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EDITORIAL

# Non-pharmacological intervention for posterior cortical atrophy

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## Abstract

Posterior cortical atrophy (PCA) is a rare neurodegenerative condition characterized by progressive visual-perceptual deficits. Although the neurocognitive profile of PCA is a growing and relatively well-established field, non-pharmacological care remains understudied and to be widely established in clinical practice. In the present work we review the available literature on non-pharmacological approaches for PCA, such as cognitive rehabilitation including individual cognitive exercises and compensatory techniques to improve autonomy in daily life, and psycho-education aiming to inform people with PCA about the nature of their visual deficits and limits of cognitive rehabilitation. The reviewed studies represented a total of 7 patients. There is a scarcity of the number of studies, and mostly consisting of case studies. Results suggest non-pharmacological intervention to be a potentially beneficial approach for the partial compensation of deficits, improvement of daily functionality and improvement of quality of life. Clinical implications and future directions are also highlighted for the advancement of the field, in order to clarify the possible role of non-pharmacological interventions, and its extent, in PCA.

**Key words:** Cognitive rehabilitation; Posterior cortical atrophy; Alzheimer's disease; Non-pharmacological intervention; Neuropsychological rehabilitation



**Core tip:** Non-pharmacological interventions remain

scarcely explored as therapies for posterior cortical atrophy (PCA). Preliminary evidence suggests the potential of cognitive rehabilitation and psychoeducation. There is a need for randomized controlled trials evaluating the efficacy and cost-effectiveness of non-pharmacological approaches in PCA.

Weill-Chounlamountry A, Alves J, Pradat-Diehl P. Non-pharmacological intervention for posterior cortical atrophy. *World J Clin Cases* 2016; 4(8): 195-201 Available from: URL: http://www.wjgnet.com/2307-8960/full/v4/i8/195.htm DOI: http://dx.doi.org/10.12998/wjcc.v4.i8.195

## INTRODUCTION

Posterior cortical atrophy (PCA) or Benson's syndrome[1] is a rare neurodegenerative syndrome mainly characterized by progressive visual-perceptual deficits. The precise prevalence and incidence of PCA are yet to be established, due to an overall lack of knowledge of this syndrome[2,3]. However, Snowden *et al*[4] reported a 5% prevalence of PCA in a population of Alzheimer's disease (AD) subjects. PCA is often described as a visual variant of AD in which there are predominant neurovisual impairments[5] with the presence of common AD brain changes such as senile and neurofibrillary plaques[6]. This latter classification is controversial because PCA can also occur as a result of other neurodegenerative diseases such as cortico-basal degeneration, Lewy body dementia or prion disease[7-9]. In those individuals with PCA with underlying Alzheimer pathology, the distribution of plaques and tangles differs from the common amnestic AD variant due to their predominance in posterior cerebral regions, sparing the middle regions of the temporal lobes[10] and also involving the white matter lateralized on the right, along visual pathways[11].

The course of PCA is characterized by insidious and progressive impairment of cognitive functions, primarily consisting of central visual deficits and excluding peripheral visual deficits or acquired focal lesions[5]. PCA patients typically present with a mean age of onset of 60 years and an average diagnostic delay of 4 years[12].

Homonymous lateral hemianopsia is often reported anecdotally in PCA, whereas this sign could be an early indicator in some patients[13]. Praxic and spatial disorders (dressing apraxia, constructional apraxia or ideomotor apraxia) are often associated[5,11,12,14]. Some studies have reported the presence of a significant reduction in verbal fluency as well as an anomia[10,15,16] related to anatomical and functional abnormalities of the left temporal-parietal junction in some patients[10,16] and deficits in working memory[15]. In the early stage of PCA, episodic memory and executive functions are relatively preserved, when comparing to typical/amnestic AD[5,11].

Daily life is severely affected by impairments in visuospatial orientation or visual recognition, and in the beginning of the disease, complaints of subjects with PCA encompass daily functioning. Difficulties in reading are the most frequently reported complaints[3,9,17-25], occurring in 80% of PCA patients[26]. In this regard, reading of text is more impaired than reading of isolated words or letters, with patients losing lines while reading and overlapping words, failing in using a "letter by letter" strategy[26] and sometimes not even being able to read their own writing[17,25]. As it can be inferred, visuospatial impairments might lead to the inability to perform simple activities of daily life [dressing[9,19,20,23,25] (how to orientate clothes to dress)] and instrumental activities such as finding the handle of a car[21], using a telephone[18] or looking at an analogue watch[18,22]. Patients can experience limitations such as be hesitating on how to sit[19], difficulties to find a way in unfamiliar surroundings[9,20,27] or even sometimes in familiar surroundings[25,28]. Gradually, PCA patients lose the ability to draw or write[20,24] and to drive a car[9,11,24,25], which might contribute to losing their job[9,18,28] when patients are of working age.

Despite a relatively well-known neurocognitive profile, non-pharmacological intervention in PCA is still rarely described or implemented, even though it is recommended[29,30] since its benefits are encouraging for the PCA patient's daily life[25,31-33].

In the available literature, two types of intervention approaches have been reported previously: (1) cognitive rehabilitation programs[25,31,32], aiming at maximizing patient cognition and functionality; and (2) psycho-educative programs[33] that consist of a didactic and therapeutic approach for people with PCA and their caregivers with the aim of facilitating coping, understanding of the disease, and reducing its impact in daily life.

Cognitive rehabilitation aims to address impaired cognitive functions (memory, executive functions, attention, *etc.*) and can be performed individually or in a group. Cognitive rehabilitation is a therapeutic intervention approach that aims to improve functioning of patients in daily life, whether in limitation of activities or in restriction of participation, as referenced by the International Classification of Functioning, Disability and Health (ICF). Furthermore, cognitive rehabilitation requires identifying individual needs and goals with suitable assessments in order to implement restorative or compensatory interventions.

Cognitive rehabilitation has shown evidence of efficacy in the treatment of cognitive disorders acquired after stroke[34,35]. Indeed, this intervention approach has also shown some evidence of efficacy in people with AD[36-39]. In a pilot study, Clare *et al*[38] has shown that people with early-stage dementia could benefit from cognitive rehabilitation and these subjects could personally identify individual goals of daily life. The research was carried out as a single-blind, randomized controlled study, in which the three following interventions (during eight sessions) were applied to 69 subjects with dementia at an early stage: (1) cognitive

rehabilitation ($n$ = 23); (2) relaxation therapy, as a placebo condition ($n$ = 24); and (3) treatment as usual (mainly pharmacological) ($n$ = 22). Goal performance improved for subjects who received cognitive rehabilitation with maintenance beyond 6 mo. without any intervention. Conversely, no change was noticed for the other two groups.

## CURRENT STATE OF ART

### *Cognitive rehabilitation*

Presently, only three case studies on three patients[25,31,32] fall within the scope of cognitive rehabilitation approaches. These described similar comprehensive approaches, which included: (1) improving autonomy in daily life as a goal; (2) individual cognitive training exercises aimed at reducing cognitive deficits; (3) introduction of compensatory techniques; and (4) a psycho-educational aspect aiming to explain to people with PCA the nature of their visual deficits and to inform them about the limits of cognitive rehabilitation as a comprehensive remediation in degenerative diseases. The first case was reported by Roca *et al*[32] and involved a 64-year-old man with PCA characterized by visual agnosia and with a complete Balint's syndrome (simultagnosia, optic ataxia and oculomotor disorders). Namely, there was a dorsal simultagnosia responsible for difficulties such as in discerning more than one object at the same time due to an attentional limitation (so that visual recognition was focusing on an isolated part of the object), optic ataxia, as well as oculomotor disorders and reading difficulties. A second case was reported by Weill-Chounlamountry *et al*[25] and involved a 60-year-old woman who presented with progressive visual disorders since age 54. She presented with visual agnosia, simultagnosia, visual-constructive apraxia, left spatial neglect and impaired visuospatial working memory, and her reading and writing abilities were affected as well. The third case was reported by Alves *et al*[31] and involved a 57-year-old man who presented with progressive decline of visuospatial and perceptive abilities, with praxic deficits and also impairment in written language. An early-stage visual variant of AD had been diagnosed 2 years earlier in this patient, following difficulties in driving, writing and reading. As it can be inferred, for these three patients, difficulties were predominantly visual, whereas memory and executive abilities were comparatively more preserved in agreement with previous descriptions[5].

Indeed, there were many similarities between those three patients. They shared a common semiology of occipitoparietal dorsal visual pathway conjugated with visual agnosia due to a disturbance of the occipitotemporal ventral visual pathway and also a relative preservation of cognitive performance without major executive functions disorder or memory impairment. For patients SS and LO (see below), the beginning of their clinical history was marked by various ophthalmological consultations before consulting neurologists. All three had preserved awareness of their disorders, likely responsible for some of the anxiety, as it is often described in PCA subjects[2,22,40].

SS, Roca's patient[32], received a cognitive intervention whose goals were selected in collaboration with the patient and his family. They aimed to improve the functioning of activities in daily life which they had considered important, such as being able to find nearby objects, diminishing difficulties in pouring drinks and being able to read messages left by his family. The cognitive rehabilitation program contained psycho-educative intervention, cognitive rehabilitation selected to reinforce preserved functions (*e.g.*, recognition of objects and visual exploration strategies) and also compensatory intervention (*e.g.*, use of tactile afferents to offset some visual problematic situations, like pouring a liquid in a glass). Weill-Chounlamountry's patient, LO, benefited from similar interventions in a multidisciplinary approach (speech therapy, occupational therapy and physiotherapy) in terms of reinforcement of residual visual abilities and compensation strategies; the patient also received psycho-educative intervention[25]. The reinforcement of residual visual abilities contained training of visual recognition (objects, pictures and scenes) and of visual exploration (where to look and how to explore in various tasks, with light pursuit as an example), with the additional aim of decreasing simultagnosia. One of the major complaints of LO was the loss of reading, which was regained once the simultagnosia and inabilities in visual exploration decreased. In addition, compensation strategies were also used in those exercises, such as the use of a rule and "finger-cursor" in order to guide the visual exploration when reading or sewing back-labels on the clothes of the patient to recover autonomy of dressing. Further activities have been conducted to provide a more comprehensive intervention and transfer of training to daily life, such as using public transport as well as planning and organizing projects. Similarly, Alves *et al*[31] have proposed a cognitive rehabilitation program with specific cognitive training sessions for written language and numbers, temporal and spatial orientation, and promotion of autonomy in daily life; these were complemented by psycho-educative intervention. After an intensive intervention of 3 sessions per week (totaling 60 h), this patient showed small neuropsychological improvements and a modest improvement in daily functioning, with the patient being better able to resort to environmental cues, such as daylight, for temporal orientation.

### *Psychoeducation*

Regarding psycho-educational interventions, Videaud *et al*[33] proposed use of a psycho-educative program for four patients with PCA and their caregivers. There were six, 2-h sessions given every 2 mo during 1 year. The program included, in order of the sessions: (1) information about the disease to enhance the understanding of PCA subjects and their caregivers; (2)

an assessment of repercussion of PCA on the activities of daily life; (3) a speaking time; (4) a use of technical aids to improve the quality of life; and (5) strengthening the knowledge and information about available help (financial and human aids). After the program, results were generally positive: The quality of life appeared unchanged, but knowledge about the disease and exchanges between participants reduced the anxiety of caregivers.

### *Motor interventions and vision training*

Lastly, to our best knowledge, no studies are available that focus on other non-pharmacological interventions, such as vision therapy supervised by orthoptists or single-component physical therapy, or physical exercise for PCA patients.

## CONCLUSION

### *Summary of findings*

Cognitive rehabilitation programs have been successful at partially remediating cognitive impairments and improving functionality in PCA, whereas the contribution of isolated psycho-educative intervention was moderate. Many studies have already shown efficacy of cognitive rehabilitation in brain injury[34,35,41] and a recent study shows that such interventions may benefit people exhibiting initial to moderate dementia[38], as is the case with the three clinical case studies of patients with PCA discussed herein[25,31,32]. Strengthening residual abilities might contribute to decreased errors in daily life and, as profiled above, to enhance the quality of life. Possibly, an awareness of some of their preserved abilities and incitement to use them allowed these patients to regain some autonomy. Following their respective interventions, the patients have thus learned to understand their disease and to develop compensatory strategies (and use them) when they were needed with a consequent improvement of the goals they have set. It is our understanding that cognitive rehabilitation intervention can be beneficial as long the overall cognitive abilities are preserved and may, thus, allow for a transfer to daily life.

### *Clinical implications for current non-pharmacological care*

In light of the aforementioned results, some prerequisites seem to be crucial to reach individual functional goals and focused requests of people with PCA: (1) it appears important to ensure that patients have a sufficient overall cognitive functioning level to follow cognitive rehabilitation[42] and to implement strategies proposed by therapists; and (2) cognitive rehabilitation should be focused on life plans of the patient and should also involve caregivers. A previous study indicated[38] that goal-oriented intervention can be helpful to people with AD, since they are able to identify goals and can provide information about their needs in daily life or in order to reduce memory deficits. In the same way, the definition of functional goals in daily life can be a key to success for cognitive rehabilitation in people with PCA. Subjects must, therefore, have realistic functional goals that are shared with therapists and caregivers and which concern either the activity, or the participation, in improving their quality of life and their environment, as referenced by the ICF.

Therefore, based on our current knowledge, cognitive rehabilitation programs designed for PCA subjects could include the following: (1) a psycho-educative intervention component, with the aim of explaining neurological mechanisms underlying the troubles experienced by the patients and their caregivers; (2) stimulation/maximization/development of preserved abilities, either in activities of daily life and/or in visual situations. Patients with PCA might underuse their residual abilities because there is sometimes a real gap between observed performance and complaints expressed. Patients should learn to reuse their skills that are preserved but underused. Psycho-educative intervention will clarify these residual abilities[33]. One example of such residual ability is the gaze. Spontaneously, patients with PCA stare and do not explore their environment, even though they retain the ability to do so. Through dedicated training of exploration with vanishing cues, patients can relearn how to explore visually, first in constrained situations and limited space (for example, a computer screen), and then transfer these trainings to larger environments ("vanishing cues," which are defined as facilitating the task being performed with cues that fade gradually until they disappear completely); (3) dedicated, focused and intensive training determined according to the goals shared by the multidisciplinary team, patients with PCA and their families (for example, writing a shopping list and being able to read it); and (4) the use of compensatory strategies for praxic disorders or spatial disorders. A standardized occupational therapy program has been previously shown to produce positive effects in stroke patients[43-45]. It uses strategy control and contains three successive phases: (1) initiation and orientation, which encompasses formulating a plan of action and selecting the correct objects; (2) execution of the selected plan; and (3) control of the result, followed by correction, if necessary. Patients learn actions with verbal aids and they can use the verbalization of the action plan during task performance. For example, cues can be labels on clothes for dressing, or a color card displayed on doors to aid in orientation in the home. The therapist teaches systematic spatial orientation of clothes before dressing, and then uses strategy control (*i.e.*, choice of clothes, orientation of clothes with a verbalization by the patient with PCA, dressing, and finally control if the dressing is performed correctly).

### *Future directions*

In the present work we reviewed the existing data on non-pharmacological interventions for PCA. Although

evidence is scarce, preliminary findings do exist for cognitive rehabilitation and psychoeducation, suggesting their potential beneficial role/impact. Moreover, present studies suggest and serve as a proof of concept for their implementation feasibility in PCA patients. These findings support related evidence in the field of dementia. For example, in a recent meta-analysis, Alves *et al*[39] showed that cognitive intervention might lead to benefits in global cognitive status. Moreover these interventions can be developed to be cost-effective and feasible options for ameliorating cognition, functionality and quality of life and/or to provide relevant experiences[46,47].

As has been observed in the global field of Alzheimer's disease and other dementias[46,48], non-pharmacological approaches might play a pivotal/relevant role within the clear need for complementing pharmacological management of PCA. Further studies assessing the potential of non-pharmacological intervention for PCA must rely on systematic enquiry through solid research design. In this regard, randomized controlled studies are considered the gold standard. A concerted and systematic effort of researchers and practitioners in the field should focus on conducting clinical research with short-term applied/applicable value that would be expected to bring clarification of both scientific and potential clinical value. For example, vision therapy studies could be conducted in order to assess their specific efficacy on the compensation, or even amelioration, of neurovisual impairments of these patients and its potential impact on daily life functionality. Indeed, recent evidence suggests that visual rehabilitation might play a relevant role in the neurorehabilitation field, both in terms of aiming at promoting recovery or compensation, and also based on underlying functional and biological neuroplasticity[49,50]. Similarly, cognitive training might delay/slow cognitive dysfunction progression in early stages and should be explored for this purpose.

Taking into account the current state of the field, we propose the following steps: (1) to conduct group studies for interventions that have thus far showed promising results, such as cognitive rehabilitation. This will also aid in clarifying possible differential effects of each therapy; (2) whenever randomized controlled studies or other group studies are not possible, due to participant number or other constraints, case studies[51] should be used, or quasi-experimental methods (*e.g*., ABAB designs with statistical methods, such as Significant Change); (3) likewise, case studies can provide a feasible option for exploring the potential role of "experimental" non-pharmacological therapies, such as vision therapy, and efforts should be developed for testing each of the available non-pharmacological therapies; and (4) studies should, therefore, sequentially focus on assessing implementation feasibility, efficacy, cost-effectiveness and differential/compared efficacy for symptoms/difficulties/functionality.

In summary, the current research in the field of dementia suggests that PCA patients show relative preserved insight in the early and moderate stages, and preliminary evidence showing promising effects for non-pharmacological interventions in PCA warrant future research.

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ORIGINAL ARTICLE

Retrospective Study

# Lateral patellofemoral ligament reconstruction to restore functional capacity in patients previously undergoing lateral retinacular release

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Author contributions: Beckert M helped design and perform the research and helped write the paper; Crebs D helped with research and manuscript editing; Nieto M helped with research and manuscript editing; Gao Y did statistical analysis and manuscript editing; and Albright J helped with study design and helped write the paper.

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## Abstract

**AIM:** To study patient outcomes after surgical correction for iatrogenic patellar instability.

**METHODS:** This retrospective study looked at 17 patients (19 knees) suffering from disabling medial patellar instability following lateral release surgery. All patients underwent lateral patellofemoral ligament (LPFL) reconstruction by a single surgeon. Assessments in all 19 cases included functional outcome scores, range of motion, and assessment for the presence of apprehension sign of the patella to determine if LPFL reconstruction surgery was successful at restoring patellofemoral stability.

**RESULTS:** No patients reported any residual postoperative symptoms of patellar instability. Also no patients demonstrated medial patellar apprehension or examiner induced subluxation with the medial instability test described earlier following LPFL reconstruction. Furthermore, all patients recovered normal range of motion compared to the contralateral limb. For patients with pre and postoperative outcome scores, the mean overall knee injury and osteoarthritis outcome score increased significantly, from 34.39 preoperatively (range: 7.7-70.12) to 69.54 postoperatively (range:

26.82-91.46) at final follow-up ($P < 0.0001$).

**CONCLUSION:** This novel technique for LPFL reconstruction is effective at restoring lateral restraint of the patellofemoral joint and improving joint functionality.

**Key words:** Lateral patellofemoral ligament; Knee; Sports medicine; Patellar instability; Orthopedics



**Core tip:** This is a case series of patients presenting with an initial history of anterior knee pain who underwent lateral capsular surgical release procedure at an outside institution. They were referred to us after a dramatic increase in their knee problems following this procedure, including recurrent medial patellar instability and pain. There are two techniques in the current literature that describe lateral patellofemoral ligament reconstruction. Here we present a third technique, as well as the specific physical examination that indicated each patient for surgery. This is an important topic because of the debilitating nature of these iatrogenic symptoms, and the 100% relief of medial patellar subluxation we were able to accomplish in the postoperative period.

Beckert M, Crebs D, Nieto M, Gao Y, Albright J. Lateral patellofemoral ligament reconstruction to restore functional capacity in patients previously undergoing lateral retinacular release. *World J Clin Cases* 2016; 4(8): 202-206 Available from: URL: http://www.wjgnet.com/2307-8960/full/v4/i8/202.htm DOI: http://dx.doi.org/10.12998/wjcc.v4.i8.202

## INTRODUCTION

Lateral retinacular release (LR) is an arthroscopic or open procedure of the lateral patellofemoral ligament (LPFL) and capsule designed to relieve pressure in the joint for some patients presenting clinically with anterior knee pain. Indications leading surgeons to pursue LR include anterior knee pain secondary to a "tight lateral band", chondromalacia patella, and "patellofemoral syndrome". Once a common procedure, LR can leads to unfavorable outcomes namely medial apprehension of the patella, which was first reported in the literature by Hughston and Deese[1]. While it is unclear how many LR procedures are performed today, the purpose of this case series is illustrate several patients referred to our tertiary care center with a dramatically worsened clinical presentation immediately following LR due to recurrent medial subluxations.

Medial subluxation is a debilitating condition characterized by the patella translating horizontally out of the trochlear groove in the medial direction, in this case due to the compromised lateral restraints during LR surgery. Hughston *et al*[2] reported 85% of patients suffering from medial patellar subluxation could not perform "light recreational activities", and 69% of patients had "severe" or "disabling" knee pain. It is for these reasons why patients seek treatment to decrease pain and increase function. Previous studies have shown LPFL reconstruction in patients with iatrogenic medial patellar instability significantly improved pain and functionality[3,4].

Two techniques currently describe LPFL reconstruction in the literature. Teitge *et al*[5] describes a technique using a patellar tendon graft, while Saper and Shneider[6] describe a technique using a quadriceps tendon graft. Using a third technique described below, it is hypothesized that restoration of the lateral capsule and LPFL will solve the sudden deteriorated state that followed the excessive lateral release in the immediate postoperative period. We also look to explore specific preoperative clinical exam findings that indicate the patient will significantly benefit from LPFL reconstruction.

## MATERIALS AND METHODS

This was a retrospective case series done at the University of Iowa, with all data obtained by a single investigator (Beckert MW) following Institutional Board Review (IRB) approval between July 2013 and August 2014. Data was collected during standard follow-up care in an outpatient clinic setting, however three patients had no record of post-operative functional outcome scores and these were administered by telephone. All patients were seen clinically for follow-up after LPFL reconstruction, with an average final follow-up of 2.05 years. The senior author (Albright JP) identified the study population during the patient's clinical evaluation for symptoms following LR. Clinical evaluations were conducted by Albright JP in all cases. Twenty-three consecutive LPFL reconstructions following LR conducted between 2009 and 2014 were eligible for the study. All patients demonstrated medial apprehension of the patella preoperatively, and a majority experienced frank medial subluxation. The study excluded patients with concurrent lateral patellar apprehension to focus on the iatrogenic medial instability caused by prior lateral release.

Chief complaints during preoperative evaluation were pain, instability, and frank medial patellar subluxations or dislocations, frequently while walking on flat ground. The diagnosis of medial subluxation is made by beginning with the leg relaxed in full extension. The examiner then pushes and holds the patella in a medial position as the free hand is placed in the popliteal space and passively flexes the patient's knee with relaxed quadriceps. Within the first 20-30 degrees the examiner observes a biomechanical acceleration ("jerk") as the patella slides back into the trochlear groove as the knee is flexed further. This "jerk" is recognized by the patient as what happens to them frequently; often with every step as they are walking. This is opposed to the smooth re-entry gliding of a non-subluxating patella that can be observed in the patient's opposite leg. The process is

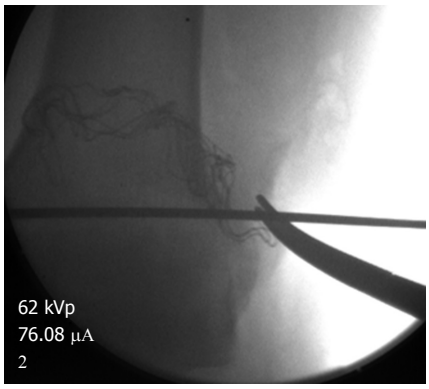


**Figure 1 Start position of the guide pin, placed in the lateral femoral epicondyle.**

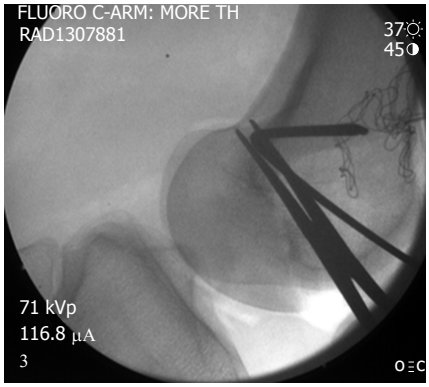


**Figure 2 Position of the entrance tunnel from lateral X-ray compared to the Blumensaat line and the posterior cortex in that area.**

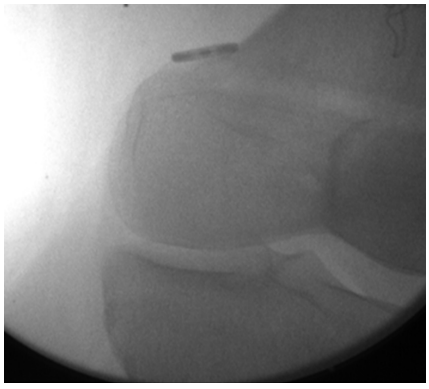

**Figure 3 EndoButton type device fixed on the medial femoral condyle.** Site of graft fixation.

then repeated with the leg again starting relaxed in full extension, pushing the patella medially and then ask the patient to actively create an active quadriceps contraction prior to the passive flexion of the knee. Here it is observed that muscle contraction aligns the extensor mechanism to the point that there is smooth patellar movement back into the trochlear groove when the knee is subsequently flexed by the examiner. A similar examination and technique was previously described by Fulkerson[7].

In addition to medial patellar subluxation and/or apprehension, two clinical indications were used by the senior author to pursue LPFL reconstruction. In all instances, patients experienced at least some noticeable improvement in joint functionality from using a patellar-stabilizing sleeve with a medial buttress and walking across the exam room. Additionally, in some patients the examiner could restore patellar stability and decrease pain by placing a finger medially on their patella during gait. Both scenarios provided objective evidence that LPFL reconstruction would prove beneficial for the patient.

### *Procedure*

An initial incision was made lateral to the patella, dissecting down to the lateral retinaculum, allowing the exposure of both the patellar surface and posterior surface of the lateral femoral condyle. In all cases a loose encapsulated layer of scar tissue was filling the gap between the edges of the capsule. A lateral parapatellar arthrotomy was performed by incising this scar tissue. At that point the soft tissues of the joint were inspected. It was determined whether or not the re-approximation of the edges of the lateral retinaculum might cause too much tension on the patellofemoral articulation. Therefore, the reconstruction procedure was performed with an allograft hamstring tendon.

LPFL reconstruction was conducted using fluoroscopy to check the start position of the guide pin, placed in the lateral femoral epicondyle in an isometric point that mimics the ideal location of an medial patellofemoral ligament (MPFL) reconstruction (Figure 1). This location is confirmed by: (1) position of the entrance tunnel from lateral X-ray compared to the Blumensaat line and the posterior cortex in that area (Figure 2); (2) checking the isometry of the potential graft from 100 degrees of flexion out to full extension; and (3) stimulation of the femoral nerve to achieve quadriceps contraction as described by McDermott *et al*[8]. The length between the guide pin entry point and the patella was checked from extension to flexion using a free suture and allograft, proceeding once satisfied. The extensor muscle was stimulated *via* femoral nerve catheter with the leg in full extension to access the effect of the quadriceps activity on the length of the graft itself. The semitendinosus allograft was secured to the lateral femoral condyle using an EndoButton type device fixed on the medial femoral condyle (Figure 3). The allograft was then sutured to the patella in isometric position with the knee in flexion, using a FiberWire and Krachow suture. The graft was passed through the EndoButton loop to allow a two-tailed graft suturing as described by Csintalan *et al*[9] for MPFLs. A decompression window was created in the iliotibial band at the femoral origin of the LPFL re-construction as it exited the femoral condyle on its way to the patella (Figure 4). This prevents the anterior and posterior motion that occurs naturally with the iliotibial band from interfering with the reconstruction. Once the graft was in place the isometry was then checked as

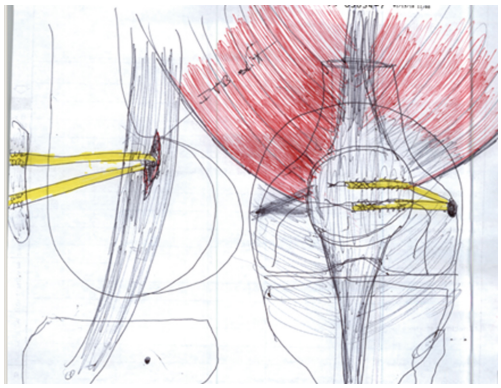

**Figure 4 Decompression window illustration in both AP and lateral view.**

well as the quadriceps activity on the length of the graft. The FiberWire attached to the allograft was securely fixed to the anterior aspect of the patella with no bone suture anchors. After observing neutral patella tracking through a full range of motion with an absence of medial apprehension, wounds were thoroughly irrigated and closed with a 2-0 Vicryl suture.

There have been reports of simply reattaching the capsule, however in this series we chose to reconstruct the LPFL allograft, because reattachment of the atrophied sides of the release was thought to create too much patellofemoral tension in these cases.

Patients began passive and active motion on the first postoperative day with the goal of reaching 90 degrees by 14 d postoperative. Patients were locked in extension in a hinged brace during ambulation and sleeping for the first 2 wk postoperatively. Active straight leg raising and eccentric quadriceps contraction allowing knee flexion to occur as far as tolerated were also encouraged starting early after surgery.

All patients returned to clinic for postoperative physical examination. During physical examination, testing for both medial apprehension and subluxation was conducted, as described previously. Other outcomes included range of motion assessed by the senior author and knee injury and osteoarthritis outcome scores (KOOS) survey questionnaire[8]. Physical examination data used in the study was taken during patient's most recent follow-up appointment.

## RESULTS

Between August 2009 and August 2014, the senior author (Albright JP) performed LPFL reconstruction with or without partial synovectomy and plicectomy on 20 patients (23 knees) who previously had LR surgery done at an outside institution. Two patients were excluded from the study due to both medial and lateral patellar instability, while a third patient declined to participate in the study when contacted. This brought the total study population to 17 patients (19 knees). The average patient age at the time of LPFL reconstruction was 29.46 years (15.4-54.35). There were 18 females and one male. All patients completed postoperative physical examination. Postoperative KOOS were obtained for 89.5% of patients. Twelve of the 19 knees (63.2%) had both pre and postoperative KOOS scores available for statistical comparison using one-way T scores. The threshold for statistical significance was $P < 0.05$[10].

No patients reported any residual postoperative symptoms of patellar instability. Also no patients demonstrated medial patellar apprehension or examiner induced subluxation with the medial instability test described earlier following LPFL reconstruction. Furthermore, all patients recovered normal range of motion compared to the contralateral limb. For patients with pre and postoperative outcome scores, the mean overall KOOS score increased significantly, from 34.39 preoperatively (range: 7.7-70.12) to 69.54 postoperatively (range: 26.82-91.46) at final follow-up ($P < 0.0001$).

## DISCUSSION

LR surgeries extensive enough to compromise the lateral restraints of the patella can indeed lead to medial patellar subluxation. Although the quadriceps muscles can provide stability by contracting to keep the patella within the trochlear groove in some circumstances such as getting up out of chairs or walking stairs, on flat surfaces these muscles are normally silent during the swing phase of gait, allowing the patella to drift medially into a subluxed position. As the knee passively flexes in subsequent stages, the patella violently re-enters the groove as seen clinically during the novel subluxation exam in our patients as described above. These patients had great difficulty with the mere act of walking on flat ground because their patella subluxes with nearly every step.

The restoration of the lateral capsule and LPFL was 100% effective in treating the sudden deteriorated state that followed the excessive lateral release in the immediate postoperative period by eliminating the patient's medial apprehension. Reconstruction of the LPFL also significantly improved knee pain and function in these patients, as determined by: (1) the postoperative physical exam in all patients; (2) postoperative functional outcome scores; and (3) pre-*vs* postoperative outcome scores when available.

This study had a number of limitations. Although 17 of 19 knees completed postoperative outcome scores, only 12 knees completed both pre and postoperative outcome scores and were made available for data analysis. This only eliminated the quantification of how poorly patients were doing preoperatively, but from a clinical standpoint it was impressive beyond quantification. Their major complaint was that they had an operation for anterior knee pain but made dramatically worse following the procedure. Post LPFL reconstruction however, 89.5% patients completed functional outcome scores, and our findings agree with that of other literature analyzing the outcomes of restoring lateral restraint following LR surgery[3,4]. This,

along with the fact that all 19 knees completed the physical exam portion of postoperative evaluation, leads us to believe the limitations of the data analysis did not have a major effect on our conclusions. Other outcome measures were also used to strengthen our findings, including range of motion, and the presence of medial apprehension and subluxation to objectively determine the success of LPFL reconstruction.

This is a case series of patients presenting with an initial history of anterior knee pain who had undergone a lateral capsular surgical release procedure. They were referred because of a dramatic increase in their knee problems due to an additional appearance of postoperative patellar instability. Our preoperative clinical exam assessment found that patellar instability existed, and the restoration of patellar stability with LPFL reconstruction led to a significant improvement in patient outcomes.

## COMMENTS

### Background

Patellar instability is a severely debilitating pathology of the patellofemoral joint that is relatively common, especially in adolescence. Lateral release is an arthroscopic or open procedure though to reduce tension on some of the lateral restraints of the knee that are believed to cause pain in some patients, but often causes unintended patellar instability. In these cases, it is imperative that lateral structures of the knee joint be repaired to correct for this recurrent medial instability.

### Research frontiers

The literature only supports two prior methods of lateral patellofemoral ligament (LPFL) reconstruction for iatrogenic patellar instability. The authors present a third technique along with outcome measures in a series of patients.

### Applications

The authors' results show favorable outcomes with the technique described for LPFL reconstruction and justifies its future use in this specific patient population.

### Peer-review

This is an important topic with excellent results of the described technique.

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ORIGINAL ARTICLE

Retrospective Study

# Abdominal tuberculosis: Diagnosis and demographics, a 10-year retrospective review from a single centre

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Author contributions: Nayagam JS wrote the manuscript; Nayagam JS and Mullender C collected and analysed the data; Nayagam JS, Cosgrove C and Poullis A convened the idea; Mullender C drafted the manuscript; Cosgrove C edited the manuscript; Cosgrove C and Poullis A supervised the project; Poullis A finalised the manuscript in its current version.

Institutional review board statement: In line with national guidelines in the United Kingdom ethics committee approval is not required for this type of study (as a retrospective analysis of a previously investigated clinical cohort) according to the United Kingdom National Research Ethics Service.

Conflict-of-interest statement: No potential conflict of interest; no financial support.

Data sharing statement: Dataset is available from the corresponding author. Consent was not obtained but the presented data are anonymized and risk of identification is low.



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## Abstract

**AIM:** To review all cases of abdominal tuberculosis (ATB) for demographic details, diagnostic work up and evidence of vitamin D deficiency.

**METHODS:** This was a retrospective analysis of all patients diagnosed with ATB from June 2003 to August 2013 at St George's Hospital, London. Demographic data was available from the local tuberculosis database. Further clinical information was collected from electronic patient records, including radiology, endoscopy, microbiology, histology, biochemistry and serology. Patients were classified as either confirmed ATB [if mycobacteria tuberculosis (MTB) was cultured from abdominal site] or presumed ATB (if suggestive findings or high clinical suspicion). Subtypes of ATB were classified as tuberculosis (TB) peritonitis, luminal TB, solid organ TB or from a combination of sites.

**RESULTS:** There were a total of 65 cases identified in this time period, with a mean of 6.5 cases per year (range 4-9). Mean age 42 years, 49.2% females. Fifty-two point three percent were South Asian, 38.5% African. Forty-nine point two percent had gastrointestinal endoscopy, 30.8% paracentesis and 24.6% surgery in order to obtain samples. Forty-seven point seven percent were defined as confirmed ATB with positive culture of MTB from abdominal sites, the rest were treated as presumed ATB. Twenty-four point six percent had co-existing sputum culture positive

for MTB, and 30.8% had an abnormal chest X-ray. Subtypes of ATB: 35.4% had TB peritonitis; 27.7% luminal TB; 3.1% solid organ TB; and 33.8% TB at a combination of abdominal sites. Thirteen point nine percent were human immunodeficiency virus positive, all with CD4 count less than 300 cells/μL. Seventy point five percent had severe vitamin D deficiency, and 25% were vitamin D deficient.

**CONCLUSION:** ATB mainly affects young South Asian and African patients, with difficulties in confirming diagnosis despite a range of non-invasive and invasive diagnostic tests.

**Key words:** Abdominal; Gastrointestinal; Tuberculosis; Vitamin D; Human immunodeficiency virus



**Core tip:** This is a single centre retrospective study of all cases of abdominal tuberculosis (ATB) from a single centre in the developed world. ATB remains a rare condition in the United Kingdom, which mainly occurs in young South Asians and African patients, and remains difficult to diagnose. When suspected, endoscopic biopsies must be taken in normal saline for microbiological assessment to help confirm the diagnosis. Chest radiology and sputum analysis should be performed as nearly a quarter had co-existent pulmonary tuberculosis. Vitamin D deficiency is common, and often severe, in ATB. Patients with human immunodeficiency virus and ATB present with low CD4 counts.

Nayagam JS, Mullender C, Cosgrove C, Poullis A. Abdominal tuberculosis: Diagnosis and demographics, a 10-year retrospective review from a single centre. *World J Clin Cases* 2016; 4(8): 207-212 Available from: URL: http://www.wjgnet.com/2307-8960/full/v4/i8/207.htm DOI: http://dx.doi.org/10.12998/wjcc.v4.i8.207

## INTRODUCTION

Abdominal tuberculosis (ATB) is a rare form of extra-pulmonary tuberculosis which can prove to be clinically challenging. It remains difficult to diagnose due to the non-specific presentation, variable anatomical location and lack of sensitive diagnostic tools[1]. ATB may occur anywhere within the abdomen, involving the gastrointestinal tract, visceral organs or peritoneum. There can be difficulty differentiating ATB from Crohn's disease clinically, endoscopically and histologically[2,3]. Both diseases have a predilection for the small bowel, and cause chronic granulomatous inflammation[4]. There are significant clinical implications of incorrectly diagnosing tuberculosis (TB) and committing patients to a prolonged course of toxic chemotherapy; or missing TB with public health implications and causing life-threatening disseminated TB if immunosuppressant therapy is erroneously initiated.

Although TB rates in the United Kingdom have plateaued in recent years, there is still a high prevalence in the non-United Kingdom born population, predominantly in urban areas[5]. The number of extra-pulmonary cases, including ATB, is increasing with figures in England and Wales rising from 175 cases of gastro-intestinal TB in 1999, to 315 cases in 2006[6]. This increase is largely attributable to an increase in the number of non-United Kingdom-born cases, in whom extra-pulmonary TB is much more common. In London, 5% of all cases of TB were ATB in 2012[7].

There has been an emergence of a role for vitamin D beyond bone health, as an immune regulator[8]. Supplementation of vitamin D is now routine practice in the treatment of pulmonary TB (PTB), although clinical data is not conclusive and there may only be a clinical benefit in a subgroup of patients[9-11]. The association between inflammatory bowel disease (IBD) and vitamin D deficiency is well recognised[12] and has become of great interest. Animal models suggest that mice with vitamin D deficiency suffer from more severe colitis, potentially due to compromised mucosal barrier[13]. The role of vitamin D deficiency in ATB has yet to be investigated.

We report a retrospective study of all cases of ATB from an urban area, with a large migrant population, over a 10-year period. The objectives of this study were to: (1) describe the demographic profile of patients with ATB; (2) review the use of diagnostic modalities, both non-invasive and invasive, and the certainty of diagnosis of ATB; and (3) report vitamin D status of patients diagnosed with ATB.

## MATERIALS AND METHODS

### *Patient selection*

We performed a retrospective review of patients treated for ATB at St George's Hospital, London, from June 2003 to August 2013. Cases were identified from a local TB database, which encompasses all patients who have received treatment for TB at St George's Hospital. Patients from this database were included in our study if they were reported as having TB involvement at an abdominal site. Cases were excluded if they were not investigated at St George's Hospital, or if there was no evidence of involvement at an abdominal site.

### *Clinical information*

Demographic data was available from the TB database. Further information on clinical investigations was collected from the electronic patient records: Radiology [including chest radiograph, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), small bowel series], endoscopy, methods by which samples were obtained, microbiology, histology, vitamin D level and human immunodeficiency virus (HIV) status.

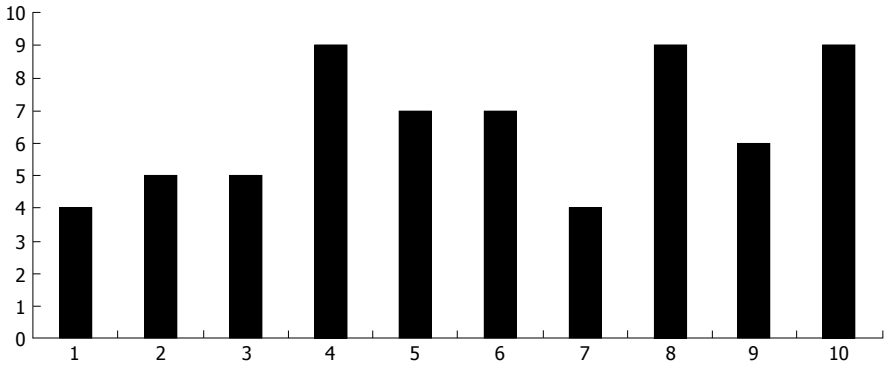


**Figure 1 Number of cases of abdominal tuberculosis by year of the study.**

**Table 1 Age and ethnicity of patients with abdominal tuberculosis**

| | Number | Mean age | Median age |
|---|---|---|---|
| South Asian | 34 (52.3%) | 42.3 | 39.5 |
| African | 25 (38.5%) | 36.1 | 35 |
| European | 5 (7.7%) | 72.4 | 69 |
| Caribbean | 1 (1.5%) | 28 | 28 |

**Table 2 Chest radiograph findings *n* (%)**

| Findings | Number of patients (*n* = 64) |
|---|---|
| Normal | 44 (68.9) |
| Consolidation | 11 (17.2) |
| Pleural effusion | 3 (4.7) |
| Lymphadenopathy (para-tracheal, hilar) | 6 (9.4) |
| Apical scarring | 1 (1.6) |
| Nodularity | 5 (7.8) |
| Focal lesion | 1 (1.6) |
| Pleural thickening | 1 (1.6) |
| Multiple radiographic features | 7 (10.9) |
| Mention of tuberculosis in differential | 6 (9.4) |

### *Definitions*

Ethnicity was defined as European, South Asian (Indian, Pakistani, Bangladeshi, Sri Lankan, any other Asian background), African, and Caribbean.

The reference range for vitamin D at our hospital is from 75-200 nmol/L. Vitamin D levels were classified as deficient (25-50 nmol/L) or severe deficiency (< 25 nmol/L). Vitamin D analysis was carried out using the immunodiagnostic systems total 25 OH vitamin D2 and D3 (25 hydroxy-vitamin D) assay according to manufacturer's instruction.

In defining the accuracy of diagnosis of ATB we sub-grouped into: (1) confirmed ATB if mycobacterium tuberculosis (MTB) was cultured from an abdominal site; and (2) presumed ATB if there was suggestive histology, suggestive history, suggestive imaging. MTB was isolated from an extra-abdominal site, or if there was high clinical suspicion.

TB peritonitis was defined as ascites, peritoneal thickening or intra-abdominal lymph nodes; luminal TB was defined as TB from the oesophagus to the anus, including perianal disease; solid organ TB was hepatic or biliary involvement; combination of sites was when TB was isolated from one site, but imaging suggested concurrent involvement at other sites.

### *Statistical analysis*

Due to small sub-group numbers comparative statistical analysis was not carried out.

### *Ethics approval*

Ethics committee approval was not required (as a retrospective analysis of a previously investigated clinical cohort) according to the United Kingdom National Research Ethics Service[14].

## RESULTS

### *Number of cases*

A total of 65 adults were treated at St George's Hospital for ATB from June 2003 to August 2013. By our case definition, 31 (47.7%) were confirmed ATB, and 34 (52.3%) were presumed ATB. The number of cases of ATB over the 10-year period has remained stable, with a mean of 6.5 cases per year (range 4-9), which is demonstrated in Figure 1.

### *Demographics*

The mean age was 42 years (range 16-97 years). There were 32 females (49.2%) and 33 males (50.8%). Age and ethnicity split is shown in Table 1.

### *Radiology*

Sixty-four (98.5%) were screened for pulmonary TB with a chest X-ray, with 20 (30.8% of total) reported as abnormal (Table 2).

Prior to diagnosis with ATB patients underwent the following abdominal imaging modalities: 42 (64.6%) ultrasound, 46 (70.8%) CT, 2 (3.1%) MRI, and 7 (10.8%) barium small bowel series. The main findings of these are shown in Table 3.

### *Endoscopy*

Prior to diagnosis 32 (49.2%) underwent gastrointestinal endoscopy (GIE): 18 had upper GIE; 21 lower GIE;

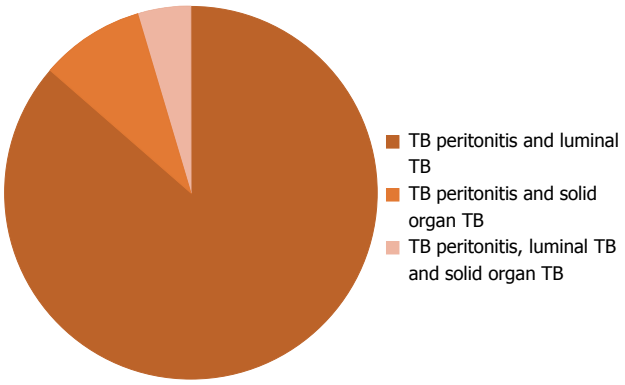


**Figure 2 Breakdown of sites of abdominal tuberculosis involvement where combination of sites.** TB: Tuberculosis.

**Table 3 Ultrasound and computed tomography findings prior to diagnosis with abdominal tuberculosis *n* (%)**

| | |
|---|---|
| Ultrasound findings (*n* = 42) | |
| Mention of TB as differential | 3 (7.1) |
| Normal | 16 (38.1) |
| Ascites | 16 (38.1) |
| Intra-abdominal lymphadenopathy | 6 (14.3) |
| Bowel thickening | 7 (16.7) |
| Abdominal collection | 1 (2.4) |
| 2 ultrasound findings[1] | 4 (9.5) |
| CT findings (*n* = 46) | |
| Mention of TB as differential | 22 (47.8) |
| Normal | 3 (6.5) |
| Ascites | 20 (43.5) |
| Intra-abdominal lymphadenopathy | 25 (54.3) |
| Bowel thickening | 27 (58.7) |
| Peritoneal thickening | 9 (19.6) |
| 1 CT finding[2] | 17 (37.0) |
| 2 CT findings | 15 (32.6) |
| 3 or more CT findings | 11 (23.9) |

[1]Four cases of intra-abdominal lymphadenopathy and bowel thickening; [2]Three had only ascites, 7 only intra-abdominal lymphadenopathy, 6 only bowel thickening, 1 only peritoneal thickening. TB: Tuberculosis; CT: Computed tomography.

and 7 both upper and lower GIE (Table 4).

### Methods of obtaining samples

The main invasive modality undertaken to obtain samples was endoscopy in 49.2% of subjects, paracentesis was carried out in 30.8% and surgery in 24.6%, other samples were acquired under radiological guidance, from swabs and from peritoneal dialysis fluid. The majority of specimens were sent for histology, however there was variability in numbers sent for microbiology, with endoscopic specimens being sent less frequently, and also having a lower yield (Table 5).

### Microbiology

MTB was cultured from abdominal sites in 31 (47.7%) patients. Of those with culture positive ATB, 30 (96.8%) patients had fully sensitive organisms, 1 (3.2%) patient had an organism resistant to isoniazid and streptomycin.

Forty-four (67.7%) had sputum samples sent for AFB testing and TB culture, with 16 (24.6% of total) obtaining positive cultures for MTB. Of the positive MTB sputum cultures, 15 patients (93.8%) were fully sensitive and 1 (6.3%) resistant to pyrazinamide.

The site of positive cultures was 7 (11%) isolated TB from abdominal and pulmonary specimens, 24 (37%) cultured from abdominal specimens alone, 9 (14%) cultured from pulmonary specimens alone, and 25 (38%) with no positive culture.

**Table 4 Endoscopic findings prior to diagnosis with abdominal tuberculosis *n* (%)**

| | |
|---|---|
| Upper GI endoscopy findings (*n* = 18) | |
| Normal | 10 (55.5) |
| Oesophageal ulcers | 3 (16.7) |
| Gastritis | 1 (5.6) |
| Gastric ulcer | 1 (5.6) |
| Duodenitis | 3 (16.7) |
| Duodenal scalloping | 1 (5.6) |
| 2 endoscopic findings[1] | 1 (5.6) |
| Lower GI endoscopy findings (*n* = 21) | |
| Normal | 4 (19.0) |
| Colonic inflammation | 11 (52.4) |
| Ileocolonic ulcers | 5 (23.8) |
| Ileocolonic nodularity | 1 (4.8) |
| Colonic stricture | 2 (9.5) |
| Colonic polyps | 2 (9.5) |
| 2 endoscopic findings[2] | 4 (19.0) |

[1]Oesophageal ulcer and gastritis; [2]Tow had colonic inflammation and ulcers, 2 had colonic inflammation and an inflammatory colonic stricture. GI: Gastrointestinal.

### Site of ATB

The sites are shown in Figure 2: TB peritonitis in 23 (35.4%), luminal TB in 18 (27.7%), solid organ TB in 2 (3.1%), combination of sites in 22 (33.8%).

### HIV

Fifty (77%) of the patients were tested for HIV, and 9 (13.9%) were HIV positive. All HIV positive patients were non-Europeans (1 South Asian, 8 Africans). Five were diagnosed with ATB within 1 year of their HIV diagnosis. All had low CD4 counts (below 300 cells/μL), 7 (77.8%) had a CD4 count of less than 200 cells/μL, 4 had been started on antiretrovirals prior to diagnosis and had undetectable viral load.

### Vitamin D

Vitamin D levels were measured within 1 year of diagnosis (mean 1.4 mo, median 1 mo, range 0-8 mo) in 44 patients (67.7%), with a mean of 23 nmol/L (range undetectable-102 nmol/L). Of those who had measurements, 31 (70.5%) had severe deficiency (< 25 nmol/L), 11 (25%) were deficient (25-50 nmol/L).

## DISCUSSION

In this study, we have reported a large modern urban case series of ATB in the developed world, where the number of cases per year has remained stable. It has

**Table 5 Breakdown of histology and microbiology according to route of specimen acquisition**

| | *n* | Cytology/histology sent | Cytology/histology suggestive of tuberculosis | Microbiology sent | Culture + *ve* |
|---|---|---|---|---|---|
| Paracentesis | 20 | 20 (100%) | 7/9 (77.8%) had lymphocytic effusion[1] | 19 (95%) | 11/19 (57.9%) |
| Endoscopy | 32 | 28 (87.5%) | 14/28 (50%) | 10 (31.3%) | 3/10 (30%) |
| Surgery | 16 | 15 (93.8%) | 14/15 (93.3%) | 13 (81.3%) | 9/13 (69.2%) |

[1]For ascitic fluid which was culture positive a lymphocyte count was not provided.

mainly been detected in young minority ethnic groups, with a small group of elderly Europeans. As part of their diagnostic work up they have undergone multiple investigations, and despite this the confirmation by MTB culture occurs in less than half of cases. Nearly a quarter of patients had co-existent active pulmonary tuberculosis. Vitamin D deficiency is common and often severe in patients with ATB, and includes the whole range of demographics and phenotypes of disease.

The majority of patients were South Asian, however there was a significant cohort of African origin. Previous studies in United Kingdom investigating ATB, from Leicester[15], Blackburn[16] and Bradford[17] have shown the majority of ATB occurring in South Asians, and in London particularly in the Bangladeshi population[18]. Our series demonstrates a sizeable young African population with ATB in London, a demographic not previously reported.

Confirming a diagnosis of abdominal TB is notoriously difficult, with the rate of positive culture from abdominal sites below 50% in our series, which is similar to previously reported rates in the United Kingdom[17]. Non-invasive imaging is useful to characterise the phenotype of abdominal TB and suggest sites for sampling, however it does not assist in obtaining a definitive diagnosis, with sampling for microbiological confirmation the gold standard for diagnosis. Only 61.8% of samples acquired from invasive procedures (paracentesis, endoscopy, surgery) were sent for micobiological assessment. In our series ascitic fluid and surgically acquired biopsies had a highest diagnostic yield. There was low rate of endoscopic biopsies being sent for microbiological assessment. If TB is part of the differential diagnosis then endoscopists must ensure microbiological samples are routinely taken into normal saline solution rather than the standard formalin histopathology pots and sent for MTB culture[1]. The identification of resistant strains highlights the importance of appropriate sampling and microbiological analysis. Despite this, if ATB is suspected then empirical treatment is warranted[5], as even with extensive interventions it is not always possible to obtain positive cultures.

The clinical implications of vitamin D deficiency, and replacement in ATB, is yet to be reported. In the absence of this, data can be extrapolated from vitamin D deficiency linked with pulmonary TB[19] and inflammatory bowel disease[20], both conditions which have clinical and pathological similarities to ATB. Of particular interest is whether, as suggested in animal models, there is a compromised colonic mucosal barrier with vitamin D deficiency[13], which could exacerbate luminal and peritoneal TB in particular. Further work needs to be carried out to identify if vitamin D deficiency play a pathological role in abdominal TB and if supplementation improves treatment outcomes, however in the interim, testing and treatment of any deficiency appears to be advisable.

There are limitations to our study. The first being the retrospective design which is subject to recall bias and confounding variables, as the data set was not specifically designed for research purposes. However, our data was collected from interrogation of clinical and electronic records making this less likely and the variables studied (vitamin D, demographics and HIV) have independently been described as important factors in TB[19,21]. The second limitation is based on the definition of vitamin D deficiency which despite multiple studies has no robust classification and therefore the accepted ranges of vitamin D deficiency are variable. Also the vitamin D levels taken for our patients were not always from the time of diagnosis, and hence could be subject to other factors, such as the effect of treatment. Due to the small numbers in each sub-group (for sites, ethnicity, vitamin D levels and HIV status) comparative statistics was not possible, larger studies are needed to explore these findings further. Unfortunately, the time that different ethnic groups had been resident in the United Kingdom was unknown.

In summary, this large retrospective series reminds us that ATB is still a diagnosis to consider in individuals presenting with abdominal symptoms in the developed world, particularly in patients from ethnic minorities. Diagnosis can be challenging and requires a multidisciplinary approach with involvement from Radiology, Microbiology, Gastroenterology, Surgery, Infectious Diseases and Respiratory teams. An increase in invasive samples being sent for microbiology may assist in improving the rates of a positive diagnosis.

## COMMENTS

### Background

Abdominal tuberculosis (ATB) accounts for 5% of all cases of tuberculosis (TB) in London. There is a high prevalence of TB in non-United Kingdom born population, in previous United Kingdom based studies this has been predominantly in patients of South Asian origin. Positive confirmation of a diagnosis of ATB through culture of mycobacterium tuberculosis was achieved in 29 of 50 patients in a previous United Kingdom based series. Vitamin D

replacement has been historically used in the treatment of TB, however vitamin D supplementation in the treatment of pulmonary TB (PTB) has not been shown to improve clinical outcomes.

### Research frontiers

Vitamin D has emerged as an immune regulator, with associations between vitamin D deficiency and both inflammatory bowel disease and pulmonary TB, however benefits from supplementation in PTB are not clear, and its role in ATB has not yet been identified.

### Innovations and breakthrough

This is the first United Kingdom based series which has identified patients of African origin with ATB. This is the first series of patients with ATB which has identified a prevalence of vitamin D deficiency.

### Applications

This study confirms the difficulties in diagnosing patients with ATB despite a number of invasive investigations, and reinforces the importance of sending tissue for microbiological assessment. It suggests that all patients with ATB should be screened for PTB, human immunodeficiency virus and vitamin D deficiency.

### Peer-review

This retrospective study, conducted with a large sample, is a valuable contribution to the literature on ATB. This is an interesting case series that is presented in a concise and balanced manner.

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ORIGINAL ARTICLE

Retrospective Study

# Prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis by pancreatic duct stenting using a loop-tipped guidewire

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## Abstract

**AIM:** To examine whether it is possible to prevent the occurrence of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis in patients experiencing difficulties with selective biliary duct cannulation by pancreatic duct stenting using a loop-tipped guidewire.

**METHODS:** Procedure success rate, frequency of unintended insertion of the guidewire into side branches of the pancreatic duct, and incidence of procedural accidents were examined using a loop-tipped guidewire (Group A, 20 patients), and a conventional straight-type guidewire (Group B, 20 patients).

**RESULTS:** The success rate of the procedure was 100% in both groups. Unintended insertion of the guidewire into a side branch of the pancreatic duct occurred 0.056 ± 0.23 (0-1) times in Group A and 2.3 ±

1.84 (0-5) times in Group B; thus, unintended insertion of the guidewire into a side branch of the pancreatic duct was seen significantly less frequently in Group A. There were no procedural accidents in Group A, whereas pancreatitis occurred in one Group B patient; however, the difference between the two groups was not statistically significant. The serum amylase level after ERCP was 257.15 ± 136.4 (88-628) IU/L in Group A, and 552.05 ± 534.57 (101-2389) IU/L in Group B, showing a significantly lower value in Group A. Hyperamylasemia was found in two patients (10%) in Group A, and nine (45%) in Group B, showing a significantly lower value in Group A.

**CONCLUSION:** The results suggest that in patients who experience difficulties with biliary cannulation, the use of a loop-tipped guidewire for pancreatic duct stenting may assist with the prevention of post-ERCP pancreatitis, and thereby to a reduction of the risk of post-ERCP pancreatitis or hyperamylasemia.

**Key words:** Hyperamylasemia; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Guidewire



**Core tip:** The results suggest that a loop-tipped guidewire inserted in the pancreatic duct during stenting in patients who experience difficulties with selective biliary duct cannulation has the potential to assist with prevention of unintended insertion of the guidewire into side branches of the pancreatic duct, and thereby contribute to a reduced risk of post-endoscopic retrograde cholangiopancreatography pancreatitis or hyperamylasemia.

Sakai Y, Tsuyuguchi T, Sugiyama H, Hayashi M, Senoo J, Sasaki R, Kusakabe Y, Nakamura M, Yasui S, Mikata R, Miyazaki M, Yokosuka O. Prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis by pancreatic duct stenting using a loop-tipped guidewire. *World J Clin Cases* 2016; 4(8): 213-218 Available from: URL: http://www.wjgnet.com/2307-8960/full/v4/i8/213.htm DOI: http://dx.doi.org/10.12998/wjcc.v4.i8.213

## INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is no longer a purely diagnostic technique. It has developed into an exclusively therapeutic procedure to treat pancreatic and biliary disease. Post-ERCP pancreatitis is the commonest early side effect of this procedure. Although its frequency varies according to the patient, technique employed, definition of pancreatitis, and method of investigation, it is generally reported to occur in about 4.5% of patients based on the results of large-scale prospective studies[1-7]. Although in many cases post-ERCP pancreatitis abates after admission and treatment for a few days, it may aggravate. It is reported that about 0.04% of patients need surgery, while about 0.03% of them die[1,2,4,5]. Elimination of post-ERCP pancreatitis is a goal that has not been achieved, despite various attempts, since the adoption of ERCP. Pancreatic duct stenting is one strategy for preventing the occurrence of pancreatitis caused by duodenal papilledema resulting from difficult selective biliary cannulation. Its usefulness is frequently reported[8-12].

However, in some patients who experience difficult selective biliary duct cannulation, pancreatic duct stenting fails to prevent pancreatitis. One past report describing the occurrence of pancreatitis in spite of pancreatic duct stenting suggests that pancreatitis might have occurred due to frequent unintended insertion of the guidewire into side branches of the pancreatic duct when placing the guidewire into the pancreatic duct[8]. In this study, we aimed to prevent post-ERCP pancreatitis by placing a loop-tipped guidewire into the pancreatic duct during pancreatic duct stenting in patients experiencing difficult selective biliary duct cannulation.

## MATERIALS AND METHODS

Of 1218 patients undergoing ERCP from and of 502 patients who had not undergone ERCP from experiencing difficulty with selective biliary cannulation were April 2013 to April 2015, 20 patients included in our test group (Group A). Of these 20 patients, 1 underwent diagnostic ERCP and 19 underwent therapeutic ERCP. We decided whether the patients had experienced difficulties with selective biliary cannulation 15 min after cannulation had been attempted employing a contrast method using a conventional imaging catheter and directly examining the duodenal papilla. ERCP was conducted by doctors who are accredited as specialists by the Japan Gastroenterological Endoscopy Society and have experience with ERCP in more than 3000 patients (Y.S., T.T.). Group A consisted of 10 male patients and 10 female patients, whose mean age was 71.68 ± 9.53 years old (43 to 85 years old), and included 12 with bile duct stones, three with cholangiocarcinoma, 3 with pancreatic cancer, 1 with intraductal papillary mucinous neoplasm (IPMN) and one with gallbladder cancer.

Before ERCP, all patients were given the standard premedication consisting of intravenous administration of midazolam (3-10 mg), with the dose adjusted for age and tolerance. Scopolamine butylbromide or glucagon was used to induce duodenal relaxation. During ERCP, arterial oxygen saturation was continuously monitored using a pulse oximeter. Patients were kept fasting for at least 24 h after the procedure and remained as inpatients for at least 72 h. They received an 8-h infusion of a protease inhibitor (nafamostat mesylate, 20 mg/d) and antibiotics (SBT/CPZ, 2 g/d) for 2 d.

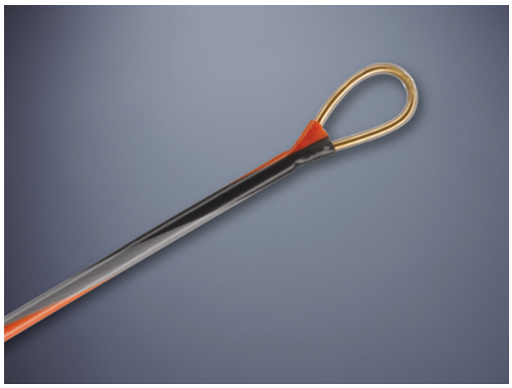

**Figure 1 Loop-tipped guidewire.** A 0.035-inch guidewire (Loop tip: Cook Medical Corp., Winston-Salem, NC).

Serum amylase level was measured before and about 18 h after ERCP. The reference range for amylase was 42-135 IU/L. Patients were clinically evaluated for symptoms (abdominal pain, nausea, *etc*.) and physical findings (abdominal tenderness).

The procedures were carried out using side-viewing duodenoscopes (JF240, 260V, TJF260V: Olympus Corp., Tokyo, Japan). For cannulation, catheters PR-104Q, PR-110Q-1 and PR-233Q were used. A 0.035-inch guidewire (Loop tip: Cook Medical Corp., Winston-Salem, NC) was employed (Figure 1). In patients experiencing difficult selective biliary duct cannulation, cannulation of the biliary duct was attempted using the pancreatic duct guidewire-placing method (P-GW) or transpancreatic precut papillotomy (TPPP) by inserting the guidewire into the pancreatic duct. In such cases, the guidewire was first inserted up to the caudal segment of the main pancreatic duct to keep the guidewire stable during the procedure. Since the pancreatic duct was imaged by contrast imaging, close attention was paid to its morphology to prevent the guidewire from being inserted into any side branches. If any resistance was encountered during insertion, the guidewire was moved forward carefully so as to avoid labored insertion. Patients were excluded from this study if cannulation of both the biliary and pancreatic ducts failed. The loop tip guidewire was inserted into the pancreatic duct *via* the cannula to stabilize the papilla of Vater and straighten the bile duct terminal (Figure 2). In P-GW, biliary cannulation was tried with the guidewire placed in the pancreatic duct. After successful cannulation of the biliary duct, additional procedures such as endoscopic sphincterotomy (EST), biliary stent placement, intraductal ultrasonography (IDUS), biopsy of the biliary duct, *etc*., were performed as necessary. If selective biliary cannulation was not successful using the P-GW method, even when tried for 15 min, TPPP was selected instead. TPPP was conducted using a Clever-Cut3V (Olympus Corp.) at the discretion of the operator. A papillotome was inserted under induction with a guidewire. Dissection was conducted using an Olympus PSD-20 Electrosurgical Unit (Olympus Corp.) at a power of 25 W. Dissection was conducted by directing the dissection blade toward the 11 or 12 o'clock direction of the bile duct. After dissection, biliary cannulation was attempted using the bile discharged from the opening in the biliary duct and the biliary mucosa as marks. After successful biliary cannulation, the target procedure was conducted; thereafter, pancreatic duct stenting was carried out. A 5-Fr 3-cm straight unilateral-flapped stent (Geenen Pancreatic Stent: Cook Medical Corp.) was placed using a pushing tube under induction of the guidewire in a configuration that crossed the duodenal papilla. Cannulation was conducted employing a conventional imaging catheter. No wire-guided cannulation was performed. We did not use nonsteroidal anti-inflammatory drugs (NSAIDs) in all cases. All the patients had provided their written informed consent before these diagnostic and therapeutic procedures. Iatrogenic morbidity was assessed according to the criteria of Cotton *et al*[13]. Hyperamylasemia was defined as serum amylase $\geqslant$ 3 times the normal level (42-135 IU/L), independent of the presence or absence of abdominal pain. The results obtained using the loop-tipped guidewire were compared with those obtained in 20 patients (Group B) who had experienced difficult selective biliary duct cannulation and in whom the procedures had been successful after the placement of a guidewire (0.025-inch VisiGlide, straight type: Olympus Corp.) in the pancreatic duct. These 20 patients were selected from among 188 patients who had undergone ERCP for the first time between December 2010 and May 2012. All the procedures were recorded on video, and the success rate, incidence of procedural accidents, and frequency of unintended insertion of the guidewire into a side branch of the pancreatic duct were examined. This study was conducted after obtaining the approval of the Institutional Ethics Committee.

### *Statistical analysis*

Data were analyzed using Statistical Package for Social Science (SPSS) software version 18 (SPSS, Chicago, IL). Fisher's exact probability test, Student's *t* test, and the Mann-Whitney *U*-test were used for statistical analyses to compare the blood test findings and patient background. A *P* value of $< 0.05$ was regarded as significant.

## RESULTS

There were no significant differences in clinical background between patients who underwent ERCP using the loop-tipped guidewire (Group A) and those who underwent ERCP using the straight-type guidewire (Group B) (Table 1). In Group A, 5 patients underwent P-GW, and 15 patients underwent P-GW + TPPP. Selective biliary duct insertion was successful in all these patients. EST was then conducted in 19 patients, lithotomy in 12, biliary stent placement in 7, IDUS in 1, and biopsy of the biliary duct in 1. No significant

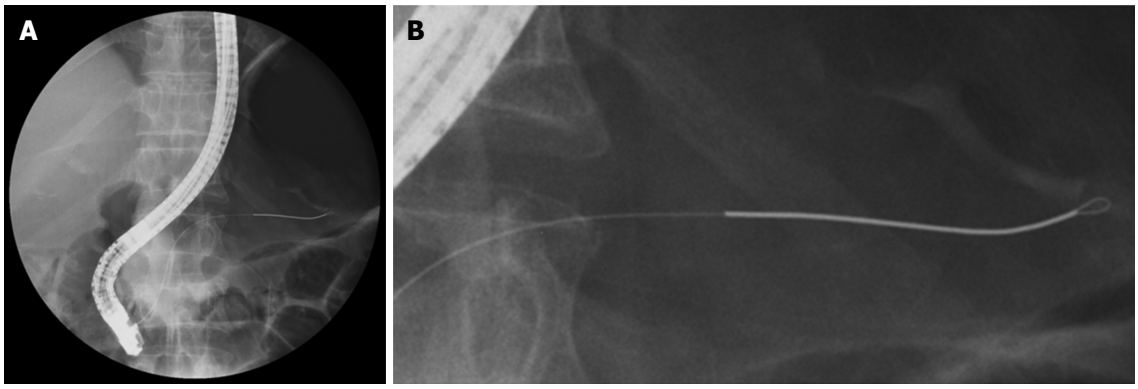


**Figure 2 Fluoroscopic image of loop-tipped guidewire.** A: Fluoroscopic image showing a loop-type guidewire inside the pancreatic duct; B: Enlarged image of the tip of the guidewire.

**Table 1 Patient clinical background**

| | Loop-type guidewire (Group A) | Straight-type guidewire (Group B) | *P*-value |
|---|---|---|---|
| *n* | 20 | 20 | |
| Age | 71.68 ± 9.53 (43-85) | 71.63 ± 10.36 (39-80) | NS |
| Sex | Males 10, females 10 | Males 10, females 10 | NS |
| Disease | | | |
| Bile duct stone | 12 | 12 | NS |
| Cholangiocarcinoma | 3 | 3 | NS |
| Pancreatic cancer | 3 | 2 | NS |
| Gallbladder cancer | 1 | 2 | NS |
| Intraductal papillary mucinous neoplasm | 1 | 1 | NS |
| Diagnostic ERCP | 1 | 1 | NS |
| Therapeutic ERCP | 19 | 19 | NS |

ERCP: Endoscopic retrograde cholangiopancreatography; NS: Not significant.

**Table 2 Procedures conducted**

| | Loop-type guidewire (Group A) | Straight-type guidewire (Group B) | *P*-value |
|---|---|---|---|
| P-GW | 5 | 6 | NS |
| P-GW + TPPP | 15 | 14 | NS |
| Endoscopic sphincterotomy | 19 | 19 | NS |
| Lithotomy | 12 | 12 | NS |
| Biliary stenting | 7 | 7 | NS |
| Intraductal ultrasonography | 1 | 1 | NS |
| Biopsy of the bile duct | 1 | 1 | NS |
| Pancreatic duct stenting | 20 | 20 | NS |
| Pancreatic duct injection | 1.263 ± 0.562 (1-3) | 1.286 ± 0.588 (1-3) | NS |
| Cannulation time (min) | 33.45 ± 9.72 (16-50) | 34.9 ± 97.04 (16-50) | NS |
| Procedure time (min) | 44.2 ± 13.22 (23-70) | 46.8 ± 14.03 (20-63) | NS |

TPPP: Transpancreatic precut papillotomy; NS: Not significant; P-GW: Guidewire-placing method.

differences were observed in the procedures conducted, cannulation time, or even procedure time when compared with Group B (Table 2). The target procedures were accomplished in both groups of patients. After completion of the procedure, pancreatic duct stenting was attempted and proved successful in all the patients in both groups. No procedural accidents, such as bleeding, perforation, or pancreatitis were observed in Group A. In Group B, there were no cases of bleeding or perforation, but mild pancreatitis was observed in one patient, who was treated conservatively. The serum amylase level at baseline was 72.84 ± 20.63 (41-112) IU/L in Group A, and 72.75 ± 20.40 (43-120) IU/L in Group B, showing no significant difference between the two groups. After ERCP, the level of serum amylase was 257.15 ± 136.44 (88-628) IU/L in Group A, and 552.05 ± 534.57 (101-2389) IU/L in Group B, showing a significantly lower value in Group A. The frequency of unintended insertions of the guidewire into a side branch of the pancreatic duct was 0.056 ± 0.23 (0-1) times in Group A, and 2.3 ± 1.84 (0-5) times in Group B, showing a significantly reduced frequency in Group A. Hyperamylasemia was observed in two patients (10%) in Group A, and in nine (45%) patients in Group B: A significantly lower value in Group A (Table 3).

## DISCUSSION

According to past reports on the prevention of post-ERCP pancreatitis, it is currently impossible to completely suppress its occurrence. Post-ERCP pancreatitis is thought to occur due to various factors. It is suspected that one or more concomitant factors may cause pancreatitis. With regard to its prevention, pancreatic duct stenting has been reported to be useful in reducing the increased inner pressure associated with buildup of pancreatic juice caused by postoperative papilledema. However, pancreatitis cannot as yet be entirely eliminated. According to our experience, pancreatitis occurs in patients who experience difficulties with selective biliary duct cannulation: These patients are more likely to develop postoperative papilledema despite pancreatic duct stenting, probably because the reason for the development of post-ERCP pancreatitis is

**Table 3 Complications and other events**

| | Loop-type guidewire (Group A) | Straight-type guidewire (Group B) | *P*-value |
|---|---|---|---|
| Bleeding | 0 | 0 | - |
| Perforation | 0 | 0 | - |
| Pancreatitis | 0 | 1 | NS |
| Pre-ERCP amylase level | 72.84 ± 20.63 (41-112) | 72.75 ± 20.40 (43-120) | NS |
| Post-ERCP amylase level | 257.15 ± 136.44 (88-628) | 552.05 ± 534.57 (101-2389) | < 0.05 |
| Frequency of unintended insertion of the guidewire into a side branch of the pancreatic duct | 0.056 ± 0.23 (0-1) | 2.3 ± 1.84 (0-5) | < 0.05 |
| Hyperamylasemia | 2 | 9 | < 0.05 |
| Others | 0 | 0 | - |

ERCP: Endoscopic retrograde cholangiopancreatography; NS: Not significant.

multifactorial. Examination of patients who experience difficult selective biliary duct cannulation and who developed pancreatitis even after pancreatic duct stenting showed that in some patients the guidewire was unintentionally inserted into a side branch of the pancreatic duct multiple times: This may have stimulated or damaged the pancreatic duct, leading to the onset of pancreatitis[8]. Since the pancreatic duct is S-shaped and has branches, it is difficult to insert a guidewire through the main pancreatic duct toward its caudal segment without any problems. Since the guidewire we employed in this study is the loop-tipped type, we anticipated a very low risk of inserting the guidewire into a branch of the duct. Video recording of the actual procedure revealed that unintended insertion of the guidewire into a branch did not occur unless the branched pancreatic duct was markedly dilated due to IPMN. Since the conventional straight-type guidewire is reported to be too frequently, although unintentionally, inserted into side branches of the pancreatic duct, it appears that amylase levels after ERCP tended to be significantly lower in the A group, although no significant difference was observed in the incidence of pancreatitis. These results suggest that pancreatic duct stenting after inserting the loop-tipped guidewire into the pancreatic duct can prevent stimulation or damage to the pancreatic duct by unintended insertion of the guidewire into branched ducts and thus reduce the risk of pancreatitis. Another type of guidewire, the J-type tip guidewire, is associated with a lower risk of insertion into branched ducts. However, its tip may be unintentionally inserted into the branched ducts while retracting the guidewire. Therefore, the loop-tipped guidewire is currently the design with the lowest risk of unintended insertion into side branches of the pancreatic duct[14,15]. This study was conducted in a small number of patients, but the results warrant future studies using larger samples that would include randomized controlled trials. Although this study was conducted using the contrast method and a catheter, inevitably examination by wire-guided cannulation will become necessary. With regard to the contrast method, since a contrast radiograph of the pancreatic duct is often taken when inserting the guidewire into the pancreatic duct, the openness of the pancreatic duct can be assessed to some degree. Contrast medium is not used for wire-guided cannulation, however: The guidewire is advanced blindly, without assessing the openness of the pancreatic duct[14-17], and if the loop-tipped guidewire is not inserted easily into the side branches of the pancreatic duct, this method can be considered even more useful. Various examinations may be necessary to further evaluate the usefulness of this type of guidewire.

Our results suggest that a loop-tipped guidewire inserted into the pancreatic duct during stenting in patients who experience difficulty with selective biliary duct cannulation could assist with the prevention of unintended insertion of the guidewire into side branches of the pancreatic duct, and thereby to a reduced risk of post-ERCP pancreatitis or hyperamylasemia.

## COMMENTS

### Background

Preventing post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis is a task that has not been resolved since the introduction of ERCP, despite numerous attempts. As one of such attempts, pancreatic duct stenting is used to prevent the occurrence of pancreatitis caused by duodenal papilledema resulting from difficult selective biliary cannulation, and its usefulness is frequently reported. In this study, the authors aimed to prevent post-ERCP pancreatitis by placing a loop-tipped guidewire into the pancreatic duct while pancreatic duct stenting is attempted in patients who experienced difficulty with selective biliary duct cannulation.

### Research frontiers

Procedure success rate, frequency of unintended insertion of the guidewire into side branches of the pancreatic duct, and incidence of procedural accidents were examined using a loop-tipped guidewire (Group A, 20 patients), and a conventional straight-type guidewire (Group B, 20 patients).

### Innovations and breakthroughs

Unintended insertion of the guidewire into a side branch of the pancreatic duct occurred 0.056 ± 0.23 (0-1) times in Group A and 2.3 ± 1.84 (0-5) times in Group B: Thus, unintended insertion of the guidewire into a side branch of the pancreatic duct was seen significantly less frequently in Group A. Hyperamylasemia was found in two patients (10%) in Group A, and in nine patients (45%) in Group B, showing a significantly lower value in Group A. Pancreatic duct stenting using a loop-tipped guidewire may assist with the prevention of post-ERCP pancreatitis, and thereby to a reduction in the risk of post-ERCP pancreatitis or hyperamylasemia.

### Applications

Pancreatitis caused by duodenal papilledema due to difficult selective biliary cannulation.

### Terminology

The results suggest that in patients experiencing difficulty with biliary cannulation, pancreatic duct stenting using a loop-tipped guidewire can assist with the prevention of post-ERCP pancreatitis, and thereby to a reduction in the risk of post-ERCP pancreatitis or hyperamylasemia.

### Peer-review

This is very interesting manuscript from the clinical point of view.

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CASE REPORT

# Coronary artery occlusion after arterial switch operation in an asymptomatic 15-year-old boy

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## Abstract

A 15-year-old boy with transposition of the great arteries (TGA) and neonatal arterial switch operation (ASO) presented with complete occlusion of the left main coronary artery (LMCA). Intra-operatively, an intramural left coronary artery was identified. Therefore, since age 7 years he had a series of screening exercise stress tests. At 13 years old, he had 3 to 4 mm ST segment depression in the infero-lateral leads without symptoms. This progressed to 4.2 mm inferior ST segment depression at 15 years old with normal stress echocardiogram. Sestamibi myocardial perfusion scan and cardiac magnetic resonance imaging was inconclusive. Therefore, a coronary angiogram was obtained which showed complete occlusion of the LMCA with ample collateralization from the right coronary artery system. This was later confirmed on a computed tomogram (CT) angiogram, obtained in preparation of coronary artery bypass grafting. The case illustrates the difficulty of detecting coronary artery stenosis and occlusion in young patients with rich collateralization. Coronary CT angiogram and conventional angiography were the best imaging modalities to detect coronary anomalies in this adolescent with surgically corrected TGA. Screening CT angiography may be warranted for TGA patients, particularly for those with known coronary anomalies.

**Key words:** Transposition of the great vessels; Arterial switch operation; Coronary angiography; Ergometry; Coronary occlusion

**Core tip:** In complete transposition of the great arteries (TGA), neonatal arterial switch operation offers excellent long term survival. Yet there can be late coronary artery complications. In this case, an asymptomatic teenager had an abnormal screening exercise-stress test leading to the identification of complete left coronary occlusion. This case illustrates how rich coronary collateralization can obscure even complete coronary occlusion. As such, young patients pose a unique diagnostic challenge. Coronary computed tomogram (CT) angiogram and conventional angiography were the best imaging modalities to detect the problem. Screening CT angiography may be warranted for TGA patients, particularly for those with known coronary anomalies.

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## INTRODUCTION

Complete transposition of the great arteries (TGA) is the most common cyanotic heart defect and lethal unless treated during infancy. Currently, most patients undergo an arterial switch operation (ASO) which involves transfer of the coronary arteries from the native to the neo-aorta. Successful coronary transfer during the ASO is crucial for long term morbidity and mortality of this operation[1]. There is increasing awareness of late coronary artery complications in long-term survivors following the ASO[1-4]. Patients with these late coronary lesions may be asymptomatic. Therefore, adult guidelines have recommended routine screening coronary angiography but this approach is not widely accepted in Pediatrics[5]. This case illustrates the limitations of the different other diagnostic techniques available to detect myocardial ischemia in this scenario.

## CASE REPORT

A 15-year-old boy presented with an abnormal screening exercise stress test. He had undergone ASO for complete TGA as a newborn. Intra-operatively, he was found to have an intramural course of the left main coronary artery (LMCA) and also required revision of the operation for bleeding a day later. During serial follow up, he was asymptomatic. Physical examination was unremarkable except for obesity and a grade 2/6 systolic ejection murmur at the left sternal border with radiation to the back. The murmur was consistent with mild branch pulmonary artery stenosis, documented on baseline echocardiogram. He underwent his first maximal exercise stress test (EST) using the Bruce protocol at 7 years of age. Initially, he showed non-specific infero-lateral ST segment depression of up to 2 mm. Repeat EST at age 13 showed 3 to 4 mm inferolateral ST segment depression. This was deemed incidental in the absence of clinical symptoms and with a normal stress echocardiogram. Serial screening Holter electrocardiograms were also reassuring with rare isolated unifocal premature contractions. At age 15, follow up EST revealed up to 4.2 mm inferior and lateral ST segment depression, again with a normal stress echocardiogram. The patient was restricted from competitive sports and started on beta blocker therapy. He subsequently reported resolution of the palpitations that he had felt but never mentioned before. On follow up, sestamibi stress test after one months of atenolol, the ST segment changes were reproducible and unchanged. Myocardial perfusion didn't show ischemia or wall motion abnormalities. However, there was a fixed anterior and antero-septal defect with no evidence of ischemia. Cardiac magnetic resonance imaging (MRI) with late gadolinium enhancement was negative. The coronary arteries were not seen well on MRI. A coronary angiogram then revealed complete ostial occlusion of the LMCA (Figure 1). There was with ample collateralization from the right coronary artery system retrograde supplying the LMCA (Figure 1). A computer tomography angiogram (obtained in preparation for the surgical revascularization procedure) also showed diffuse hypoplasia of the left coronary artery system (Figure 1B-D). The patient underwent coronary artery bypass grafting with the left internal mammary artery to the left anterior descending (LAD). He is now a year out from his bypass surgery and is doing well clinically. However, there is persistent mild inferolateral ST segment depression on maximal EST with normal stress echocardiogram.

## DISCUSSION

Occult coronary artery obstruction has been increasingly recognized in long-term survivors following the ASO[1-4]. Therefore, lifelong follow-up is recommended after ASO, and a one-time evaluation of the patency of the coronary arteries has to be considered according to the current American Heart Association/European Society of Cardiology (AHA/ESC) guidelines for adults with congenital heart disease[5,6]. This case illustrates the difficulties encountered in diagnosing late coronary events years after the ASO in young patients without atherosclerosis. Many patients with late coronary lesions are asymptomatic or are not aware of the significance of symptoms (like this patient who didn't report his palpitations). If coronary stenosis developed slowly in young patients, collaterals can develop. Myocardial ischemia then may manifest itself late, well into teenage years. Occult coronary problems may be unmasked by growth spurts and increased oxygen demand as the adolescents challenge themselves more in sports and other activities. Although retrograde perfusion from

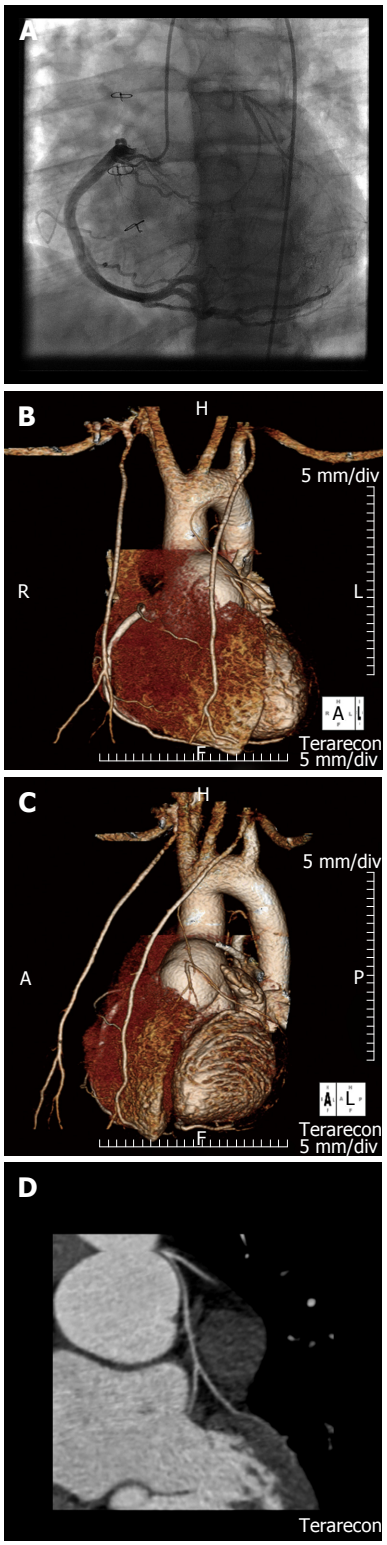


**Figure 1 Conventional and computer tomographic coronary angiogram in a 15-year-old patient with infero-lateral ST segment changes on exercise stress test following arterial switch operation for complete transposition of the great arteries.** Aortic root injection at catheterization demonstrates retrograde filling of the completely occluded LMCA from ample collaterals vessels from the right (A). CT angiographic views of the antero-posterior (B), left anterior oblique (C) and coronary views (D) indicates ostial occlusion and hypoplasia of the LMCA with collateralization from at the enlarged right coronary artery. CT: Computed tomogram; LMCA: Left main coronary artery.

collateral circulation may initially provide sufficient perfusion of the myocardium, coronary blood flow can become insufficient with growth and during periods of increased myocardial demand. This puts these patients at risk for sudden cardiac death as first sign of their coronary problem.

Adult congenital heart disease guidelines now comprise a recommendation for coronary angiography after ASO[2]. However, in Pediatric Cardiology, the practice of routine coronary angiography in ASO survivors has not been widely implemented as the risk benefit ratio for cardiac catheterization in asymptomatic ASO survivors is unclear[7]. Computed tomogram (CT) angiogram now offers a more acceptable screening method that is equally highly sensitive and specific. In children, non-invasive methods to assess coronaries are preferable. This case shows that a CT angiogram provided optimal visualization of the coronary anatomy. Based on this experience, CT angiograms could potentially become the screening test of choice to assess coronary anatomy following the ASO for TGA. It also allows excellent interrogation of the branch pulmonary arteries following the Lecompte maneuver.

Treatment of coronary artery problems following ASO for TGA can be challenging. Surgical and percutaneous coronary revascularization has been employed in patients with evidence of myocardial ischemia with mixed results[8]. Based upon the experience with surgical intervention for anomalous origin of the coronary artery from opposite sinus in the absence of structural heart disease, we know that nearly half of the children still had abnormal stress testing electrocardiogram (ECG) findings with normal stress echocardiograms post-operatively[9,10]. Therefore, further follow up of these patients is challenging.

This case calls attention to the potential of coronary CT angiogram in diagnosing late coronary obstruction in patients post arterial switch operation for transposition of the great arteries. Screening with exercise stress testing helped to raise suspicion of a problem but this standard method was ultimately non-diagnostic in this scenario. Therefore, CT angiogram or coronary angiogram should be considered in teenagers, as recommended by current guidelines for the management of adults with surgically corrected transposition of the great arteries.

## COMMENTS

### *Case characteristics*

The 15-year-old male patient was asymptomatic but had a severe coronary artery problem putting him at risk for sudden cardiac death following arterial switch operation for complete transposition of the great arteries as a newborn.

### *Clinical diagnosis*

Complete occlusion of the left coronary artery.

### *Differential diagnosis*

Nonspecific ST segment changes.

### *Imaging diagnosis*

Complete occlusion of left coronary artery.

### Treatment
Coronary artery bypass operation.

### Related reports
Late coronary artery complications are a recognized complication of the arterial switch operation for complete transposition of the great arteries. However, the optimal diagnostic work up is still unclear.

### Term explanation
Computed tomogram computer tomography.

### Experiences and lessons
Treatment of coronary artery problems following arterial switch operation for transposition of the great arteries (TGA) can be challenging due to their atypical presentation compared to adults with ischemic heart disease.

### Peer-review
The authors present a case report of complete left main coronary artery occlusion after arterial switch operation in an asymptomatic15-year-old boy. They have concluded that coronary computed tomography angiogram or coronary angiogram (CAG) should be considered in patients with TGA. This manuscript is nicely structured and well written.

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CASE REPORT

# Electroconvulsive therapy and/or plasmapheresis in autoimmune encephalitis?

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## Abstract

Autoimmune encephalitis is a poorly understood condition that can present with a combination of neurological and psychiatric symptoms, either of which may predominate. There are many autoantibodies associated with a variety of clinical syndromes - anti-N-Methyl-D-Aspartate receptor (NMDAR) is the commonest. Currently, the most widely used therapy is prompt plasmapheresis and steroid treatment (and tumour resection if indicated), followed by second line immunosuppression if this fails. Given the growing awareness of autoimmune encephalitis as an entity, it is increasingly important that we consider it as a potential diagnosis in order to provide timely, effective treatment. We discuss several previously published case reports and one new case. These reports examined the effects of electroconvulsive therapy (ECT) on patients with autoimmune encephalitis, particularly those in whom psychiatric symptoms are especially debilitating and refractory to standard treatment. We also discuss factors predicting good outcome and possible mechanisms by which ECT may be effective. Numerous cases, such as those presented by Wingfield, Tsutsui, Florance, Sansing, Braakman and Matsumoto, demonstrate effective use of ECT in anti-NMDAR encephalitis patients with severe psychiatric symptoms such as catatonia, psychosis, narcolepsy and stupor who had failed to respond to standard treatments alone. We also present a new case of a 71-year-old female who presented to a psychiatric unit initially with depression, which escalated to catatonia, delusions, nihilism and auditory hallucinations. After anti-NMDAR antibodies were isolated, she was treated by the neurology team with plasmapheresis and steroids, with a partial response. She received multiple sessions of

ECT and her psychiatric symptoms completely resolved and she returned to her premorbid state. For this reason, we suggest that ECT should be considered, particularly in those patients who are non-responders to standard therapies.

**Key words:** Autoimmune encephalitis; Electroconvulsive therapies; Autoantibodies; Plasmapheresis



**Core tip:** Although there are still only a small number of reports supporting the theory that electroconvulsive therapies is effective in treating symptoms of autoimmune encephalitis, it is reasonable to suggest that it should be considered as an alternative/adjunct to standard immunosuppressive therapies. There is a difficulty in differentiating between "functional" causes of psychosis and psychosis seen in anti-N Methyl D Aspartate receptor encephalitis, which may lead to some patients being treated inappropriately with anti-psychotics rather than immunomodulatory treatments. It is crucial for clinicians to be aware of the potential for patients to present to either psychiatry or neurology services to allow timely diagnosis and prompt, appropriate treatment.

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## INTRODUCTION

It has been established that autoantibody mediated encephalitides can present with altered mental states[1-3]. Psychiatric presentation of autoimmune encephalitis has attracted considerable interest since the association with autoantibodies was discovered, particularly as many of these syndromes have demonstrated excellent responses to immunomodulatory therapies and may be underdiagnosed[1]. Anti N-Methyl-D-Aspartate receptor (NMDAR) encephalitis appears to be the commonest form, followed by anti-Voltage Gated Potassium Channel (VGKC) mediated encephalitis [which actually encompasses a number of subtypes including anti Leucine-rich Glioma Inactivated 1 (LGI1) and Contactin-Associated Protein 2 (CASPR2)]. Other antibodies associated with encephalitis with psychiatric presentations are anti Gamma-Aminobutyric Acid A (GABA-A), Gamma-Aminobutyric Acid B (GABA-B), Glutamate Decarboxylase (GAD) and α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid (AMPA) receptor antibodies[4].

Presentation appears to differ according to the associated antibody. Anti LGI1 encephalitis presents with "a classic limbic encephalitis" but also rapid eye movement (REM) sleep disorders and occasionally movement abnormalities. Patients with anti-CASPR2 encephalitis tend to develop Morvan syndrome which is characterized by a limbic encephalitis, neuromyotonia and autonomic features[5,6]. Anti-GAD associated encephalitis presents as "stiff man syndrome", with cerebellar ataxia and seizures, although psychiatric symptoms may also feature[5,7]. Those with anti-GABA-B encephalitis develop seizures early on in their presentation, alongside memory loss, confusion and hallucinations[5,8]. Anti-AMPA encephalitis is predominantly a paraneoplastic phenomenon, which presents with limbic encephalitis, confusion, memory impairment, seizures and psychosis[5,9].

The presentation in anti-NMDAR mediated encephalitis initially appeared to follow a predictable timeline, with a viral-type prodrome followed by neuropsychiatric symptoms, then subsequent movement abnormalities and autonomic dysfunction[4,10]. Short term memory loss, personality and behavioural changes, language disintegration (including reduced verbal output or mutism), psychosis, paranoia, agitation and catatonia have been the most commonly described psychiatric presentations in this type of autoimmune encephalitis[10-13]. However, further studies have shown that anti-NMDAR encephalitis may not follow this progressive stepwise presentation and can present with isolated psychiatric symptoms[2,11], or have relapses with isolated psychiatric symptoms[14] which then makes consideration of possible autoimmune aetiology in the psychiatric setting even more crucial.

Early treatment in autoimmune encephalitis accelerates recovery, reduces ongoing disability and prevents relapse[1,3]. It is important to initially exclude an underlying neoplastic process with computed tomography (CT), magnetic resonance (MR) or positron emission tomography (PET) imaging. In the absence of any malignancy, the recommended treatment is prompt and aggressive immunotherapy[1,3]. Plasmapheresis or intravenous immunoglobulins in combination with corticosteroids is the first line therapy. A review of over 500 patients with anti-NMDAR encephalitis showed that 53% of those treated with immunosuppression (and tumour removal if indicated) made improvement within 4 wk[15]. Further immunosuppressive drugs are often required if this first line therapy fails - cyclophosphamide and rituximab are the most commonly used[2].

Interestingly, other treatments including electroconvulsive therapy (ECT) have also been used and found to be at least partially effective in a number of cases[9,16-18]. Indeed, several patients have made extraordinary recoveries after ECT administration, with improvement in stupor, catatonia, psychosis and delusions[15].

Braakman presented a case of a 47-year-old previously healthy male who presented with progressive psychiatric symptoms following an upper respiratory tract infection[19]. Extensive investigations were performed,

including multiple CT and MR images, which did not reveal any abnormality. Cerebrospinal fluid (CSF) showed a pleocytosis and the patient received therapy initially for a viral encephalitis and subsequently for encephalitis lethargica (with intravenous lorazepam and 3 d of intravenous methylprednisolone). His psychiatric symptoms failed to resolve and he therefore underwent 7 sessions of bilateral ECT, which eventually induced remission. All symptoms, including mutism, hallucinations, oculogyric crises and extrapyramidal symptoms resolved and he returned to work within 2 years. Retrospective analysis of his CSF revealed anti-NMDAR antibodies and this was therefore concluded to be anti-NMDAR encephalitis. A further case reported by Matsumoto described an 18-year-old Japanese male who presented with delusions, catalepsy, convulsions and involuntary tongue movements following influenza[20]. Initial investigations did not reveal a diagnosis and he was treated initially for catatonic schizophrenia with antipsychotics, lorazepam and valproate, which failed to provoke sufficient clinical response. He proceeded to receive 13 sessions of ECT and made a complete recovery. Again, CSF results only became available after discharge, which were also positive for anti-NMDAR antibodies.

## CASE REPORT

A 71-year-old previously healthy female presented to her general practitioner (GP) in October 2013 with malaise and bilateral shoulder pain. Her erythrocyte sedimentation rate (ESR) was raised at 45 mm/h and C-reactive protein (CRP) levels were noted to be raised and she was therefore commenced on treatment for presumed Polymyalgia Rheumatica with Prednisolone at 15 mg once per day (OD) for 3 wk and continued on a reducing dose. She started to show signs of low mood at the start of her course of steroids, accompanied by obsessional thoughts about her boiler exploding and paranoid thoughts about her husband wanting to harm her. She presented to her GP following completion of her steroids and was prescribed Fluoxetine, Buspirone and Diazepam to alleviate these symptoms following advice from a psychiatrist.

The patient's mental health continued to deteriorate despite these measures in the community. She lost 2 stones in weight and was unable to fulfil her activities of daily living (ADLs). She developed severe depressive symptoms with catatonia, posturing with psychotic symptoms, paranoid thoughts nihilistic delusions and auditory hallucinations, so was admitted informally to a psychiatric ward in November 2013.

At the time of admission she appeared withdrawn, confused, disorientated and was responding to auditory hallucinations. General physical examination was normal and there were no abnormal neurological findings. Her bloods on admission revealed a raised ESR, white cell count (with neutrophilia), raised urea and creatinine and raised alanine transaminase (ALT) and bilirubin. Lumbar puncture for CSF analysis was not felt to be indicated at this time. A CT scan of her head did not demonstrate any abnormality.

The patient received a trial of several psychotropic medications initially - Risperidone and Sertraline, which were titrated up to 5 mg and 100 mg respectively. Shortly afterwards, she became dizzy and had an unresponsive episode so was admitted to the emergency department for further investigations. No physical cause was identified and her Risperidone and Sertraline were stopped. She was subsequently treated with maximal doses of Mirtazapine, Venlafaxine and Olanzapine, which also failed to significantly improve her symptoms. She remained severely depressed with persistent catatonia and psychotic features so she was commenced on an ECT regime. She received 4 cycles of ECT until she unfortunately fell, sustaining a fractured neck of femur, which required an operation and a 2 wk admission to an orthopaedic ward.

On return to the psychiatric unit in January 2014, the results of the autoantibody screen sent on admission became available which showed that her serum sample was low positive for anti-NMDAR antibodies. She was therefore referred to the Neurology team for their input in management in light of the new diagnosis of anti-NMDAR encephalitis.

Magnetic Resonance Imaging (MRI) of her head at this time was normal. A CT scan of her chest, abdomen and pelvis did not identify an ovarian teratoma or any other evidence of malignancy. Electroencephalogram (EEG) performed indicated a post-central dominant Rhythm at 9 Hz up to 90 mV, which spread to the anterior regions. A considerable amount of theta activity was noted which was diffusely present, especially over the temporal regions and a slight slowing was occasionally noted over the temporal areas bilaterally.

The patient was transferred to a Neurology unit to receive plasmapheresis in March 2014 after careful consideration that this was a new onset severe psychiatric syndrome that was treatment resistant. She received 5 d of plasma exchange and was administered Methylprednisolone 1 g IV for 3 d, followed by Prednisolone at 1 mg/kg OD, which was soon tapered down. Her anti-NMDAR antibody levels remained at a "low positive" level post-plasmapheresis. Her mood and speed of thinking were noted to improve and this was corroborated by an improvement in serial addenbrooke's cognitive examination revised (ACE-R) tests, although she remained severely depressed and her paranoia worsened after 1-2 mo. She was transferred back to the psychiatric unit and received Quetiapine, Lithium and further Venlafaxine. She continued on reducing doses of Prednisolone.

Even despite the plasmapheresis, corticosteroids and multiple psychotropics, the patient's symptoms remained severe. The psychiatric team therefore decided to embark on a second course of ECT. The patient received a further 8 cycles of ECT in May 2014 (approximately 2 mo after completion of plasmapheresis) and made a rapid and

**Table 1 Table demonstrating changes in the patient's addenbrooke's cognitive examination-III scores throughout admission and after discharge**

| ACE-III | During admission | Later during admission | 1 mo post plasma exchange | 6 mo post ECT and discharge date |
|---|---|---|---|---|
| | 13/01/2014 | 24/02/2014 | 17/04/2014 | 30/01/2015 |
| Total score | 82/100 | 79/100 | 68/100 | 92/100 |
| Attention | 15/18 | 15/18 | 10/18 | 16/18 |
| Memory | 22/26 | 23/26 | 17/26 | 26/26 |
| Fluency | 10/14 | 3/14 | 3/14 | 9/14 |
| Language | 23/26 | 24/26 | 23/26 | 25/26 |
| Visuospatial | 12/16 | 14/16 | 15/16 | 16/16 |

ECT: Electroconvulsive therapy; ACE-III: Addenbrooke's Cognitive Examination-III.

**Table 2 Table illustrating the change in geriatric depression scale and brief psychiatric rating scale scores from admission to post-electroconvulsive therapy and discharge**

| | Geriatric depression scale | | Brief psychiatric rating scale | |
|---|---|---|---|---|
| | 23/01/2014 | 30/01/2015 | 15/05/2014 | 30/01/2015 |
| | During admission | 6 mo post electroconvulsive therapy and discharge date | During admission | 6 mo post ECT and discharge date |
| Score | 20/30 (severe depression) | 0/30 (Normal) | 84 (moderate to severe psychosis) | 18 (Normal) |

marked recovery. Her mood improved significantly with no psychotic symptoms or perceptual abnormality. Her anti-NMDAR antibody titres were repeated and were undetectable. She began to function at her premorbid level and she was discharged home in July 2014 with Lithium, Venlafaxine, Quetiapine and Prednisolone. The improvement in the patient's symptoms after the second course of ECT was remarkable. It is difficult to know how much improvement was due to either her immunosuppressive therapies or the ECT - it is more likely that the combination of both led to her recovery.

At 6 mo follow up, the patient presented well with no significant affective, psychotic or cognitive symptoms. She was compliant with her medication, had good insight into her illness and had made further progress since discharge, corresponding with an improvement in her scores in the addenbrooke's cognitive examination, Geriatric Depression Scale and Brief Psychiatric Rating Scale (Tables 1 and 2).

## DISCUSSION

Diagnosis of these encephalitides is supported by identification of antibodies in CSF or serum, however the decision to embark on immunotherapy is usually made depending on the patient's clinical condition rather than the actual antibody titres. Of note, the identification of NMDAR antibodies does not automatically confirm a diagnosis of anti-NMDAR encephalitis- this result should always be considered with the clinical presentation in mind. Research by Zandi *et al*[21] showed that NMDAR-Abs were higher in patients with associated tumours. Low positive and positive results were found in a spectrum of patients including those classified as having a possible NMDAR encephalitis and in unlikely cases. Some of those with low positive results were later diagnosed with neurodegenerative disorders and responded poorly to immunotherapy.

There is very little research that has explored how best to monitor patients and whether serial serum or CSF titres are needed but they appear to correlate with clinical progress[5]. Predictors of good outcome are less severe clinical symptoms at onset, no admission to an intensive care unit and timely initiation of immunomodulatory therapy[15]. Interestingly, Titulaer *et al*[15] in 2013 suggested that the rate of recovery can be extremely variable - some patients in this study stopped attending follow up assessments due to an accelerated recovery phase, whereas others were still making more modest progress two years later.

The exact mechanism behind ECT in autoimmune encephalitis is unclear. ECT has previously been shown to upregulate NMDAR in animal models. Watkins *et al*[22] showed that ECT caused an elevation in mRNA for some NMDA subunits (NR2A and NR2B) in rats, mainly in the dentate gyrus of the hippocampus, although these changes only lasted for 48 h. A study done by Fumagalli *et al*[23] in 2010 suggested that ECT may aid regeneration of NMDAR damaged by autoantibodies by improving binding of the glutamate subunit on NMDA in the hippocampus[22]. Another idea is that use of ECT results in partial resolution of symptoms, leading to exposure of other features of the disease which can then be targeted and treated[13].

At present, the concept of autoimmune encephalitis is relatively new and poorly understood. It is important for clinicians working in both psychiatry and neurology to be aware of the potential for patients to present to either specialty. Education in this field is needed to raise awareness of these treatable, but potentially fatal conditions - for example one could easily mistakenly treat those presenting to a psychiatric setting with antipsychotics and those presenting to a medical

setting may not receive ECT. "Red flags" for these diagnoses should be noted so that the appropriate investigations can be performed promptly, to allow early commencement of treatment and to secure the best outcomes. Furthermore, many of these patients will require joint neurology and psychiatry input, depending on which symptoms are present and which of these predominate.

In view of several case studies demonstrating the role in autoimmune encephalitis, ECT may be emerging as a viable alternative or adjunct to immunomodulatory therapies, particularly in those with prevailing psychiatric symptoms. Further studies are needed to establish its role either alone or in combination with other treatments.

## COMMENTS

### Case characteristics

A 71-year-old previously well female presented with low mood and psychotic features.

### Clinical diagnosis

The patient developed severe depressive symptoms with catatonia, psychotic symptoms, paranoid thoughts, nihilistic delusions and auditory hallucinations and so was admitted informally to a psychiatric ward. Examination was normal, with no abnormal neurological findings.

### Differential diagnosis

Mood disorder, steroid-induced psychosis and other autoimmune encephalitides.

### Laboratory diagnosis

Blood tests on admission revealed a raised erythrocyte sedimentation rate, white cell count (with neutrophilia), raised urea and creatinine and raised alanine transaminase (ALT) and Bilirubin. The serum sample sent on admission, which was available later, was low positive for anti-N-Methyl-D-Aspartate receptor (NMDAR) antibodies.

### Imaging diagnosis

A computed tomography (CT) scan of the head did not demonstrate any abnormality. Magnetic resonance imaging of the head was normal. A CT scan of her chest, abdomen and pelvis did not identify an ovarian teratoma or any other evidence of malignancy.

### Treatment

Multiple anti-depressants, benzodiazepines and anti-psychotics were initially trialled. She later received high dose steroids and plasmapheresis, followed by several sessions of electroconvulsive therapies (ECT).

### Related reports

There are emerging case reports that demonstrate effective use of ECT in autoimmune encephalitis, either as an alternative or as adjunctive treatment with steroids and plasma exchange.

### Term explanation

Anti-NMDAR encephalitis is the commonest of the autoimmune encephalitides. "Autoimmune encephalitides" represent conditions which may present with either psychiatric or neurological symptoms and require prompt and aggressive treatment (previously with steroids and plasmapheresis alone).

### Experiences and lessons

It is important that the diagnosis is made swiftly so that the appropriate treatment can be commenced. ECT should be considered, particularly in those patients with psychiatric symptoms refractory to standard immunosuppressive therapies.

### Peer-review

The authors make a great case advocating awareness for the disease, its diagnosis and treatment. This case report is a good contribution for treatment considerations.

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CASE REPORT

# Extraordinary sneeze: Spontaneous transmaxillary-transnasal discharge of a migrated dental implant

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## Abstract

This case report describes an extraordinary case of the spontaneous transmaxillary-transnasal discharge of a dental implant, which occurred during a sneeze. The patient was complained of symptoms of acute sinusitis. She underwent a computed tomography scan that revealed a dental implant dislocated in the maxillary sinus. Medical treatment based on antibiotics and mucolytics was administered to the patient in order to prepare her for endoscopic endonasal surgery. The implant was spontaneously discharged two days after during a sneeze. Mucociliary clearance in combination with a local osteolytic inflammatory process and mucolytics therapy are the likely causes of this unusual discharge.

**Key words:** Complications; Dental implant; Acute sinusitis; Implant surgery



**Core tip:** Iatrogenic dislocation of dental implants into paranasal sinuses is not a rare pathological finding. Dental implants dislocation are commonly related to a wrong operating procedure or diagnostic clinical planning. Functional endoscopic sinus surgery has been widely described as the first option to remove foreign bodies from the paranasal sinuses, while the Caldwell-Luc approach to the maxillary sinuses still represents an option if the patients wants to avoid general anesthesia. Up-today just one case of spontaneous nasal discharge was reported in the literature. Therefore this case report describes a really uncommon clinical finding.

Procacci P, De Santis D, Bertossi D, Albanese M, Plotegher C, Zanette G, Pardo A, Nocini PF. Extraordinary sneeze: Spontaneous transmaxillary-transnasal discharge of a migrated dental implant. *World J Clin Cases* 2016; 4(8): 229-232 Available from: URL: http://www.wjgnet.com/2307-8960/full/v4/i8/229.htm DOI: http://dx.doi.org/10.12998/wjcc.v4.i8.229

## INTRODUCTION

Implant-supported prosthetic rehabilitation represents one of the most common procedures in dental clinical practice[1]. In surgical dental treatment that includes the posterior maxillary region, such as implant placement or impacted third molar extraction, the maxillary sinus should be taken into account because of its anatomical position[2,3]. Implant displacement into paranasal sinuses has been reported frequently in the literature[4-9]. According to the associated complications (implant displacement, implant displacement with or without reactive sinusitis and/or with or without associated oro-antral communication), such approaches as functional endoscopic sinused surgery (FESS), intraoral approach to the sinus, or FESS associated with an intraoral approach could be considered[10]. To the authors' knowledge, this is the second report of a migrated dental implant spontaneous transnasal-transmaxillary discharge[11].

## CASE REPORT

A 63-year-old woman was referred to our Department complaining of pain in the right cheek, malar rubor and edema, fever and nasal purulent discharge. Symptoms and signs appeared one week before her first visit. When the patient visited her private dentist with those symptoms, he promptly performed a radiological examination. The panoramic radiography revealed that an endosseous dental implant previously located at the posterior aspect of the right upper maxillary alveolar ridge had disappeared (Figure 1). On her arrival in our department, the patient immediately underwent a computed tomography scan which revealed that the dental implant was located inside the right maxillary sinus. The anterior aspect of the implant was completely inside the maxillary sinus while the posterior part was positioned throughout the osteomeatal complex. A massive right odontogenic sinusitis with ethmoid involvement was noticed (Figures 2 and 3). The clinical examination did not show any kind of oroantral communication at the superior aspect of the right maxillary ridge and the implant-supported prosthesis was stable without evidence of any kind of pathological signs. An endoscopic endonasal removal of the implant was then planned. A preoperative medical treatment [Ciprofloxacin (500 mg) and Acetylcysteine (600 mg)] twice a day for 7 d was administered in order to prepare her for surgery. Unexpectedly, 2 d after she reported that she had discharged the dental implant in the early morning during a sneeze (Figure 4). No bleeding took place. Surgery was then cancelled and the patient completed her medical treatment. Signs and symptoms disappeared without any kind of late complications within 7 d.

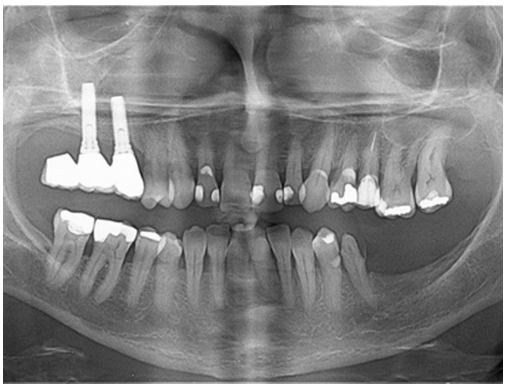

**Figure 1 The preoperative panoramic radiography showed an unknown disappearance of an upper endosseous dental implant previously located in the posterior aspect of the right upper maxilla.**

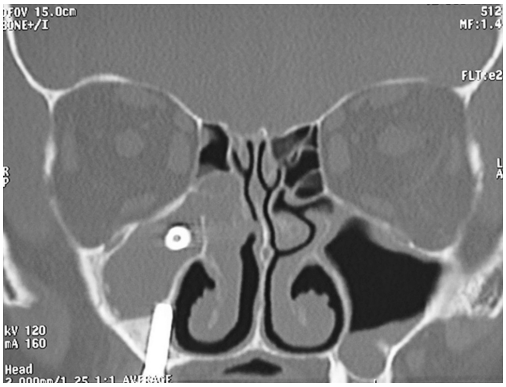


**Figure 2 Coronal computed tomography scan clearly revealed the dental implant located in the upper third of the maxillary sinus.** Acute maxillary sinusitis and ethmoiditis are evident.

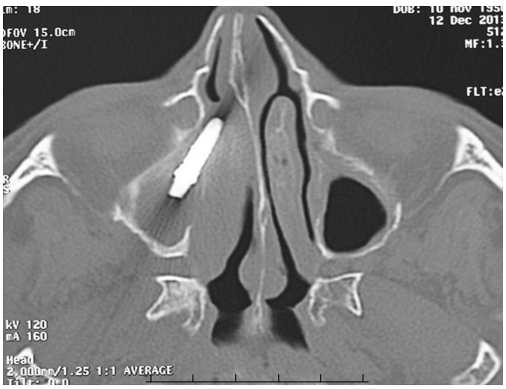


**Figure 3 Axial computed tomography scan allowed to analyze the exact position of the implant between the maxillary sinus interiorly and the osteomeatal complex posteriorly.**

## DISCUSSION

Foreign body dislocation in the paranasal sinuses is a

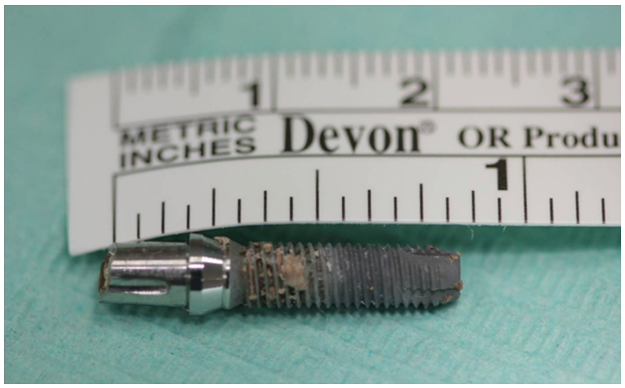


**Figure 4 The sneezed implant.** The prosthetic abutment is still engaged to the dental implant.

common event[12-14]. The presence of a foreign body inside a paranasal sinus often causes an acute inflammatory reaction of the Schneider membrane with a possible consequent obstruction of the sinus ostium. The occlusion of the osteomeatal complex and the edema of the sinusal membrane could lead to a severe alteration of the mucociliary function and, as a direct complication, an acute or recurrent sinusitis[15]. When foreign body displacement occurs, it has to be removed in order to avoid sinus pathology[10,12]. Although several different approaches to remove a foreign body from the maxillary sinus have been described, all of those should be associated with preoperative and postoperative antibiotic, mucolytics and corticosteroid treatment. The first aim of the medical therapy is to reduce the edema of the sinonasal mucosa and to limit the infection.

In the present case the patient underwent preoperative medical therapy that probably stimulated the reactivation of the mucociliary function of the maxillary sinus with a consequent dislocation of the migrated dental implant from the maxillary sinus to the osteomeatal complex. The dental implant then acted like a trigger causing subsequent multiple sneezing and the final extraordinary transnasal discharge of the foreign body.

## COMMENTS

### *Case characteristics*

The paper describes an extraordinary case of an ectopic implant spontaneously discharged during a sneeze.

### *Clinical diagnosis*

The case describes an acute maxillary sinusitis due to a dislocated dental implants into maxillary sinus.

### *Differential diagnosis*

Maxillary sinusitis *vs* rhinosinusitis.

### *Imaging diagnosis*

Computed tomography scans clearly describe the position of the ectopic implant located between the maxillary ostium and the medial meatus.

### *Pathological diagnosis*

Malar rubor and malar oedema associated with severe nasal discharge and nasal dripping allowed to make diagnosis of acute maxillary sinusitis.

### *Treatment*

The patients was candidated to functional endoscopic sinuses surgery in order to remove the foreign body but immediately before the surgical procedure she discharge the ectopic dental implant.

### *Related reports*

Please provide other contents related to the case report to help readers better understand the present case.

### *Term explanation*

To the authors' knowledge, this is the second report of a migrated dental implant spontaneous transnasal-transmaxillary discharge.

### *Experiences and lessons*

The present case showed clearly how competent could be the mucociliary clearance and helps to understand that the combined antibiotic and mucolytic therapy is always advisable before surgery.

### *Peer-review*

This case report describes an extraordinary case of the spontaneous transmaxillary-transnasal discharge of a dental implant. The implant was spontaneously discharged 2 d after during a sneeze. It is interesting and meaningfull.

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CASE REPORT

# Secondary aorto-esophageal fistula after thoracic aortic aneurysm endovascular repair treated by covered esophageal stenting

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## Abstract

Thoracic endovascular aortic repair for thoracic aortic aneurysms is an accepted alternative to open surgery, especially in patients with significant comorbidities. The procedure itself has a low risk of complications and fistulas to surrounding organs are rarely reported. An 86-year-old patient was admitted to our hospital with gastro intestinal (GI) bleeding and a suspected aortoesophageal fistula. Eight months prior, the patient had undergone a stent graft repair of a mycotic thoracic aneurysm. Computerized tomography angiography and upper GI endoscopy confirmed an aortoesophageal fistula, which was treated by esophageal stenting. With early recognition, esophageal stenting may have a role in the initial emergency control of bleeding from and palliation of aortoesophageal fistula.

**Key words:** Endovascular therapy; Bleeding; Aortic aneurysm



**Core tip:** Thoracic endovascular aortic repair (TEVAR) for thoracic aortic aneurysms is an accepted alternative to open surgery, especially in patients with significant comorbidities. The procedure itself has a low risk of

complications and fistulas to surrounding organs are rarely reported. Aortoesophageal fistula post-TEVAR is a very rare entity; however, it is a devastating and usually fatal condition. Treatment options are very restricted, as these patients are often not candidates for complex surgery. We consider the placement of a covered self-expanding esophageal stent to be useful in the management of secondary aortoesophageal fistula after TEVAR to prevent re-bleeding in the fragile patient.

Tao M, Shlomovitz E, Darling G, Roche-Nagle G. Secondary aorto-esophageal fistula after thoracic aortic aneurysm endovascular repair treated by covered esophageal stenting. *World J Clin Cases* 2016; 4(8): 233-237 Available from: URL: http://www.wjgnet.com/2307-8960/full/v4/i8/233.htm DOI: http://dx.doi.org/10.12998/wjcc.v4.i8.233

## INTRODUCTION

Thoracic endovascular aortic repair (TEVAR) is a minimally invasive and generally excellent modality to treat descending thoracic aortic aneurysms. Nevertheless, several complications including paraplegia, stroke and occasionally aortoesophageal fistula (AEF) may occur[1-4]. Aortoesophageal fistula post-TEVAR is a rare entity with a reported incidence of 1.7%-1.9%[1-3], however, it is a devastating and usually fatal condition. Treatment options are very restricted, as these patients are often not fit for complex surgery. Conservative management outcomes are almost always fatal due to recurrent hemorrhage or chronic infection and mediastinitis. In this paper, we present a case of secondary AEF post-TEVAR with insertion of a covered self-expanding esophageal stent to control gastrointestinal bleeding.

## CASE REPORT

An 86-year-old woman was admitted to hospital with back pain and investigations demonstrated lumbar spine discitis. She developed progressive dyspnea, dysphagia, bilateral swelling of the arms and a leukocytosis. Chest radiography showed a widened mediastinum, bilateral pleural effusions and tracheal deviation (Figure 1). Computed tomography of the chest with intravenous contrast showed a saccular thoracic aortic aneurysm (5.0 cm × 5.0 cm) with surrounding hematoma compressing the trachea, esophagus and superior vena cava (Figure 2A). She was transferred to our center and received an endovascular stent graft (Figure 2B).

She re-presented to hospital 8 mo later following an upper gastro intestinal (GI) bleed and computerized tomography (CT) suggested an aortoesophageal fistula (Figure 3). The patient was not a candidate for open surgery and transferred for emergency gastroscopy and esophageal stent insertion. There was a large clot in the upper mid esophagus and an 18 mm diameter × 150 mm Niti-S esophageal stent (Taewoong Medical, Seoul, South Korea) was inserted to tamponade the bleeding point. The patient had persistent nausea, reflux and vomiting for 24 h post stent insertion. Chest X-ray demonstrated the stent had migrated distally resulting in these symptoms (Figure 4). She returned for repeat gastroscopy which confirmed migration of the stent through the gastro-esophageal junction. The initial stent was repositioned into the upper esophagus and a Double Niti-S™ esophageal stent (Taewoong Medical) 20 mm × 100 mm was placed, partially overlapping with the previous stent. She was commenced on lifelong antibiotic therapy and was discharged well from hospital 7 d after presentation. Unfortunately she died from a myocardial infarction 8 mo later.

## DISCUSSION

The first report of aortoesophageal fistula was in 1818 due to a beef bone fragment[5]. A large review of 500 cases identified three major causes[6]. The main aetiologic factor identified being aortic disease with 54.2% of cases secondary to rupture of a descending thoracic aorta aneurysm into the oesophagus. Foreign body ingestion (19.2%) and advanced esophageal carcinoma (17.0%) were the next commonest causes.

Endovascular stent graft implantation procedures are performed in patients with aneurysms of the aorta or other large vessels. The goal of the procedure is to preserve vessel patency and to prevent the aneurysm from rupture. Formation of aortoesophageal and aortobronchial fistulas is a rare (0.5%-1.7%), but serious complication of stent graft implantation to thoracic aorta[3]. They are most frequently caused by infection of the prosthesis, compression, ischemia, local inflammatory reaction and subsequent necrosis[2]. Aortoesophageal fistulas are more common (68%) than aortobronchial (5%) and both types of fistulas coexist in 26% of cases.

Eggebrecht *et al*[2] followed up 268 patients undergoing TEVAR, AEF occurred in 5 (1.9%). Secondary AEF can develop late after thoracic aortic surgery in up to 1.7% of patients[7]. The incidence of post-TEVAR AEF is comparable to the incidence after open repair surgery[1]. The largest risk factor for fistula formation is infection of the prosthesis. The incidence of peri-graft infection is reported to be as high as 0.5%-5%[2]. Other factors increasing the risk of complications such as fistulas include pseudoaneurysms as in our case, emergency surgeries and intraoperative complications.

The primary presentation is massive hematemesis, often resulting in exsanguination[2]. Other presentations include: (1) severe backache[8]; (2) fever[8]; and (3) chest pain[9]. The "classic" symptom of AEF involves Chiari's triad of aortoesophageal syndrome-chest pain, episode of small hematemesis followed by massive hematemesis[10].

The exact pathophysiologic mechanisms of AEF formation secondary to TEVAR are unknown thus far. There are different theories. A pathophysiologic mechanism of secondary AEF after TEVAR has been

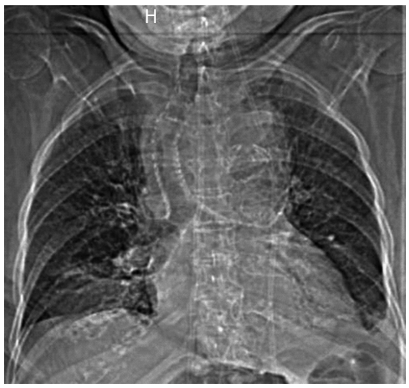

**Figure 1 Chest radiography showed a widened mediastinum and tracheal deviation.**

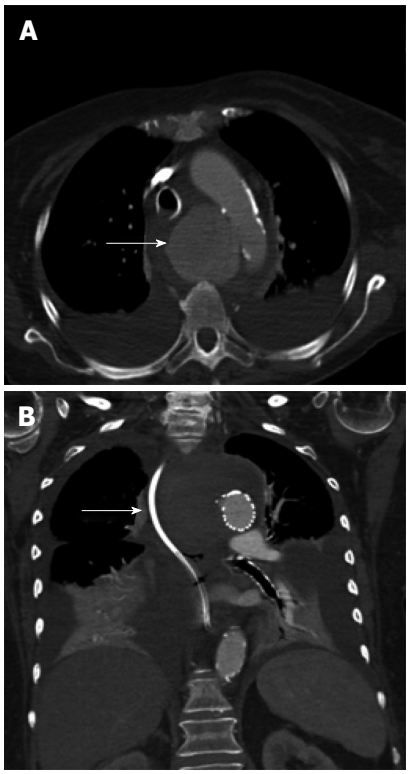


**Figure 2 Computed tomography of the chest with intravenous contrast showed a saccular thoracic aortic aneurysm (5.0 cm × 5.0 cm) (arrow).** Pre (A) and post (B) TEVAR with surrounding hematoma compressing the trachea, esophagus and superior vena cava. TEVAR: Thoracic endovascular aortic repair.

hypothesized[11]. Direct erosion of the rigid stent-graft through the aorta into the esophagus or pressure necrosis of the esophageal wall due to the ongoing forces of the self-expanding stent graft. Potential ischemic esophageal necrosis due to stent-graft occlusion of aortic side branches that feed the esophagus or most likely in our case infection of stent-graft prosthesis that eventually extends to the esophagus eroding its wall. Pressure necrosis mechanisms also occur in the presence of endoleak that enlarge the aneurysm sac or in an already large aneurysm sac prior to TEVAR[2,11,12].

Any patient with a previous history of thoracic aortic

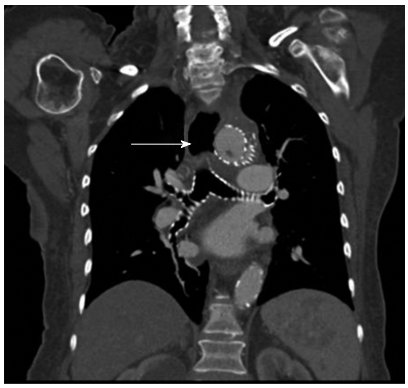

**Figure 3 Computed tomography demonstrating an aortoesophageal fistula (arrow).**

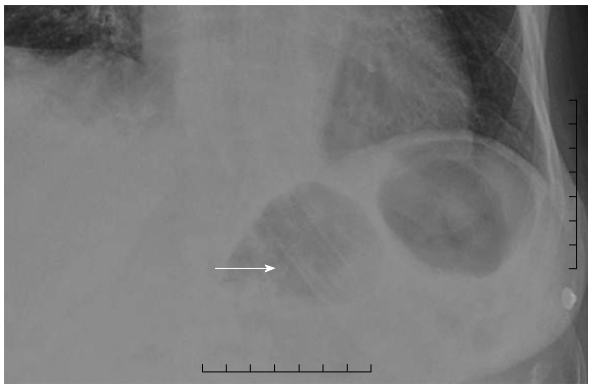

**Figure 4 Chest X-ray demonstrating migration of the esophageal stent to the level of the gastroesophageal junction (arrow).**

surgery and hematemesis should have a suspected AEF. Computed tomography angiography (CTA) is the initial investigation of choice in a case of suspected AEF looking for close approximation of the TEVAR and esophagus with or without air present. It can be confirmed by prompt upper GI endoscopy.

A treatment consensus for AEF, especially after previous TEVAR, has not been agreed upon. Conservative management of this condition almost invariably results in a fatal outcome. However, a more aggressive surgical strategy involving esophageal diversion or resection, extensive debridement, and aortic graft interposition is associated with significant mortality and morbidity[13,14]. The majority of patients who undergo TEVAR for aortic pathology have significant comorbidities precluding open surgical rescue. In this frail population management includes the use of broad-spectrum antibiotics, proton pump inhibition, and potential enteral feeding *via* percutaneous endoscopic gastrostomy (PEG) to bypass the esophageal fistula.

In our case we chose to place a self-expanding esophageal stent as a palliative measure. Esophageal diversion or resection was not possible due to her age and co-morbidities and re-stenting her aorta was not felt to be indicated. An esophageal stent may prevent re-bleeding and allow the patient to eat normally so is a good palliative option. When considering this option

it is important to understand that stenting the "normal" esophagus is not always effective. Incomplete seal or stent migration requiring repositioning or replacement may be necessary as seen in our case. In a study of 187 esophageal stents insertions, 29 (17%) patients required repositioning or replacement[3]. There are a number of reports describing the use of self-expanding esophageal stents in this setting. Eggebrecht *et al*[2] inserted self-expanding esophageal stents in three patients with secondary AEF after endovascular stent grafting, with two patients surviving for 2-6 mo[2]. Onodera *et al*[4] reported a case where a covered self-expanding esophageal stent was inserted to prevent re-bleeding, and re-bleeding did not occur for 52 d post-insertion. In our case the patient did not re-bleed and died of a myocardial infarction 8 mo post stenting. Therefore, placement of a covered self-expanding esophageal stent may be useful to prevent re-bleeding for a substantial period of time.

The Taewoong Niti-S esophageal stents, such as the one utilized in this case encompass a family of fully covered esophageal stents for various indications. The stent design consists of a self-expanding, braided nitinol (nickel titanium alloy). The stents are covered with a polyurethane membrane throughout their length designed to resist tissue ingrowth. To reduce the risk of migration the "S" esophageal stents are designed with both proximal and distal flares which are 8 mm wider than the shaft. Such flares are meant to anchor the stents in position across an obstructing esophageal lesion or resist migration through the gastroesophageal junction. In instances similar with this case where no obstructing lesion exists, there remains a significant risk of migration. The DOUBLE Niti-S esophageal stent is designed to further minimize this risk of migration. This stent has the same basic characteristics as the "S" type esophageal stent, including flared ends and a polyurethane membrane internal covering. However, the design also includes an outer layer consisting of an uncovered nitinol mesh intended to more firmly embed into the surrounding tissues. This additional second layer also increases the radial force excreted by the stent, further reducing the risk of migration[15].

During endoscopy, there is direct visualization of the pathology and a guide wire is placed in the stomach under direct vision. Guide wire choice is best individualized to the patient's overall situation for esophageal stent placement. Stents can be deployed under fluoroscopic guidance, endoscopic guidance, or a combination of the two. Ideally however, both modalities should be used and are complementary in the safe and accurate deployment of esophageal stents. Although the learning cure for placement of esophageal stents is not known a certain comfort level with both modalities is extremely useful in the management of these patients especially in the acute setting.

An aortoesophageal fistula presents a challenge for even the most experienced thoracic and vascular surgeons with a high mortality rate. We consider the placement of a covered self-expanding esophageal stent to be a valuable option for the management of secondary AEF after TEVAR and to prevent re-bleeding in the frail patient. The Taewoong Niti-S esophageal stent should be considered to reduce risk of migration. This treatment allows the patient to eat normally while providing the best palliation method in an often terminal condition.

## COMMENTS

### Case characteristics

An 86-year-old patient was admitted with gastro intestinal (GI) bleeding and a suspected aortoesophageal fistula.

### Clinical diagnosis

GI bleeding on the background of aortic surgery should always raise suspicion of aorto-enteric fistula.

### Differential diagnosis

Hemorrhagic gastritis, esophageal varices, Mallory-Weiss tear, Neoplasm, Dieulafoy lesion or Aorto-enteric fistula.

### Laboratory diagnosis

The hemoglobin was reduced.

### Imaging diagnosis

Computerized tomography angiography and upper GI endoscopy confirmed an aortoesophageal fistula.

### Treatment

A covered esophageal stent was inserted to tamponade the bleeding point.

### Related reports

Thoracic endovascular aortic repair (TEVAR) is a minimally invasive and generally excellent modality to treat descending thoracic aortic aneurysms. Aortoesophageal fistula post-TEVAR is a rare entity. There are few reports describing the use of self-expanding esophageal stents in this setting.

### Term explanation

Aortoesophageal fistula post-TEVAR is an infrequent presentation likely caused by direct erosion of the rigid stent-graft through the aorta into the esophagus or pressure necrosis of the esophageal wall due to the ongoing forces of the self-expanding stent graft.

### Experiences and lessons

The authors consider the placement of a covered self-expanding esophageal stent to be useful in the management of secondary aortoesophageal fistula (AEF) after TEVAR to prevent re-bleeding in the fragile patient.

### Peer-review

The author reported a rare case of AEF following endovascular repair of thoracic aortic aneurysm. The paper is well written.

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CASE REPORT

# Successful endoscopic closure of a colonic perforation one day after endoscopic mucosal resection of a lesion in the transverse colon

Kazuya Inoki, Taku Sakamoto, Masau Sekiguchi, Masayoshi Yamada, Takeshi Nakajima, Takahisa Matsuda, Yutaka Saito

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Author contributions: Inoki K, Sakamoto T and Saito Y designed the report, collected the patient's clinical information and wrote the paper; Sekiguchi M, Yamada M, Nakajima T and Matsuda T revised the manuscript.

Institutional review board statement: This case report was exempt from the Institutional Review Board standards at National Cancer Center Hospital, Tokyo, Japan.

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## Abstract

A 73-year-old man underwent endoscopic mucosal resection (EMR) of a 20-mm flat elevated lesion on the transverse colon. The morning after the procedure, he started to have severe right upper quadrant pain after his first meal. A computed tomography scan revealed free air and a stomach filled with food. He was diagnosed to have delayed post-EMR intestinal perforation. He underwent emergent colonoscopy and clipping of the perforated site. He was discharged 8 d after the endoscopic closure without the need for surgical intervention. The meal was not the cause of the colon transversum perforation.

**Key words:** Colonoscopy; Colorectal tumors; Endoscopic surgical procedure; Emergencies; Intestinal perforation



**Core tip:** The prompt and adequate management of post-operative gastrointestinal perforation is imperative. For delayed perforations, surgical management is the most common option. Herein we report a case of delayed colonic perforation that was successfully repaired by an endoscopic approach, even after the patient ingested food. We describe the techniques and highlight the importance of adequate bowel preparation

for a favorable outcome.

Inoki K, Sakamoto T, Sekiguchi M, Yamada M, Nakajima T, Matsuda T, Saito Y. Successful endoscopic closure of a colonic perforation one day after endoscopic mucosal resection of a lesion in the transverse colon. *World J Clin Cases* 2016; 4(8): 238-242 Available from: URL: http://www.wjgnet.com/2307-8960/full/v4/i8/238.htm DOI: http://dx.doi.org/10.12998/wjcc.v4.i8.238

## INTRODUCTION

Endoscopic mucosal resection (EMR) is a relatively safe and basic technique with a reported risk of perforation of 0%-5%[1]. The 30-d mortality rate for perforation after colonoscopy, both therapeutic and diagnostic, has been reported to be 0%-26%[2]. As a result of developments in endoscopic techniques, endoscopic closure is a considerable option for the management of perforation during endoscopic treatments[3]. However, for delayed colorectal perforation, emergency surgery is often imperative[4]. Herein we report a case of delayed colonic perforation due to EMR that was successfully treated by endoscopic closure, even though the patient had already ingested one meal after the procedure.

## CASE REPORT

A 73-year-old man was referred to the National Cancer Center Hospital in Tokyo, Japan, for the management of multiple polyps in the transverse and sigmoid colon, one of which was approximately 20 mm in size and was located in the transverse colon. Diagnostic and therapeutic colonoscopy was planned on the same day. Endoscopic submucosal dissection (ESD) was planned on the largest lesion, which was 18 mm in size and was diagnosed as adenoma, 0-IIa, laterally spreading tumor non-granular type (LST-NG) (Figure 1A and B). On the basis of these findings, we decided to proceed with EMR instead of ESD for the largest lesion (Figure 1C and D); the other smaller polyps were removed by polypectomy or biopsy. No clippings were performed after EMR. Total colonoscopy and all related procedures were performed using carbon dioxide insufflation. There were no immediate complications, and the patient was asymptomatic during the endoscopic procedure.

The day after the endoscopic treatment, his white blood cell count was noted to increase, but there was no fever. There were no abdominal symptoms in the morning, but he started to have severe right upper quadrant pain after having his first meal post-procedure. On physical examination, abdominal rigidity and mild tenderness on the right upper quadrant were observed. A computed tomography (CT) scan was immediately performed and showed free air around the right lobe of the liver and inside the adipose tissue surrounding the ascending colon. A small amount of ascites around the liver was also recognized (Figure 2A and B). He was diagnosed with post-EMR colonic perforation, and broad-spectrum antibiotics were immediately started. Prior to repair, the CT scan was reviewed, and the stomach was seen to be filled with food that had not yet reached the colon (Figure 2C and D). After discussion with the surgeons, a decision was made to perform endoscopic closure of the perforated site.

During colonoscopy, brown intestinal juice was observed, but there were no food residues (Figure 3A). The examination of the EMR site showed a reddish and edematous ulcer (Figure 3B), initially without an obvious perforation (Figure 3C). Nevertheless, we judged this as the perforated site and performed endoscopic closure using four clips (HX-610-090L; Olympus, Japan) (Figure 3D).

The day after the endoscopic closure, the patient had mild fever but no abdominal pain and a small amount of free air under the right diaphragm was seen on his chest X-ray. No fever was observed during the clinical course and white blood cell count (WBC) and C-reactive protein (CRP) declined after the endoscopic closure. Enteral feeding was resumed 5 d after the endoscopic treatment, and he was discharged eight days after the treatment.

## DISCUSSION

Castellví *et al*[5] reported several factors that can be used to recommend conservative treatment, including endoscopic closure for colonic perforation. These factors are good general condition, unobvious perforation, early diagnosis, no signs of diffuse peritonitis, and proper colonic preparation. Our patient met all these factors.

Food is considered to adversely affect the management of a delayed perforation because it may contaminate the perforated site and peritoneal cavity leading to severe peritonitis. In the present case, we confirmed that the food in the stomach did not reach the EMR site. It has been reported that the small bowel transit time is approximately 3-5 h; by responding quickly, we successfully performed endoscopic closure before the food could contaminate the site.

Adequate bowel preparation is strongly associated with detection rates for adenoma and is regarded as an indicator of a good endoscopy examination[6]. A clean environment is also essential for safe colonoscopy, and inadequate bowel preparation is related to poor outcomes of perforation after colonoscopy. In fact, with inadequate bowel preparation, endoscopists cannot observe the perforated site and inflammation would be worse. At our institution, the bowel preparation regimen for colonic ESD cases is more meticulous than that for screening cases. For this case, a segment score 3 was given based on the Boston Bowel Preparation Scale[7].

To the best of our knowledge, this is the first reported case of a successful repair of colonic perforation, even after starting a meal. It is important to confirm that food has not reached the perforated site and to immediately

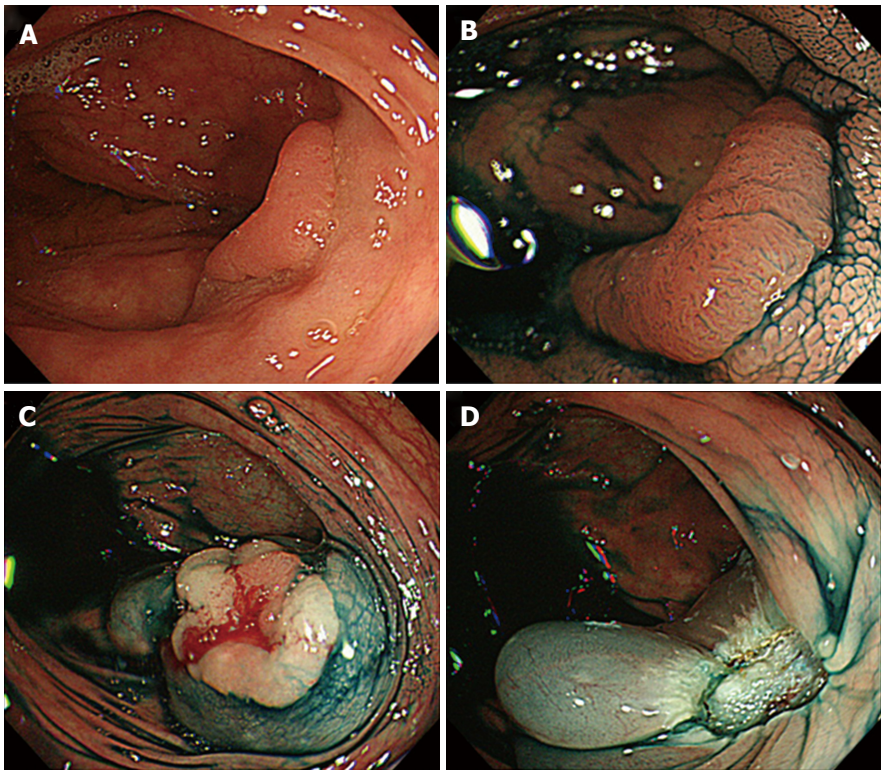


**Figure 1 Colonoscopy images when endoscopic mucosal resection was performed.** A: An 18-mm slightly reddish elevated lesion was recognized on the transverse colon; B: Type 3L pit pattern was recognized with indigo was recognized; C: Endoscopic mucosal resection (EMR) was performed; D: There were no apparent findings that suggested perforation at the ulcer floor immediately after EMR.

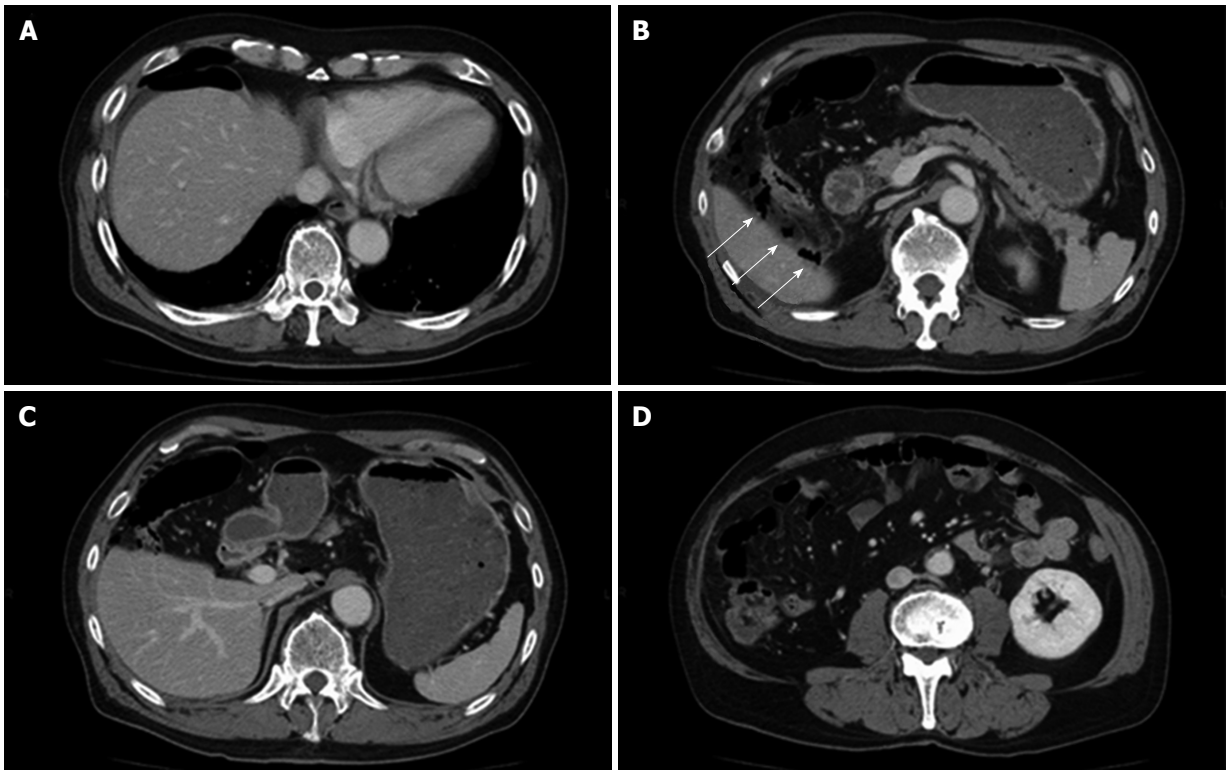


**Figure 2 Abdominal computed tomography scan images of a man in his 70s who underwent endoscopic mucosal resection of a large polyp on the transverse colon.** A: Free air and small ascites were recognized around the right lobe of the liver; B: Air density was recognized inside the adipose tissue around the ascending colon (white arrows); C: The stomach was fully occupied with food particles; D: Which had not yet reached the colon.

perform the closure.

Adequate bowel preparation is necessary for the

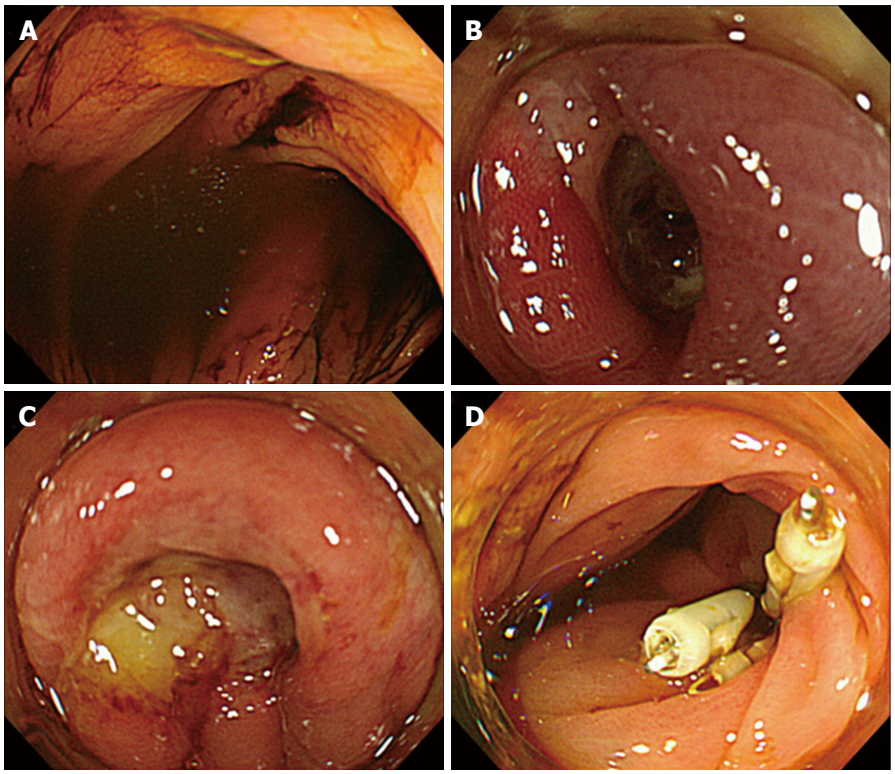


**Figure 3 Emergency colonoscopy in a man in his 70s with colonic perforation after endoscopic mucosal resection of a large polyp.** A: Brown intestinal juice was seen inside the colon, but there was no food residue; B: The endoscopic mucosal resection ulcer was reddish and edematous; C: The ulcer floor was observed, but perforation was not obvious at that time; D: Endoscopic closure with clips was successfully performed.

success of colonic endoscopic closure after delayed perforation. Understanding risk factors, quick decision-making after a discussion with surgeons, and a prompt response are of prime importance.

## COMMENTS

### *Case characteristics*

A 73-year-old man with delayed colonic perforation that was successfully repaired by an endoscopic approach, even after the patient ingested food.

### *Clinical diagnosis*

Delayed post-endoscopic mucosal resection (EMR) intestinal perforation.

### *Differential diagnosis*

Peritonitis, postpolypectomy electrocoagulation syndrome.

### *Laboratory diagnosis*

Elevated white blood cell count and C-reactive protein declined gradually after the endoscopic closure.

### *Imaging diagnosis*

Computed tomography showed free air around the right lobe of the liver and air density inside the adipose tissue around the ascending colon.

### *Pathological diagnosis*

Well differentiated adenocarcinoma, low grade atypia.

### *Treatment*

Complete endoscopic closure of perforation site.

### *Related reports*

Basically emergent surgery is considered to be necessary for delayed post-EMR intestinal perforation; therefore, consulting surgeons is imperative.

### *Term explanation*

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; LST-NG: Laterally spreading tumor non-granular type.

### *Experiences and lessons*

Adequate bowel preparation is necessary for the success of colonic endoscopic closure after delayed perforation. Understanding factors to select conservative or surgical treatment, quick decision-making after a discussion with surgeons, and a prompt response are of prime importance.

### *Peer-review*

This is a well-written manuscript describing an unusual case report and a promising alternative treatment.

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CASE REPORT

# Primary hepatic neuroendocrine tumor: A case report and literature review

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Author contributions: Song JE collected the patient's clinical data and wrote the paper; Kim BS and Lee CH designed the report.

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## Abstract

Primary hepatic neuroendocrine tumors (PHNETs) are extremely rare and difficult to distinguish from other liver tumors, such as hepatocellular carcinoma (HCC) and cholangiocarcinoma, based on medical imaging findings. A 70-year-old man was referred for evaluation of liver mass incidentally discovered on abdominal computed tomography. The characteristic finding from dynamic liver magnetic resonance imaging led to a diagnosis of HCC. The patient underwent right hepatectomy. Histopathological and immunohistochemical examination revealed grade 2 neuroendocrine tumor. The postoperative 24-h urinary excretion of 5-hydroxy-indolacetic acid was within the normal range. Further imaging investigations were performed. No other lesions were found making probable the diagnosis of PHNET. This case shows that the diagnosis of PHNET is a medical challenge, requiring differentiation of PHNETs other hepatic masses and exclusion of occult primary neuroendocrine tumors. The diagnosis of PHNET can be ascertained after long term follow-up to exclude another primary origin.

**Key words:** Primary hepatic neuroendocrine tumor; Neuroendocrine tumor; Liver; Hepatocelluar carcinoma



**Core tip:** Primary hepatic neuroendocrine tumors (PHNETs) are extremely rare and difficult to diagnose before preoperative biopsy or surgery. This case report shows that the diagnosis of PHNET is a medical challenge. Thus differentiation of PHNET from other hepatic mass and exclusion of occult primary neuroendocrine tumors are necessary. The diagnosis of PHNET can be ascertained after long term follow-up to exclude another primary origin.

Song JE, Kim BS, Lee CH. Primary hepatic neuroendocrine

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## INTRODUCTION

Neuroendocrine tumors (NETs) are a rare type of tumor, originating in the cells of the neuroendocrine system. NETs arise preferentially in the bronchopulmonary tree (30%) or gastrointestinal tract (50%) and usually metastasis to the liver[1]. However, primary hepatic neuroendocrine tumor (PHNET), first described by Edmondson in 1958[2], is extremely rare, with only 94 cases described in the literature up to 2009[3]. This scarcity of cases makes it difficult for clinicians to diagnose PHNET accurately before biopsy or surgical resection of the tumor[4]. Therefore, PHNET is difficult to differentiate preoperatively from other solid mass, especially hepatocellular carcinoma (HCC). Herein, we report a rare case of PHNET suspected to be HCC before operation.

## CASE REPORT

A 70-year-old man complained of left flank pain and gross hematuria. Abdominal computed tomography (CT) revealed a stone in the left uretero-pelvic junction and a 6.8-cm lobulated solid mass in the liver dome. He was referred for evaluation of the incidentally discovered liver mass. He did not have any other symptoms such as jaundice, vomiting, flushing, or diarrhea before admission. His medical history was not significant, except for type 2 diabetes. Physical examination and all biochemical laboratory results were within the normal limits, including tests for liver function and tumor markers (alpha-fetoprotein and carcinoembryonic antigen). No serologic evidence of hepatitis B or C virus infection was found. Endocrine studies were not performed. Liver magnetic resonance imaging (MRI) revealed a lobulated mass involving segments 7 and 8, with mild hypervascularity on arterial phase images and washout on delayed images (Figure 1). Based on the imaging findings, the presumed diagnosis was HCC.

He underwent right hepatectomy and had an uneventful postoperative course. The resected specimen revealed a solid tumor measuring 8.3 cm × 6.5 cm, outlining a heavy cell proliferation with trabecular, glandular, and solid growth patterns. Immunohistochemical staining revealed that tumor cells were diffusely positive for synaptophysin, chromogranin A and CD56, with a Ki67 index of 10%, indicating nuclear reactivity. However, the staining was negative for Heppar-1 and alpha-fetoprotein (Figure 2). Given these findings, a grade 2 neuroendocrine tumor was made. The postoperative 24-h urinary excretion of 5-hydroxyindole acetic acid (5HIAA) was within the normal range.

The tumor was considered as a metastatic NET, so further evaluation was undertaken to search for the primary tumor. Chest CT, and upper and lower gastrointestinal endoscopies were performed, and the results were negative for any tumor. The patient underwent an indium-111-Diethylenetriaminepentaacetic acid (DTPA)-octreotide scan, which revealed no lesions positive for somatostatin receptor (Figure 3). The final diagnosis was PHNET based on the pathological and imaging results. At 2-year follow-up the patients shows no signs of liver recurrence or appearance of another primary neuroendocrine tumor.

## DISCUSSION

NETs derive from neuro-ectodermal cells that are dispersed throughout the body. The incidence rate of NET is 6.25 cases per 100000 individuals per year in the United States[5]. Between 54% and 90% of all NET cases arise from the gastrointestinal tract and a primary hepatic location is extremely rare (0.3% of all NET cases)[6].

The grading system used in the 2010 World Health Organization (WHO) classification of gastroenteropancreatic NET (GEP-NET) takes into account the number of mitoses per 10 high power microscopic fields or the percentage of neoplastic cells immunolabeled for the proliferation marker Ki67. These measures indicate the rate of proliferation and correlate with prognosis. GEP-NETs are classified into three types, namely well-differentiated tumors of low-grade malignancy with an indolent development and a good prognosis (grade 1), well-differentiated tumors of intermediate-grade neoplasms (grade 2), and poorly differentiated or high-grade neoplasms that have a poor prognosis (grade 3)[7]. So far, no classification system has been established for PHNETs. However, the categorization of PHNETs according to the 2010 WHO classification of GEP-NETs is useful for the assessment of the prognosis and malignant potential of the tumors[8]. In the present case, the patient was diagnosed as having a grade 2 NET according to the 2010 WHO GEP-NET classification.

PHNETs have a clinical presentation that distinguishes them from other NETs. PHNETs typically grow slowly and become clinically obvious only at an advanced stage[9]. In most cases, they are incidentally discovered, because they most often appear as an endocrinologically silent hepatic mass. Only 6.8% of patients with PHNETs present with the classic carcinoid syndrome, such as skin flushing, diarrhea, and abdominal pain[10]. The presentation of PHNETs can be contrasted with that of hepatic metastases from extrahepatic NETs, which are more commonly related to the typical carcinoid syndrome. However, why PHNETs are frequently endocrinologically silent while their metastatic counterparts are not. PHNETs are more often discovered based on symptoms associated with mass effects on the liver and adjacent organs, such as abdominal distension, vague pain, jaundice, and palpable right upper quadrant mass. In a recently reported review of literature (124 PHNET cases), the mean age at diagnosis was 51.9 years, and no apparent

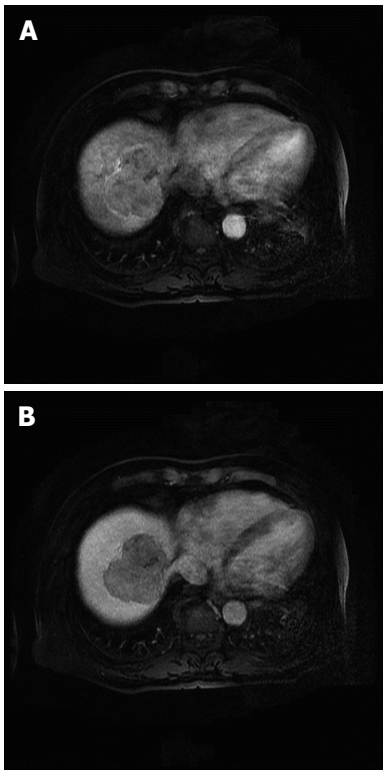


**Figure 1 Dynamic liver magnetic resonance image showing a 6.8-cm solid mass in segments 8 and 7.** A: Image obtained in the arterial phase, showing a lobulated enhancing mass; B: Image obtained in the portal phase, showing the mass evolving into a low-density mass.

sex predilection was reported (50.8% women and 49.2% men)[10]. However, in another literature, PHNET was slightly more frequent in women (58.5%)[3]. Most tumors were solitary (76.6%) but could be multicentric, with right lobar preference (46.8%)[3]. Our patient was a 70-year-old man who had nonspecific symptoms for the liver tumor, which was located in the right lobe of the liver and found incidentally.

The diagnosis of PHNET is a continuum starting from preoperative to post-surgical stage including long term follow-up to search for extra-hepatic primary[10]. In preoperative imaging study, PHNETs are frequently misdiagnosed as HCC or cholangiocarcinoma (CCC). The gross radiological features of PHNET can be highly varied, with some lesions appearing solid or cystic, as well as having diffuse or well-circumscribed margin[11]. PHNETs have a rich blood supply from the hepatic artery, which is reflected in the type of dynamic enhancement curves. Wang *et al*[12] reported that all lesions were remarkably enhanced in the arterial phase and that the reconstruction of the arterial phase confirmed a rich blood supply. HCC has the typical patterns of marked arterial enhancement and washout in the portal and delayed phases, which easily confounds the diagnosis of PHNET.

Several studies has reported that preoperative diagnosis for PHNETs with needle biopsy[13-16], but the diagnostic accuracy is not high enough. The low

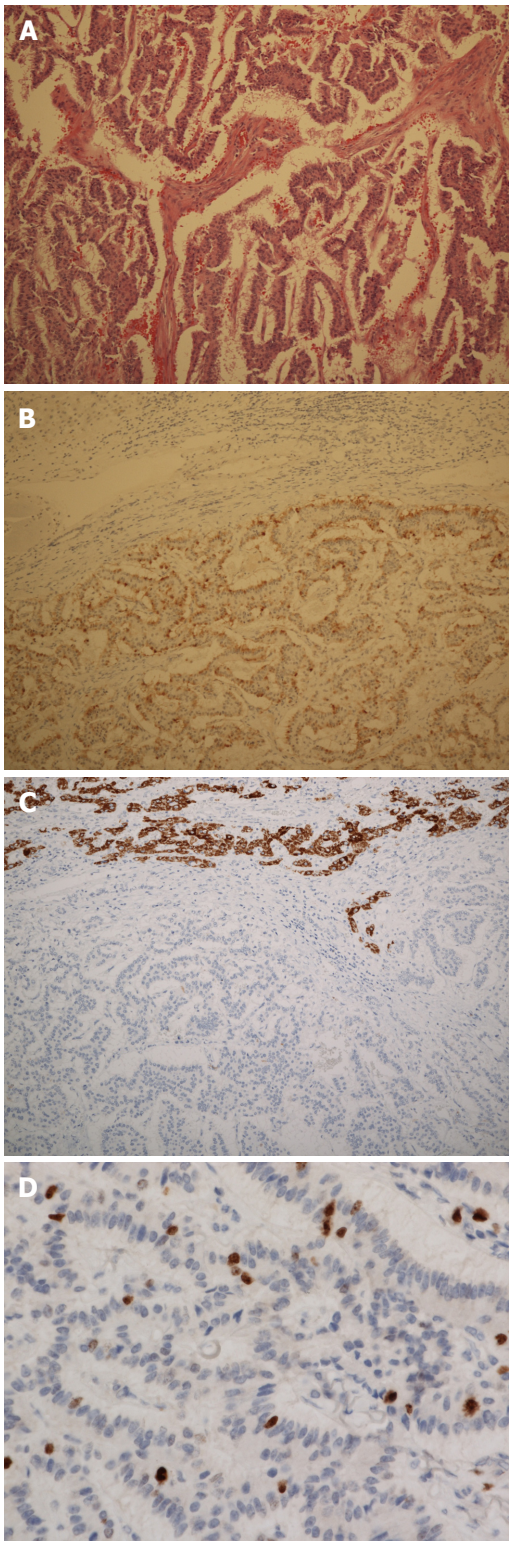


**Figure 2 Pathological findings.** A: Microscopic appearance of the tumoral lesion in the resected liver specimen. The architectural pattern is trabecular and glandular. Hematoxylin-eosin staining × 100; B: Diffuse, moderate immunoreactivity for chromogranin in the tumor cells. Immunohistochemical (IHC) staining, × 100; C: Negative immunoreactivity for Heppar-1 in tumor cells, and positive immunoreactivity occurs in normal hepatic cells. IHC staining, original magnification × 100; D: The Ki67 proliferation index is 10% in tumor cells. IHC staining, original magnification × 400.

diagnostic accuracy is obvious in reported cases that

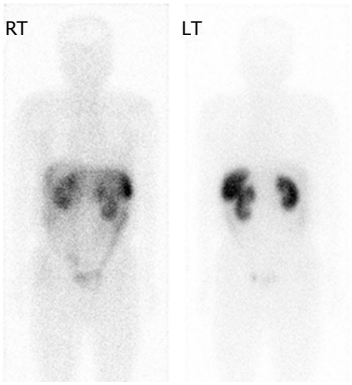


**Figure 3 Single-photon emission computed tomographic images obtained 24 h after the administration of indium-111 octreotide.** Both the anterior and posterior whole body images show, no abnormal lesions with increased uptake. RT: Right; LT: Left.

PHNETs are misdiagnosed as HCC or CCC[15,17,18]. It is still unclear on the value of liver biopsy therefore post-operative histological and immunohistochemical evaluation serves as the essential method for the definite diagnosis[10].

Radiological findings are similar for both primary and metastatic NETs[19]. Moreover, the pathological features of PHNET are difficult to distinguish from those of hepatic metastases. Therefore, careful investigations are required to exclude the presence of extrahepatic NET. These include CT, MRI, somatostatin scintigraphy, positron-emitting tomography (PET), gastroscopy, colonoscopy, bronchoscopy and operative exploration. When the primary tumor is still considered to be hepatic NET even after thorough investigation, long-term reexamination with CT, MRI, octreotide scan and PET are useful to detect a small extrahepatic tumor that may have initially been missed[20]. Occasionally, a very close post surgical long-term follow-up is needed for definite diagnosis of PHNET[21].

Gross pathological findings of PHNETs are gray-yellow in color and well demarcated mass with multiple irregular hemorrhagic lesions or with cystic area[22,23], ranging in size from 3.2 to 18 cm (mean: 8.6 ± 5.7 cm)[15]. Routine pathological examination using the hematoxylin-eosin staining method shows insular, nested, trabecular or mixed pattern of cell growth, but it is not specific for NETs and only beneficial to tumor classification. Neuron-specific enolase, chromogranin A and synaptophysin are generally accepted as highly sensitive immunohistochemical markers for the diagnosis of NETs. The tumor in our case was immunoreactive for synaptophysin and chromogranin A.

No treatment guideline for PHNET has been recently established, but surgical resection (*e.g.*, wedge resection or formal lobectomy) is the treatment of choice that can provide a complete cure[14,24]. PHNETs are associated with a resectability rate of 70% and a 5-year survival rate after hepatectomy of 78%[5]. Recent study shows that the extent of the disease and type of surgery does not affect the survival rate[23]. In patients with unresectable disease, various palliative options exist, such as systemic 5 fluorouracil[25], hepatic artery embolization[26], and octreotide therapy[27]. However, data on these are limited. Currently, liver transplantation has been suggested to be a treatment option in selected patients with multiple lesions or impaired liver function[28].

The present case shows that the diagnosis of PHNET is a medical challenge. PHNETs are rare and asymptomatic. They are quite difficult to distinguish from other liver tumors, such as HCC and cholangiocarcinoma, based on medical imaging findings. PHNET should be suspected in patients with no chronic liver disease, with normal serum alpha-fetoprotein levels, and with solitary hypervascular tumor in imaging studies. Differentiation of PHNET from other hepatic mass and exclusion of occult primary neuroendocrine tumors are necessary. The diagnosis of PHNET can be ascertained after long term follow-up to exclude another primary origin.

## COMMENTS

### *Case characteristics*

A 70-year-old man was referred for evaluation of liver mass incidentally discovered on abdominal computed tomography.

### *Clinical diagnosis*

The characteristic finding from dynamic liver magnetic resonance imaging led to a diagnosis of hepatocellular carcinoma.

### *Differential diagnosis*

Cholangiocarcinoma.

### *Laboratory diagnosis*

All biochemical laboratory results were within the normal limits, including tests for liver function and tumor markers (alpha-fetoprotein and carcinoembryonic antigen).

### *Imaging diagnosis*

Liver magnetic resonance imaging revealed a lobulated mass involving segments 7 and 8, with mild hypervascularity on arterial phase images and washout on delayed images.

### *Pathological diagnosis*

Immunohistochemical staining revealed that tumor cells were diffusely positive for synaptophysin, chromogranin A and CD56, with a Ki67 index of 10%, indicating nuclear reactivity. Given these findings, a grade 2 neuroendocrine tumor was made.

### *Treatment*

He underwent right hepatectomy.

### *Peer-review*

This is a well written case report of a rare pathology. It lacks long term follow-up in order to support the immunohistological diagnosis of primary hepatic neuroendocrine tumor.

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CASE REPORT

# Cronkhite-Canada syndrome polyps infiltrated with IgG4-positive plasma cells

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Author contributions: Fan RY designed, wrote and revised the paper; Wang XW and Xue LJ treated patient and collected clinical data from patient; An R responsible for pathologic diagnosis; and Sheng JQ responsible for endoscopic diagnosis.

Informed consent statement: The patient involved in this study gave his written informed consent authorizing use and disclosure of his protected health information.

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## Abstract

Cronkhite-Canada syndrome (CCS) is a rare but serious protein-losing enteropathy, but little is known about the mechanism. Further more, misdiagnosis is common due to non-familiarity of its clinical manifestation. A 40-year-old male patient was admitted to our hospital because of diarrhea and hypogeusia associated with weight loss for 4 mo. On physical examination, skin pigmentation, dystrophic nail changes and alopecia were noted. He had no alike family history. Laboratory results revealed low levels of serum albumin (30.1 g/L, range: 35.0-55.0 g/L), serum potassium (2.61 mmol/L, range: 3.5-5.5 mmol/L) and blood glucose (2.6 mmol/L, range: 3.9-6.1 mmol/L). The erythrocyte sedimentation rate was elevated to 17 mm/h (range: 0-15 mm/h). X-ray of chest and mandible was normal. The endoscopic examination showed multiple sessile polyps in the stomach, small bowel and colorectum. Histopathologic examination of biopsies obtained from those polyps showed hyperplastic change, cystic dilatation and distortion of glands with inflammatory infiltration, eosinophilic predominance and stromal edema. Immune staining for IgG4 plasma cells was positive in polyps of stomach and colon. The patient was diagnosed of CCS and treated with steroid, he had a good response to steroid. Both histologic findings and treatment response to steroid suggested an autoimmune mechanism underling CCS.

**Key words:** Gastrointestinal polyposis; Cronkhite-Canada syndrome; IgG4 plasma cells; Autoimmune mechanism



**Core tip:** Cronkhite-Canada syndrome (CCS) is a non-hereditary condition characterized by gastrointestinal polyposis associated with diarrhea and epidermal manifestations. It is a rare but serious disease, early

diagnosis can improve prognosis of the patients, but delay in diagnosis is common due to non-familiarity of its clinical manifestation. Here we report a case of a patient with CCS, in this report showed the patient's clinical characteristics and response to treatment.

Fan RY, Wang XW, Xue LJ, An R, Sheng JQ. Cronkhite-Canada syndrome polyps infiltrated with IgG4-positive plasma cells. *World J Clin Cases* 2016; 4(8): 248-252 Available from: URL: http://www.wjgnet.com/2307-8960/full/v4/i8/248.htm DOI: http://dx.doi.org/10.12998/wjcc.v4.i8.248

## INTRODUCTION

Cronkhite-Canada syndrome (CCS) is a rare, non-hereditary condition characterized by gastrointestinal polyposis associated with diarrhea and epidermal manifestations, such as cutaneous hyperpigmentation, alopecia and onychodystrophy[1]. So far, the pathogenesis of CCS is still not fully understood[2], and autoimmune mechanism is probably involved. We here report a case of CCS in a male patient whose polyps presented with IgG4 - positive plasma cells. This finding is consistent with the autoimmune mechanism underlying CCS.

## CASE REPORT

A 40-year-old male patient with a 4-mo history of non-bloody watery diarrhea and hypogeusia associated with weight loss was admitted to our hospital in October of 2015. He defecated 6 to 10 times daily. No blood, mucosa, fat or oil was observed in the stool. He had no fever and abdominal pain. Family history was negative. In the past 4 mo, the patient experienced a weight loss of 17 kg.

Vital signs on physical examination were normal. His nutritional status was poor. Systemic skin pigmentation, dystrophic nail changes (Figure 1A and B) and alopecia (Figure 1C) were noted, but there was no pigmentation within oral cavity. The rest of the physical examination was non-contributory.

Laboratory results revealed low levels of serum albumin (30.1 g/L, range: 35.0-55.0g/L), serum potassium (2.61 mmol/L, range: 3.5-5.5 mmol/L) and blood glucose (2.6 mmol/L, range: 3.9-6.1 mmol/L). The erythrocyte sedimentation rate was elevated to 17 mm/h (range: 0-15 mm/h). The C reaction protein was within normal ranges. Both serum IgG4 (0.42 g/L, range: 0.08-1.4 g/L), and serum total IgG were normal (6.16 g/L, range: 6.0-16.0 g/L). Antinuclear antibody, anti-mitochondrial antibody, and smooth muscle antibody were all negative. There were no abnormal findings in X-ray of chest and mandible. The patient underwent electron esophagogastroduodenal endoscopy, capsule endoscopy and electronic colonoscopy, respectively, after admission. The endoscopic evaluation revealed multiple sessile polyps in the stomach (Figure 2A), small bowel (Figure 2B), and colon and rectum (Figure 2C). Histopathologic examination of biopsies obtained from those polyps showed hyperplastic change, cystic dilatation and distortion of glands with inflammatory infiltration, esinophillic predominance and stromal edema (Figure 3A and B). The histopathology of his rectal polyp showed a serrated adenoma. Mild chronic inflammation was found in the rectal mucosa which appeared normal under endoscope. Esophago-gastroduodenal endoscopy revealed an esophageal papilloma, but did not show polyp of the esophageal mucoma.

Immune staining for IgG4 plasma cells was positive in polyps of stomach (Figure 3C) and colon (Figure 3D), and IgG4 positive cell count of each high power field was 0-3 and 10-18 in gastric and colonic polyps, respectively. Cronkhite-Canada syndrome was diagnosed based on a

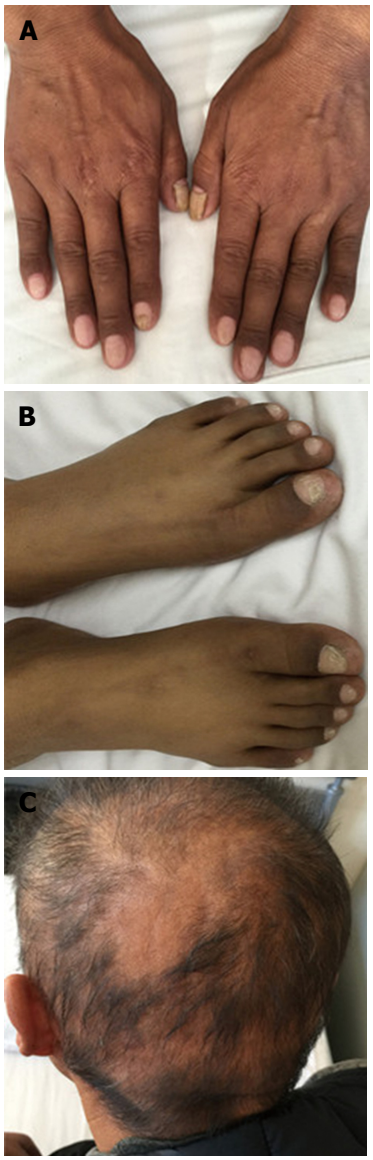


**Figure 1 Systemic skin pigmentation, dystrophic nail changes and alopecia.** A: Showing hyperpigmentation in hands and onychodystrophy in fingers; B: Showing hyperpigmentation in feet and onychodystrophy in toes; C: Showing sparse hair.

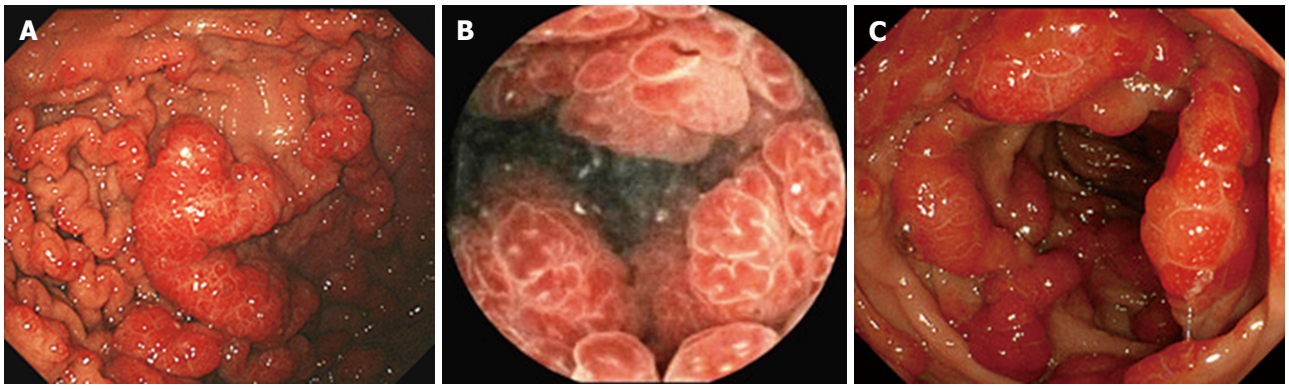


**Figure 2 Endoscopic evaluation revealed multiple sessile polyps in the stomach, small bowel and colon and rectum.** A: Electron gastroscopy revealing diffuse polyps in gastric mucosa; B: Capsule endoscopy showing diffuse polyps in small intestinal mucosa; C: Electronic colonoscopy showing diffuse polyps in colorectal mucosa.

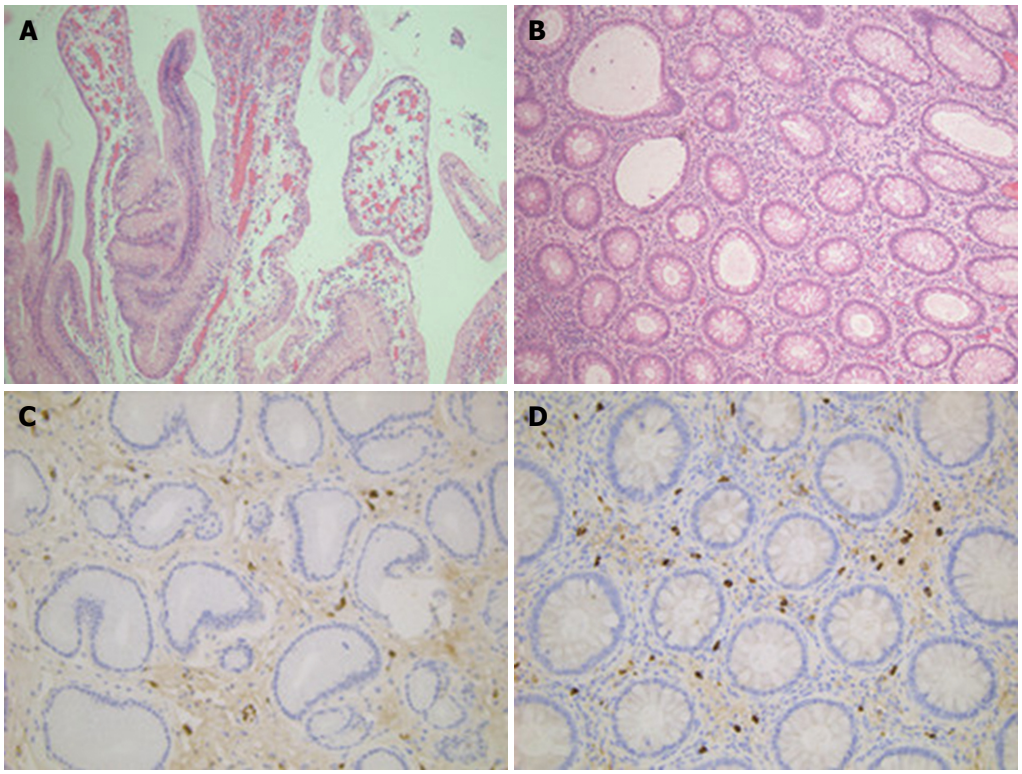


**Figure 3 Histopathologic examination of biopsies.** A: Histopathology examination of gastric polyp showing inflammatory and hyperplasia change (hematoxylin-eosin stain, × 20); B: Histopathology examination of colonic polyp showing inflammatory change (hematoxylin-eosin stain, × 10); C: IgG4 mononuclear cell staining in gastric polyp (× 20); D: IgG4 mononuclear cell staining in gastric polyp (hematoxylin-eosin stain, × 20).

combination of clinical features, endoscopic findings and histopathology of polyps. The patient was given nutrition support and symptomatic treatment, and his symptom of diarrhea improved. The patient refused steroid treatment and was discharged.

After a month, he was admitted to our hospital again because of severe diarrhea. By consent, he started on steroid treatment, and was administered methylprednisolone 40 mg/d intravenously for 6 d. His condition became much better, and was discharged. The patient was then treated with prednisone 30 mg/d orally for 4 wk, tapered by 2.5-5 mg/d every 1-2 wk. Follow-up was carried out at 8 wk after discharge, his diarrhea was improved, taste returned to normal and weight gain was 5.0 kg.

## DISCUSSION

CCS was first described in 1955 by Leonard W. Cronkhite, and Wilma J. Canada[1]. It occurs most frequently in middle-aged or older adults, with a slight male predominance, and a male-to-female ratio of 3:2[3]. CCS is a rare but serious protein-losing enteropathy, classically characterized by gastrointestinal polyposis and ectodermal features. Gastrointestinal polyposis is closely related to the malabsorption which

induced these ectodermal changes[4]. There is no strong evidence to suggest a familial aggregation and genetic predisposition. The etiology remains obscure but immune dysregulation may be important, given the increased IgG4 mononuclear cell staining in CCS polyps[5,6]. In this case, IgG4 immunostaining was positive in polyps of stomach and colon. This histologic finding further supports that autoimmune mechanism may be involved in CCS.

Differential diagnosis of CCS includes a number of polyposis syndromes, such as familial adenomatous polyposis, Peutz-Jeghers syndrome, Cowden disease, Turcot syndrome and juvenile polyposis. These can be distinguished based on the polyp histology, polyp distribution, clinical presentations, family history, and molecular genetic testing[7]. Polyps in CCS patients can develop throughout the gastrointestinal tract (except the esophagus) and are usually non-neoplastic hamartomas[5]. But polyps of CCS also displayed hyperplastic, inflammatory, or adenomatous features[8]. Watanabe *et al*[9] demonstrasted common features typical of CCS polyps, such as focal dilated cystic glands, some filled with proteinaceous fluid or inspissated mucus, the polyp and interpolyp area was edematous, with congestion and chronic inflammation of the lamina propria and submucosa, even though endoscopically the mucosa appeared normal. These findings are consistent with our case.

Optimum therapy for CCS is not known because of the rarity of the disorder and the poor understanding of the etiology. Combination therapy based on nutritional support and corticosteroids appears to lessen symptoms. The total treatment period is also not evidence-based, some recommended a range from 6 to 12 mo[10,11]. Relapse was common with steroid tapering. For some patients with CCS who initially responded to corticosteroids, long-term maintenance therapy by azathioprine may decrease its recurrence rate[5]. Our case had a good response to corticosteroids for 9 wk, but long-term efficacy is uncertain, and follow-up is needed in the future.

CCS has a rather poor prognosis, with a 5-year mortality rate of only 55%[12]. Delay in diagnosis are common primarily due to non-familiarity of physicians with this rare entity or nonspecific manifestation of early CCS, leading to poor outcome[13,14]. CCS bears a risk of malignancy development, and adenomatous polyps may occasionally occur in CCS patients, which are precursor lesions of colorectal cancer[15]. In the present case, colonoscopy showed a serrated adenoma in rectal mucosa. Intensive follow-up should be carried out in order to prevent and find canceration.

In summary, CCS is a rare disease with poor prognosis, autoimmune mechanism is probably involved in its pathogenesis. It has a good response to steroid. CCS has the risk of gastrointestinal cancer development and requires regular endoscopic surveillance.

## COMMENTS

### Case characteristics

A 40-year-old male patient with a 4-mo history of diarrhea and hypogeusia associated with weight loss.

### Clinical diagnosis

Cronkhite-Canada syndrome.

### Differential diagnosis

Familial adenomatous polyposis, Peutz-Jeghers syndrome, Cowden disease, Turcot syndrome, juvenile polyposis.

### Laboratory diagnosis

Low levels of serum albumin (30.1 g/L) and serum potassium (2.61 mmol/L).

### Imaging diagnosis

The endoscopic evaluation revealed multiple sessile polyps in the stomach, small bowel and colorectum.

### Treatment

The patient was treated with steriod.

### Related reports

Cronkhite-Canada syndrome is a rare and serious disease, but few report is related to the mechanism.

### Experiences and lessons

For the patient with Cronkhite-Canada syndrome, early diagnosis and follow-up is import to improve the prognosis. Immune staining for IgG4 plasma cells in the polpys is helpful for exploring the mechanism underling cronkhite-canada syndrome.

### Peer-review

In this manuscript, the authors demonstrated interesting Cronkhite-Canada syndrome case.

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