

# World Journal of *Clinical Cases*

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2012-2016

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## Breath-based meditation: A mechanism to restore the physiological and cognitive reserves for optimal human performance

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### Abstract

Stress can be associated with many physiological

changes resulting in significant decrements in human performance. Due to growing interests in alternative and complementary medicine by Westerners, many of the traditions and holistic yogic breathing practices today are being utilized as a measure for healthier lifestyles. These state-of-the-art practices can have a significant impact on common mental health conditions such as depression and generalized anxiety disorder. However, the potential of yogic breathing on optimizing human performance and overall well-being is not well known. Breathing techniques such as alternate nostril, Sudarshan Kriya and bhastrika utilizes rhythmic breathing to guide practitioners into a deep meditative state of relaxation and promote self-awareness. Furthermore, yogic breathing is physiologically stimulating and can be described as a natural “technological” solution to optimize human performance which can be categorized into: (1) cognitive function (*i.e.*, mind, vigilance); and (2) physical performance (*i.e.*, cardiorespiratory, metabolism, exercise, whole body). Based on previous studies, we postulate that daily practice of breathing meditation techniques play a significant role in preserving the compensatory mechanisms available to sustain physiological function. This preservation of physiological function may help to offset the time associated with reaching a threshold for clinical expression of chronic state (*i.e.*, hypertension, depression, dementia) or acute state (*i.e.*, massive hemorrhage, panic attack) of medical conditions. However, additional rigorous biomedical research is needed to evaluate the physiological mechanisms of various forms of meditation (*i.e.*, breath-based, mantra, mindfulness) on human performance. These efforts will help to define how compensatory reserve mechanisms of cardiovascular and immune systems are modulated by breath-based meditation. While it has been suggested that breath-based meditation is easier for beginning practitioners when compared to other forms of meditation more research is needed to elucidate these observations. A breath-based meditation sequence such

as Sudarshan Kriya has the potential to help develop an individual's self-awareness and support better integration of the brain (*i.e.*, mind) with other organ systems (*i.e.*, body) for enhanced human performance.

**Key words:** Meditation; Breathing technique; Cognitive reserve; Neurophysiology; Stress; Human performance; Emotional regulation

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**Core tip:** Breath-based meditation has potential benefits for patients with chronic diseases and mental health disorders to otherwise healthy individuals interested in optimizing their physical and cognitive performance.

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## INTRODUCTION

Stress can be associated with many physiological changes resulting in significant decrements in human performance. Recent innovations in medicine and wellness are currently rediscovering and validating numerous health practices such as yoga, meditation and breathing techniques from traditional cultures. While most often associated with Eastern cultures and traditions, the term "meditation" denotes emotional and reflective practices from cultural frameworks including Christianity, Judaism and Islam. More recently, breath-based meditation techniques that are a major component of routine Eastern practices, have been so called "Westernized" and are routinely suggested for better health and well-being<sup>[1]</sup>. Furthermore, a growing number of Westerners are adopting Eastern spiritual practices and mind-body therapeutic interventions such as yogic breathing<sup>[2]</sup>.

Breath-based meditation techniques generally utilize rhythmic breathing to guide practitioners to enter into a deeply meditative, relaxed mental state. We postulate that yogic breathing should not only be considered as a solution for health, but as a natural, technological solution for optimizing human performance. Human performance is generally categorized into cognitive function (*i.e.*, mind, brain) and physical performance (*i.e.*, cardiorespiratory, muscle metabolism) (Figure 1). Specifically, performance can be defined as activities and outcomes related to measurable goals and objectives that are expressed in absolute or relative terms.

As previously described, the concept of so-called "physiological reserve" is described as the compensatory

mechanisms available to sustain physiological function before the clinical expression of a disease or disorder<sup>[3]</sup>. For example, we recently demonstrated that optimizing the respiratory pump (rhythmic breathing) contributed to increasing tolerance to decreases in central blood volume by extending the body's compensatory reserve mechanisms<sup>[3]</sup>. Recently in a randomized control trial, breath-based meditation (*i.e.*, Sudarshan Kriya) significantly reduced post-traumatic stress disorder (PTSD) symptoms, hyperarousal, re-experiencing symptoms, anxiety, and respiration rate in United States military combat veterans<sup>[4]</sup>, suggesting that rhythmic breathing has the potential to restore cognitive functional reserve mechanisms. Reductions in PTSD symptoms and hyperarousal have been shown to have a positive impact on quality of life, which also may be an important component of optimized human performance. We hypothesize that yogic breathing plays a significant role in restoring the compensatory mechanisms, as it relates to mitigating PTSD and associated life stressors.

The purpose of this editorial is to introduce the notion that breath-based meditation (*i.e.*, pranayama, Sudarshan Kriya, alternate nostril, Ujjayi) may play a significant role in preserving and "restoring" both physiological and cognitive functional reserve. We discuss the proposed underlying mechanisms of yogic breathing in optimizing human performance and well-being.

## THE PHYSIOLOGICAL MECHANISMS OF YOGIC BREATHING

Yogic breathing, when practiced together with traditional meditation has been shown to reduce physiological stress. This have been previously described in detail by Brown *et al.*<sup>[1]</sup> and reviewed by Sharma *et al.*<sup>[5]</sup>. A detailed description of the fundamental breathing techniques that comprise of the Sudarshan Kriya sequence has been previously outlined by Brown *et al.*<sup>[1]</sup> and others<sup>[6]</sup>. Briefly, Sudarshan Kriya is a form of breath-based meditation which follows four breathing exercises: (1) victory breath or Ujjayi; (2) bellows breath or Bhastrika; (3) "Om" chanted three times; and (4) concluded with a series of three distinct rhythmic, circular breathing patterns<sup>[5]</sup>.

A growing body of evidence suggests that yogic breathing contributes to improved cognitive performance, better tissue perfusion, lower blood pressure<sup>[7]</sup>, glucose metabolism<sup>[8]</sup> and increased immune system<sup>[9]</sup>. It is well documented that these physiological changes are associated with optimal human performance.

Similar to routine physical activity, the daily practice of pranayama and breath-based meditation can provide moderate stimulation to the autonomic nervous system<sup>[1]</sup>. Therefore, the compensatory reserve mechanisms to defend against routine insults may be preserved by appropriate activation of the sympathetic nervous system and balancing the components of the autonomic nervous system<sup>[3]</sup>.

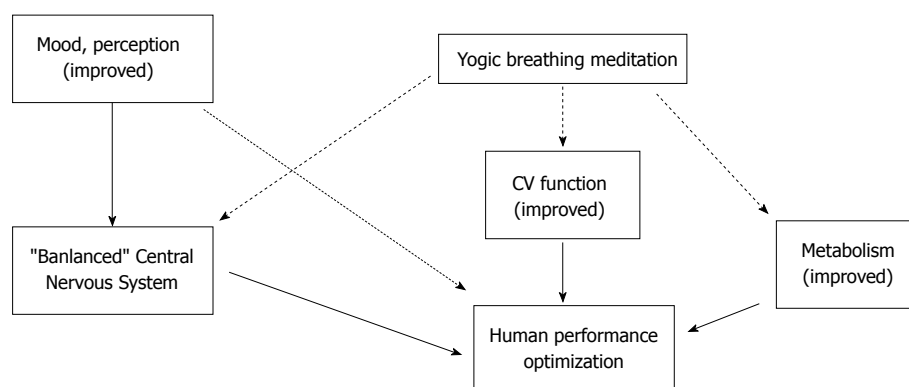


Figure 1 Proposed model of the relationship between yogic breathing meditation and human performance.

The physiological responses to physical stress (*i.e.*, exercise, hemorrhage) or cognitive stress consist of adjustments in metabolism, cardiovascular function, and the autonomic nervous system. Each of these mechanisms contribute to the physiological reserve of an individual and is specific to the genetic make-up, non-genetic factors, and event dependent (*i.e.*, the level of stress). In nature, the breathing patterns of animals reflect the presence of environmental stressors (*i.e.*, predators, drought) and the level of physical activity. While, humans are presented with numerous internal and external stressors on a daily basis, the consequences of these insults on short and long term human performance, health, and well-being are not always considered.

Brown *et al.*<sup>[1]</sup> introduced the neurophysiological mechanisms underlying yogic breathing. They suggested that a concomitant temporary state of alertness and calmness are spontaneously produced by activation of the autonomic nervous system. Breath-based meditation seems to modulate the appears to modulate metabolism and cardiovascular function through neural pathways and structures within the brain<sup>[6]</sup>. However, specifically how these physiological responses contribute to potential acute and long-term improvements in human performance and well-being are unknown. However, we postulate based on existing evidence that Sudarshan Kriya the unique sequence of breathing patterns and durations likely simulate various peripheral and central sensory pathways related compensatory mechanisms that govern balancing metabolism, cardiovascular and nerve function.

## MODULATING FACTORS ON COGNITIVE FUNCTIONAL RESERVES

The concept of functional cognitive reserves is the postulated capacity of a mature adult brain to sustain the effects of chronic stress, disease or injury (traumatic or non-traumatic) without manifesting clinically. Generally, it is hypothesized that the variability in functional reserve is related to individual differences in cognitive processes and brain neural networks which

allow some individuals to cope better than others<sup>[10]</sup>. A growing body of literature suggests that the reserve capacity is not only active and functional but modifiable with time, experience, and training<sup>[11]</sup>. This is a significant derivation from the previous concept of "brain reserve" which suggested that brain size govern the capacity of cognitive processes and reserves. Thus suggesting that individuals with similar brain neural network and baseline cognitive processes may have different functional reserves their cognitive functional reserves may be modifiable with techniques such as breath-based meditation.

Recently, enriched environment (EE), cognitively stimulating activities, cognitive training, and physical training were identified as factors for enhanced psychological resilience<sup>[12]</sup> and sustained functional cognitive reserves. It is likely that these factors may contribute to more resistance to cognitive decline, optimized human performance and improved quality of life.

### EE

There is emerging evidence that stressful environmental conditions may have a negative impact on human performance and lead to significant decrements in cognition<sup>[13]</sup>.

### Cognitive stimulating activities

Stimulating cognitive activities and training have been shown to improve neural function and lessen age-related decline in memory loss. Breath-based meditation could be considered as a cognitively stimulating activity to help promotion better brain health.

### Physical training

A study showed that physical training combined with yoga may have more benefits than exercise alone<sup>[9]</sup>. Stress may negatively affect cognition, mood, and mental status during physical training. Given that yogic breathing has been shown to reduce stress, this may be a plausible mechanism to improve physical training and human performance. Furthermore, there is emerging evidence that the ability to sustain exercise performance comes from a conscious effort and meditation may have a positive impact on this relationship.

Recently, it was demonstrated that training in meditation has significant advantages over exercise for reducing cold and flu illness, and was associated with improved immune system and quality of life<sup>[11]</sup>. While the scientific community may not fully understand the impact of mental status and perception on health and human performance, it is apparent that the compensatory reserve of each organ system responds to preserve functionality.

## CONCLUSION

Daily stress is associated with many physiological changes resulting in significant decrements in human performance. The mechanisms by which yogic breathing may positively impact our compensatory mechanisms to restore functional cognitive reserves and other physiological systems are not completely understood. It is very likely that meditation and intentional rhythmic breathing may, in part, reduce the overall physiological strain and mental workload on these human systems. By reducing the physical and cognitive workloads on the organ systems, optimal human performance is accomplishable. Physical activity training, EEs and cognitive reserve preserving activities such as meditation may have a positive impact on sustaining human performance during periods of acute or prolonged stress.

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## Posterior reversible encephalopathy syndrome following sepsis in a Crohn's disease patient: A case report

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### Abstract

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological syndrome presenting with neurological symptoms and characteristic radiologic findings. PRES occurs in the setting of various clinical conditions and requires prompt management of the causative factor for a full recovery. This is a case report of a Crohn's disease patient who developed PRES syndrome during a complicated post-operative course. In the presence of multiple causative factors, sepsis was considered as the predominant one. After prompt management, the patient recovered with no permanent neurological damage.

**Key words:** Crohn's disease; Sepsis; Posterior reversible encephalopathy syndrome; Diagnosis

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**Core tip:** We present the case of a Crohn's disease patient who suffered posterior reversible encephalopathy syndrome in the setting of a troublesome post-operative course. The etiology has not been clarified, since various



contributing factors existed, however sepsis represents the predominant reason. The patient was diagnosed early, since neurological consult was sought immediately, and after prompt management, he fully recovered without neurological deficits. Our goal is to stress out the importance of clinical suspicion in such cases, as the post-operative course in a Crohn's disease patient can often be perplexed and challenging.

Papaconstantinou I, Mantzos DS, Pantiora E, Tasoulis MK, Vassilopoulou S, Mantzaris G. Posterior reversible encephalopathy syndrome following sepsis in a Crohn's disease patient: A case report. *World J Clin Cases* 2016; 4(4): 103-107 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v4/i4/103.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v4.i4.103>

## INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a well-described clinico-radiological entity that has been associated with a variety of clinical conditions. It is characterized by neurological symptoms including seizures, visual abnormalities, altered mental status, headache and focal neurological signs. The clinical presentation is accompanied by characteristic cerebral magnetic resonance imaging (MRI) findings. Cerebral vasogenic edema represents the principal abnormality, but the underlying pathophysiological mechanisms remain controversial, as a number of etiologies have been implicated in the pathogenesis of this syndrome. As suggestive by its name it is reversible in most cases, however, permanent impairment and even death have been reported. Crohn's disease is considered a rare cause of PRES, as only a few cases have been described in the literature. The aim of this report is to underline the importance of clinical suspicion and prompt management in such cases, in order to achieve an optimal outcome.

## CASE REPORT

A 29-year-old, Caucasian male, with a long medical history of multiple surgical operations due to ulcerative colitis, was admitted to our hospital after repeated episodes of ileus and weight loss during the last nine months. The patient's previous operations included a subtotal colectomy with end-ileostomy formation and mucus fistula of the rectal stump at the age of seven, followed by rectum removal and an ileal J-pouch with a temporary loop-ileostomy. The patient underwent four reoperations over the following years due to complications and multiple episodes of ileus. Prior to his admission, two endoscopic dilatations were performed in an effort to conservatively treat existing enteral stenosis, with unsatisfactory results.

When admitted to our hospital, the patient was subjected to thorough work up, including abdominal and pelvic CT-scans and MRI-enterography which revealed ileus of the small bowel with dilatation of the ileum and obstruction of the afferent ileal loop above the pouch. Following discussion at our multidisciplinary team (MDT) meeting, a decision was reached to proceed with an exploratory laparotomy. During the operation, laborious lysis of adhesions was performed and 15 cm of jejunum along with a segment of ileum, proximal to the pouch, were removed. On inspection of the resected segments, a fistula was present between the jejunum and ileum along with multiple constricted areas. An end-ileostomy was created. The histopathological examination surprisingly revealed lesions compatible with Crohn's disease.

The postoperative period was cumbersome and complicated. From the ninth postoperative day onwards, the patient developed post-operative ileus. A few days later, due to a sudden episode of fever, blood cultures were ordered, in which *Escherichia coli* (*E. coli*) was isolated and appropriate antibiotics were administered. The patient remained stable until the twenty fifth postoperative day when he suddenly deteriorated. He presented septic profile, with fever, hypotension and tachycardia (T: 35 °C, arterial blood pressure: 7.9/5.9 kPa, 135 beats/min, 30900/IU WBCs) and underwent urgent laparotomy. During the operation a dilated bowel segment, a sizable retroperitoneal hematoma, and a pelvic abscess were discovered and drained with an adequate number of drainage tubes left in place. After the operation, the patient was unstable and therefore transferred to the intensive care unit (ICU), where he was supported with vasopressors and transfused with pRBCs, platelets and fresh frozen plasma. After a new episode of fever, new sets of blood cultures were sent and *Pseudomonas aeruginosa* was isolated. Meropenem was added to the administered antibiotics, according to cultures sensitivities. The patient's condition progressively improved and he was finally discharged from the ICU eight days later. Despite his improvement, the patient was in need of frequent platelets' transfusion due to profound and persistent thrombocytopenia.

Meanwhile, enterocutaneous fistulae had been established, following the route of draining tubes. Ten days later the patient was transferred again to the ICU due to hemorrhage from the stoma, which was treated conservatively; he returned to the ward after two days on tygecycline, fluconazole and methylprednisolone.

Five days later, the patient suddenly developed initially a right sided focal seizure with eye gaze deviation to the right for several minutes and a post critic gaze deviation to the left. This seizure was followed by a left sided one, a few minutes later, and continued for approximately an hour. During these episodes there was no impairment of consciousness, the patient was well oriented and cooperative, but complained of complete

vision loss. His vital signs were within normal ranges apart from his blood pressure which was 22/13 kPa and presented no neurological deficit. Blood tests revealed normal glucose and electrolyte levels. The patient underwent an urgent cerebral CT scan which showed hypodense areas in cortical and subcortical white matter of the occipital lobe. The antibiotics regimen was discontinued and the patient was treated with levetiracetam 500 mg bid and thiamine, instructions dictated by a specialized neurologist. The next day the patient was free of seizures but the visual impairment was scarcely improved as he could only recognize light. Head MRI revealed increased T2 and Flair signal intensity in cortical and subcortical white matter of bilateral parietal and occipital lobes with a slight contrast enhancement and restricted diffusion areas.

The magnetic resonance angiography was normal. The patient's condition improved over the next days and his vision was gradually restored. Thirty days later, the presence of infectious source was excluded and an MDT meeting was held. The patient was then commenced on infliximab and continued to receive levetiracetam. The enterocutaneous fistulae were still productive but did not cause electrolyte disorders. The patient was discharged after seventy-six days of hospitalization.

Six months later, the follow up MRI was completely normal, revealing no high intensity areas. Today the patient is in good condition, trying to improve his nutritional status; the enterocutaneous fistulae have dried up. His vision is completely restored and no other neurological manifestations have presented.

## DISCUSSION

PRES was first described by Hinchey *et al.*<sup>[1]</sup> in 1996. PRES is commonly presented with headache, altered mental status or consciousness impairment, visual disturbances and seizures in more than 90% of cases; status epilepticus is not uncommon<sup>[1,2]</sup>. Although reversible, permanent neurological impairment and death have also been reported<sup>[3]</sup>.

The pathophysiology of PRES includes abnormal alterations in cerebrum perfusion that lead to vasogenic edema<sup>[4]</sup>. The lesions are usually located in the posterior parietal and occipital lobes, such as in our case, possibly due to reduced number of sympathetic nerve fibers in this region, followed by the frontal lobe, the temporal lobe and the cerebellum<sup>[5]</sup>. Two totally different theories tend to prevail over others. The first one involves an increase in cerebral blood flow as a result of an increase in mean arterial pressure (MAP). This hyperperfusion causes a failure of the blood brain barrier, with subsequent injury of the endothelium which finally leads to vasogenic edema<sup>[6]</sup>. However, this theory fails to explain the pathogenesis of 20%-40% of PRES patients with normal blood pressure values<sup>[7]</sup>. The other theory involves hypoperfusion of the cerebrum as a result of

the damage of the blood brain barrier caused mainly by immune system activation or toxic agents in the setting of conditions such as eclampsia/preeclampsia, cyclosporine toxicity and sepsis/septic shock and may be related or not to severe hypertension<sup>[4]</sup>. The disruption of the endothelium leads to vasogenic edema. In our case, sepsis seems to be the most important factor that led to PRES. Patient presented acute hypertension during his hospitalization which is described in 67% to 80% of cases of PRES syndrome. However hypertension cannot be considered as a predominant factor in this case, considering that MAP was only slightly elevated (16 kPa) above the range that can be counterbalanced by auto regulation mechanisms. The acute onset of the symptoms, mentioned above and the presence of predisposing factors along with the exclusion of other causative factors of encephalopathy are highly suggestive of PRES. The rapid clinical and radiological improvement after the initiation of targeted therapy with levetiracetam, agrees with the diagnosis of PRES. A variety of factors causing PRES have been reported in the literature, such as toxic agents and immunosuppressive drugs, acute severe hypertension, preeclampsia/eclampsia, renal disease, transplantation, autoimmune disease and sepsis<sup>[2,3]</sup>. Our patient was exposed to several of the putative causative factors. He suffered from Crohn's disease for over two decades; Crohn's disease itself has been reported as a causative factor in 6% of the cases<sup>[5]</sup>. To the best of our knowledge there are a few reports of PRES development in Crohn's disease patients<sup>[8-11]</sup>. However, most of them have implicated immunosuppressant drugs as the main cause. Undoubtedly, sepsis played a key role in our case, as PRES occurred twenty-five days after severe infection. This is in line with the findings published by Bartynski *et al.*<sup>[12]</sup>, who described an interval of 15-30 d between sepsis and PRES development. Unlike most cases, with positive blood cultures for Gram-positive bacteria<sup>[13]</sup>, in our patient there was a bloodstream infection attributed to *E. coli* and *Pseudomonas aeruginosa*. In addition, our patient had been on corticosteroid therapy for a week before the onset of symptoms and received numerous blood transfusions during his hospitalization. Hypertension, as a result of corticosteroid therapy, has also been reported to lead to PRES<sup>[9]</sup> in several cases, while blood transfusion is considered an uncommon causative factor<sup>[14]</sup>.

MRI is the main imaging modality used for the diagnosis of PRES. Regions of high signal in T2-weighted images indicate cerebral vasogenic edema. In our case, multiple regions in bilateral parietal and occipital lobes showed abnormal signal intensity<sup>[6]</sup>. Computed tomography seems to be of less diagnostic value, with normal findings or nonspecific imaging of hypodense regions in most of the cases<sup>[15]</sup>. A normal MRI scan, six months after the incidence indicated the reversibility of the syndrome and confirmed the diagnosis in our

patient. Treatment should be initiated as soon as possible. Stabilization of the hemodynamic status and the management of the underlying causative factors are the cornerstones of the treatment of PRES. The patency of the airway should be the first priority, especially during seizure activity. Anticonvulsant agents, such as benzodiazepines or levetiracetam, should be initiated for seizure control. Progressive reduction of blood pressure, when needed, is also recommended<sup>[2]</sup>. Thiamine was given to our patient due to malnutrition.

The presence of multiple causative factors in this case, complicated the orientation towards a leading factor; however sepsis along with hypertension seemed to play a key role in the development of PRES syndrome in this patient.

PRES is a clinico-radiological entity that may be associated with a variety of clinical conditions, including Crohn's disease. In the presented case, PRES was most probably caused by the severe sepsis the patient sustained. However, whatever the reason is, PRES may confer additional morbidity with putative detrimental effects, especially in patients such as in the presented case, thus mandating a high level of awareness for the prompt identification and management of this entity.

## COMMENTS

### Case characteristics

A 29-year-old male patient with a history of Crohn's disease presented focal epileptic seizures and vision impairment in the setting of a troublesome post-operative course.

### Clinical diagnosis

Focal seizures alternating from right to left side accompanied with complete loss of vision.

### Differential diagnosis

Infective encephalitis or meningitis, hypoglycemia, venous sinus thrombosis.

### Laboratory diagnosis

All laboratory values were within normal limits.

### Imaging diagnosis

Magnetic resonance imaging revealed increased T2 and Flair signal intensity in cortical and subcortical white matter of bilateral parietal and occipital lobes with a slight contrast enhancement and restricted diffusion areas.

### Pathological diagnosis

Posterior reversible encephalopathy syndrome (PRES).

### Treatment

Administration of levetiracetam and thiamine.

### Related reports

PRES is a clinical syndrome that manifests in the setting of several conditions, such as acute hypertension, autoimmune disease, toxic agents, immunosuppressive drugs and sepsis. Crohn's disease has been reported as a rare causative factor. In a clinical setting where several factors exist, it is difficult to determine which one is responsible and target therapeutic action.

### Term explanation

PRES is a clinical entity with neurological symptoms and characteristic radiologic imaging. The pathophysiological mechanisms that lead to PRES are yet to be established.

### Experiences and lessons

Immediate diagnosis and prompt management are necessary in PRES, in order to avoid permanent neurological impairment. Even when the causative factor cannot be identified with certainty, supportive therapy and amelioration of patient's status lead to a favourable outcome.

### Peer-review

An interesting case of importance to clinicians treating inflammatory bowel disease.

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## Rare case of sclerosing mesenteritis and low grade follicular lymphoma

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**Author contributions:** Shah S and Roche E collected patient data, designed and wrote the paper; Roche E contributed in revising the work critically for important intellectual content and along with Mahy G contributed by giving final approval of the version to be published.

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### Abstract

An unusual case of long standing sclerosing mesenteritis; initially presented with recurrent abdominal pain and a mesenteric mass with surrounding fat oedema and stranding with a pseudocapsule and fat ring sign were clearly visualised on the initial computed tomography scan. Laparotomy showed diffuse thickening at the root of the mesentery and histology from this specimen revealed fat necrosis and reactive lymphoid tissue consistent with sclerosing mesenteritis. Initial treatment with steroids and tamoxifen relieved the symptoms and the mass. He was maintained on tamoxifen. Three years later he developed a recurrence of his symptoms and abdominal mass that responded to a course of steroids. Two years following this, he developed a follicular Hodgkin's lymphoma.

**Key words:** Sclerosing mesenteritis; Computerised tomography scan; Magnetic resonance imaging scans; Tamoxifen; Steroids; Hodgkin's lymphoma

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**Core tip:** Sclerosing mesenteritis is a rare disease but clinicians should be mindful of this condition that can present with various clinical symptoms including recurrent abdominal pain. The case we describe showed typical features of sclerosing mesenteritis and demonstrated good clinical and radiological response to steroids and tamoxifen. Five years later he developed a recurrence of the abdominal mass that showed transformation into a lymphoma.

Shah S, Mahy G, Roche E. Rare case of sclerosing mesenteritis and low grade follicular lymphoma. *World J Clin Cases* 2016; 4(4): 108-111 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v4/i4/108.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v4.i4.108>



## INTRODUCTION

Sclerosing mesenteritis also known as mesenteric lipodystrophy and mesenteric panniculitis is the part of the spectrum of idiopathic primary inflammatory and fibrotic process that affects mesentery<sup>[1]</sup>. This is a relatively rare condition with clinical data limited only to case reports. It has a male preponderance and generally occurs in the sixth and seventh decades of life. Pathophysiology remains unknown and various mechanisms like trauma (including surgery), autoimmune, malignant and paraneoplastic causes have been postulated. There is an association with lymphoma, breast cancer, lung cancer, melanoma and colon cancer<sup>[1-4]</sup>. In one study, prior abdominal surgery was present in about 35% of patients. There have been no reports of sclerosing mesenteritis transforming into a lymphoma, although in one case both of these lesions coexisted. We report an unusual case of long standing sclerosing mesenteritis that subsequently progressed to a follicular Hodgkin's lymphoma.

## CASE REPORT

We report a case of a 63-year-old man who presented to our department five years ago, with a five-year history of recurrent abdominal pain that had recently worsened. It was constant and increased in intensity on lying down and radiated into his back. He denied vomiting, weight loss or anorexia.

He was known to have Metabolic syndrome and his past surgical history included: (1) a laparotomy done over 10 years ago for probable cyst on pancreas; the details were not available; and (2) cholecystectomy, 5 years ago for calculus cholecystitis. On examination of his abdomen there was a long mid-line scar, mild abdominal tenderness and an impression of an ill-defined mass in his mid abdomen.

No abnormalities were noted on routine blood work up. IgG 4 and platelet serotonin were within normal limits. Computerized tomography (CT) scan of the abdomen showed a mesenteric mass with surrounding fat oedema and stranding. It was encasing superior mesenteric vessels and extending superiorly to the uncinate process. A pseudocapsule and fat ring sign were clearly visualised (Figure 1).

He had a laparotomy that showed diffuse thickening at the root of the mesentery that did not feel hard. On incising the peritoneum there was no discrete mass evident, though some discolouration and sclerosis of fat was present. There was no intra-abdominal lymphadenopathy. The histology from this specimen revealed fat necrosis and reactive lymphoid tissue. The features were consistent with sclerosing mesenteritis.

He was commenced on prednisolone 50 mg daily and Tamoxifen 10 mg twice a day and noticed significant improvement in his clinical symptoms. His steroids were tapered and discontinued and he continued on Tamoxifen 10 mg daily. He remained well and a repeat

CT scan had shown a significant improvement (Figure 2).

Three years later he developed an exacerbation of his symptoms and imaging demonstrated a recurrence of the mass. He was retreated with oral steroids and Tamoxifen was increased to 10 mg twice a day. He responded clinically and radiologically.

Two years later, he had a further recurrence in his symptoms. CT scans showed an increase in size and a change in characteristics of the mass. Positron emission tomography (PET) scan showed an intensely fluorodeoxyglucose avid heterogeneous nodal masses in the mesentery and adjacent para-aortic and aorto-caval nodes that were suspicious for a malignant process (Figure 3). He underwent a mini laprotomy for mesenteric mass biopsy. Histology revealed a follicular lymphoma/nodular sclerosing Hodgkin's disease and he has been commenced on treatment.

## DISCUSSION

The clinical presentation of Sclerosing mesenteritis varies from asymptomatic incidental diagnosis to various clinical features including abdominal pain, vomiting, diarrhoea, constipation, anorexia, weight loss, fatigue, fever of unknown origin, ascites, pneumoperitoneum, pleural and pericardial effusion<sup>[1-6]</sup>.

The diagnosis of sclerosing mesenteritis requires appropriate clinical and radiological analysis with multidetector CT and MRI being the modality of choice. Biopsy is necessary for definitive diagnosis. The two main CT features are the "fat ring" sign consisting of area of fat around the mesenteric vessels and presence of a pseudocapsule around the tumour. Other CT findings consist of increased attenuation in mesentery, foci of fat necrosis and fibrosis appearing as low-attenuation areas and a solid mass encasing the mesenteric vessels<sup>[7,8]</sup>. Magnetic resonance imaging and PET scans are upcoming modalities used to diagnose this condition. A negative PET has a high diagnostic accuracy in excluding tumoural mesenteric involvement while increased uptake suggests the co-existing mesenteric deposits, particularly in patients with lymphoma<sup>[9,10]</sup>.

Management of sclerosing mesenteritis is based on expert opinion with no recognised standard therapy. Treatment is generally guided by symptoms. Various treatments have been mentioned in case reports including immunosuppressive therapy with glucocorticoid and tamoxifen as first line therapy while colchicine, azathioprine or cyclophosphamide may be used as adjunct therapy. For refractory cases thalidomide can be considered. Surgery and radiation therapy both have a limited role. Surgery is best reserved for obstructive cases. The largest series was published from the Mayo Clinic in 2007 and based on their advice it is recommended that tamoxifen be continued indefinitely as the rate of recurrence and complications is significant<sup>[5]</sup>. A combination of steroids (40-60 mg) and Tamoxifen 10 mg BD tapered over

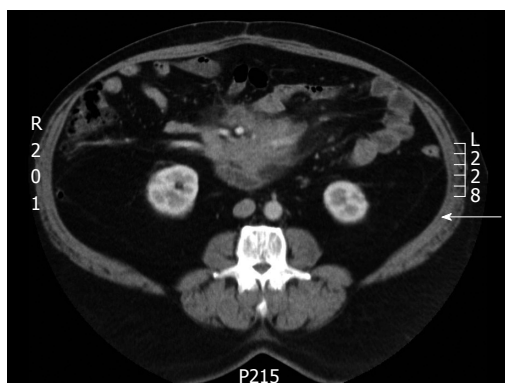


Figure 1 Pseudocapsule and fat ring sign were clearly visualised on initial computerised tomography scan.



Figure 2 Follow up computerised tomography scan showed significant improvement after treatment with prednisolone and tamoxifen.

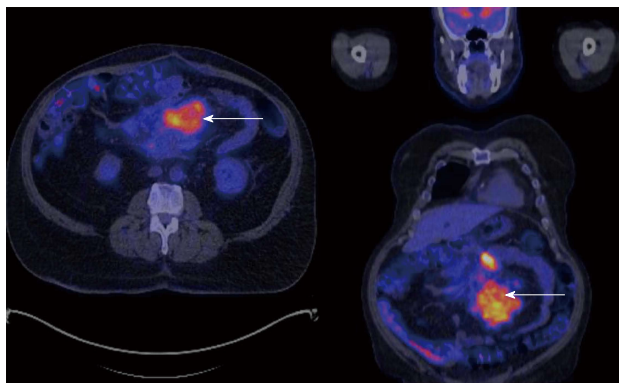


Figure 3 Positron emission tomography scan shows an intensely fluorodeoxyglucose avid heterogeneous nodal masses in the mesentery and adjacent lymph nodes.

three months has been the regimen most widely used. Tamoxifen apparently decreases inflammation and down regulates fibroblast proliferation<sup>[1-5,10]</sup>.

The case we describe showed typical features of sclerosing mesenteritis and demonstrated good clinical and radiological response to steroids and tamoxifen. Over the years he had follow up by imaging techniques to check the progress of mesenteric mass after treatment with Tamoxifen and steroids to which he

responded well initially. Three years later he developed an exacerbation of his symptoms and a recurrence of the abdominal mass on imaging that was treated again with steroids and tamoxifen. After 5 years he presented with recurrent symptoms and increase in size and a change in characteristics of the mass that was proved to be follicular Hodgkin's Lymphoma on histology.

## COMMENTS

### Case characteristics

A 63-year-old man with metabolic syndrome and previous abdominal surgery presented with a five-year history of recurrent abdominal pain that had recently worsened.

### Clinical diagnosis

There was a long mid-line scar, mild abdominal tenderness and an impression of an ill-defined mass in his mid-abdomen.

### Differential diagnosis

Differential diagnosis is quite broad and includes multiple causes of recurrent abdominal pain and abdominal masses including any intra-abdominal malignancy, carcinomatosis, lymphoma, pancreatitis, retroperitoneal fibrosis, vasculitis and granulomatous diseases.

### Laboratory diagnosis

All laboratory investigations were within normal limits.

### Imaging diagnosis

Initial computerised tomography scan of the abdomen showed a mesenteric mass with surrounding fat oedema, stranding and pseudocapsule with fat ring sign. Subsequent positron emission tomography scan on an intensely fluorodeoxyglucose avid heterogeneous nodal masses in the mesentery and adjacent para-aortic and aorto-caval nodes that were suspicious for a malignant process.

### Pathological diagnosis

Histology revealed a follicular lymphoma/nodular sclerosing Hodgkin's disease.

### Treatment

He was commenced on prednisolone 50 mg daily and tamoxifen 10 mg twice a day for treatment of symptomatic sclerosing mesenteritis. Later on after the diagnosis of lymphoma he underwent chemotherapy.

### Peer-review

In this study, the authors report a case of a man with a metabolic syndrome story. The patient got a dual treatment with glucocorticoid and tamoxifen which evolved through a lymphoma. This case study is interesting.

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## Chronic pancreatic pain successfully treated by endoscopic ultrasound-guided pancreaticogastrostomy using fully covered self-expandable metallic stent

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### Abstract

One of the most common symptoms presenting in patients with chronic pancreatitis is pancreatic-type pain. Obstruction of the main pancreatic duct in chronic pancreatitis can be treated by a multitude of therapeutic approaches, ranging from pharmacologic, endoscopic and radiologic treatments to surgical interventions. When the conservative treatment approaches fail to resolve symptomatic cases, however, endoscopic retrograde pancreatography with pancreatic duct drainage is the preferred second approach, despite its well-recognized drawbacks. When the conventional transpapillary approach fails to achieve the necessary drainage, the patients may benefit from application of the less invasive endoscopic ultrasound (EUS)-guided pancreatic duct interventions. Here, we describe the case of a 42-year-old man who presented with severe abdominal pain that had lasted for 3 mo. Computed tomography scanning showed evidence of chronic obstructive pancreatitis with pancreatic duct stricture at genu. After conventional endoscopic retrograde pancreatography failed to eliminate the symptoms, EUS-guided pancreaticogastrostomy (PGS) was applied using a fully covered, self-expandable, 10-mm diameter metallic stent. The treatment resolved the case and the patient experienced no adverse events. EUS-guided PGS with a regular biliary fully covered, self-expandable metallic stent effectively and safely treated pancreatic-type pain in chronic pancreatitis.

**Key words:** Endoscopic ultrasound-guided; Endoscopic



ultrasound; Pancreaticogastrostomy; Pancreatic duct drainage; Chronic pancreatitis; Self-expandable metallic stent

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**Core tip:** Endoscopic treatment for chronic pancreatitis is one of the most challenging advanced therapeutic interventions applied in clinical practice. While endoscopic retrograde pancreatography remains the preferred treatment option, alternative therapeutic approaches are available for application upon failure of the first-line approach, including endoscopic ultrasound (EUS)-guided pancreatic interventions, radiological interventions, or surgery. Here, we describe a case of chronic pancreatitis that failed first-line therapy and was effectively and safely resolved by EUS-guided pancreaticogastrostomy using a biliary-type, fully covered, self-expandable metallic stent.

Chang A, Aswakul P, Prachayakul V. Chronic pancreatic pain successfully treated by endoscopic ultrasound-guided pancreaticogastrostomy using fully covered self-expandable metallic stent. *World J Clin Cases* 2016; 4(4): 112-117 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v4/i4/112.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v4.i4.112>

## INTRODUCTION

Chronic pancreatitis is characterized by chronic progressive inflammation, destruction and scarring of the pancreatic tissue, all of which can lead to permanent loss of pancreatic function in both the exocrine and endocrine glands of the organ. As a condition with appreciable prevalence and incidence worldwide, accumulated research efforts have provided substantive insights into its etiology, pathophysiological course, and clinical manifestations<sup>[1]</sup>. The resultant advancements in radiologic and endoscopic techniques for examining this condition have increased the rate of diagnosis and helped to identify cases eligible for treatment in a more timely manner.

The most common clinical signs of chronic pancreatitis are deficiencies in pancreatic exocrine and endocrine enzymes (known as pancreatic insufficiency) and chronic abdominal pain. The pancreatic-type pain manifests from major pancreatic duct obstruction consequent to ductal stone blockade, peri-pancreatic ductal fibrosis, or parenchymal calcification. A multitude of therapeutic approaches are available for treatment of main pancreatic duct (MPD) obstruction in chronic pancreatitis, and range from pharmacologic, endoscopic and radiologic approaches to surgical intervention<sup>[2-4]</sup>. These approaches are also applied to resolve obstructions of the MPD associated with post-operative anastomotic stricture resulting from the Whipple procedure or surgeries to address disconnected

pancreatic tail syndrome or necrotizing pancreatitis with complete duct rupture<sup>[5]</sup>. Until resolution, the obstruction of drainage of pancreatic juices causes ductal hypertension which manifests as pancreatic-type pain<sup>[6,7]</sup>.

The pharmacologic treatments, such as pancreatic enzyme supplementation and analgesics, can relieve the pain symptom but do not resolve the obstruction-induced ductal hypertension<sup>[4,8]</sup>. Resolutive treatments, on the other hand, include physical interventions, using surgical or the less-invasive endoscopic approaches. Endoscopic retrograde pancreatography (ERP) with pancreatic duct drainage is the current preferred first line treatment<sup>[5-9]</sup>, and reportedly leads to complete or partial relief of the pain symptom in up to 80% of cases<sup>[9,10]</sup>; however, the ERP intervention reportedly fails to achieve pancreatic duct drainage in 5%-10% of cases, even when performed by experienced endoscopists<sup>[11,12]</sup>. The reported reasons for failure of pancreatic drainage are various and include chronic inflammation-related changes in the tissues of the perampullary region, complete MPD obstruction, post-surgical anastomotic changes, tortuous configuration of MPD, and obstructions of the gastric outlet and duodenum<sup>[11,13-15]</sup>. Surgery remains the most effective intervention for chronic pancreatitis since it can resolve ductal hypertension while facilitating resection of pathologic foci; in addition, the surgical approach allows for localized disease treatment in the absence of ductal dilatation<sup>[11]</sup>. When MPD dilatation is present, however, the surgical drainage is most frequently achieved by longitudinal pancreaticojejunostomy; although, this procedure carries high rates of complications (reportedly up to 30%) and mortality (reportedly up to 2%)<sup>[4,16-20]</sup>.

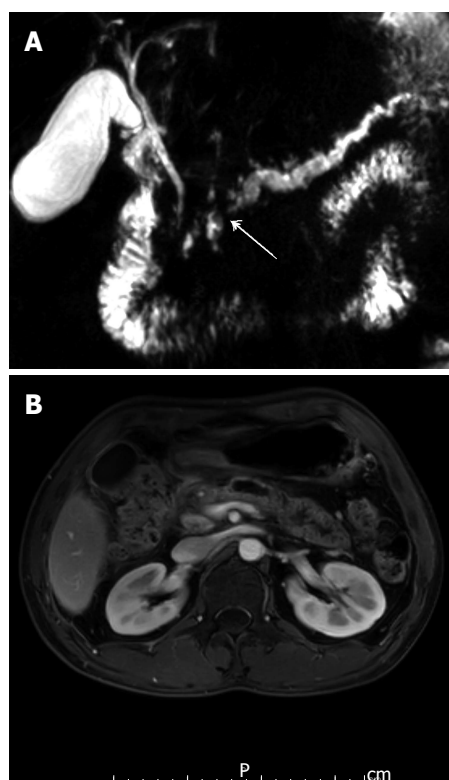
For patients with contraindications for surgery or who decline the surgical treatment, endoscopic intervention is considered. ERP with pancreatic duct drainage is the least invasive of the available endoscopic treatments and is often offered as the first line treatment for this alternative therapeutic approach<sup>[21-23]</sup>. However, if pancreatic duct cannulation by the standard ERP approach fails, alternative endoscopic techniques are available; these techniques include the endoscopic ultrasound (EUS)-guided rendezvous technique using a transpapillary approach or antegrade stenting and the EUS-guided transmural drainage technique<sup>[24]</sup>.

Here, we report the successful application of EUS-guided pancreaticogastrostomy (EUS-PGS) using a fully covered, self-expandable metallic stent (SEMS) to resolve a case a chronic pancreatitis.

## CASE REPORT

A 42-year-old man presented to our clinic with complaint of post-prandial chronic epigastric pain that had lasted for 3 mo. At intake, the patient reported no pre-existing illness but revealed a 14-year history of heavy alcohol intake. The patient described the abdominal pain as very severe and radiating into his back. Other

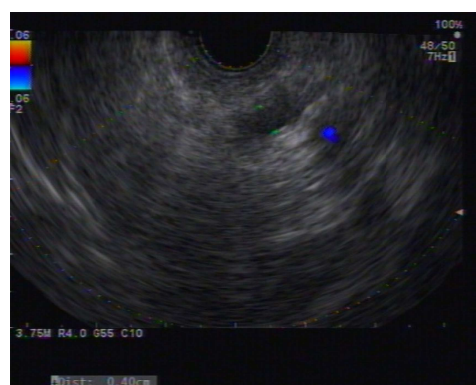




**Figure 1** Radiologic imaging finding showing an atrophic pancreatic parenchyma dilatation of pancreatic duct to 7 mm in diameter. A: Magnetic resonance image; B: Magnetic resonance cholangiopancreatography.

reported symptoms included anorexia, nausea and vomiting, with unintentional weight loss of a few kilogram. Physical examination revealed mild epigastric tenderness without rebound tenderness or abdominal mass. Blood workup showed complete blood count in the normal range, high fasting glucose (115 mg/dL; reference range: 74-99 mg/dL), normal total/direct bilirubin (0.6/0.2 mg/dL; reference range: 0.0-1.2 mg/dL), normal serum glutamic oxaloacetic transaminase/serum glutamic pyruvic transaminase (SGOT/SGPT) (21/15 U/L; reference range: 0-41 U/L), normal alkaline phosphatase (75 U/L; reference range: 40-130 U/L), low amylase (25 U/L; reference range: 28-100 U/L), and low lipase (12 U/L; reference range: 13-60 U/L). Coagulation tests were normal.

The patient underwent esophagogastroduodenoscopy, which showed unremarkable findings. Radiologic examinations of the upper abdomen by computed tomography and magnetic resonance imaging demonstrated atrophic pancreatic parenchyma with heavy calcification; in addition, the pancreatic duct showed a beaded appearance and dilation, with duct size measuring 7 mm at the maximal diameter. Accumulation of pancreatic juices was detected in the MPD adjacent to the pancreatic head, and multifocal narrowing and focal wall thickening was detected in the cystic duct and extrahepatic common bile duct. The collective radiologic findings strongly suggested a diagnosis of chronic pancreatitis (Figure 1).



**Figure 2** Echoview of the main pancreatic duct, from the body to tail, showing irregular and tortuous configuration and dilation up to 7 mm.

Pharmacological treatment was initiated and consisted of pancreatic enzyme supplements, tricyclic anti-depressant, and analgesic agents. When the nearly 1-year treatment produced no improvement in symptoms, including of the abdominal pain, the patient was referred for endoscopic pancreatic duct decompression. Initially, ERP with transpapillary drainage was attempted but the procedure could not be completed due to tight stricture of the pancreatic duct at the pancreatic genu that hindered passage of the guidewire.

The patient developed post-ERP pancreatitis and at day 3 post-ERP was offered the alternative treatment options of EUS-guided pancreatic duct drainage (rendezvous or PGS) as well as surgery. The patient and his family were informed of all procedure-related risks, benefits and long-term outcomes. At this time, the patient was discharged for decision-making and he returned 14 d later to undergo the selected EUS-guided intervention. Upon admission for the procedure, the patient provided informed consent for the procedure and publication of any and all data related to his case. For the treatment, the patient was positioned on the left lateral decubitus in the supine position and was put under intravenous sedation using propofol.

A curvilinear echoscope (GF-UCT 140-AL5; Olympus, Tokyo, Japan) was used for scanning. The endoview was unremarkable, and the echoview demonstrated non-homogeneous pancreatic parenchyma with hyperechoic foci and strands, lobulation, and parenchymal calcifications. The MPD, from the body to tail, was irregular, tortuous, and dilated up to 7 mm (Figure 2). An optimal puncture site was located to access the full MPD, from the body to tail, and a 19-gauge needle (Expect™ Slimline; Boston Scientific Corp., Spencer, IN, United States) was inserted. The aspirated liquid was clear. Contrast media was injected for the pancreatography, and the MPD was observed to be tortuous and dilated to between 6 mm and 8 mm in diameter (Figure 3). A 0.025 stiff guidewire (VisiGlide™; Terumo Medical Corp., Somerset, NJ, United States) was negotiated proximally, but passage down through



Figure 3 Pancreatography showing the main pancreatic duct to be irregular, tortuous, and dilated.



Figure 4 Fluoroscopic view showing the guidewire at the point it was hindered from passing through the papilla.

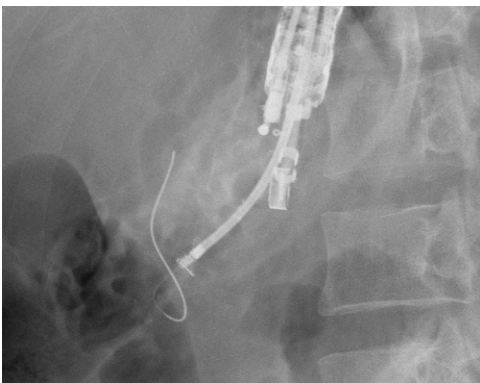


Figure 5 Fluoroscopic views during the neo-tract dilation.

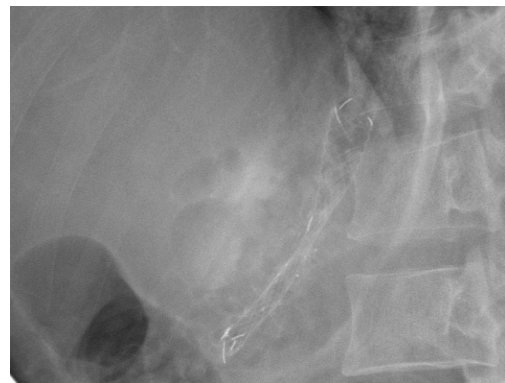


Figure 6 Fluoroscopic views after stent deployment.

the papilla was not possible (Figure 4). Therefore, the endoscopist decided to perform PGS. The neo-tract was created using a needle knife (MicroKnife™; Boston Scientific Corp., El Coyoil, Alajuela, Costa Rica), followed by dilation using a 5 Fr Soehendra biliary dilation tapered tip catheter (Wilson-Cook Medical, Inc., Winston-Salem, NC, United States), a 7 Fr Soehendra dilation catheter, a Soehendra stent retriever size 8.5 Fr, and an 8.5 Fr Soehendra dilator (Figure 5). Then, a 10 mm × 60 mm fully covered metallic stent (Niti-S Biliary Covered Stent™; TaeWoong Medical Co, Ltd., Gimposi, Gyeonggi-do, Korea) was inserted and deployed between the MPD and gastric cavity; good position and satisfactory drainage was achieved (Figure 6). After 5 d of uneventful in-hospital recovery, the patient was discharged.

At the 6-mo follow-up appointment, the patient reported no recurrence of abdominal pain and weight gain of 3 kg. The blood workup showed results within normal range for complete blood count and for all liver function markers. The patient continued taking the pancreatic enzyme supplement, but analgesics and anti-depressants were deemed unnecessary and discontinued. At the last follow-up (attended at 6 mo), the patient was healthy and had gained an additional 3 kg. The blood workup again showed results within the normal ranges, including those for lipase, amylase, and

CA19-9. Pancreatic stent removal was planned for 6 mo to 9 mo following this appointment.

## DISCUSSION

When conventional endoscopic techniques for pancreatic drainage fail, two alternative endoscopic approaches may be considered. The first technique is the rendezvous technique followed by transpapillary approach, and is recommended by some expert endoscopists as the first line option due to its general safety and efficacy<sup>[24-27]</sup>. For the case described herein, we attempted to perform this technique initially but the attempt failed when the guidewire could not be negotiated down through the stricture point, possibly due to the patient's complete MPD obstruction at the pancreatic genu. The second technique is the EUS-PGS. Since its first description in the literature in 1995 by Harada *et al.*<sup>[28]</sup> several case series successfully treated by this technique have been reported, but with the majority having used plastic stents<sup>[24,26,29-34]</sup>. However, the safety profile of plastic stents is negatively impacted by their potential to migrate from the intrapancreatic location<sup>[35]</sup>, the not infrequent failure rate of achieving stent placement, and the association with pancreatic fluid leakage following placement<sup>[36,37]</sup>.

Recent case reports have demonstrated the adv-

antages of using fully covered SEMs, which include longer stent patency, applicability to larger sized pancreaticogastric fistula, reduced rates of re-intervention, and increased ease of re-intervention to resolve cases of stent obstruction<sup>[38,39]</sup>. Moon *et al.*<sup>[40]</sup> reported a case series of 25 patients with painful obstructive pancreatitis, including 10 cases of chronic pancreatitis, all of who failed the initial ERP treatment and then underwent EUS-guided pancreatic drainage using fully covered SEMs. The study showed a 100% technical success rate and 100% clinical success rate, without any occurrences of stent-related adverse events (mean follow-up: 221.1 d).

The stents used in the study by Moon *et al.*<sup>[40]</sup> were either 6 mm or 8 mm in diameter, which are not readily available in the global medical device market. For example, our hospital did not have ready access to stents of those sizes and only a regular-sized biliary stent, of 10-mm, was available. Therefore, we performed the EUS-PGS using the 10-mm biliary stent and drainage was achieved without occurrence of any stent-related adverse event during the 6-mo follow-up period.

In conclusion, we have shown that a regular biliary fully covered SEMs can be used effectively and safely for EUS-PGS.

## COMMENTS

### Case characteristics

A 42-year-old man presented with severe abdominal pain that had lasted for 3 mo. Computed tomography scanning showed evidence of chronic obstructive pancreatitis with pancreatic duct stricture at genu. After conventional endoscopic retrograde pancreaticography failed to eliminate the symptoms, endoscopic ultrasound (EUS)-guided pancreaticogastrostomy (PGS) was applied using a fully covered, self-expandable, 10-mm diameter metallic stent.

### Clinical diagnosis

Chronic pancreatitis with pancreatic duct stricture.

### Differential diagnosis

Pancreatic duct stone.

### Laboratory diagnosis

Increased blood glucose (115 mg/dL; reference range: 74-99 mg/dL); Liver chemistry results: normal total/direct bilirubin (0.6/0.2 mg/dL; reference range: 0.0-1.2 mg/dL), normal serum glutamic oxaloacetic transaminase/serum glutamic pyruvic transaminase (21/15 U/L; reference range: 0-41 U/L), normal alkaline phosphatase (75 U/L; reference range: 40-130 U/L), low amylase (25 U/L; reference range: 28-100 U/L), low lipase (12 U/L; reference range: 13-60 U/L).

### Imaging diagnosis

Magnetic resonance imaging showed trophic pancreatic parenchyma with heavy calcification and the pancreatic duct with a beaded appearance and dilatation of 7 mm at the maximal diameter; in addition, multifocal narrowing and focal wall thickening was observed in the cystic duct and extrahepatic cystic bile duct.

### Treatment

EUS-guided PGS using a 10-mm, fully covered self-expandable metallic stent (FCSEMS).

### Term explanation

EUS is a novel endoscopic intervention applied through the gastrointestinal

tract for diagnostic evaluation and therapeutic interventions. EUS-guided PGS is a therapeutic intervention used to create a new connection between the main pancreatic duct and stomach to achieve pancreatic drainage.

## Experiences and lessons

A 10-mm FCSEMS represents a feasible and safe tool for achieving drainage of the pancreatic duct via the EUS-guided PGS procedure.

## Peer-review

This is an interesting case report aimed at describing and explaining the treatment of pancreatic duct obstruction by EUS-guided PGS using a fully covered metallic stent that is 10 mm in diameter.

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## Primary extragastrointestinal stromal tumor arising in the vaginal wall: Significant clinicopathological characteristics of a rare aggressive soft tissue neoplasm

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**Author contributions:** Liu QY participated in collecting case information about the patient and drafted the manuscript; Kan YZ, Zhang MY and Sun TY performed the literature review and provided the experimental technical assistance; Kong LF assisted in revising the manuscript; all the authors read and approved the final manuscript.

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### Abstract

Gastrointestinal (GI) stromal tumor is the most common mesenchymal neoplasm of the GI tract but also occurs with a lower frequency in extragastrointestinal regions and is called extragastrointestinal stromal tumor (EGIST). We report an unusual case of EGIST presenting as a vaginal mass. A 41-year-old woman presented with a gradually enlarging vaginal mass for the last 2 years. Physical examination revealed an elliptical, non-tender mass about 7.5 cm × 7 cm in size in the posterior vaginal wall and was resected completely. Under histological examination, the tumor showed a spindle cell type with coagulation necrosis, hemorrhage and high mitotic count. Immunohistochemical analysis revealed tumor cells were positive for DOG1, CD117, CD34 and p53 protein. Ki-67 labeling was 8%. Genetic analysis showed a deletion of exon 11 of the *c-kit* gene at codons 557-558. EGISTs should be kept in mind in the differential diagnosis in patients presenting with solid mass of the vaginal wall.

**Key words:** Platelet derived growth factor receptor alpha; Extragastrointestinal stromal tumors; Vagina; *c-kit*; Mutation

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**Core tip:** Gastrointestinal (GI) stromal tumor is the most common mesenchymal neoplasm of the GI tract but also occurs with a lower frequency in extragastrointestinal



regions and is called extragastrointestinal stromal tumor (EGIST). We report an unusual case of EGIST presenting as a vaginal mass and describe its clinicopathological, immunohistochemical and genetic features. Our data shows that this case was a primary malignant EGIST in the vaginal wall but few cases of primary vaginal EGIST have been reported to date. EGISTs should be kept in mind in the differential diagnosis of patients presenting with a solid mass of the vaginal wall.

Liu QY, Kan YZ, Zhang MY, Sun TY, Kong LF. Primary extragastrointestinal stromal tumor arising in the vaginal wall: Significant clinicopathological characteristics of a rare aggressive soft tissue neoplasm. *World J Clin Cases* 2016; 4(4): 118-123 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v4/i4/118.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v4.i4.118>

## INTRODUCTION

Gastrointestinal (GI) stromal tumors (GISTs) are the most common mesenchymal neoplasms of the GI tract. They affect all segments of the digestive tract, usually originate in the wall of the stomach or small intestine and develop from the interstitial cells of Cajal<sup>[1]</sup>. The pathogenesis of GISTs is related to *c-kit* gene mutation, which results in activation of a *c-kit* receptor tyrosine kinase (KIT, also called CD117 or stem cell factor receptor), then cell proliferation induction and apoptosis inhibition. Most GISTs harbor gene mutations in either the *c-kit* or platelet-derived growth factor receptor alpha (*PDGFRA*) gene. Rarely, GISTs arise primarily in the omentum, mesentery, retroperitoneum or undefined abdominal sites, which are referred to as "extragastrointestinal stromal tumors" (EGISTs)<sup>[2]</sup>. To the best of our knowledge, few cases of primary EGIST have been reported arising in the vaginal wall. In this study, we present a rare case of vaginal EGIST and a brief literature review.

## CASE REPORT

A 41-year-old woman complained of a painless mass in the perineal region which had gradually increased in size, initially from about 3 cm × 3 cm to 7.5 cm × 7 cm over a period of 2 years. The patient had no significant past medical or surgical history.

The gynecological examination revealed that the vagina was unobstructed and found a mass measuring about 7.5 cm × 7 cm in size with poor mobility and tenderness in the posterior vaginal wall. Its interior pole was closed to the vaginal opening with no discomfort symptoms such as bearing down. The ultrasonograph diagnosed cervix leiomyoma. The magnetic resonance imaging (MRI) revealed an elliptical mass in the cervix and posterior vaginal wall with a clear margin measuring about 9 cm × 7 cm × 6 cm in size, with equal T1 and T2 signals and a few punctate long T2 signal. The MRI also

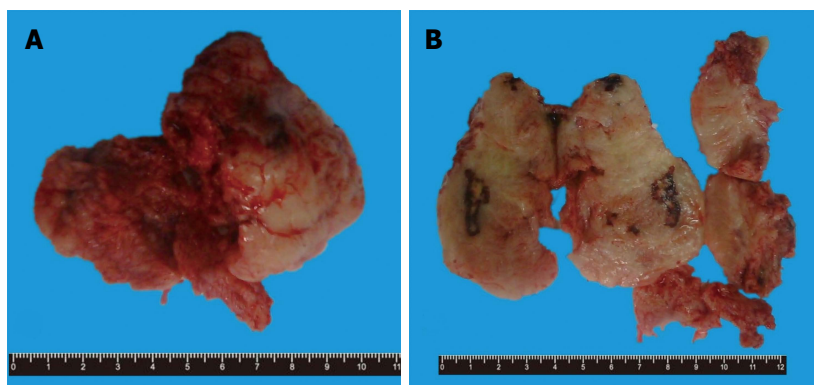
diagnosed leiomyoma. Other laboratory examinations were normal. The mass was completely removed along with part of the vaginal wall using vaginal resection and during the operation gynecologists found the margin of the mass was from the vaginal opening to the fornix vaginae, which was close to the rectum but the mass did not invade the bowel wall.

Grossly, the mass was elliptical, gray-white and grey-red, about 8 cm × 7.5 cm × 5 cm in size. The specimen was a well circumscribed mass and was surrounded by a fibrous capsule with pushing borders. Its section was also gray-white and grey-red in color with medium texture, containing multiple hemorrhages and necrosis (Figure 1).

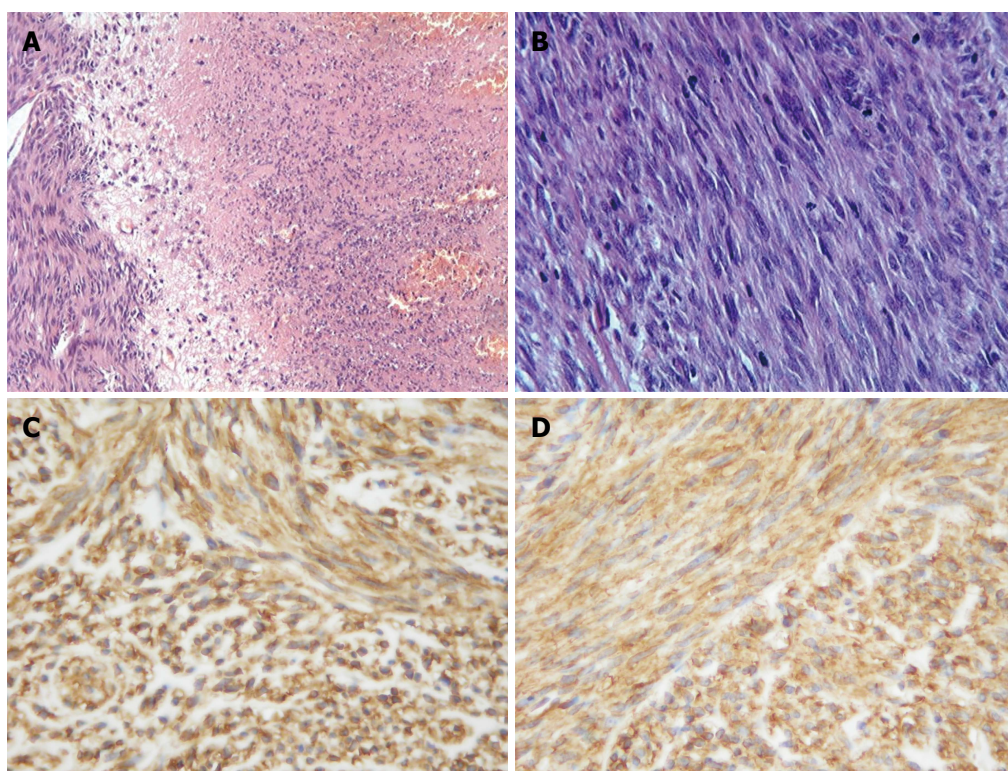
The fresh specimen was fixed in 10% formalin buffer solution and embedded in paraffin. Sections (3-4 μm) were cut from the block and stained with hematoxylin and eosin. Microscopic examination showed that the mass was mainly composed of spindle cells which were arranged in fasciculation or paliform, like leiomyoma or neurilemmoma. The cytoplasm of the tumor cells was eosinophilic and some had clear cytoplasm or paranuclear vacuoles. The nucleus of tumor cells was oval or rod shape with some vesicular chromatin and small prominent nucleoli. There were multiple large or small areas of coagulation necrosis and hemorrhage, accompanied by variable amounts of myxoid stroma (Figure 2A and B). Average mitotic figures were about 25 mitoses per 50 HPFs.

Immunohistochemical study was performed and the following antigens were used. CD117 (*c-kit* oncogene product, No.A4502, polyclonal, 1:70), CD34 (QBEND10, No.M7165, monoclonal, 1:150), S-100 protein (No.Z0311, polyclonal, 1:300), smooth muscle antibody (SMA, No.M0851, monoclonal, 1:200), desmin (No.M0760, monoclonal, 1:150), p53 protein (DO-7, No.M7001, monoclonal, 1:300) and Ki-67 (No.M7248, monoclonal, 1:100) were purchased from Dako Corp. Discovered on GIST 1 (DOG1) (DOG1, clone SP31, Cat.#RM-9132, monoclonal, ready to use) was applied by LabVision Corp. The slides were inserted in 10 mmol/L citrate buffer solution, pH 6.0 and heated in a microwave oven at a high setting for 5 min for epitope retrieval. The slides were incubated with 3,3'-diaminobenzidine tetrahydrochloride, following the use of the EnVision staining technique, and counterstained with hematoxylin. The tumor cells showed diffusely strong positivity for DOG1, CD117 (Figure 2C and D) and CD34 at both the cytoplasmic and membranous components and p53 protein at the nucleus, while tumor cells were completely negative for SMA, desmin and S-100 protein. Ki-67 labeling was about 8%.

Direct sequencing of polymerase chain reaction (PCR) productions was applied to detect the gene mutations of the *c-kit* gene (exons 9, 11, 13, 17) and the *PDGFRA* gene (exons 12, 18). Sections (10 μm) were cut and DNA was extracted from paraffin embedded tissue, according to the protocol of the Dneasy Tissue Kit (Cat.69504, Qiagen, Hilden, Germany). The product was



**Figure 1 Gross findings of the specimen.** A: Elliptical gray-white and grey-red soft tissue mass with fibrous capsule; B: Medium texture with multiple hemorrhage and necrosis on the cut surface.



**Figure 2 Histological findings of the tumor.** A: The tumor was composed of cellular spindle cells with a large area of necrosis. Hematoxylin and eosin (× 200); B: Active mitosis of tumor cells. Hematoxylin and eosin (× 400). Immunohistochemical findings of the tumors; C: Diffusely and strongly DOG1 positive in the tumor cells (× 400); D: Diffusely and strongly CD117 (*c-kit* pro-oncogene product) positive in the tumor cells (× 400).

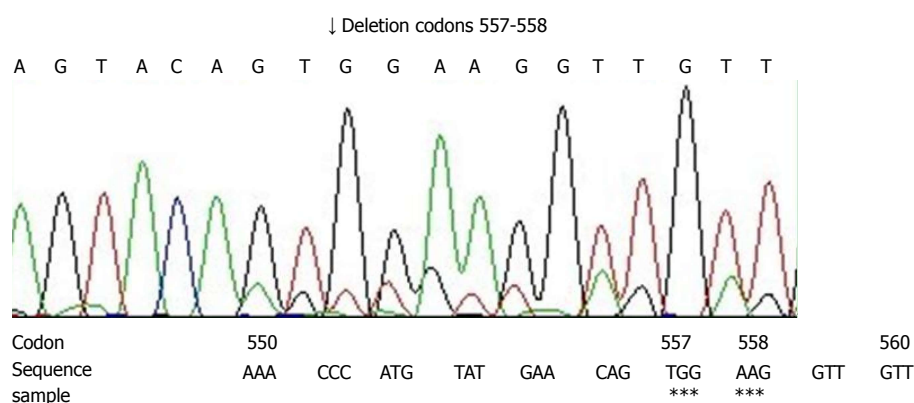
stored at -20 °C. Based on the *c-kit* gene and *PDGFRA* gene, 6 pairs of primers were designed and are shown in Table 1<sup>[3]</sup>. The PCR reaction conditions, recommended by Perkin Elmer, were the standard ones. The annealing temperature was set at 55 °C. PCR productions were fractionated on 50 g/L polyacrylamide gels and then stained with ethidium bromide. The ABI Prism 310 DNA sequencer (Applied Biosystems) was used to perform the direct sequencing by use of the same primers mentioned above. The Big Dye Terminator cycle sequencing ready reaction kit (Applied Biosystems Inc., Foster City, Calif.) was used for the sequencing reactions, according to the manufacturer's instructions.

PCR amplification and DNA sequencing revealed exon 11 mutation of *c-kit* gene. Sequence analysis showed the deletion of 6 bp at codons 557-558 (Figure 3). Other mutations were not found.

The maximal diameter of this mass was 8 cm and average mitotic figures were about 25 mitoses per 50 HPFs. There was multiple coagulation necrosis and hemorrhage. According to the results of immunohistochemistry and genetic mutation in exon 11 of *c-kit* gene, the histopathological diagnosis of this case was primary malignant EGIST in the vaginal wall. The patient was well after surgery and discharged with imatinib (STI-571) treatment. After 5 mo of follow-up,

**Table 1** Primer sequences for gene mutation analysis in our case

Forward	Reverse
<i>c-kit</i> exon 9	
5'-TCCTAGAGTAAGCCAGGGCTT-3'	5'-TGGTAGACAGAGCCTAAACATCC-3'
<i>c-kit</i> exon 11	
5'-CCAGAGTGTCTCTAATGACTG-3'	5'-TGACATGGAAAGCCCCTGTT-3'
<i>c-kit</i> exon 13	
5'-GCTTGACATCAGTTTGCCAG-3'	5'-AAAGGCAGCTTGGACACGGCTTTA-3'
<i>c-kit</i> exon 17	
5'-CTCCTCCAACCTAATAGTGT-3'	5'-GTCAAGCAGAGAATGGGTAC-3'
<i>PDGFRA</i> exon 12	
5'-TTGGATATTCACCAGTTACCTGTC-3'	5'-CAAGGGAAAAGCTCTTGG-3'
<i>PDGFRA</i> exon 18	
5'-ACCATGGATCAGCCAGTCTT-3'	5'-TGAAGGAGGATGAGCCTGACC-3'



**Figure 3** Computer analysis of a part of exon 11 of the *c-kit* gene in the tumor. Deletion of codons 557-558 was noted. Asterisks showed the deletion.

no recurrence or metastasis was found by clinical or radiological examination.

## DISCUSSION

GIST is the most common mesenchymal tumor of the GI tract and can occur anywhere in the GI-tract, most commonly in the stomach (60%) and small intestine (30%)<sup>[4]</sup>. The occurrence of most EGIST is related to the metastasis of primary GIST. Primary EGIST is very rare and occurs in the omentum, mesentery, retroperitoneum, pleura, liver, spleen, pancreas, pelvis, rectovaginal septum and vagina with clinicopathological and molecular features similar to GISTs<sup>[5]</sup>. However, little is known about their actual origin and pathogenesis. There are three reported cases of primary vaginal EGIST<sup>[6-8]</sup> and Weppner *et al*<sup>[7]</sup> supposed they might be derived from the rectovaginal septum. Our case was a primary vaginal EGIST because it was an isolated tumor with a clear boundary and no adherence to the intestine. Furthermore, there was no abnormal affect in other organs, especially the GI tract.

The diagnosis of GIST is established based on the morphology characteristics, distinctive immunophenotype and molecular genetic features. Histologically, GIST usually presents as a nodular mass and is solid on cross section, frequently with hemorrhage. There are three types of GISTs: Spindle cell (70%), epithelioid

(20%) and mixed<sup>[9]</sup>. The spindle type often presents with paranuclear vacuoles and is similar to leiomyoma or neurilemmoma. The National Institute of Health developed a new classification system for GIST for the risk of malignant behavior in 2001, which ranged from very low to high risk and was based on tumor size, mitotic counts and anatomical position, the three factors that are the most important reference index for judging malignant degree and prognosis<sup>[4,10,11]</sup>. In general, tumors larger than 5 cm in size with more than 5 mitoses per 50 HPFs are considered to be high risk. The tumor in our case was 8 cm in diameter with active mitotic counts about 25 mitoses per 50 HPFs and Ki-67 labeling was about 8%, so it was considered a high risk tumor and presented with malignant biological behavior. Hou *et al*.<sup>[12]</sup> reported that most EGISTs from the abdominal cavity or retroperitoneum were borderline or malignant. Two of the three reported cases of primary vaginal EGISTs were malignant. Our present case was also malignant.

Approximately 95% of GISTs show a distinctive immunohistochemical feature of positive staining for CD117 on membrane, cytoplasm and the paranuclear region (Golgi pattern)<sup>[1]</sup>. CD117 is the product of proto-oncogene *c-kit*, a tyrosine kinase transmembrane receptor located on chromosome 4 (4q11-q12)<sup>[9]</sup>. CD117 positive tumors are most responsive to the treatment with *c-kit* selective tyrosine kinase inhibitor,



imatinib (STI-571). DOG1, known also as TMEM16A and ANO1, is currently considered the most specific and sensitive marker of GIST<sup>[13]</sup>. Also, its expression does not depend on the gene mutation state of *c-kit* or *PDGFRA* gene and it is a very valuable marker, especially in CD117-negative cases<sup>[14]</sup>. In molecular genetics, 86% of GISTs present with mutations in the *c-kit* gene and 15% in *PDGFRA* gene<sup>[1]</sup>. In our case, immunohistochemical analysis showed diffusely strong positivity for DOG1, CD117, CD34 and p53 protein, while it was completely negative for SMA, desmin and S-100 protein. Mutational analysis revealed exon 11 mutation of *c-kit* gene that was deletion mutation at codons 557-558. He *et al.*<sup>[15]</sup> reported that *c-kit* mutations were identified in 76.1% of CD117 positive GISTs and most were mutations of exon 11 (67.1%). Hou *et al.*<sup>[16]</sup> discovered that many mutational sites of exon 11 were not fixed and had a central tendency. Point mutations and frame deletions were most frequently concentrated at codons 550-560 but duplications were most observed at codons 570-585. Terada<sup>[3]</sup> reported that primary EGIST of the omentum showed a deletion mutation of exon 11 of the *c-kit* gene at codons 552-558. Zheng *et al.*<sup>[17]</sup> analyzed gene mutations from 25 cases of EGIST and found that the pattern of *c-kit* and *PDGFRA* mutation in EGISTs was essentially similar to that in GISTs, that is, *c-kit* mutations were detected in 44% of EGISTs and all were exon 11 mutations. The *c-kit* gene mutation state and type was not only correlated to malignant degree and prognosis of GIST, but also a predictive factor of imatinib (STI-571) therapeutic reaction, which has important significance in the clinical diagnosis of GIST. Exon 11 gene mutation occurred especially in malignant GISTs and might be a clinical useful adjunct marker in the evaluation of GISTs<sup>[16]</sup>. In our case, exon 11 mutation also occurred and presented with deletion mutations at codons 557-558, identical to those reported in the literature.

The diagnosis of primary EGIST should be based on morphology, immunophenotype and molecular genetic features, and at the same time differentiated from other mesenchymal tumors of GI tract. The present data on EGIST is insufficient to make a final conclusion regarding pathogenesis, biological behavior, treatment, prognosis and recurrence. Thus, follow-up for a long period of time is required.

## COMMENTS

### Case characteristics

A rare extragastrointestinal stromal tumor (EGIST) arising in the vaginal wall.

### Clinical diagnosis

Leiomyoma.

### Differential diagnosis

Leiomyoma, malignant peripheral nerve sheath tumor and stromal sarcoma.

### Pathological diagnosis

EGIST.

### Treatment

Excision and administration of imatinib.

### Related reports

In early reports, extragastrointestinal stromal tumor presented as a recurrent vulvar mass.

### Term explanation

EGIST is a subtype of GIST and occurs in extragastrointestinal regions.

### Experiences and lessons

EGIST mostly has the same biological behavior as GIST.

### Peer-review

This case (GIST in the vaginal wall) is an extremely rare case and well organized. The presentation of the case is clear and the discussion conducted well with updated references.

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