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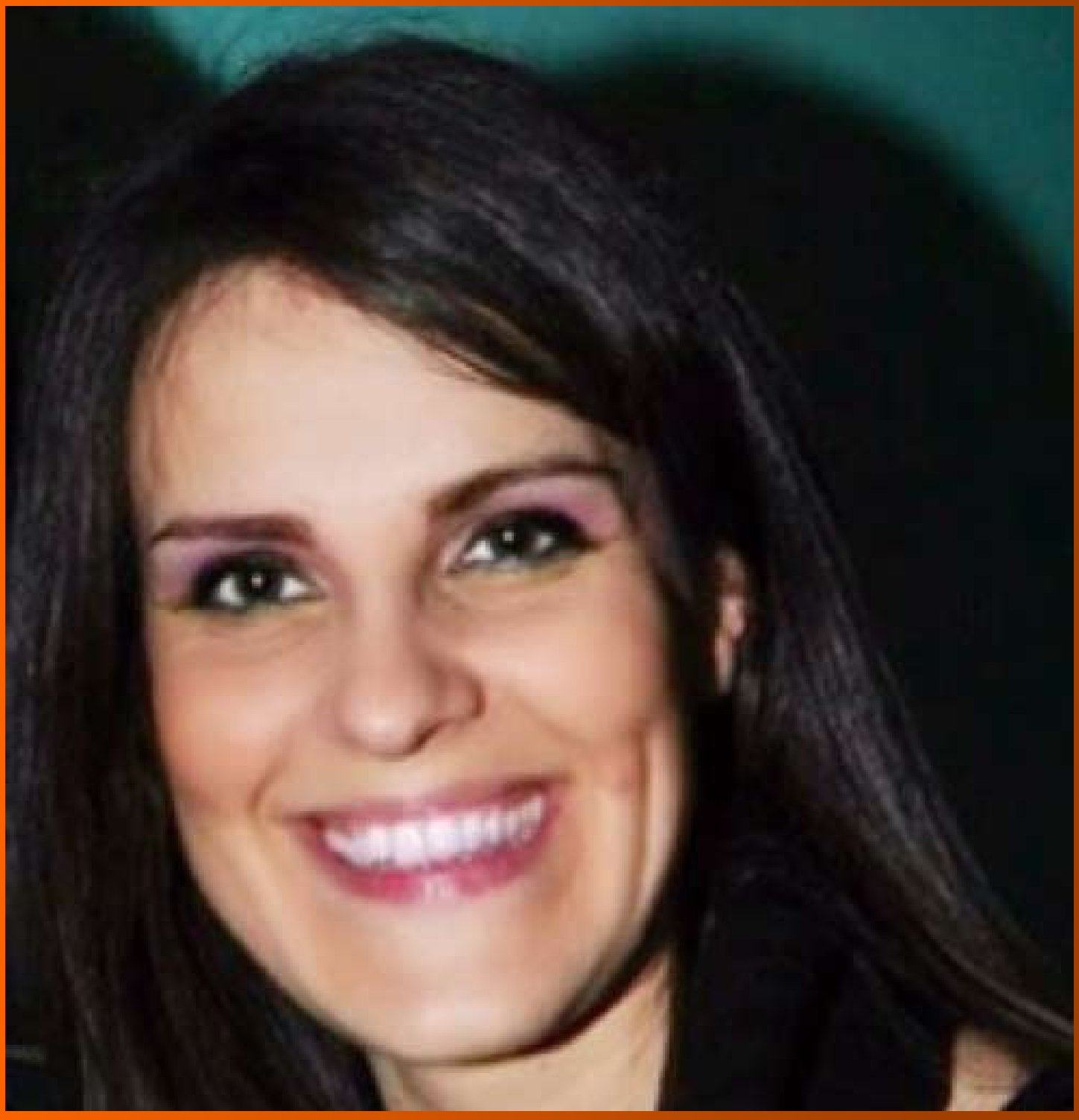

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EDITORIAL

Ultrasound: A promising tool for contemporary airway management

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Abstract

Airway evaluation and its management remains an ever emerging clinical science. Present airway management tools are static and do not provide dynamic airway management option. Visualized procedures like ultrasound (US) provide point of care real time dynamic views of the airway in perioperative, emergency and critical care settings. US can provide dynamic anatomical assessment which is not possible by clinical examination alone. US aids in detecting gastric contents and the nature of gastric contents (clear fluid, thick turbid or solid) as well. US can help in predicting endotracheal tube size by measuring subglottic diameter and diameter of left main stem bronchus. US was found to be a sensitive in detecting rotational malposition of LMA in children. Also, US is the fastest and highly sensitive tool to rule out a suspected intraoperative pneumothorax. In intensive care units, US helps torule out causes of inadequate ventilation, determine the tracheal width and distance from the skin to predict tracheotomy tube size and shape and assist with percutaneous dilatational tracheostomy. US can help in confirming the correct tracheal tube placement by dynamic visualisation of the endotracheal tube insertion, widening of vocal cords (children), and bilateral lung-sliding and diaphragmatic movement. Thus, ultrasonography has brought a paradigm shift in the practise of airway management. With increasing awareness, portability, accessibility and further sophistication in technology, it is likely to find a place in routine airway management. We are not far from the time when all of us will be carrying a pocket US machine like stethoscopes to corroborate our clinical findings at point of care.

Key words: Airway; Ultrasound; Evaluation; Difficult; Management

Core tip: Airway evaluation and its' management is conventionally based on clinical examination and

radiological imaging. They remain static and do not provide dynamic airway management option. Visualized procedures like ultrasound (US) provide point of care real time dynamic views of the airway in perioperative, emergency and critical care settings. US also aids in detecting gastric contents and the nature of gastric contents (clear fluid, thick turbid or solid). This detection is important for preventing complication of aspiration during airway management. The ultrasonography has brought a paradigm shift in the practise of airway management. With increasing awareness, portability, accessibility and further sophistication in technology, it is likely to find a place in routine airway management. We are not far from the time when all of us will be carrying a pocket US machine like stethoscopes to corroborate our clinical findings at point of care.

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Contemporary anaesthesia practise is richly blessed with technology based solutions. Technology has served to reduce human error in enumerable ways. Ultrasonography is one such extremely useful tool which is finding increasing applications in anaesthesia. It is already being considered as "gold standard" for central venous cannulations and peripheral nerve blockade. Visualized procedures improve safety and outcomes as compared to conventional techniques. In recent past, accumulated evidence is favouring its utility for various aspects of airway management for preoperative airway assessment, intraoperative management, predicting weaning from ventilation and successful extubation[1-3]. Various closed claim database and national level audits continue to implicate failure in airway management as a major contributor to perioperative morbidity and mortality[4-6]. Hence, constant efforts have been directed towards finding a "fail-safe" device for assisting us with airway management. Ultrasound (US) is turning out to be one such promising tool.

US provides point of care real time dynamic views of the airway inperioperative, emergency and critical care settings. It is free of ionizing radiation, painless, portable, convenient, reproducible, accurate and easily mastered skill and anaesthesiologist need not be dependent on their radiology colleagues. Because of superficial location of larynx, US can provide images of even higher resolution than advanced imaging modalities like computed tomography (CT) or magnetic resonance imaging (MRI)[6].

Conventional airway assessment fails predict difficult intubation in all patients. US can provide dynamic anatomicalassessment which is not possible by clinical examination alone. Various studies have suggested that US can help in predicting difficult airway by measuring the soft tissue thickness measured on anterior aspect of trachea along with neck circumference[1], hyomental distance ratio[7], width of tongue base and lateral pharyngeal wall thickness[8]. Intraoral sublingual approach to US is being investigated as a useful approach to predict difficult airway[9]. If difficult airway is suspected US can assist in preparing the airway (superior laryngeal and recurrent laryngeal) for awake intubation[10] and identify the cricothyroid membrane so that transtracheal cricothyrotomy cannula can be placed in a "cannot ventilate cannot intubate" (CVCI) scenario[11,12]. Though fasting guidelines are well known, however, gastric emptying is quite variable. US aids in detecting gastric contents and thenature of gastric contents (clear fluid, thick turbid or solid) as well[13].

US can help in predicting endotracheal tube size by measuring subglottic diameter and diameter of left main stem bronchus (for placement of double lumen tube) and help in deciding the appropriate size of the endotracheal tube (ETT)[14,15]. US can also be used to confirm correct laryngeal mask airway (LMA) placement[16]. Its use instead of fiberoptic confirmation averts the hypercapnia associated with the later[17]. US was found to be a sensitive in detecting rotational malposition of LMA in children[18]. Also, US is the fastest and highly sensitive tool to rule out a suspected intraoperative pneumothorax[2].

In intensive care units, US helps to rule out causes of inadequate ventilation, determine the tracheal width and distance from the skin to predict tracheotomy tube size and shape and assist with percutaneous dilatational tracheostomy (PDT)[19,20]. US guided PDT provides real time visualisation of the needle path and guide wire placement using linear array probe. It permits visualisation of pretracheal blood vessels, selection of puncture site, decreases posterior tracheal wall puncture, decreases injury to thyroid isthmus and increases the overall success[21-23]. US has been found to be a better alternative to FOB guided PDT and may replace it in coming years.

US scan help in confirming the correct tracheal ETT placement by dynamic visualisation of the ETT tube insertion, widening of vocal cords (children), and bilateral lung-sliding and diaphragmatic movement[23-25]. Additional advantage of US guided ETT placement is that esophageal intubation can be diagnosed prior to initiation of mechanical ventilation, thus reducing gastric insufflations and its consequences. Recent studies have suggested that bedside US is feasible and faster substitute to conventional techniques (auscultation and waveform capnography) and may replace them in future[24].

Expanding literature in recent years is indicating the utility of US in diagnosing various pathologies that can have implication in clinical decision making, *e.g.*, vocal cord malfunction[3], swallowing abnormalities[25], sialolithiasis[26], supraglottic hemangiomas[27], respi-

ratory papillomatosis[28], laryngeal stenosis[29], Zenker's diverticulum[30-34], *etc*.

Recent advances in airway US include transesophageal US which can provide distal airway images from mid-trachea to bronchi[33]. Additionally, endoscopic high frequency US of larynx has been described where a thin catheter high frequency probe with rotating mirror can produce 360° image of larynx[34]. With advent of multiplanar 3D US in airway imaging, spectrum of its application has further widened as spatial information obtained is more detailed and measurements obtained are more precise[35]. A recent report describing the use of 3D US concluded that airway anatomy, anteroposterior diameter of subglottic area and transverse diameter of upper trachea can be accurately measured and correlated with MRI findings[35]. Pocket sized smartphone based system can increase its applicability even in remote areas[36].

US has steep learning curve as depicted by many studies[37]. Inexpensive training models like gel phantom model can help improve US assessment and interventional skills and safety[38]. However, like and any other skill based technique, a degree of manual dexterity and knowledge is required to be proficient in its use. Hence, its accuracy remains operator dependent.

To conclude, ultrasonography has brought a paradigm shift in the practise of airway management. With increasing awareness, portability, accessibility and further sophistication in technology, it is likely to find a place in routine airway management. We are not far from the time when all of us will be carrying a pocket US machine like stethoscopes to corroborate our clinical findings at point of care.

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MINIREVIEWS

Physician disruptive behaviors: Five year progress report

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Abstract

Disruptive behaviors in health care can have a significant adverse effect on staff interactions that can negatively impact staff satisfaction, staff performance, and patient outcomes of care. As referenced in a previously published article, the Obstetrics and Gynecology specialty is one of the service areas where these behaviors occur more frequently. Despite growing evidence of the ill effects of these types of behaviors many organizations are still having a difficult time in addressing these issues in an effective manner. Gaining a better understanding of the nature, causes, and impact of these behaviors is crucial to finding the right remedies for solution. Nobody intentionally starts the day planning to be disruptive, it's just that things get in the way. A combination of deep seated factors related to age and gender preferences, culture and ethnicity, life experiences, and other events that help shape values, attitudes and personalities, and more external factors related to training, environmental pressures, stress and burnout, and other personal issues all contribute to the mix. Given the complexities of today's health care environment, each person needs to recognize the importance of being held accountable for appropriate actions and behaviors that affect work relationships and care coordination that impact patient care. Early recognition, early intervention, and taking a pro-active supportive approach to improve individual behaviors will result in better relationships, less disruption, more satisfaction, and better outcomes of care.

Key words: Disruptive behaviors; Patient safety; Patient outcomes; Staff relationships; Communication; Teamwork

Core tip: Disruptive behaviors in health care can have a significant adverse effect on staff interactions that can negatively impact staff satisfaction, staff performance, and patient outcomes of care. Disruptive incidents are more likely to occur in high risk settings such as the Obstetrical arena. Despite growing evidence of the ill effects of these types of behaviors many organizations are still having a difficult time in addressing these issues in an effective manner. Gaining a better understanding of the nature, causes, and impact of these behaviors and providing appropriate early and supportive interventions is crucial to finding the right remedies for solution.

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INTRODUCTION

It's been several years since I published a paper on the impact of disruptive behaviors in the Obstetrical setting highlighting its negative impact on staff relationships, care coordination, and patient outcomes of care[1]. Follow up reactions to the article have been very positive, but due to the nature of problem, and issues around reporting, internal organizational dynamics, and confidentiality, it's difficult to assess valid statistics as to how this has impacted the frequency of occurrence or consequences of these episodes. There have been a number of recent reports suggesting that the problem continues despite recurring evidence linking disruptive behaviors to patient harm[2-4]. Further evidence of its continued recurrence comes from research we conducted for an upcoming article in a law journal where we found a large number of cases reaching the appeal courts for incidents related to physician disruptive behaviors. The question is, why does this continue to be an ongoing problem?

HISTORY

We first reported on the impact of physician disruptive behaviors in 2002 highlighting the types of disruptive behaviors, the frequency, the specialties most involved, and its impact on nurse satisfaction and retention[5,6]. Phase two of our research extended the scope of analysis to include the incidence of disruptive behaviors in nursing and other disciplines and its impact on behaviors affecting communication and task performance leading to medical errors and other adverse events negatively impacting patient care. Our article in *The Joint Commission Journal of Quality and Patient Safety* was timed with the release of the Joint Commission Sentinel Event Alert #40 and the initiation of the new Joint Commission accreditation standard requiring hospitals to have a disruptive policy in place and to provide resources for its support as one of the leadership standards for accreditation[7,8]. During our research we noted that disruptive behaviors had the greatest likelihood of occurrence in high risk settings such as Obstetrics, Surgery, and the Emergency Department, and we reported on special studies conducted specifically in these areas[1,9,10]. In actuality, disruptive behaviors can occur anytime and anywhere across the full spectrum of care with similar detrimental effects on organizational culture, patient and staff satisfaction, morale, work relationships, task accountability, care efficiency, patient safety, and quality of patient care.

Table 1 Barriers

Organizational responsiveness (code of silence)
Reluctance to act (financial/hierarchy)
Structure and process (policy/reporting)
Process review (bias/conflicts of interest)
Intervention (skill sets)
Recommended action
Physician liabilities (personality)

PROGRESS?

We have definitely made some progress in this area. Many organizations have initiated a culture of zero tolerance for disruptive behaviors supported by setting appropriate behavioral standards described in either a code of conduct or disruptive behavior policy holding individuals accountable for their actions with set ramifications for non-compliance. Some organizations have taken a more pro-active approach in trying to reduce the incidence of disruptive behaviors by providing specific training programs in diversity management, cultural competency, emotional intelligence, conflict management and/or additional training to improve communication and team collaboration skills[11]. Programs focusing on skills taught in the airline industry (crew resource management), NASCAR (pit crew mechanics), and the nuclear power industry have shown significant benefit for team based care in Obstetrics, Surgery and Critical Care[12]. But problems still persist.

BARRIERS

Table 1 lists a number of different barriers that influence organizational effectiveness in addressing disruptive behaviors.

One of the first barriers is the issue of organizational responsiveness. This starts with organizational awareness. Many events go unnoticed or are not reported due to a hidden code of silence, an inconsistent reporting system, or fears of repercussion or retaliation for making a report. Ways to enhance organizational awareness include distributing a confidential internal survey assessment and making it safe for individuals to speak up. The second part is responsiveness. The underlying organizational culture and leadership need to develop and support a zero tolerance policy for disruptive behaviors and be willing to take the necessary steps to intervene when they occur.

A second more disturbing barrier is that of tolerance and acceptance. Many of these behaviors occur in physicians who are high revenue producers and the organization may be reluctant to confront the physician in fear of an antagonistic response and threats to bring his or her patients elsewhere. There may also be issues related to hierarchy, boundaries, or "sacred saints" leading to an unwillingness to

Table 2 Risks of non-action

Organizational morale
Recruitment and retention
Staff/patient satisfaction (HCAHPS)
Community reputation
Patient complaints/malpractice
Care efficiency (process flow/delays/utilization/productivity)
Poor compliance (documentation/metric based performance)
Communication gaps/medical errors/adverse events

HCAHPS: Hospital Consumer Assessment of Healthcare Providers and Systems.

intervene.

A third issue is that of structure and process. Do you have the right policies and procedures in place? Do you have a consistent reporting process? Do you have a standardized intervention plan where evaluation, assessment, and recommendations can be made in professional non- biased manner?

One of the key liabilities of any disruptive behavior policy is the process for event review, assessment, and follows up intervention. Some organizations may turn the issues over to the Chief Medical Officer, a Department Chair, or another delegated individual or task force, but do they have the right skills necessary to adequately assess the full situation, avoid preconceived biases or conflicts of interest, diffuse anger, resolve conflict, maintain focus on the key issues, offer support, and provide appropriate recommendations for next steps? In many cases the success of the intervention is more dependent on the effectiveness of the individual doing the intervention than the scope of the disruptive behavior described.

Probably the biggest challenge has to do in dealing with the underlying personality traits of the physician involved. Physicians are by nature very competitive, task driven, perfectionists, with very strong egocentric personalities. Medical training further accentuates the problem with its focus on gaining scientific knowledge (at the expense of developing interpersonal skills) which breeds a sense of autonomy, dominance, and need to control (at the expense of emotional sensitivity). All these factors can lead to a challenging personality who may at time be difficult to deal with.

As far as the question as to whether or not disruptive behavior will go away, recent changes in the health care environment may actually make the situation worse. Issues around Health Care Reform, changing models, metrics, and financial incentives for care, and greater accountability for performance outcomes have dramatically increased physician frustration, dissatisfaction, and levels of stress and burnout which can lead to both physical and emotional states that adversely affect attitudes and behaviors[13,14]. Recognizing these underlying issues are critically important when it comes to making appropriate recommendations for improvement.

Table 3 Recommendations

Awareness and responsiveness
Address organizational culture
Solicit project champions
Develop policies and procedures
Implement a consistent reporting and review process
Follow established process
Document all interactions
Intervention with trained personnel
Prevention
Provide physician/staff education (recognition/accountability)
Provide physician training (diversity/conflict management/communication skills)
Offer physician assistance and support (coaching/counseling/behavioral intervention)
Enhance physician engagement (input/motivation/alignment/satisfaction)
Recognize efforts

RISKS OF NON-ACTION

Sometimes we have to deliver a wake-up call for the organization to take appropriate action. Budget issues, resource issues, and the naïve sense of "no harm done" may override thoughts and willingness for organizational time and investment. Actually, it's quite the opposite[15]. Table 2 lists a number of different "costs" that may result from inaction.

One of the most obvious impacts is on employee morale. Perceptions of working in a "toxic" non-caring work environment leads to problems with staff retention and turnover and problems in recruiting new staff. The average cost to recruit a new nurse is over $60000 and at least twice as much to recruit a new physician. Anger and frustration lead to not only staff dissatisfaction, but also filters through to patient dissatisfaction which for Medicare is a key metric affecting hospital reimbursement[16]. With the growing public focus on the effects of workplace bullying, a further consequence is a tarnished community reputation which may impact market share and contract negotiations. More extreme situations may lead to patient complaints and a higher risk of costly malpractice suits[17].

Care efficiency can also suffer. Failure to follow best practice guidelines, failure to comply with hospital policies and procedures, failure to return calls, failure to collaborate, and failure to document can lead to wasted dollars related to inappropriate utilization, waste, duplication, process delays, mistakes, and reduced reimbursement.

The most serious effects occur when these behaviors disrupt care leading to costly medical errors and adverse events[15].

RECOMMENDATIONS

The discussion above highlights opportunities for improvement which are summarized in Table 3.

The first and most obvious need is organizational awareness of what is happening and the willingness to respond. The case for inaction is inexcusable.

At the core of reaction is organizational willingness to endorse and support a culture that values staff contributions and work ethic and reinforce the importance of a positive work environment which will not tolerate inappropriate behaviors. There are many articles emphasizing the importance of organizational culture and its relationship to staff satisfaction and patient outcomes of care[18]. Soliciting the help of project champions (both clinical and non- clinical) provide an excellent opportunity to further advance organizational initiatives.

Policies and procedures need to be developed to define appropriate standards of behavior and establish a consistent process for review. The organization then needs to follow due process in how it moves forward with the intervention. Not following due process and/or lack of documentation are two key issues to be considered if subsequent legal action is initiated.

The actual intervention process is probably the most critical part of the entire process and should be conducted by individuals trained in facilitation and conflict resolution techniques. The degree of intervention will depend upon the circumstances. Many disruptive behaviors occur unknowingly by the physician. In these cases just raising awareness and discussing alternative reactions will often help them self-correct. These types of informal interventions are often described as "coffee time" discussions. For more serious and repetitive disruptive behaviors the organization needs to take a more formal approach concluding with specific recommendations of what the physician needs to do to avoid these types of behaviors in the future. Depending on the circumstances additional training in diversity management, anger management, stress management, or conflict management may be appropriate. More severe cases may require individualized coaching or counseling services. These interventions can either be conducted internally or through a variety of outside programs offered by organizations that specialize in dealing with disruptive individuals. In some cases more intense behavioral modification therapy is needed which may includes assessment of possible substance abuse. In cases where the physician is resistant to change, sanctions, suspension, or termination of privileges may be the only alternative.

The best overall strategy is prevention. Most physicians don't plan to be disruptive, it's just that things may get in the way. Training in emotional intelligence, communication, and team collaboration skills will help provide essential tools to improve staff relationships and lower the incidence of disruptive events. If stress and burnout is an issue providing support services through either human resources, Physician Wellness Committees, a Physician EAP (Employee Assistance Program), or through the use of outside agencies to help the physician better adjust to the pressures of today's health care environment will ease some of their emotional liabilities.

Even better, take a proactive stance in trying to increase overall physician engagement. Take time to educate them about Health Care Reform and other current issues impacting their medical practice. Provide opportunities for discussion, listen to them, and respond to some of their needs and concerns. This can be done through discussion forums or town hall meetings, agenda items at Department meetings, or though one on one discussions[19]. Allowing physician input and participation around health care matters will increase physician alignment, engagement, satisfaction, and compliance, all of which will reduce the likelihood of a disruptive event. Be responsive to their needs and when possible offer appropriate administrative, operational, or clinical support to help ease the burden of running a demanding clinical practice.

In the end, physicians, and all staff, should be regarded as a precious resource. Show them respect, recognize and thank them for what they do, and work with them to re-invigorate their passion for providing medical care.

CONCLUSION

Disruptive behaviors can have a significant impact on patient care. Most physicians are just trying to do their job and in many cases don't even recognize the downstream effects of inappropriate behaviors. Many of these problems occur with strong personality traits further perpetuated by medical training that results in dominant, authoritative, egocentric, demanding behaviors with little emotional intelligence about the world around them. The current changes in today's medical environment are putting even more pressures on physicians which are increasing levels of stress and burnout that can change attitudes, perspectives, and behaviors that impact patient care. Physicians often don't recognize that they're under stress or what it does, and even if they do, feel like they can handle it themselves. Egos and concerns about competency and confidentiality with further limit their willingness to seek outside help. All of these issues can lead to disruptive behaviors. Yes organizations need to have policies and procedures in place to address the issue and definitely need to intervene when staff relationships and patient care may be compromised. Unfortunately, that's the punitive approach. Better yet would be for the organizations to take a different direction by taking a more pro-active approach to gaining insight into physician concerns, providing education, training, guidance, and behavioral support, and providing additional resources to help ease the burden of medical care. We can't leave it up to physicians to take care of themselves. Compassion and early intervention will do the job.

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Cost-effectiveness in *Clostridium difficile* treatment decision-making

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Abstract

AIM: To develop a framework for the clinical and health economic assessment for management of *Clostridium difficile* infection (CDI).

METHODS: CDI has vast economic consequences emphasizing the need for innovative and cost effective solutions, which were aim of this study. A guidance model was developed for coverage decisions and guideline development in CDI. The model included pharmacotherapy with oral metronidazole or oral vancomycin, which is the mainstay for pharmacological treatment of CDI and is recommended by most treatment guidelines.

RESULTS: A design for a patient-based cost-effectiveness model was developed, which can be used to estimate the cost-effectiveness of current and future treatment strategies in CDI. Patient-based outcomes were extrapolated to the population by including factors like, *e.g.*, person-to-person transmission, isolation precautions and closing and cleaning wards of hospitals.

CONCLUSION: The proposed framework for a population-based CDI model may be used for clinical and health economic assessments of CDI guidelines and coverage decisions for emerging treatments for CDI.

Key words: *Clostridium difficile* infection; Guidance; Cost-effectiveness; Model; Standardisation; Decision making

Core tip: Current clinical guidelines seldom include cost-effectiveness evaluations. Conclusions are typically based on clinical data only and sometimes referral is made to prices of therapies for justification of the treatment sequence advised. However, the price of a therapy as such is just a single criterion and does not reflect the balance between effectiveness and costs associated with the application of that therapy. This results often in a restricted position of new therapies in the treatment algorithm. Integration of cost-effectiveness using the population-based variant of cost-effectiveness evaluations as an instrument in guidelines for *Clostridium difficile* infection may be provide better decision making framework.

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INTRODUCTION

Escalating costs resulting from ageing of the population and an increase of innovative, expensive, medical technologies have become a major concern for health care professionals, decision-makers and the public. In addition to considering clinical benefits and the price of the new treatment, decision makers have taken a broader perspective by including cost-effectiveness evaluations, which also include related costs in the health care system.

Clostridium difficile infection (CDI) is considered a hospital-acquired infection. Diarrhea due to pathogenic *Clostridium difficile* (*C. difficile*) can occur if the bowel microbiota (bacterial content of the bowel) of a patient is disturbed, which is usually the result of antibiotic use prior to the CDI. With the increasing use of broad-spectrum antibiotics over the past two decades, the incidence of CDI has risen[1,2] and CDI is responsible for 15%-25% of cases of antibiotic associated diarrhea (AAD)[1]. CDI is usually self-limiting, but severe disease leading to colectomy and intensive care admission may occur. Mortality rates of 2%-7% have been reported[2,3], and seem even higher with the hypervirulent strain polymerase chain reaction (PCR) ribotype 027[4-6]. The chance of contracting CDI increases with a longer hospital stay[7] and both spread of *C. difficile* between patients as well as auto-re-infection, by this spore forming bacterium, have been demonstrated. In 55% of hospitalized patients with CDI, hospital stay was prolonged to more than 4 wk[8].

Pharmacotherapy of an initial episode of CDI with oral metronidazole or oral vancomycin is the recommended treatment in most guidelines[9-11]. However, following antibiotic treatment of CDI, recurrence and re-infection within 30 d occurs in approximately 15%-35% of patients, while 33%-65% of patients with > 2 previous CDI episodes will recur[12]. Recurrence of CDI is a serious and difficult-to-treat problem, impacting on the length and overall cost of hospitalisation[13]. The guidelines of the European *Society of Clinical Microbiology and Infectious Diseases* (ESCMID) have identified recurrence as being the most important challenge in the treatment of CDI[14].

Recently published guidelines[11-13] have incorporated relatively new treatments strategies with the antibiotic fidaxomicin and fecal microbiota transplantation (FMT or donor feces infusion), although their role is restricted because of the high price of fidaxomicin and the complexity (unconventional and unstandardized nature) of FMT. The latest Netherlands guideline suggests weighing fidaxomycin's high price versus the advantage of fewer recurrences[10,12,15]. English guidelines also recommends oral metronidazole for initial treatment in non-severe CDI, because it is cheaper than oral vancomycin, and because of concern about the selection of vancomycin resistant enterococci[13]. The median cost to treat a patient with CDI was €33840, showing an almost five fold higher and significant difference compared with the non-infected matched controls[16]. The estimated cost of CDI within the European Union (EU) is about €3 billion per year[17], and may further increase with aging. In most studies, hospitalisation is the main cost driver in patients with CDI[18]. Patients with CDI spend on average an extra 7-21 d in hospital, compared with non-infected controls[16,19,20]. The high rates of treatment failure and high rates of currently recommended antibiotics (metronidazole and vancomycin)[15,21,22] significantly affects costs[23]. The influence on clinical outcome and costs of this limited treatment efficacy is particularly apparent for patient groups with multiple comorbidities and a high risk of recurrence. In addition, minimizing the risk of person-to-person transmission of *C. difficile* in hospital wards seems of utmost importance. Taken together it is evident there is a large socio-economic and clinical unmet need to evaluate all these different factors in a single decision support model[1].

MATERIALS AND METHODS

Classic patient-based cost effectiveness model for infectious diseases tend to ignore the supra-patient social-economic consequences such as, for example, person-to-person transmission and closing of hospital wards due to infectious outbreaks. Preparing for an

Table 1 Summary of the most relevant therapeutic issues in *Clostridium difficile* infection

Level	Issues
Patient level	Recurrence of CDI is a serious and difficult-to-treat problem[26]
	Patient groups at high risk of recurrence or those for whom the impact of recurrence would be most dramatic include those with multiple comorbidities, who are immunocompromised, who are receiving certain concomitant antibiotics[26], who have had CDI previously, who are renally impaired, who are aged 65 yr or over, patients awaiting further treatment (for example chemotherapy) or rehabilitation (for example after cerebrovascular event)
Population level	The rate of person-to-person transmission of *C. difficile* is a complicating problem
	The risk for development of vancomycin-resistant enterococci or other antibiotic induced resistant bacteria, although it is not a major issue in daily practice

CDI: *Clostridium difficile* infection.

Table 2 Summary of the most relevant economic issues in *Clostridium difficile* infection

Level	Issues
Patient level	The cost of recurrence of CDI is high
	CDI leads to additional costs: extra diagnostic tests, extra antibiotics and other medication, time spent by nurse and physician on the ward
	The additional circumstances of these seriously ill patients (*e.g.*, not completing primary therapy, thereby complicating cure or improvement of their disease state) due to CDI should be reflected in the CEA
Population level	The rate of person-to-person transmission of *C. difficile* is a complicating problem with high costs
	The increased length and overall cost of hospitalization with CDI, including the costs of measures to isolate the patient and other clinical measures to prevent person-to-person transmission, as well as the costs of closing and cleaning wards
	The consequences of developing vancomycin-resistant enterococci or other antibiotic induced resistant enterococci are not integrated in standard cost-effectiveness evaluations

CDI: *Clostridium difficile* infection; CEA: Carcinoembryonic antigen.

all-inclusive model an expert procedure was convened considering the clinical and economic issues supposed to have an influence on cost-effectiveness evaluation of preventive and therapeutic measures for CDI. Step one was an extensive literature search on all different aspects of such a model. Subsequently, a base model was constructed and presented to experts. Next, the therapeutic and economic issues that were mentioned by the individual experts were incorporated in the model. This model was the input for a plenary discussion. The most relevant therapeutic and economic issues were defined and discussed. Based on scientific sources (literature and professional guidelines) as well as practice based sources, the issues were validated and a framework for the integration of these relevant issues into cost-effectiveness modeling was finalized. The outcomes of the expert procedure are described below.

Clinical and economic relevant issues

Clinical and economic relevant issues are shown in Tables 1 and 2.

The clinical and economic consequences of CDI in terms of morbidity, survival and costs underline the therapeutic need for innovative cost-effective solutions. Payers require cost-effectiveness analyses when deciding whether or not to reimburse new therapies/approaches for CDI. In such an analysis the first step is typically to develop a patient-based cost-effectiveness model. Such a model for CDI is shown in Figure 1.

Instructions are defined possible different stages for a CDI patient (health states).

Treatment stages hospital setting: (1) In the hospital, discontinuation of the antibacterial therapy that may have precipitated CDI is often not possible; (2) Patients with CDI are usually treated with antibiotics (metronidazole); (3) Patients may die or stay alive and surviving patients may or may not respond to metronidazole; (4) Patients who respond to metronidazole may be cured or experience a recurrence (or re-infection), which may occur during the hospitalization period or after discharge. In both cases the initial treatment with metronidazole is restarted, or vancomycin or fidaxomicin is prescribed instead; (5) If no response to metronidazole is seen, patients may be switched to vancomycin or fidaxomicin; (6) Then again patients may die or stay alive and surviving patients may respond or not respond to vancomycin or fidaxomicin; (7) Patients who respond to vancomycin or fidaxomicin may be cured or experience a recurrence (or re-infection), which may occur during hospitalization or after discharge. In both cases the initial treatment with vancomycin or fidaxomicin is restarted; and (8) Patients not responding will be switched to third-line treatment. For patients failing on third-line treatment, not many treatment options are left. If third line treatment is FMT, this can be repeated several times. Otherwise, patients may have to use vancomycin more or less continuously.

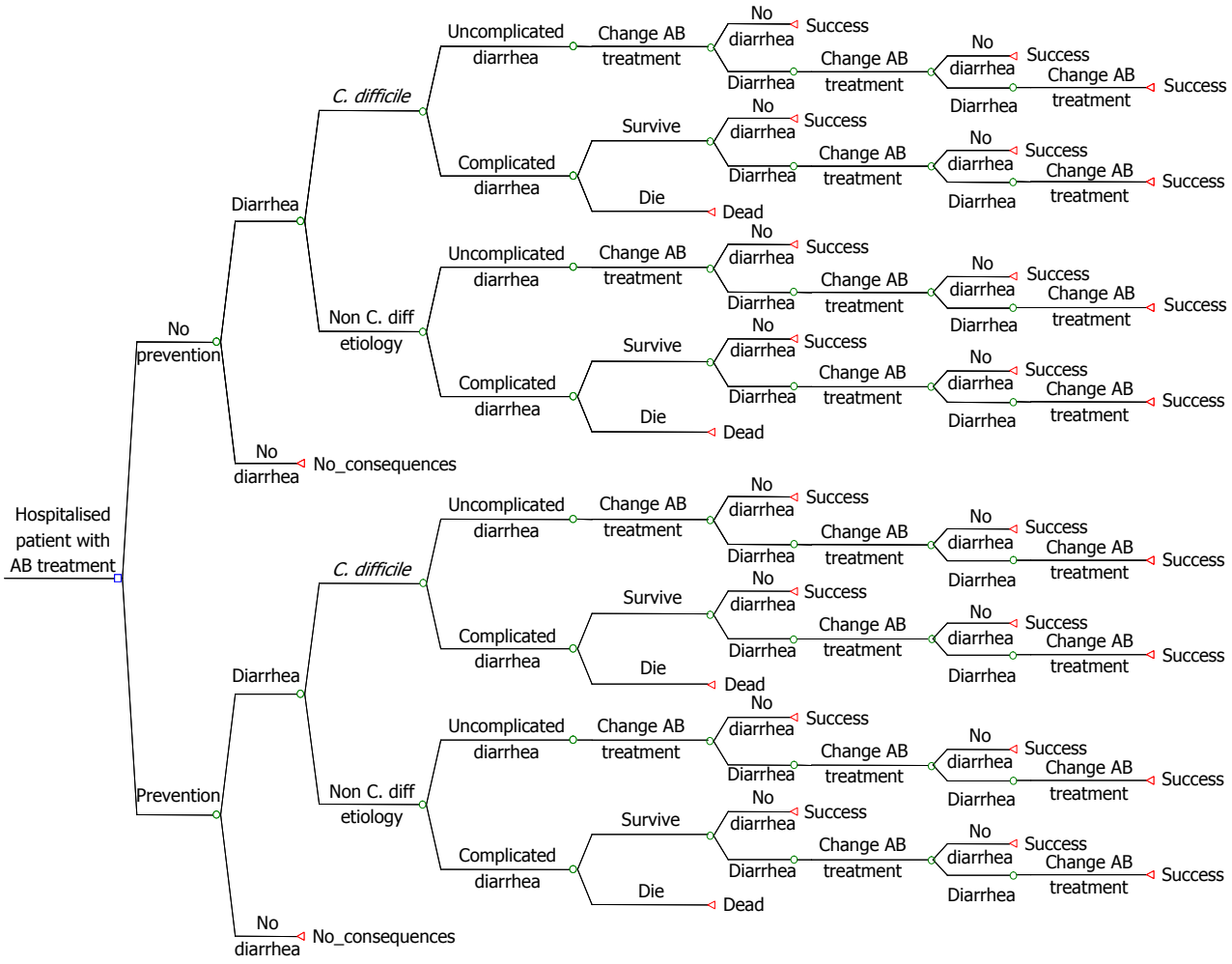

Figure 1 Flow diagram for cost-effectiveness modeling for Clostridium difficile infection.

Treatment stages community setting: The treatment stages are similar, as described above, but the difference is that patients may or may not be hospitalized, whereas in the previous section patients are already hospitalized.

The incremental cost per QALY gained is seen as the preferred cost-effectiveness outcome, but is often of limited value in a health economic analysis, which only covers the hospitalization period. The QALY gain is calculated by combining the utility gain (quality of life gain) with the number of life years gained. QALY gained may therefore be the result of longer life expectancy, utility gain, or both. If the cost per QALY gained is not viewed as the most appropriate outcome (for example when transmission and/or ward contamination are a problem), other cost-effectiveness outcomes may be considered, for example, the cost per recurrence avoided, which reflects the additional costs for the prevention of one recurrence. As recurrence is not only a clinical issue, but also may have major economic consequences, this outcome might be relevant for decision makers.

Population-based model for cost-effectiveness analysis

The cost-effectiveness outcome based on the patient-based model only provides a limited health economic outcome in terms of time horizon and perspective and more importantly, disregards the impact on other patients. The relevant economic issues, such as resistance, person-to-person transmission, isolation measures and closing of wards of hospitals, are all supra-patient effects. These consequences of CDI on hospitals, payers and society, that go beyond the individual scope of the patient, are not integrated in standard CEA's. Therefore, the outcomes of a patient-based cost-effectiveness model should be considered cautiously because they present only a conservative and limited outcome. For all-encompassing cost-effectiveness evaluations of CDI therapies, these supra-patient economic aspects cannot be disregarded. Therefore, we propose performing cost-effectiveness analyses for CDI using a population-based model, which incorporates all of the clinically important elements of the patient-based model as well as the supra-patient therapeutic and economic issues (Table 3).

RESULTS

The flow diagram (Figure 1) does not contain a particular choice for a specific therapy but serves as

Table 3 Similarities and differences between a patient-based and population based cost-effectiveness model

Patient-based cost-effectiveness model	Population-based cost-effectiveness model
Similarities	
Patient-related therapeutic and economic measures for clinical and economic evaluations	
Differences	
	The relevant economic issues, as indicated for CDI like: increasing incidence of CDI, person-to person transmission of CDI, development of vancomycin-resistant enterococci (VRE), or other antibiotic induced resistant bacteria, impact for department of microbiology diagnostic testing isolation measures and closing of wards of hospitals other supra-patient effects
Limited health economic outcome in terms of time horizon and perspective	
The patient-based cost-effectiveness model only captures the short-term time horizon of the CDI episode within the hospital setting at a patient level	

CDI: *Clostridium difficile* infection.

a blueprint for cost-effectiveness modeling. Based on the developments in CDI treatment, we suggest applying different treatment sequences for testing the effects on cost-effectiveness outcomes. Other suggestions for application are stratification of the patient population according to potential co-variables, such as risk factors for recurrence (for example, prolonged hospital stay or ICU admission) or underlying diseases (for example, patients after surgery, patients with a malignancy receiving chemotherapy, and renally impaired patients).

Three types of recent therapies could be candidates for comparison using a population-based model: the antibiotic fidaxomicin, fecal microbiota transplantation (FMT), and preventive use of probiotics.

Fidaxomycin is a novel antibiotic with targeted activity against *C. Difficile* with a similar safety profile as vancomycin. After treatment of an initial episode of CDI, the cure rate after 30 d was increased after fidaxomycin (82%) compared to vancomycin (70%)[16,17,24]. FMT helps restore the normal colonic micro flora in patients with refractory and recurrent CDI[25,26]. The procedure involves single or multiple infusions (*e.g.,* by enema) of a feces based solution from a healthy donor. A recently published randomized trial confirmed the efficacy of FMT in patients with recurrent CDI. For assessment of preventive treatments, the framework (Figure 1) can be used to estimate the costs and benefits of co-prescription of probiotics with antibiotics to prevent CDI. Recently, a patient-based cost-effectiveness evaluation for probiotics showed probiotics "could lead to substantial cost savings"[27]. To further investigate the economic consequences of the use of probiotics to prevent CDI, a population-based model could be applied and although the expected clinical benefit may be limited, total cost savings compared to no preventive treatment, and a predicted (Cochrane) drop in therapy induced side effects, may still be relevant.

DISCUSSION

Current clinical guidelines seldom include cost-effectiveness evaluations. Conclusions are typically based on clinical data only and sometimes referral is made to prices of therapies for justification of the treatment sequence advised. However, the price of a therapy as such is just a single criterion and does not reflect the balance between effectiveness and costs associated with the application of that therapy. This results often in a restricted position of new therapies in the treatment algorithm.

Among health authorities, it is common to include evidence of cost-effectiveness in decision-making about coverage under the health insurance package. Even though the cost per QALY outcome might fall below the threshold of a country, health authorities might decide to reject coverage based on the high weight they place on the budget impact[28]. This may be considered a paradox, because the cost-effectiveness guidelines were written by the same authorities and payers.

Estimates of the cost-effectiveness of a medicine may only have a limited impact on the use of that medicine within a hospital, as a result of a "silo mentality" found within the hospital as well as within the budget management structure existing at the payer, local and national levels. In that case, a treatment (medication or medical therapy) that is more expensive than existing treatments may exceed the amount of money reserved within the hospital budget or the pharmacy budget.

Another paradox, since exceeding this "local" budget might generate a multiplier and create substantial savings in the total system/hospital.

Achieving changes in the "silo structure" within hospitals as well as the budget management structure by payers depends on the generation of basic information on these cost-effective aspects. We propose that usage of the current flow diagram will

generate facts and figures, as well as enable motivated implementation of these facts into guidance documents from professional societies to policy makers and payers (locally or regionally as well as nationally).

Integration of cost-effectiveness using the population-based variant of cost-effectiveness evaluations as an instrument in guidelines for CDI should be considered.

This may help healthcare professionals, patients, hospitals, payers and society to make better decisions about the optimal way to reduce the health and economic impact of CDI.

COMMENTS

Background

Current clinical guidelines seldom include cost-effectiveness evaluations. Conclusions are typically based on clinical data only and sometimes referral is made to prices of therapies for justification of the treatment sequence advised. However, the price of a therapy as such is just a single criterion and does not reflect the balance between effectiveness and costs associated with the application of that therapy. This results often in a restricted position of new therapies in the treatment algorithm.

Research frontiers

Recent high rates of treatment failure and recurrent infection have vast economic consequences emphasizing the need for innovative and cost effective solutions in *Clostridium difficile* infections (CDI). The price of new therapies and approaches cannot always compete with the relatively low, generic prices of current standard therapies with metronidazole and vancomycin. The question is then, how should professional societies integrate new and more effective, but also more expensive, remedies into their guidelines and how health authorities make reimbursement decisions.

Innovations and breakthroughs

The cost-effectiveness outcome based on the patient-based model only provides a limited health economic outcome in terms of time horizon and perspective and more importantly, disregards the impact on other patients. The relevant economic issues, such as resistance, person-to-person transmission, isolation measures and closing of wards of hospitals, are all supra-patient effects. These consequences of CDI on hospitals, payers and society, that go beyond the individual scope of the patient, are not integrated in standard cost-effectiveness analyses. Therefore, we developed a guidance model for coverage decisions and guideline development in CDI based on a population-based cost-effectiveness model.

Applications

The authors propose performing cost-effectiveness analyses for CDI using a population-based model, which incorporates all of the clinically important elements of the patient-based model as well as the supra-patient therapeutic and economic issues.

Terminology

CDI is responsible for 15%-25% of cases of antibiotic associated diarrhea (AAD) and is typically seen in elderly hospitalised patients, resulting in significant morbidity and mortality. Pharmacotherapy of an initial episode of CDI with oral metronidazole or oral vancomycin is the mainstay for pharmacological treatment of CDI and is recommended by most treatment guidelines.

Peer-review

This guideline article is interesting and has a high scientific value.

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CASE REPORT

Contrast induced neurotoxicity following coronary angiogram with Iohexol in an end stage renal disease patient

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Author contributions: All authors contributed to the acquisition of information, writing and revision of this case report.

Institutional review board statement: This case report was exempt from the Institutional Review Board standards at East Carolina University.

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

Conflict-of-interest statement: All the authors have no conflicts of interests to declare.

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Abstract

Neurotoxicity is an infrequent adverse reaction to iodinated contrast agents. Contrast induced neurotoxicity following coronary angiogram is very rare. Renal disease is a risk factor for contrast induced neurotoxicity. We report a case of contrast induced neurotoxicity following coronary angiogram and intervention using Iohexol (Omnipaque 350) in an end stage renal disease patient on peritoneal dialysis who had prior exposure to iodinated contrast without any adverse reaction. Hemodialysis had to be initiated for rapid removal of the contrast agent with subsequent complete resolution of neurological deficits. This case highlights the need for interventionalists to be aware of an important adverse reaction to iodinated contrast agents, especially in individuals with renal dysfunction, and that neurotoxicity is a possibility even with prior uneventful exposures. The role and timing of hemodialysis in contrast induced neurotoxicity in patients with chronic kidney disease and in those without chronic kidney disease needs further deliberation.

Key words: Coronary angiogram; End stage renal disease; Hemodialysis; Iodinated contrast agent; Neurotoxicity

Core tip: Contrast induced neurotoxicity following coronary angiogram is very rare. Interventionalists should be aware of this rare complication especially in patients with end stage renal disease (ESRD). Iodinated contrast media can be effectively removed from the blood by dialysis. Hemodialysis is a better modality for rapid removal of contrast agent compared to peritoneal

dialysis. Hemodialysis should be considered in life-threatening adverse reactions when supportive care alone is not sufficient. More studies are needed to further delineate the role and timing of hemodialysis following coronary angiogram and the optimal dosage of contrast media in ESRD patients to prevent this infrequent but potentially life threatening adverse reaction.

Gollol Raju NS, Joshi D, Daggubati R, Movahed A. Contrast induced neurotoxicity following coronary angiogram with Iohexol in an end stage renal disease patient. *World J Clin Cases* 2015; 3(11): 942-945 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i11/942.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i11.942

INTRODUCTION

Iodinated contrast agents are an important tool in medical practice. It is estimated that nearly 75 million doses are administered worldwide every year[1]. Modern iodinated contrast agents are mostly nonionic and low osmolar (2-3 times the osmolality of serum) or iso-osmolar (same osmolality of serum). They are safe and adverse reactions, when occur, are mild and self-limiting but serious and life threatening reactions can occur occasionally[2]. Here we describe a case of contrast induced neurotoxicity (CIN) following coronary angiogram in a patient with end stage renal disease (ESRD).

CASE REPORT

A 44-year-old African American female with coronary artery disease, hypertension, severe functional mitral regurgitation, ESRD on peritoneal dialysis, status post failed renal transplant on slow taper of immunosuppressants and diabetes mellitus type 2, was admitted for unstable angina. A month prior to this presentation patient had undergone a diagnostic right and left heart catheterization revealing 70% stenosis of first obtuse marginal branch and 80% stenosis of mid right coronary artery. Seventy ml of Iohexol (Omnipaque 350), a low-osmolar nonionic contrast media, had been used during the procedure. A coronary angiogram with percutaneous coronary intervention was planned. Three days prior to the cardiac intervention, a computerized tomography (CT) of abdomen and pelvis with and without contrast was performed for evaluation of hematuria. Seventy milliliter of Iodixanol (Visipaque 320), an iso-osmolar nonionic contrast media, was used. Patient tolerated this without any untoward events. Three days later patient underwent coronary angiogram and percutaneous intervention with drug eluting stent to first obtuse marginal branch of left circumflex and right coronary artery. Around 190 mL of Iohexol (Omnipaque 350) was used during the procedure. Patient tolerated the procedure without any immediate complications but within few hours developed headache with left sided weakness. A non-contrast head CT, four hours after the coronary intervention, showed extensive intravascular contrast with cortical staining, primarily over the right cerebral hemisphere and left cerebral hemisphere watershed territories (Figure 1). No other acute abnormalities were noted. Subarachnoid hemorrhage was considered unlikely and the clinical picture was considered likely secondary to contrast induced neurotoxicity. Supportive care and manual peritoneal dialysis exchanges were initiated. During this process, patient became more encephalopathic with subsequent seizure like activity. Antiepileptic medications, lorazepam and levetiracetam, were given to control seizures. Patient was transitioned to hemodialysis for rapid removal of contrast agent. A magnetic resonance imaging (MRI) of the brain taken 24 h after the coronary intervention showed hyperintense cortical signal on T2, fluid attenuated inversion recovery (FLAIR) and diffusion weighted images throughout the right greater than left cerebral hemisphere (Figure 2). No definite restricted diffusion was observed. There was mild mass effect without hemorrhage or herniation. An electro encephalogram was negative for seizure

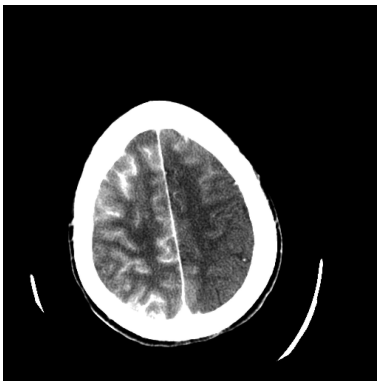

Figure 1 Non-contrast head computerized tomography showing extensive intravascular contrast with cortical staining, primarily over the right cerebral hemisphere.

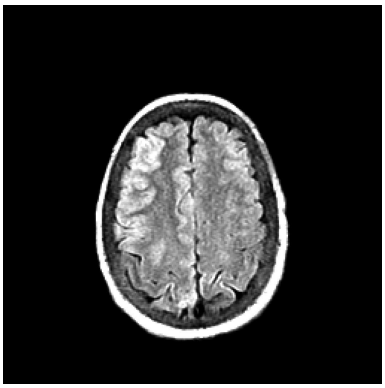

Figure 2 Magnetic resonance imaging fluid attenuated inversion recovery image showing hyperintense cortical signal of the cerebral hemispheres.

activity. These findings were considered consistent with contrast induced neurotoxicity (CIN). Supportive care and hemodialysis were continued for the next three days with gradual improvement and complete resolution of neurological abnormalities. Patient was transitioned back to peritoneal dialysis and discharged from the hospital in stable condition. Repeat imaging was not performed prior to discharge.

DISCUSSION

CIN is an infrequent adverse reaction to iodinated contrast agents. Intraarterial and neurointerventional procedures are more commonly associated with CIN[3]. CIN following coronary angiogram is very rare and the reported incidence is 0.06%[4]. This adverse reaction following coronary angiogram using Iohexol has been noted before[5]. All types of iodinated contrast agents irrespective of their ionic state or osmolality can cause CIN[3]. Neurological deficits are either focal or global. The exact etiology of CIN is unclear. Prior and subsequent exposure may not cause the same complication[4]. It is considered to be an idiosyncratic reaction to the contrast agent. An intact blood brain barrier is impermeable to contrast agents under normal conditions. Direct chemotoxic effects and hyperosmolality result in increased permeability of blood brain barrier and resultant cerebral edema, and also the possibility of increased hydrostatic pressure transmitted during neurointerventional procedures and subsequent changes in cerebral autoregulation predisposing to contrast extravasation has also been postulated[4,6]. Symptoms range from headache to seizures, hemiparesis, ophthalmoplegia, transient global amnesia, and transient cortical blindness. Neurological deficits are mostly transient but could also be persistent, especially with ophthalmic involvement[3,4]. Symptoms appear within 2 to 12 h of contrast injection and usually resolve in 24 to 72 h[7]. Imaging studies are recommended to rule out thromboembolic or hemorrhagic complications. Unenhanced CT images may be normal or show combination of poorly localized cortical and or subcortical enhancement, cerebral edema, and hyperdensity in the subarachnoid space similar to subarachnoid hemorrhage. MRI imaging may demonstrate hyperintense areas on T2, FLAIR, and diffusion weighted images[5]. Risk factors for CIN include renal disease, hypertension, and route, number of administration, and duration of exposure[3,7]. Larger dose of contrast is considered a risk factor but CIN has been reported even with very small doses[4]. Kocabay *et al*[3] recommend a maximum of 170 mL contrast agent for coronary angiograms to prevent CIN but none of the patients in their case series had ESRD. Our patient had ESRD and had prior exposure to iodinated contrast agents including Omnipaque 350 and to Visipaque 320 without any adverse events supporting the concept of CIN being an idiosyncratic reaction. In our case, for the culprit coronary angioplasty procedure, 190 mL of Omnipaque 350 had been utilized. General consensuses for preventive measures include adequate hydration prior to contrast exposure and using lowest possible contrast dose. Treatment is mostly supportive and hydration. Contrast media can be effectively removed from the blood by dialysis[8].

Contrast induced neurotoxicity following coronary angiogram is very rare. Interventionalists should be aware of this rare complication especially in patients with ESRD. Iodinated contrast media can be effectively removed by dialysis. Hemodialysis is a better modality for rapid removal of contrast agent compared to peritoneal dialysis. Hemodialysis should be considered in life-threatening adverse reactions when supportive care alone is not sufficient. More studies are needed to further delineate the role and timing of hemodialysis following coronary angiogram, and the optimal dosage of contrast media in ESRD patients to prevent this infrequent but potentially life threatening adverse reaction to iodinated contrast agents.

COMMENTS

Case characteristics

A 44-year-old female with coronary artery disease and end-stage renal disease on peritoneal dialysis underwent coronary angiogram and intervention for unstable angina.

Clinical diagnosis

Status post coronary angiogram and intervention, patient developed acute encephalopathy with no focal neurological deficits.

Differential diagnosis

Cerebrovascular accident, contrast neurotoxicity.

Imaging diagnosis

A non-contrast computerized tomography of the head showed extensive intravascular contrast with cortical staining, primarily over the right cerebral hemisphere. A magnetic resonance imaging showed hyperintense cortical signal of the cerebral hemispheres.

Treatment

Hemodialysis and supportive care.

Related reports

Contrast induced neurotoxicity is very rare following coronary angiogram. Correct diagnosis will avoid erroneous treatment for cerebrovascular accident.

Term explanation

Contrast induced neurotoxicity (CIN) is an infrequent adverse reaction to iodinated contrast agents. End stage renal disease (ESRD) is a risk factor for the development of CIN.

Experiences and lessons

Contrast induced neurotoxicity is very rare following coronary angiogram. Prior exposures to iodinated contrast agents may not have resulted in any adverse reaction supporting CIN to be an idiosyncratic reaction. Hemodialysis is an effective tool in contrast removal and management of CIN, especially in ESRD patients.

Peer-review

Very good case report about contrast induced neurotoxicity. It is very well written, summarized but completed.

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CASE REPORT

First description of cervical intradural thymoma metastasis

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Author contributions: All the authors contributed to this manuscript.

Institutional review board statement: The study was reviewed and approved by the Department of Neurology and Psychiatry, Division of Neurosurgery, University of Rome "Sapienza" Institutional review board.

Informed consent statement: The study participant provided informed verbal consent prior to study enrollment.

Conflict-of-interest statement: The authors declare no conflicts of interest.

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Abstract

Thymoma and thymic carcinoma are rare epithelial tumors, which originate from the thymus gland. According to the World Health Organization there are "organotypic" (types A, AB, B1, B2, and B3) and "non-organotypic" (thymic carcinomas) thymomas. Type B3 thymomas are aggressive tumors, which can metastasize. Due to the rarity of these lesions, only 7 cases of extradural metastasis are described in the literature. We report the first and unique case of a man with cervical intradural B3 thymoma metastasis. A 46-year-old man underwent thymoma surgical removal. The year after the procedure he was treated for a parietal pleura metastasis. In 2006 he underwent cervical-dorsal extradural metastasis removal and C5-Th1 stabilization. Seven years after he came to our observation complaining left cervicobrachialgia and a reduction of strength of the left arm. He underwent a cervical spine magnetic resonance imaging, which showed a new lesion at the C5-C7 level. The patient underwent a surgery for the intradural B3 thymoma metastasis. Neurological symptoms improved although the removal was subtotal. He went through postoperative radiation therapy with further mass reduction. Spinal metastases are extremely rare. To date, only 7 cases of spinal extradural metastasis have been described in the literature. This is the first case of spinal intradural metastasis. Early individuation of these tumors and surgical treatment improve neurological outcome in patients with spinal cord compression. A multimodal treatment including neoadjuvant chemotherapy, surgery and postoperative radiation therapy seems to improve survival in patients with metastatic thymoma.

Key words: Thymoma; Metastasis; Intradural lesion; Spinal tumor; Spinal surgery

Core tip: To date, only 7 cases of spinal extradural thymoma metastasis have been described in the literature. We report the first case of spinal intradural thymoma metastasis. Early individuation of these tumors and surgical treatment improve neurological outcome in patients with spinal cord compression. A multimodal treatment including neoadjuvant chemotherapy, surgery and postoperative radiation therapy seems to improve survival in patients with metastatic thymoma.

Marotta N, Mancarella C, Colistra D, Landi A, Dugoni DE, Delfini R. First description of cervical intradural thymoma metastasis. *World J Clin Cases* 2015; 3(11): 946-950 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i11/946.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i11.946

INTRODUCTION

Thymoma and thymic carcinoma are uncommon epithelial lesions, which originate from the thymus gland. To date, the true incidence is not known, but it is estimated to be 0-15 cases/100000 people. Between the fifth and sixth decades of life, this pathology represents 0.2%-1.5% of all malignancies[1]. According to the World Health Organization there are "organotypic" (types A, AB, B1, B2, and B3) and "non-organotypic" (thymic carcinomas) thymomas. Types A, AB, B1 and B2 thymomas are benign tumors. Type B3 thymomas are aggressive tumors of intermediate malignancy[2]. Spinal metastases are very uncommon. In the literature, only 7 patients with spinal extradural metastasis have been described. We report the first and unique case of a man with cervical intradural B3 thymoma metastasis.

CASE REPORT

A thymoma was resected in a 46-year-old male in 1989. He did not submit himself to adjuvant therapy. A year after the procedure he underwent parietal pleura metastasis resection. The patient remained disease-free until 2006, when he complained a reduction of strength of the left arm, for the presence of a cervico-dorsal extradural metastasis. He underwent resection of the lesion and C5-Th1 stabilization (Figure 1). The lesion was totally removed (R0) and the dura mater appeared intact.

In 2013, the patient came to our observation complaining left cervicobrachialgia and a reduction of strength of the left arm. A cervical spine magnetic resonance imaging (MRI) showed a new lesion at the C5-C7 level (Figure 2). The lesion showed a homogeneous enhancement after gadolinium administration in the T1-weighted sequences, and enclosed the spinal cord, especially on the left side. From the imaging, it was not clear if the lesion was extradural or intradural. Intraoperatively, there was not pathological tissue in the epidural space; it appeared only after opening the dura mater. The patient underwent a sub-total resection, in order to preserve the spinal cord from the surgical manipulation. The lesion was intradural-extramedullary. It was adherent to the spinal cord surface in its lateral and anterior portions.

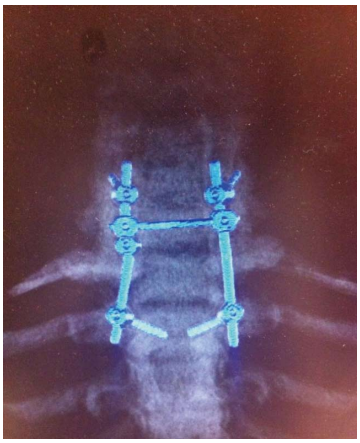

Figure 1 Maximum intensity projection reconstruction from computed tomography images shows C5-Th1 stabilization after the first intervention.

A spinal metastasis of the type B3 thymoma according to the World Health Organization 2004 was diagnosed (well-differentiated thymic carcinoma according to Marino and Muller-Hermelick)[3]. The immunohistochemical examination demonstrated positivity of neoplastic cells for CK19 and p63 and CD1a positive T-cells (Figure 3). Even if the resection was not total, no postoperative neurological deficits were observed. After 3 mo, the cervico-thoracic spine MRI showed a small residual tumor, especially anteriorly to the cervical spinal cord (Figure 4). Subsequently, focal radiotherapy (25.5 grays) was given. Cervical MRI after radiation treatment showed almost total disappearance of the mass (Figure 5). The patient is free of symptoms.

A search was carried out about spinal thymoma metastasis in the English language literature. We excluded one work because it is available only in Japanese language[4] and another because it did not report sufficient data to be included in our series. We used the following key words: "thymoma metastasis", "thymic carcinoma", "spinal cord compression", and "spinal metastasis". The data were extracted according to these parameters: (1) author and year of publication; (2) age; (3) sex; (4) time to spinal metastasis; (5) site of spinal metastasis; (6) sign and symptoms; (7) surgery; (8) follow-up; (9) radiotherapy; and (10) classification of histological type of the thymoma[5-9].

DISCUSSION

We found 6 papers, in which 7 cases were described.

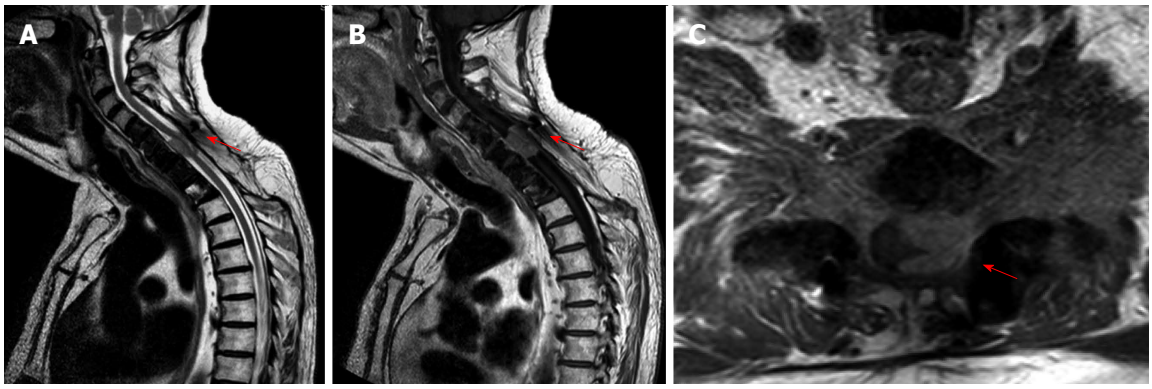

Figure 2 Cervical spine magnetic resonance imaging. A: A C5-C7 lesion with homogeneous enhancement after gadolinium administration in the T1-weighted sequences; B: T2 weighted sequences showing the enclosed spinal cord; C: Especially on the left side (red arrow).

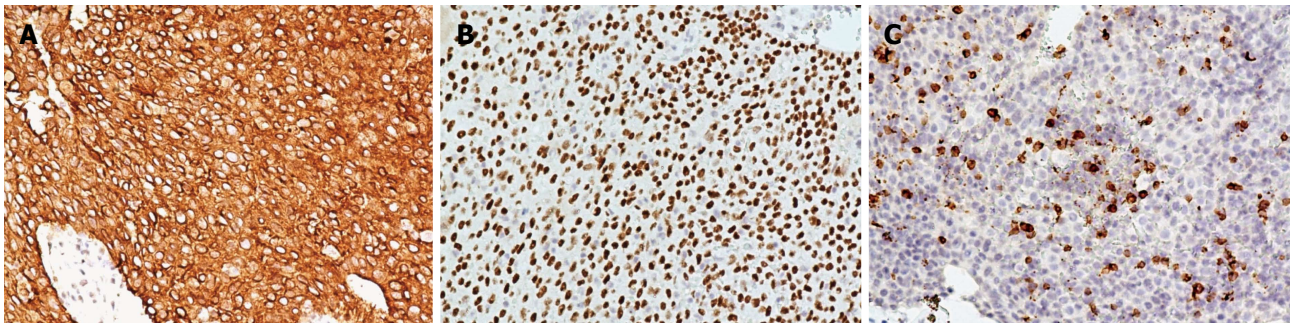

Figure 3 The immunohistochemical examination demonstrated positivity of neoplastic cells for (A) CK19, (B) p63 and (C) CD1a positive T-cells.

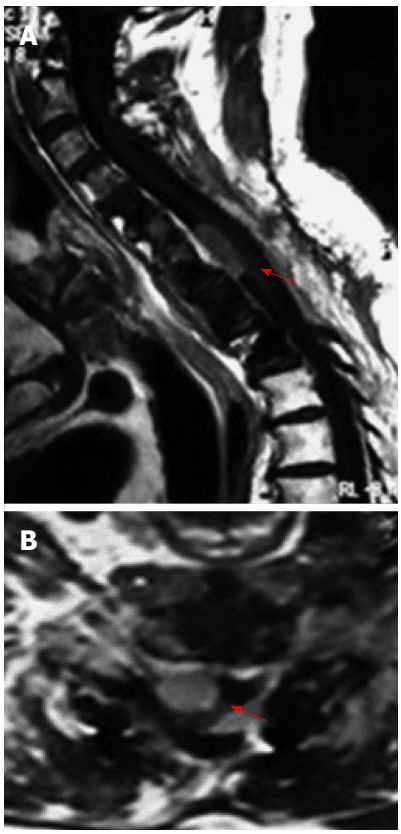

Figure 4 Magnetic resonance imaging of the cervico-thoracic spine at 3-mo follow-up showing (A) a small residual tumor, especially anteriorly to the cervical spinal cord and (B) axial view (red arrow).

We included our case in the review, for a total number of 8 cases of spinal thymoma metastasis. Four patients were male and 3 were female. About the age, the average was 51.4 years old (range, 29-70 years). The median time from thymoma diagnosis to spinal metastasis was 7.9 years (range, 1-17 years); in one case the spinal metastasis was diagnosed before primary tumor; the case with longer time to spinal metastasis was our case. The spinal metastases were localized at the thoracic level in 4 cases, at the cervico-thoracic site in 1 case, cervical level in 2 cases, and lumbar level in 1 case. Patients presented symptoms related to the thymoma in 2 cases (myasthenia gravis); in all cases they had neurological symptoms related to the spinal metastasis (motor deficit, sensitive deficit or pain). All patients underwent surgical treatment. During the follow-up, 3 patients died after 3 mo, 5 mo and 2 years, respectively; 4 patients survived with a time of follow-up from 9 mo to 8 years (our case). Five patients did not receive radiation therapy, and 2 underwent RT. Histological diagnosis was not based on the actual WHO classification in 2 cases; the histological subtype was B2 in 1 case, B3 in 2 cases, and C in 2 cases.

Thymoma and thymic carcinoma are uncommon epithelial lesions, which originate from the thymus gland. Thymoma is a rare tumor, commonly associated with the myasthenia gravis (15%); local dissemination occurs quickly, but distant spinal metastasis may occur up to 16 years after the diagnosis of thymomas. They

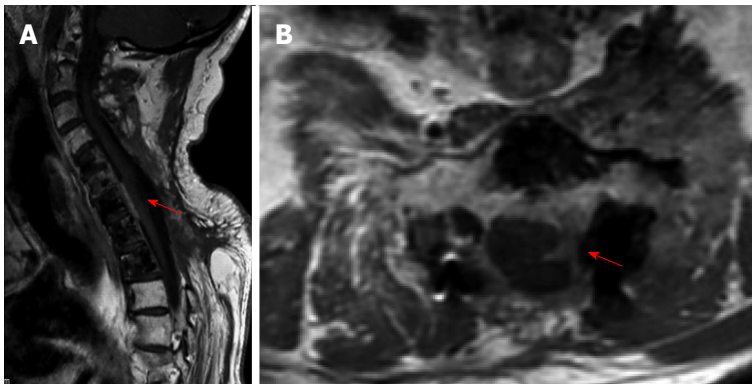

Figure 5 Cervical magnetic resonance imaging after radiation treatment showing (A) almost total disappearance of the mass and (B) axial view (red arrow).

can metastasize to the pleura regional nodes, liver and lung. Spinal metastases are very uncommon. In the literature, only 7 patients with spinal extradural metastasis have been described. We report a unique case of spinal intradural metastasis. On MRI, the vertebral metastases appear hypointense on T1-weighted images and hyperintense on T2-weighted images. Infiltration of the paravertebral muscles and vertebral elements, evident on axial views, is possible. Imaging after gadolinium administration shows an important enhancement. A computed tomography scan shows infiltration of the vertebral body, with both osteolytic and osteoblastic lesions. The spinal metastasis can cause, in fact, vertebral collapse, spinal instability and neurological deterioration. Early diagnosis and surgery have the goal to control pain and reduce motor deficits. It is fundamental to take in account that an invasive thymoma can metastasize both extradurally and intradurally, because patient's survival may be extended by an early diagnosis followed by an appropriate treatment.

We report the first case of spinal intradural metastasis. It is not yet known the gold standard of treatment, but a multimodal treatment which includes neoadjuvant chemotherapy, surgery and postoperative radiotherapy seems to improve survival in patients with metastatic thymoma.

COMMENTS

Case characteristics

Left cervicobrachialgia and a reduction of strength of the left arm.

Differential diagnosis

It is fundamental to take in account that an invasive thymoma can metastasize both extradurally and intradurally.

Imaging diagnosis

The lesion showed a homogeneous enhancement after gadolinium administration in the T1-weighted sequences, and enclosed the spinal cord, especially on the left side.

Pathological diagnosis

A spinal metastasis of the type B3 thymoma according to the World Health Organization 2004 was diagnosed (well-differentiated thymic carcinoma according to Marino and Muller-Hermelick).The immunohistochemical examination demonstrated positivity of neoplastic cells for CK19 and p63 and CD1a positive T-cells.

Treatment

Surgical sub-total resection and focal radiotherapy.

Related reports

The spinal metastasis can cause, in fact, vertebral collapse, spinal instability and neurological deterioration. Early diagnosis and surgery have the goal to control pain and reduce motor deficits.

Term explanation

Extradural, outside the dura mater.

Experiences and lessons

Multimodal treatment which includes neoadjuvant chemotherapy, surgery and post-operatory radiotherapy seems to improve survival in patients with metastatic thymoma.

Peer-review

The present case report is worth publishing, as it documents an extremely rare case of an intradural thymoma metastasis.

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CASE REPORT

Laparoscopic splenectomy for a littoral cell angioma of the spleen: Case report

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Abstract

A littoral cell angioma (LCA) is a primary vascular tumor of the spleen, that can have malignant potential and may present association with other malignancies. This is a case of LCA that was discovered incidentally in a 79-year-old woman who presented with a polycythemia at the time of consultation. The neoplasm was evaluated by ultrasound and computed tomography. The patient underwent a splenectomy that revealed LCA by pathological evaluation. The post-operative outcome was favorable with no complications or recurrent disease. This case presentation, clinical, radiographic, and pathological features of an uncommon splenic tumor can be studied in order to advance our knowledge in our understanding of LCA.

Key words: Laparoscopy; Splenectomy; Splenomegaly; Angioma; Littoral cell

Core tip: We invite readers to read "laparoscopic splenectomy for littoral cell angioma of the spleen: Case report", because we understand how pathological evaluation, after splenectomy, allows the definite diagnosis of this rare vascular neoplasm and given its

potential malignancy and its association with other cancer types, splenectomy should be always performed.

Marzetti A, Messina F, Prando D, Verza LA, Vacca U, Azabdaftari A, Rubinato L, Reale D, Favat M, Barbujani M, Agresta F. Laparoscopic splenectomy for a littoral cell angioma of the spleen: Case report. *World J Clin Cases* 2015; 3(11): 951-955 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i11/951.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i11.951

INTRODUCTION

LCA was first reported by Falk *et al*[1] in 1991. They reviewed 200 surgical specimens of benign vascular tumors of the spleen and described 17 similar tumors correlated to the cells lining the red pulp splenic sinuses[1]. The littoral cell, the original one, presents both epithelial and histiocytic features[1].

Both sexes at any age are affected by this tumor. Usually patients are asymptomatic and the dignosis leads to an incidental founding. When patient presents symptoms they arise later and are splenomegaly, thrombocytopenia and anemia.

The neoplasm take its origin in the sinus of the red pulp of the spleen. These endothelial cells show the same immunoreactivity for markers CD31 and factor Ⅷ, as showed by hemangiomas situated in different places.

Pathogenetic mechanism of this tumor is still uncertain, but has been thought as a possible one an immune system dysfunction because it has been observed an important association with autoimmune disorders like Crohn's disease and metabolic diseases like Gaucher's one[2,3].

CASE REPORT

Our patient, a 79-year-old woman, entered to the hospital for a polycythemia and during medical examinations it was discovered an hypointense lesion of the spleen and splenomegaly without hypersplenism (Figure 1). The patient did not present abdominal pain, nausea, episodes of vomite and changes in bowel habits. Her BMI was 35.8. The evaluation of EPO (5 IU/L) and genetic mutation of Jak2 (30%) revealed a chronic myeloproliferative syndrome. Ultrasound and computed tomography (CT) scan were performed. The ultrasound showed a round, solid, hypoechogenic mass of 45 mm of size at the superior pole of the spleen (Figure 2). A large, solitary, low-density lesion appeared in the early arterious phase of the contrast-enhanced CT (Figure 1). Laboratory tests showed normal liver enzymes and renal function, they only revealed an elevated count of platelets (587000/mcL) and a polycythemia (RBC = 5920000/mm, Hb = 17 g/dL) that was the primary reason why the patient entered to the Hospital.

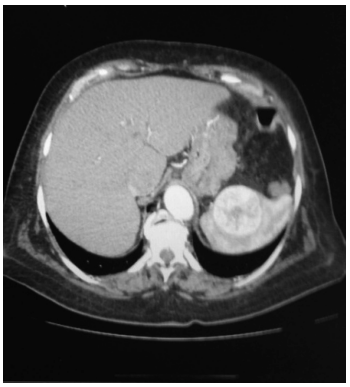

Figure 1 Computed tomography scan.

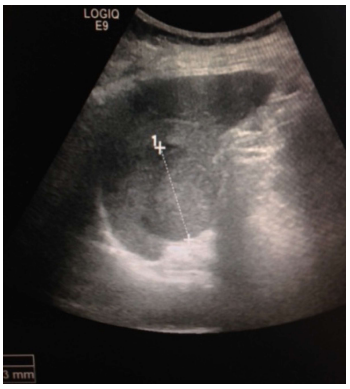

Figure 2 Ultrsound.

Imaging

Our patient underwent CT scan, that showed a hypoattenuating nodule of 4 cm × 5 cm of size with contrast enhancement on the arterious phase (Figure 1) and a hypointense lesion at Ultrasonography (Figure 2). Several studies have described the contrast-enhanced sonographic findings of various splenic lesions[4-6]. Characteristically benign vascular tumors show isoenhancement or a little hyperenhancement during the arterial phase and isoenhancement or hypoenhancement during the venous phase.

Rarely imaging can dignose the benign vascular neoplasm because many other splenic tumors mimic LCA. It is important a differential diagnosis with other splenic tumors that have a similar appearance with LCA like lymphangiomatosis, hamartoma, hemangiomatosis, hemangioendothelioma, hemangiopericytoma, and angiosarcoma; it has to be included in the differential diagnosis also lymphoma, metastases, Kaposi sarcoma and infectious diseases like Pneumocystis and Mycobacterium.

Histopathologic features

The neoplasm arises from the littoral cells in the splenic red pulp sinuses. Hemangiomas of other sites share

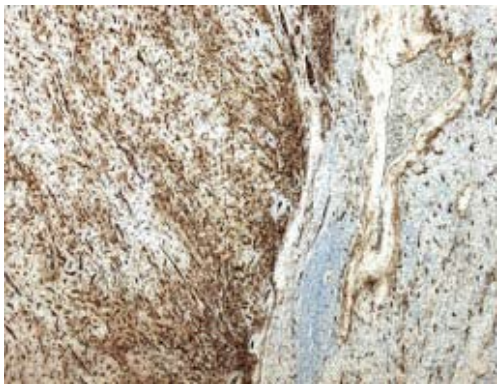

Figure 3 Positivity of vascular proliferation for immunohistochemical marker CD34; on right side there is normal splenic parenchyma (CD3450X).

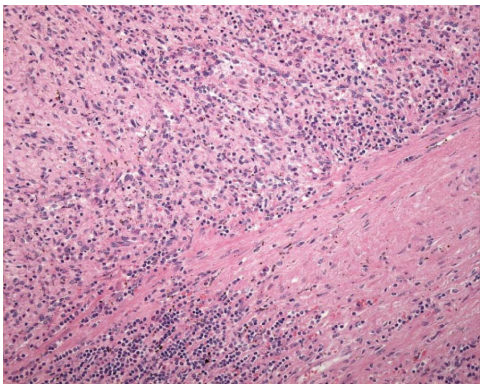

Figure 4 Vascular structures anastomosed (E-E 200 ×).

the same immunoreactivity for vascular endothelial markers CD31 and factor Ⅷ. It is interesting to observe that the tumor cells express histiocytic marker CD68 that explain why this neoplasm may begin in the splenic sinus lining cells or littoral cells.

DISCUSSION

Pathological evaluation, after laparoscopic splenectomy, allowed the definite diagnosis of this rare vascular neoplasm.

The surgical outcome was favorable without post-operative complications or recurrence.

Given certain diagnosis by pathological evaluation, associated to clinical features and imaging of an uncommon splenic tumor can be studied in order to advance our knowledge in our understanding of LCA.

The pathogenesis of LCA is nowadays still indefinite. We speculate as a possible pathogenic mechanism an immune system dysfunction, as demonstrates the association with autoimmune disorders like Gaucher's disease and Crohn's disease.

Pathological evaluation, after splenectomy, allows the definite diagnosis of this rare vascular neoplasm. Given its potential malignancy, splenectomy is usually performed.

The lining of vascular splenic sinuses, made by endothelial cells, presents both phagocytic and hematopoietic characteristics, that is the reason why they are thought to be unique since the 1930s[2].

The littoral cell of the spleen, the cell of origin, presents both epithelial and histiocytic features[7,8]. Overall the incidence of hemangioma of the spleen changes from 0.003% to 14% in autopsy reports[9], however the real incidence of LCA is unrecognized.

From a clinical point of view, the majority of patients with LCA are asymptomatic, while usually symptoms are anemia, thrombocytopenia both can be hypersplenism associated, splenomegaly, or unrecognized fever[10].

Abdominal pain can be also the main symptom at the time of consultation, otherwise the neoplasm is an incidental finding[11].

Our patient infact, entered to the hospital for a polycythemia and during medical examinations it was discovered an hypointense lesion of the spleen and splenomegaly without hypersplenism. She did not describe episodes of abdominal pain.

Normally, splenectomy performed for other reasons leads to diagnosis of LCA.

Only a minority of patients presents with splenomegaly, fever and features of hypersplenism like anemia and thrombocytopenia[12].

The vascular neoplasm can look like a single or multiple lesions in the spleen, while a massive splenomegaly can mimic a pancreatic tumor.

Recently LCA has been associated with tumors of the colon, kidney, pancreas, lung and ovary[13]. Have been described also associations with leiomyosarcoma, melanoma and lymphoma. Considering this malignancy association in patients with LCA, it should be always excluded visceral tumor.

The laparoscopic approach permitted to operate an old age, obese and cardiopathic patient and to dismiss her in 6 d without any postoperative complication.

Reports[10] comparing laparoscopic splenectomy to open splenectomy for diagnosed diseases like idiopathic thrombocytopenic purpura, reveal superiority of miniinvasive procedure because of its several benefits of lower post-operative pain and quicker post-operative recovery. Kercher *et al*[11] found that a laparoscopic approach was beneficial for massive splenomegaly (defined as craniocaudal dimension $\geqslant$ 17 cm and weight $\geqslant$ 600 g), which is also supported by our experience with this patient. Brodsky *et al*[12] also support laparoscopic splenectomy for several splenic diseases, also in case of splenomegaly. Rosen *et al*[13] found laparoscopic splenectomy to be safe for benign and malignant hematologic conditions, including Idiopathic Thrombocytopenic Purpura and a case of LCA, with a conversion rate of 5%.

Our patient was discharged by postoperative day 2 and did not present any complication, so

that splenectomy allowed the definite dignosis of LCA, without compromise the outcome in an old, cardiopathic, obese patient.

Pathological evaluation, after splenectomy, allows the definite diagnosis of this rare vascular neoplasm and given its potential malignancy, even though most of LCAs are benign, and its association with other cancer types, splenectomy should be always performed. So their differential diagnosis must observe primary and secondary malignancy.

This rare case shows the interest of studying vascular tumors of the spleen even most of all are incidental foundings.

Considering these concepts, gold standard management appears to be splenectomy (in our experience and in literature, laparoscopic approach reveals a better surgical outcome) and a strict follow-up to recognize synchronous tumors or metastatic lesions.

COMMENTS

Case characteristics

The authors' patient, a 79-year-old woman, entered to the hospital for a polycythemia and during medical examinations it was discovered an hypointense lesion of the spleen and splenomegaly without hypersplenism (Figure 1). The patient did not present abdominal pain, nausea, episodes of vomite and changes in bowel habits.

Clinical diagnosis

Splenomegaly, polycythemia, chronic myeloproliferative syndrome, elevated counts of platelets.

Differential diagnosis

Lymphangiomatosis, hamartoma, hemangiomatosis, hemangioendothelioma, hemangiopericytoma and angiosarcoma; lymphoma, metastases, Kaposi sarcoma and infectious diseases like Pneumocystis and Mycobacterium.

Laboratory diagnosis

Laboratory tests showed normal liver enzymes and renal function, they only revealed an elevated count of platelets (587000/mcL) and a polycythemia (RBC = 5920000/mm, Hb = 17 g/dL) that was the primary reason why the patient entered to the Hospital.

Imaging diagnosis

CT scan showed a hypoattenuating nodule of 4 cm × 5 cm of size with contrast enhancement on the arterious phase, and US revealed an hypointense splenic lesion.

Pathological diagnosis

Splenectomy revealed at the pathological examination vascular structures anastomosed and positivity of vascular proliferation for immunohistochemical marker CD34 , diagnosing LCA (Figures 3 and 4).

Treatment

Laparoscopic splenectomy.

Related reports

Recently LCA has been associated with neoplasms of the colon, kidney, pancreas, lung and ovary. Have been described also associations with leiomyosarcoma, melanoma and lymphoma. Considering this malignancy association in patients with LCA, it should be always excluded visceral tumor.

Term explanation

LCA is primarily a benign tumor, however may be associated with others visceral neoplasms and may have malign potential.

Experiences and lessons

Pathological evaluation, after splenectomy, allows the definite diagnosis of this rare vascular neoplasm because radiological and clinical foundings do not lead to a certain diagnosis. So, given its potential malignancy, even though the vast majority of LCAs are benign, and its association with other cancer types, splenectomy remains the golden standard in the managment of this disease.

Peer-review

Best management of this disease remains splenectomy (in our experience and in literature, laparoscopic approach reveals a better surgical outcome) and a strict follow-up to recognize synchronous tumors or metastatic lesions.

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CASE REPORT

Differential diagnosis of a vanishing brain space occupying lesion in a child

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Author contributions: All the authors equally contributed to this work.

Institutional review board statement: This study was reviewed by and received exemption from the Assiut University Hospital Institutional Review Board.

Informed consent statement: The study participant provided written informed consent for inclusion in this case report.

Conflict-of-interest statement: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Abstract

We describe clinical, diagnostic features and follow up of a patient with a vanishing brain lesion. A 14-year-old child admitted to the department of Neurology at September 2009 with a history of subacute onset of fever, anorexia, vomiting, blurring of vision and right hemiparesis since one month. Magnetic resonance imaging (MRI) of the brain revealed presence of intra-axial large mass (25 mm × 19 mm) in the left temporal lobe and the brainstem which showed hypointense signal in T1W and hyperintense signals in T2W and fluid attenuated inversion recovery (FLAIR) images and homogenously enhanced with gadolinium (Gd). It was surrounded by vasogenic edema with mass effect. Intravenous antibiotics, mannitol (2 g/12 h per 2 d) and dexamethasone (8 mg/12 h) were given to relief manifestations of increased intracranial pressure. Whole craniospinal radiotherapy (brain = 4000 CGy/20 settings per 4 wk; Spinal = 2600/13 settings per 3 wk) was given based on the high suspicion of neoplastic lesion (lymphoma or glioma). Marked clinical improvement (up to complete recovery) occurred within 15 d. Tapering of the steroid dose was done over the next 4 mo. Follow up with MRI after 3 mo showed small lesion in the left antero-medial temporal region with hypointense signal in T1W and hyperintense signals in T2W and FLAIR images but did not enhance with Gd. At August 2012, the patient developed recurrent generalized epilepsy. His electroencephalography showed the presence of left temporal focus of epileptic activity. MRI showed the same lesion as described in the follow up. The diffusion weighted images were normal. The seizures frequency was decreased with carbamazepine therapy (300 mg/12 h). At October 2014, single voxel proton (1H) MR spectroscopy (MRS) showed

reduced N-acetyl-aspartate (NAA)/creatine (Cr), choline (Cho)/Cr, NAA/Cho ratios consistent with absence of a neoplasm and highly suggested presence of gliosis. A solitary brain mass in a child poses a considerable diagnostic difficulty. MRS provided valuable diagnostic differentiation between tumor and pseudotumor lesions.

Key words: Vanishing brain mass; Gliosis; Unconfirmed diagnosis; Lymphoma; Granuloma

Core tip: A vanishing brain space occupying lesion is defined as reduction or disappearance of a brain lesion spontaneously or after steroid treatment to ⩽ 70% of its size before establishing its definitive diagnosis. A vanishing solitary neoplastic/non-neoplastic (pseudotumor) (*e.g.*, infection/abscess, granuloma, radiation necrosis, multiple sclerosis) brain mass in a child poses a considerable diagnostic difficulty particularly deeply seated lesions in which tissue diagnosis is difficult to be done. In clinical practice, neuroimaging has to be done every 6-12 mo for at least 3-5 years to follow up after complete remission of the patient. Magnetic resonance spectroscopy (MRS) has been proved to be valuable for diagnostic differentiation between tumor and pseudotumor lesions. MRS provides information related to the metabolic activity in the culprit lesion (*e.g.*, neoplastic processes, demyelination, cell necrosis or gliotic changes).

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INTRODUCTION

Cases with solitary brain space occupying lesions (*e.g.,* tumor, intracranial infection/abscess, granuloma, neurocystocercosis, tuberculoma, multiple sclerosis) may pose a diagnostic difficulty particularly when brain biopsy can't be done due to deep location of the lesion. For such cases, clinicians often start corticosteroids to reduce manifestations of increased intracranial pressure (ICP) (caused by the intracranial mass and the surrounding vasogenic edema) and to give brain radiation if there is a high suspension for the presence of malignant lesion[1,2]. Also such patients should be routinely followed by magnetic resonance imaging (MRI) even after the disappearance of the enhancing lesion for at least 3-5 years[3]. The disappearance or decrease of the initial brain space occupying lesion (SOL) volume to ⩽ 70% either spontaneously or after steroid treatment before establishing the definitive diagnosis, has been referred as a vanishing brain lesion[4].

In the last decade, magnetic resonance spectroscopy (MRS) has been considered as a diagnostic test which helped to distinguish normal from abnormal brain tissue. Proton (1H) MRS measures some unique tissue metabolites which provide valuable information regarding the severity of the brain lesion, pathogenesis, prognosis and response to therapy. Briefly, in MRS, peaks which are proportional to the concentration of the given metabolite, are arranged along a flat baseline according to their radiofrequency (measured in units called parts per million or ppm)[5]. The most commonly defined brain metabolites (^{1}H-MRS spectrum) in which their patterns can be observed and correlate with different types of lesions (from right to left) include: free lipids (Lip), lactate (Lac), N-acetyl-aspartate (NAA), glutamate/glutamine (Glx), creatine (Cr)/phosphocreatine (the Cr peak), choline (Cho; the Cho peak), and myo-inositol (mI). In spectra obtained at long echo time (⩽ 135 ms), the peaks for NAA, Cr, Cho, and lactic acid are prominent and sharp. They are also detected and quantified at short echo time (⩾ 30 ms) MRS. In contrast, Lip, Glx and mI signals are detected only in short echo time MRS. In normal brain, NAA is synthesized in neurons, diffuses along axons and broken down in oligodendrocytes. In MRS, NAA is a marker of intact number of neurons in gray matter and the density of intact axons in white matter. The most prominent peak of NAA in MRS is the resonance at 2.0 ppm and it has concentration of 7.9-16.6 mmol/kg. NAA is a non-specific marker as its value is reduced in any disease associated with neuronal or axonal loss[6]. Cr is present at higher concentrations in the glia and it is a marker of brain energy. The most prominent peak of Cr in MRS is the resonance at 3.0 ppm and concentration of 5.1-10.6 mmol/kg[7]. Cho is a marker of brain injury of non-specific type. Cho level reflects the brain membrane metabolism with cellular turnover. The most prominent peak of Cho in MRS is the resonance at 3.2 ppm and concentration of 0.9-2.5 mmol/kg[6]. Lipids comprise about 20% of brain weight. Lipids are normally absent from 1H spectrum, and its appearance at 0.9-1.4 ppm resonances indicates presence of necrotic tissue (*i.e.*, breakdown of cell membrane and release of fatty acids)[8]. The mI is a marker of glial proliferation. It resonates at 3.6 ppm and concentration of 3.8-8.1 mmol/kg[9]. The glutamate/glutamine peak represents a mixture of excitatory and inhibitory brain neurotransmitters. Glutamate is mainly stored in neurons whereas glutamine concentration is higher in astrocytes. Both, Glx have two groups of resonances, the first group resonances at 3.6-3.9 ppm whereas the second group resonances at 2.0-2.6 ppm and concentration of 6.0-12.5 mmol/kg for glutamate and 3.0-5.8 mmol/kg for glutamine. Excess glutamate in active lesions could contribute to axonal damage, brain atrophy and neurological disability[10].

Malignant brain tumors are differentiated from other focal lesions, including multiple sclerosis (MS), radiation necrosis and infections/abscess by absent

NAA, excess Cho and lip. Spectra with elevated Cho, a Cho/Cr index greater than 1.3 and diminished NAA levels are associated with aggressive neoplasms (*e.g.,* malignant lymphoma and glioma). Tumor recurrence is characterized by high Cho/Cr and Cho/NAA ratios. A multi-voxel Cho/Cr ratio of > 1.54 and Cho/NAA ratio of > 1.05 was found to have 93.1% and 89.7% accuracies for diagnosis of tumor recurrence, respectively[11,12]. In MS, the abnormal increases in total Cr, total Cho, mI, Lac, lipids and macromolecules are markers for acute demyelination in MS. NAA is reduced in acute MS lesions and in normal appearing white matter, even distant to acute and chronic-lesions. Increased NAA to subnormal values occurs during remyelination. mI is increased in chronic MS (a marker for astrocytic gliosis). Reduced NAA peak represents neuronal/axonal dysfunction or loss. Elevated Cho peak represents enhanced cell-membrane turnover and is seen in demyelination, remyelination, inflammation, or gliosis[13]. In radiation necrosis (defined as a death of normal brain tissue caused by radiation therapy), in which the pathological features include progressive cellular necrosis (coagulative necrosis), inflammatory changes and reactive glial cell proliferation and gliosis, MRS shows elevated Cho, mI, lactate and lipid peaks[14].

This paper described a child with a symptomatic parenchymal brain mass but showed marked clinical recovery and disappearance of the original brain mass shortly after starting treatment. In this case report, the phenomenon of a tumor/or pseudo-tumor remission and the problems related to its differential diagnosis and treatments were discussed. The significance of using MRS to distinguish neoplastic from non-neoplastic nature of the intra-axial lesion in our patient was also discussed.

CASE REPORT

At September 2009, a 14-year-old child presented with a history of fever, anorexia, generalized body ache, loss of weight and headache since two months, which progressed to repeated vomiting, nausea, lethargy and blurring of vision in the last month. Prior to neurologic consultation, the patient was admitted to a fever hospital for one week because of the unexplained high grade fever. One year ago, the patient had past history of body aches and recurrent arthritis which was attributed to recurrent tonsillitis and based on the advice of the ear, nose and throat (ENT) physician, the patient did tonsillectomy. The mother said that although it was expected that the patient will be better after tonsillectomy but unfortunately, he had recurrent fever and generalized body aches till the time of presentation. On neurological examination, the child was feverish and looked toxic. He was alert, oriented and his higher mental functions testing were normal. He had right hemiparesis and right upper motor neuron facial paralysis. His fundus examination was normal. MRI-brain [1.5-Tesla, standard (T1W) pre- and post-contrast, T2W, fluid attenuated inversion recovery (FLAIR) brain imaging] revealed presence of a large intra-axial mass (25 mm × 19 mm) in the left temporal lobe with extension to the adjacent brainstem. It showed hypointense signal in T1W, hyperintense signals in T2W and FLAIR images and homogenous enhancement with gadolinium (Gd). It was surrounded by moderate perifocal vasogenic edema with mass effect in the form of compression of the third ventricle with midline shift (Figure 1). The clinical and radiological findings were highly suggestive of a neoplastic lesion (malignant lymphoma or glioma). The patient was examined for lymphadenopathy and organomegaly. He underwent laboratory workup [for complete blood count, erythrocyte sedimentation rate (ESR), glucose, electrolytes, lactic dehydrogenase (LDH), liver and renal functions], abdominal ultra-sonography and chest radiographs to rule out the presence of systemic lymphoma but no bone marrow evaluation was done. Blood tests revealed leukocytosis (16000 cells/μL) and elevated ESR (30/52). In view of the presence of fever, manifestations of increased intracranial pressure (ICP) and the prominent cerebral edema associated with the intracranial lesion; intravenous antibiotics (cefotax 1 g/12 h per 7 d), mannitol (2 g/12 h per 48 h) and dexamethasone (8 mg/12 h) were initiated. The oncologist recommended whole craniospinal irradiation (brain = 4000 CGy/20 settings per 4 wk; spine = 2600CGy/13 settings per 3 wk) which was started 10 d after presentation. Within 15 d and even before the start of radiotherapy, the patient exhibited marked clinical recovery (up to complete improvement) but he developed subjective cognitive deterioration as a side effect of radiotherapy which was recovered after its discontinuation. Tapering of steroids was done over the next 4 mo. Follow up of the patient was done every 3 mo. The follow up MRI after 3 mo from onset showed disappearance of the original mass but presence of small lesion with hypointense signal in T1W and hyperintense in T2W and FLAIR signals in the antero-medial part of the left temporal lobe but did not show enhancement with Gd. At further follow up (September 2010) the patient condition was unremarkable and his MRI had the same small non-enhanced lesion (Figure 2). At August 2012, the patient developed recurrent generalization tonic-clonic convulsions. His EEG showed left temporal focus of epileptic activity. His MRI had the same small non-enhanced lesion (as that of 2010) with no restricted diffusion in diffusion weighted images (DWI) (Figure 3). The seizures frequency was reduced with carbamazepine therapy (300 mg/12 h). At October 2014, his follow up MRI had the same small non-enhanced lesion (as that of 2010 and 2012) with no restricted diffusion in DWI. Single voxel proton (1H) spectroscopy at long and short echo times showed reduced values of choline to creatine (Cho/Cr: long ET = 0.05; short ET = 0.907), N-acetyl-aspartate to

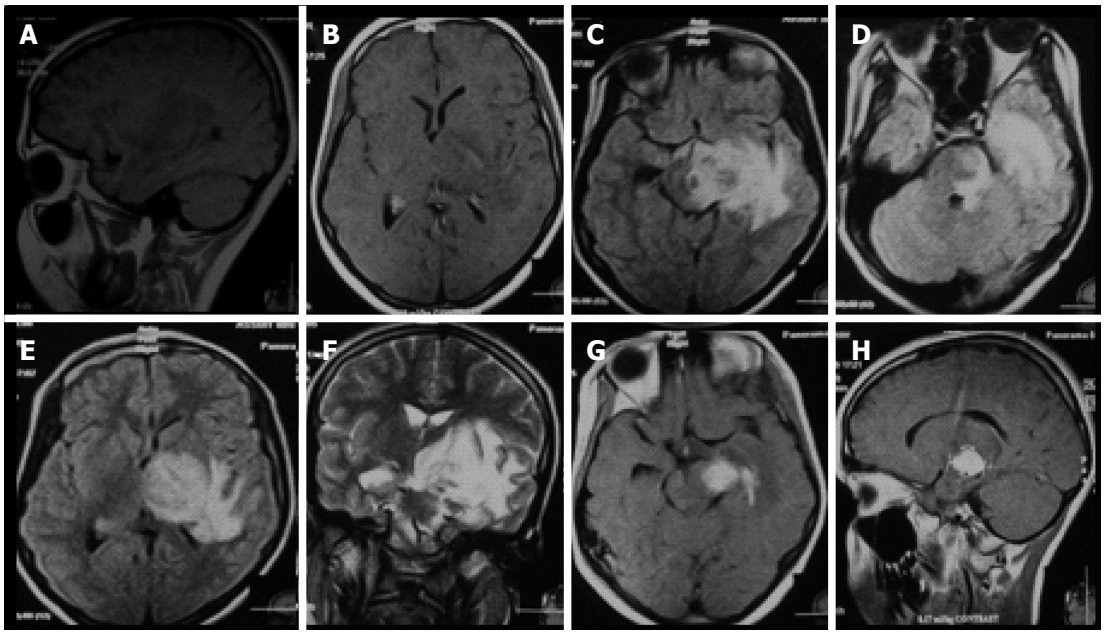

Figure 1 Cranial magnetic resonance imaging brain (on admission at September 2009) showing (A, B) sagittal and axial T1-weighted views with a solitary hypointense lesion in the left temporal lobe; (C-E) axial fluid attenuated inversion recovery and T2-weighted (F) images showing hyperintense lesion in the left temporal lobe encroaching on the adjacent brainstem with perifocal edema and mass effect; (G, H) axial and sagittal T1-weighted views showing homogenous solitary enhanced lesion in the left temporal lobe encroaching on the adjacent brainstem and surrounded by a moderate hypointensity.

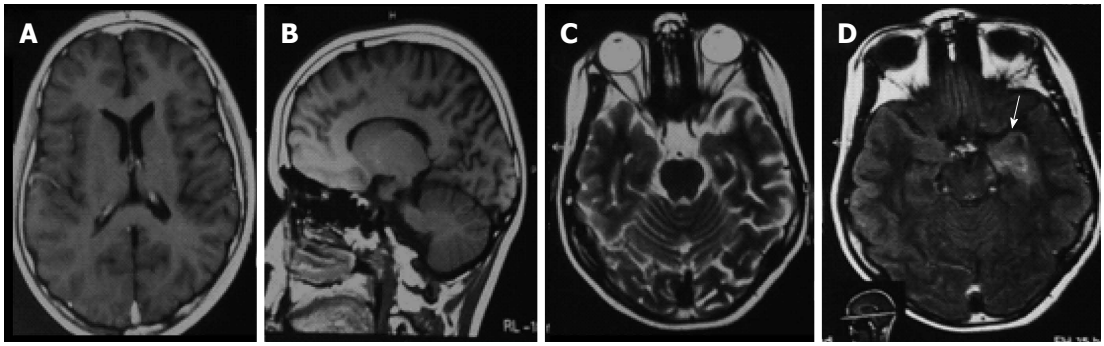

Figure 2 Cranial magnetic resonance imaging brain (September 2010) showing (A, B) normal axial and sagittal TIW and (C) axial T2W images but (D) hyperintense lesion in the antero-medial region of the left temporal lobe (white arrow) in fluid attenuated inversion recovery image.

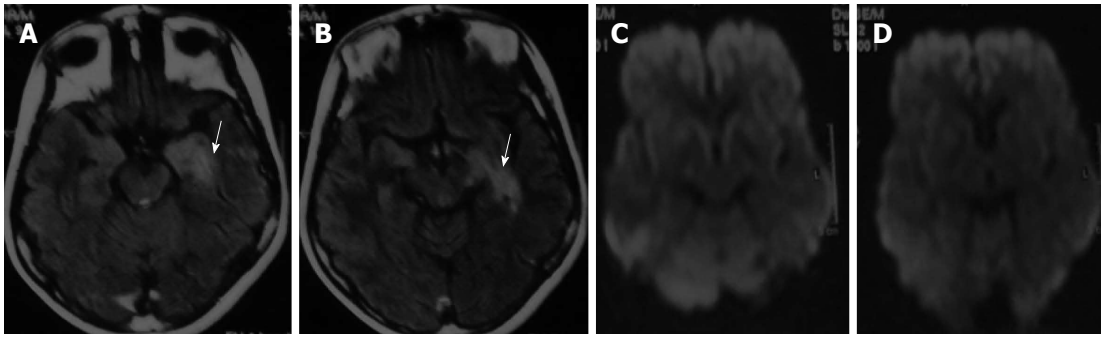

Figure 3 Cranial magnetic resonance imaging brain (August 2012) showing (A, B) hyperintense lesion in the antero-medial region of the left temporal lobe (white arrow) in axial fluid attenuated inversion recovery images (white arrow) and (C, D) normal diffusion weighted axial images.

creatine (NAA/Cr: long ET = 1.31; short ET = 1.107) and N-acetyl-aspartate to choline (NAA/Cho: long ET = 0.037; short ET = 0.38) ratios which confirmed the absence of neoplastic activity but highly suggestive of gliotic lesion (Figure 4).

This study was conducted according to the principles established in Helsinki and approved by Assiut University Hospital ethics committee. Informed written

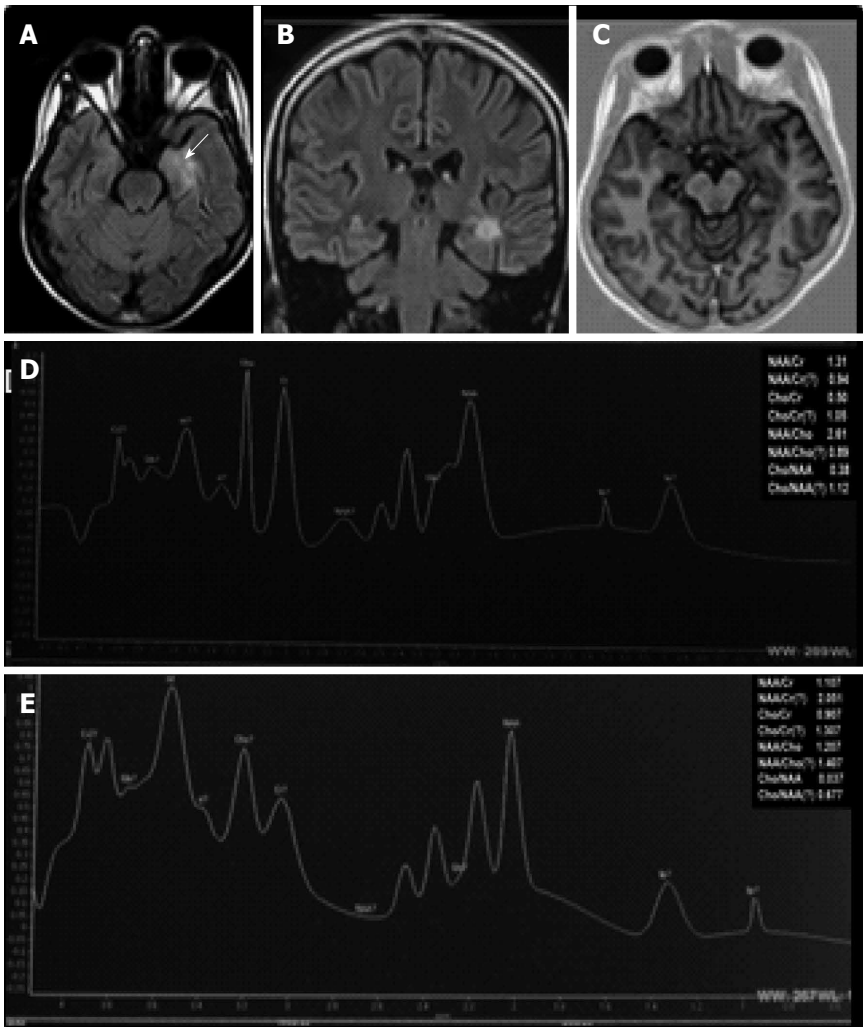

Figure 4 Cranial magnetic resonance imaging and magnetic resonance spectroscopy (MRS) brain (October 2014) showing (A, B) hyperintense lesion in the antero-medial region of the left temporal lobe in axial and coronal fluid attenuated inversion recovery images (white arrow); and (C) no restricted diffusion in axial diffusion weighted axial images; (D, E) long and short time echo MRS showing reduced values of Cho/Cr (long ET = 0.05; short ET = 0.907), NAA/Cr (long ET = 1.31; short ET = 1.107) and NAA/Cho (long ET = 0.037; short ET = 0.38) ratios. NAA: N-acetyl-aspartate; Cr: Creatine; Cho: Choline.

consent was obtained from the patient and his parents to publish the details of his clinical history, laboratory and imaging data.

DISCUSSION

This case is significant as the parenchymal brain mass could not be distinguished from a neoplastic space occupying lesion (*e.g.,* glioma or lymphoma) at presentation. Brain biopsy was not done due to deep location of the lesion. Complete clinical improvement was observed within 15 d on medical treatment including steroids and even before the start of radiotherapy. Corticosteroids were used empirically to reduce the manifestations of increased ICP and improve the surrounding vasogenic edema caused by the intracranial mass. The decision to give whole craniospinal irradiation was based on the high suspicion of a neoplastic lesion (*e.g.,* lymphoma or glioma). Marked reduction of the intracranial mass with disappearance of enhancement was observed in MRI within 3 mo of the onset. Follow up of the patients up to 5 years showed absence of recurrence of the original lesion.

Based on the above findings, the suggestive differential diagnosis of the vanishing space occupying lesion in this child at presentation include: (1) tumor [*e.g.,* primary central nervous system lymphoma (PCNSL) or glioma]; (2) tumor like demyelinating lesion or tumefactive multiple sclerosis (TMS); in clinical practice, most vanishing brain masses are frequently diagnosed as malignant tumors or multiple sclerosis (MS); and (3) intracranial infection/abscess/granulomas or tuberculoma.

For our patient, earlier at presentation, PCNSL was suggested. In patients presented with unclear intra-axial brain masses which regress with steroids, the diagnosis of PCNSL has to be considered[15]. PCNSL is a rare extranodal non-Hodgkin's lymphoma[16]. PCNSL represents approximately 3%-4% of newly diagnosed

central nervous system (CNS) tumors[17]. The typical MRI features of PCNSL include the presence of intra-axial single or multiple masses adjacent to cerebrospinal fluid space (CSF) with intermediate- to low-signal-intensity in T1W images and hypointense signal relative to the gray matter on T2W images, surrounding vasogenic edema, mass effect, restricted diffusion in DWI and intense homogenous enhancement with Gd[18,19]. Although, PCNSL is extremely rare in children and immunocompetent individuals[20,21], we suggested the diagnosis of PCNSL based on the MRI appearance of large solitary deep hemispheric infiltrative lesion[22] and rapid remission with steroid even before the start of radiotherapy. However, PCNSL is a malignant neoplasm and never considered as a self-limiting and recurrence is common within 18 mo. No cases have been reported yet for malignant brain tumors that recurred more than 5 years after spontaneous regression[23]. For our patient, the lacks of recurrence on follow ups for more than 5 years making such diagnosis less likely. This was also confirmed by the findings of MRS which will be discussed in the following section.

Also for our patient, the presence of fever prior to presentation and rapid remission with Ⅳ antibiotics and steroid suggest the diagnosis of TMS[24] or abscess/granuloma[25] but not the diagnosis of tuberculoma[26]. TMS is defined as a solitary large intracranial lesion larger than 2.0 cm in diameter associated with peri-lesional edema and mass effect[24]. TMS represents 1-2/1000 of cases of MS. TMS has been reported to be extremely rare in children in comparison to tumors and abscesses[27]. Diagnosis of MS depends on combination of clinical, neurophysiological, elevation of CSF immunoglobulin G (IgG) index and oligoclonal bands, and MRI of the brain and spine. Immunosuppressants (including steroids) and immunomodulators are the main therapies of TMS[28]. TMS lesion usually appears as open-ring (directed toward the cortical surface or to the basal ganglia) or closed ring or has diffuse, homogeneous, punctate, or concentric enhancement with Gd[29]. Although, CSF examination and gadolinium-enhanced MRI scan should differentiate between the MS and PCNSL, however, CSF may also be normal in fulminant conditions and short duration of the disease[30].

Furthermore, for our patient inflammatory pseudotumors or non-neoplastic lesions (*e.g.,* abscess/granulomas) of unknown etiology and respone to steroids was also suggested[25]. Patients with intracranial infection/abscess/granulomas commonly have history of risk factors (*e.g.,* immunocompromised state, dental, pulmonary or ear abscesses and intravenous drug use), fever, abnormal labs (as high erythrocytic sedemintation rate or C-reactive protein) and abnormal CSF suggesting CNS infection. Presentation is usually of acute onset with manifestations of increased ICP, seizures and focal neurological deficits. MRI-brain of brain abscess usually shows ring enhancement which is often complete with regular margin[31].

Magnetic resonance spectroscopy (MRS) was not done to the patient at presentation (2009) to distinguish neoplastic from non-neoplastic nature of the mass due to lack of availability. However and fortunately, it was available later and was done to the patient when he developed epilepsy (2012). For our patient, the focal lesion in the left antero-medial region of the temporal lobe found in the MRI (2010-2014) is the cause of the patients' left temporal lobe epilepsy with secondary generalization. The suggested differential diagnosis of the lesion according to the conventional MRI include: (1) tumor recurrence; (2) radiation necrosis; (3) multiple sclerosis; and (4) post-infective/inflammatory gliosis. MRS helped to distinguish tissue changes due to different brain lesions as discussed below.

For our patient, the reduced Cho/Cr (short ET = 0.907; long ET = 0.05), NAA/Cr (short ET = 1.107; long ET = 1.31) and NAA/Cho (short ET = 0.38; long ET = 0.037) ratios confirm the absence of tumor recurrence. Furthermore, the lack of reduced diffusion in DWI also confirms the absence of tumor recurrence[32].

For our patient, the diagnosis of radiation necrosis was suggested based on the facts that children are more susceptible to radiation necrosis than adults[33] and it usually occurs approximately 2-32 mo after radiotherapy, with 85% of cases occurring within 2 years. Delayed radiation-induced brain injury is a relatively common complication of radiation therapy representing 3%-24%[34]. Radiation necrosis is usually presented as a solitary periventricular white matter lesion, because of excess oligodendrocytes in these areas and a poor blood supply that produces ischemia[35]. The typical MR appearance of radiation necrosis is a soap bubble or Swiss cheese-like enhancing periventricular mass[36-38] and elevated Cho, mI, lactate and lipid peaks in MRS[39,40]. Radiation necrosis is related to both the volume of irradiated brain and the total administered radiation dose[41]. It has been reported radiation necrosis is extremely rare (5%) at doses < 45 Gy given over 25 fractions, or when the fractional dose is < 2 Gy/d but often occurs with total doses of > 60-70 Gy[34] or when the fractional dose is ⩾ 2 Gy/d. Our patient was given whole brain radiotherapy in a dose of 4000 CGy/20 settings per 4 wk (*i.e.,* < 2 Gy/d) making the diagnosis of radiation necrosis less likely. Also the absence of enhancement of the new lesion further confirms that the lesion in our patient is not a radiation necrosis.

Although, the results of MRS of our patients may suggest remyelination and gliosis following TMS, however, the presentation with seizures and lack of relapse with enhanced lesions after 5 years of follow up makes the diagnosis of MS less likely[13].

For our patient, the reduced values of Cho/Cr, NAA/Cr and NAA/Cho and lack of enhancement of the lesion are consistent with the diagnosis of gliosis. Gliosis is the process of scarring in the central nervous

system[42]. It results from the proliferation of glial cells or in a damaged brain tissue. It represents a healing process of brain injury whatever its nature. When neurons are injured, astrocytes proliferate in the region and manufacture glial-fibrillary acidic protein. This compound causes the astroglia to form a dense and fibrous tissue: The glial scar. Gliosis can take from a few days to many months to reach its final form. Gliosis is diagnosed by immunohistochemistry or MRI[43]. Gliosis occurred as a result of an acquired brain injury (most likely abscess, granuloma, inflammation) and it is the cause of temporal lobe epilepsy. Cr and Cho are glial markers. Gliosis typically presents with reduced levels of Cho, NAA, and Cr and observed lip peaks. Moderate levels of Cho and/or a Cho/Cr index < 1.3 are frequent with gliosis. This is supported by the followings: (1) the development of epilepsy in our patient occurred as a result of a focal lesion in the antero-medial region of the left temporal lobe which is suggestive of gliosis with no evidence of neoplastic activity as confirmed by MRS; and (2) mesial temporal lobe epilepsy (due to hippocampal sclerosis) is characterized by hippocampal atrophy, decreased NAA, and a low NAA/Cr ratio which are attributed to neuron loss and gliosis[39].

ACKNOWLEDGMENTS

I would like to thank the patient's parents for their cooperation and providing approval to publish the clinical, laboratory and imaging results of this case presentation.

COMMENTS

Case characteristics

A 14-year-old child with history of acute manifestations of increased intracranial pressure and right sided hemiparesis which improved completely within two weeks and followed after 3 years by epilepsy.

Clinical diagnosis

The patient was having right sided hemiparesis due to brain space occupying lesion which was complicated by recurrent generalized epilepsy.

Differential diagnosis

Brain tumor (*e.g.,* primary central nervous system lymphoma or glioma); tumor like demyelinating lesion or tumefactive multiple sclerosis and intracranial infection or abscess/granulomas.

Laboratory diagnosis

Blood tests revealed mild leukocytosis and elevated erythrocyte sedimentation rate (ESR).

Imaging diagnosis

Initially at presentation, magnetic resonance imaging-brain showed a large intra-axial mass (25 mm x 19 mm) in the left temporal lobe with hypointense signal in T1W, hyperintense signals in T2W and fluid attenuated inversion recovery (FLAIR) images and homogenous enhancement with Gd suggesting neoplastic lesion (malignant lymphoma or glioma) while follow up after 5 years, MRI showed small non-enhanced lesion in the antero-medial part of the left temporal lobe with hypointense signal in T1W and hyperintense in T2W and FLAIR signal and reduced choline (Cho)/creatine (Cr), N-acetyl-aspartate (NAA)/Cr and NAA/Cho ratios in magnetic resonance spectroscopy (MRS) which confirmed absence of neoplastic activity but suggestive of gliosis.

Pathological diagnosis

Inflammatory brain space occupying lesion complicated by gliotic lesion in the antero-medial part of the left temporal lobe.

Treatment

Brain dehydrating measures, antibiotics, corticosteroids and a course of craniospinal irradiation.

Related reports

In clinical practice; a vanishing brain space occupying lesion is commonly diagnosed as a neoplasm (*e.g.,* lymphoma) or multiple sclerosis.

Term explanation

A vanishing brain space occupying lesion is defined as reduction or disappearance of a brain lesion spontaneously or after steroid treatment to ⩽ 70% of its size before establishing its definitive diagnosis.

Experiences and lessons

In clinical practice, neuroimaging [including MRS or magnetic resonance imaging (MRI)] has to be done every 6-12 mo for at least 3-5 years to follow up after complete remission of the patient with a vanishing brain lesion.

Peer-review

The case report presents a vanishing brain space occupying lesion in a child over 5 years course of recovery and MRI follow-up. The prognosis was fortunately better. Text is well wrote and easily comprehensible with clear figures. The authors discussed the potential differential diagnosis, and recommended that MRS may be helpful to identify a potential vanishing brain space occupying benign lesion from tumor lesion in clinic.

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CASE REPORT

Case of Fitz-Hugh-Curtis syndrome in male without presentation of sexually transmitted disease

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Abstract

Fitz-Hugh-Curtis syndrome is a type of perihepatitis that causes liver capsular infection without infecting the hepatic parenchyma or pelvis. Fitz-Hugh-Curtis syndrome is known to occur commonly in women of childbearing age who do not use oral contraceptives and have sexual partners older than 25 years of age. However, the syndrome has been reported to occur rarely in males. The clinical symptoms are right upper quadrant pain and tenderness, and pleuritic right sided chest pain. The clinical presentation is similar in male and female. We experienced a case of Fitz-Hugh-Curtis syndrome in a 60-year-old man with the chief complaint of right upper quadrant abdominal pain. Despite a previous history of gonorrhea, we have also described our experiences of improved symptoms and recovery with allopathic medicines and have thereby reported the present case with a literature review.

Key words: Male; Right upper quadrant pain; Fitz-Hugh-Curtis syndrome; Perihepatitis; Sexually transmitted disease; Liver capsular infection

Core tip: Fitz-Hugh-Curtis syndrome is known to occur commonly in sexually active women and very rarely in males. We experienced a case of Fitz-Hugh-Curtis syndrome in a 60-year-old man with the chief complaint of right upper quadrant abdominal pain on inspiration. Despite of negative laboratory result, we diagnosed as Fitz-Hugh-Curtis syndrome by symptom and liver computed tomography scan. We have also described our experiences of improved symptoms and recovery with allopathic medicines.

Yi H, Shim CS, Kim GW, Kim JS, Choi IZ. Case of Fitz-Hugh-Curtis syndrome in male without presentation of sexually transmitted disease. *World J Clin Cases* 2015; 3(11): 965-969 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i11/965.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i11.965

INTRODUCTION

Fitz-Hugh-Curtis syndrome is a type of perihepatitis that causes liver capsular infection without infecting the hepatic parenchyma or pelvis. In 1920, Carlos Stajano first described the surgical confirmation of an adhesion that connected the anterior peritoneum and hepatic parenchyma in a gonorrheal patient who had complained of right upper quadrant abdominal pain. In 1930, Curtis[1] reported an adhesion of the peripheral hepatic parenchyma in a patient with salpingitis. In 1934, Fitz-Hugh[2] identified *Neisseria gonorrhoeae* (*N. gonorrhoeae*) on a peripheral liver adhesion in a patient complaining of right upper quadrant abdominal pain and reported that these findings were associated with the violin string-shaped adhesions around the liver observed in female patients with pelvic infection and salpingitis, which was at that time suggested as a new syndrome in terms of the pathophysiology of venereal diseases. Initially, only *N. gonorrhoeae* was considered a causative bacterium; however, in recent years, additional causative bacteria such as *Chlamydia trachomatosis* (*C. trachomatosis*) have been reported, and this condition was also found to be caused by other bacterial sexually transmitted diseases in addition to gonorrhea[3-5].

Traditionally, Fitz-Hugh-Curtis syndrome is known to occur commonly in women of childbearing age who do not use oral contraceptives and have sexual partners older than 25 years of age; because of unclear statistical results, it is uncertain whether this condition is accompanied by pelvic inflammation. However, since its detection in men after the 1970s[6], more extensive studies of this disease have been performed.

Based on the diagnostic criteria of a disease history and clinical patterns, cases in which a violin string-shaped abdominal adhesion is confirmed through laparoscopy or laparotomy to exclude other diagnoses and in which causative bacteria are identified in the liver capsule exudate are generally diagnosed as Fitz-Hugh-Curtis syndrome. In 2003, Nishie *et al*[7] and colleagues observed more definite hepatic capsule enhancement in the arterial phase relative to other phases during a computed tomography (CT) scan. Using abdominal dynamic CT scans, Joo *et al*[8] detected Fitz-Hugh-Curtis syndrome with a sensitivity of 88% and specificity of 95%, and Woo *et al*[9] diagnosed Fitz-Hugh-Curtis syndrome with 95.5%. In recent years and in consideration of surgical complications, non-invasive diagnoses not requiring surgery have increased for cases with mild symptoms by integrating the outcomes of clinical patterns, culture tests, and CT scan results.

In South Korea, Fitz-Hugh-Curtis syndrome was previously reported in women; however, in 2010, *Mycoplasma genitalium* was first identified *via* blood testing, an abdominal dynamic CT scan, and urine culture testing in a 35-year-old male patient complaining of right upper quadrant abdominal pain[10]. In addition to a literature review, the authors herein report a case of non-invasively diagnosed Fitz-Hugh-Curtis syndrome in a sexually inactive, hepatitis B virus (HBV)-positive elderly patient who presented with right upper quadrant abdominal pain; this diagnosis was achieved *via* blood testing and an abdominal dynamic CT scan, and excluded other diseases despite the inability to identify the causative bacteria.

CASE REPORT

A 60-year-old male patient was admitted to the emergency room with right upper quadrant abdominal pain that had gradually increased in severity beginning three days earlier. This pain was not affected by meals, and became sharp and severe upon inhalation. The patient had a disease history of gonorrhea while in his 20s, although this had completely recovered, and had no family medical history. He was divorced, a non-smoker, drank 1 bottle of soju 3-4 times a week, and had no external injuries. At the time of admission, his vital signs were as follows: Blood pressure, 140/70 mmHg; pulse rate, 80 times/min; respiration, 20 times/min; and body temperature, 36.5 ℃. He presented with acute symptoms, no specific sphygmoscopic findings, a soft abdomen, normal bowel sounds, oppressive pain in the right upper abdominal quadrant, no rebound tenderness or abdominal distension, and Murphy's sign negativity. He did not present with shifting dullness or fluid waves indicative of ascites, enlarged organs or masses, or bilateral costovertebral pain.

Peripheral blood tests revealed the following (Table 1). The following serum biochemical test results (Table 1) were observed: Increased C-reactive protein, aspartate aminotransferase, and alanine aminotransferase. Urine tests revealed no specific findings, and the results of simple chest and abdominal radiography were normal.

An abdominal pelvic CT scan was performed, and linear capsular enhancement of the inferior segment of the liver was observed in the arterial phase (Figure 1A). No specific findings were observed in other abdominal and pelvic organs, including the hepatic parenchyma, gallbladder, biliary tract, and pancreas. Hepatitis virus tests were planned to evaluate the increased hepatosomatic index, and a fluid treatment involving daily intravenous levofloxacin administration (500 mg) as well as experimental antibiotics were planned to treat suspected Fitz-Hugh-Curtis syndrome. Based on the findings observed in known cases of this disease, examinations of previous urinary tract

Table 1 Clinical value on initial admission

Peripheral blood test	
Leukocyte	3610/mm^3
Neutrophils	50.90%
Lymphocytes	35.50%
Hemoglobin	146 g/L
Platelet	164000/mm^3
Erythrocyte sedimentation rate	25 mm/h
Serum biochemical test	
C-reactive protein	15.6 mg/L
Total protein	67 mg/L
Albumin	37 mg/L
Total bilirubin	5.8 mg/L
Aspartate aminotransferase	52 IU/L
Alanine aminotransferase	47 IU/L
Alkaline phosphatase	93 IU/L
Blood urea nitrogen	148 mg/L
Creatinine	6.1 mg/L
Na	134 mmol/L
K	4.01 mmol/L
Cl	98.3 mmol/L
Creatine kinase-myocardial band	2.27 ng/mL
Troponin-T	0.003 ng/mL
Amylase	61 U/L

Table 2 Tumor marker test

Carbohydrate antigen 19-9	0.6 U/mL
Alpha-fetoprotein	19.28 ng/mL
Carcinoembryonic antigen	4.69 ng/mL
Protein induced by vitamin K absence or antagonist Ⅱ	17 nAU/mL

infections or venereal diseases, blood tests, and urine culture tests were performed. In a subsequent examination, the patient reported having 1 sexual relationship 20 d earlier; all results for the following tests were negative: Human immunodeficiency virus (HIV) Ag/Ab combi test, urine culture test, and PCR for *N. gonorrhoeae*, *C. trachomatis*, Ureaplasma urealyticum, M. genitalium, M. hominis, Trichomonis vaginalis, Treponema palladium, *Candida albicans*, Herpes simplex Ⅵ and Ⅶ, Haemophilus ducreyi, and Condyloma 6, 11, which was performed after prostate massage. The hepatitis virus test indicated the following: Hepatitis A virus IgM, HBV surface antibody (enzyme-linked immunoassay; EIA), HBV extracellular antigen (HBeAg), and hepatitis C virus Ab negativity; HBV surface antigen (EIA) and HBV extracellular antibody (HBeAb) positivity; and an HBV DNA copy number of 1.59×10^7/mL. A tumor marker test measured to exclude cancer and showed no abnormalities (Table 2). Gastroscopy and colonoscopy were performed to exclude cancer, and no specific findings were observed besides chronic superficial gastritis and a gastric ulcer. No findings indicative of liver cancer besides the previously observed capsular enhancement of the inferior segment of liver were observed on a liver abdominal dynamic CT scan.

On the second day of hospitalization, the right upper quadrant abdominal symptoms improved and on the third day of hospitalization, the patient's pain upon inhalation had decreased. The patient requested outpatient clinic care and he was discharged from the hospital. Two weeks after the initial medical treatment, the right upper quadrant abdominal pain disappeared during outpatient clinic care, and pain during inhalation decreased to 1-2 times per day. After four weeks of antibiotic treatment, the right upper quadrant abdominal pain improved, and the liver capsule enhancement completely disappeared on a liver abdominal dynamic CT scan performed three months after treatment (Figure 1B).

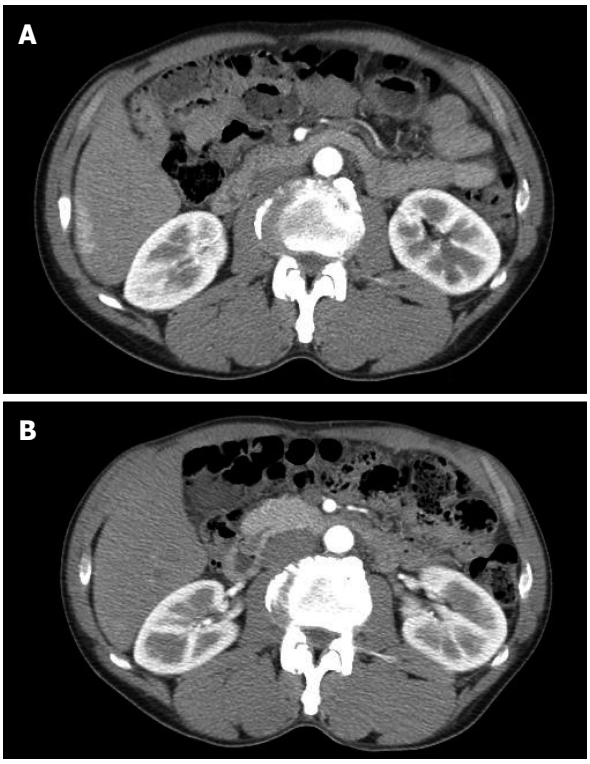

Figure 1 Abdominal computed tomography findings. A: Linear capsular enhancement of the inferior segment of the right lobe is visible on an arterial phase image; B: On an arterial phase image obtained 3 mo after treatment, the liver capsule enhancement over the right lobe has disappeared completely.

DISCUSSION

Fitz-Hugh-Curtis syndrome refers to perihepatitis accompanied by pelvic inflammation in 5%-15% of cases; young women of childbearing age are mainly affected by this disease. The symptoms can be divided into acute and chronic phases. Patients in the acute phase have characteristic pathologic findings of exudative hepatic capsule inflammation with inflammatory reactions and bleeding of the inferior liver and vessels in the abdominal wall adjacent to the liver[11]. Accordingly, in the acute phase, the right upper quadrant abdominal pain is sharp and pleuritic and occasionally radiates to the right shoulder or inside of the arm. In the chronic phase, exudative inflammation causes a violin string-like adhesion between the

hepatic capsule and inferior abdominal wall or between the hepatic capsule and diaphragm. Although this adhesion rarely causes clinically significant symptoms, laparoscopic synecotomy can be performed in cases involving persistent right upper quadrant abdominal pain that are refractory to antibiotic therapy[12].

Previously, *N. gonorrhoeae* was identified as the causative bacterium of Fitz-Hugh-Curtis syndrome, but in recent years *C. trachomatis* has also been identified as a major causative bacterium. In the present case, the patient had a previous history of gonorrhea and was an HBV carrier; however, there are no previous reports of secondary Fitz-Hugh-Curtis syndrome onset resulting from a previous gonorrheal infection and HBV positivity.

Regarding the infection route, traditionally direct infection has been dominant as determined *via* culture tests of the uterine tubes and hepatic lesions. However, blood-mediated infection has been reported in other cases[13] *via* blood culture tests, supporting the use of antibiotic treatment. However, most case reports remain controversial because of a lack of positive culture test results. Infection *via* lymphatic vessels could explain the cases of perihepatitis in both men and women without gonohemia, although as yet there is no clear evidence to support this. Money *et al*[14] suggested an immune reaction-based pathophysiology following a comparison of IgG values in the context of chlamydia infection, but currently this hypothesis remains unconfirmed.

Long-term complications of Fitz-Hugh-Curtis syndrome are rare and include pelvic inflammatory complications, chronic pain, small intestinal obstruction due to adhesion, and infertility.

A suspicion of Fitz-Hugh-Curtis syndrome is most important when diagnosing and detecting pleural or right upper quadrant abdominal pain in young, sexually active women in the absence of clear evidence for other diseases such as acute cholecystitis. As mentioned earlier, invasive surgical procedures such as laparoscopic surgery or laparotomy are required to confirm a diagnosis of Fitz-Hugh-Curtis syndrome, but these are not desirable or practically feasible in many cases. Therefore, in actual clinical settings, it is common to diagnose and treat this syndrome under only a presumptive diagnosis and the identification of characteristic strains after excluding other diagnoses. Blood tests mostly reveal a normal or elevated leukocyte count and erythrocyte sedimentation rate and a normal or slightly increased hepatosomatic index, which assist with the diagnosis. CT scans reveal hepatic capsule contrast enhancement, a characteristic finding of perihepatitis, in the arterial phase and are thereby used as a non-invasive method for diagnosing Fitz-Hugh-Curtis syndrome. Although cervical exudate is mainly used for stain identification, vaginal, anal, urethral, and pharyngeal exudates may also be used. Generally, culture tests are most widely used although genetic tests such as PCR or gene amplification provide better sensitivity and specificity. According to recent studies, however, increasing numbers of cases have been observed with *C. trachomatosis* negative PCR results but positive antigen-antibody reactions, and it is therefore recommended that antibody tests for causative bacteria identification should be performed concurrently[15]. In the present case, both culture tests and PCR were conducted to identify sexually transmitted microbes; however, an antigen-antibody test was not performed and the causative bacteria could not be identified.

Fitz-Hugh-Curtis syndrome can be treated experimentally with antibiotics, according to the principle of using antibiotics suitable for each identified causative bacterium. However, because of the rejection of some patients with venereal diseases, some cases have reportedly been treated with experimental antibiotics in the absence of causative bacteria identification or even attempted identification. Experimental antibiotics use is based on pelvic inflammatory treatment, and antibiotics such as cefotetan, doxycycline, clindamycin, gentamicin, and ofloxacin have been used[16]. Cefotetan and doxycycline are mainly administered intravenously, and levofloxacin and metronidazole can also be used. Intravenous antibiotics are continued for 48 h after the improvement of clinical symptoms, and metronidazole or levofloxacin are used orally for 2 wk. If pain persists even with proper treatment, a peripheral liver adhesion should be confirmed *via* laparoscopy[17].

Fitz-Hugh-Curtis syndrome is known to be extremely rare in men. In 1970, Kimball and Knee first reported a case of Fitz-Hugh-Curtis syndrome caused by *N. gonorrhoeae* in a 22-year-old man[6]. In 1982, Davidson and Hawkins[18] reported the development of this syndrome from gonorrheal sepsis concomitant with pustular bacterid in a 35-year-old bisexual man with an identified *N. gonorrhoeae* infection. In 1985, Winkler *et al*[19] reported a case of Fitz-Hugh-Curtis syndrome and discussed the possibility that *N. gonorrhoeae* entered *via* damaged rectal mucous membranes and directly spread through the abdominal cavity in a 35-year-old homosexual man with a history of acquired immune deficiency syndrome.

In the present case, we have reported a diagnosis of Fitz-Hugh-Curtis syndrome *via* blood tests and abdominal dynamic CT in a 60-year-old man with the chief complaint of right upper quadrant abdominal pain. Blood culture tests, urine culture tests, and PCR of sexually transmitted disease-causing microbes were performed to identify the causative agent, although *N. gonorrhoeae* was not proven to be the causative bacterium, despite a previous history of gonorrhea. We have also described our experiences of improved symptoms and recovery with allopathic medicines and have thereby reported the present case with a literature review.

COMMENTS

Case characteristics

A 60-year-old male patient was admitted to the emergency room with right upper quadrant abdominal pain that had gradually increased in severity beginning 3 d earlier.

Clinical diagnosis

Fitz-Hugh-Curtis syndrome.

Differential diagnosis

Hepatocellular carcinoma (right upper quadrant abdominal pain) -gastroscopy, colonoscopy, abdominal computed tomography (CT), and tumor marker test.

Laboratory diagnosis

Aspartate aminotransferase was 52 IU/L and Alanine aminotransferase was 47 IU/L.

Imaging diagnosis

Abdominal CT showed linear capsular enhancement of the inferior segment of the right lobe is visible on an arterial phase.

Pathological diagnosis

Blood culture tests, urine culture tests, and PCR of sexually transmitted disease-causing microbes were negative.

Treatment

Empirical intravenous antibiotics were administered, maintained oral medication.

Related reports

Fitz-Hugh-Curtis syndrome occurs rarely in male. Cases reported in English and Korean literature were reviewed.

Term explanation

Fitz-Hugh-Curtis syndrome is a type of perihepatitis that causes liver capsular infection without infecting the hepatic parenchyma or pelvis is known to be locally aggressive and requires extensive surgical resection.

Experiences and lessons

Fitz-Hugh-Curtis syndrome was considered as sexually transmitted disease. Although causative pathogen was not proven, we diagnosed and treated patient.

Peer-review

This article can nicely contribute to increasing the awareness of Fitz-Hugh-Curtis syndrome.

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CASE REPORT

Lower gastrointestinal tract bleeding caused by dieulafoy-like lesion synchronous meckel diverticulum: A rare case report

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Author contributions: Li SH, Wu GY contributed the main work of this article, they are both co-first authors; the study was guided by Yu SP; the endoscopy operation was performed by Wen ZQ, assisted by Lin XD; Zhang H performed the colectomy and exploring laparotomy; data were obtained by Li SH, Wu GY, Lin XD and Huang MT; data were analyzed by Wu GY; the report was written by Li SH and Wu GY; all authors approved the final version.

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Abstract

Meckel diverticulum is an embryonic remnant of the Gastrointestinal duct which causes symptoms < 5% in the 2% population. Painless bleeding and abdominal pain are the most often reported symptoms. Dieulafoy lesion/dieulafoy-like lesion often cause upper gastrointestinal (GI) tract bleeding, but massive lower gastrointestinal bleeding is rare. We reported a 19-year-old male presented massive lower GI tract bleeding caused by Meckel diverticulum synchronous dieulafoy-like lesion.

Key words: Lower gastrointestinal tract; Bleeding; Dieulafoy-like lesion; Meckel diverticulum; Endoscopy

Core tip: Dieulafoy-like lesion often causes upper gastrointestinal (GI) tract bleeding, and meckel diverticulum is another common cause of GI tract bleeding. The two of them happened at the same person is rare. We observed a 19-year-old man complained of upper stomachache was admitted to hospital. He underwent left hemi-colectomy on day 5 after admitted. Pathology confirmed the diagnosis of dieulafoy-like lension of descending colon. The bleeding ceased for 2 d. But another attack came on day 3 after surgery. He underwent a second laparotomy which united endoscopy, a 2 cm × 1.5 cm meckel diverticulum

in terminal ileum was detected. Resection was performed. Pathology revealed meckel diverticulum. He was fully recovered with no sign of bleeding in the next year's following up.

Li SH, Wu GY, Lin XD, Wen ZQ, Huang MT, Yu SP, Zhang H. Lower gastrointestinal tract bleeding caused by dieulafoy-like lesion synchronous meckel diverticulum: A rare case report. *World J Clin Cases* 2015; 3(11): 970-972 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i11/970.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i11.970

INTRODUCTION

A 19-year-old man was admitted to hospital due to upper stomachache for 6 d, hematochezia for 3 d and syncope twice. He had recurrent massive hematochezia and conservative therapy was inefficacy. He had left hemi-colectomy on day 5 after admitted. Pathology confirmed the diagnosis of dieulafoy-like lesion of descending colon. The bleeding ceased for 2 d. He had another attack of hematochezia on day 3 after surgery (day 7 after admitted). He underwent a second laparotomy which united colonoscopy, a 2 cm × 1.5 cm meckel diverticulum in terminal ileum was detected. Resection was performed. Pathology revealed meckel diverticulum, atopia gastric mucosa polyp accompany with chronic ulcer. He recovered well and was discharged 20 d later. The next year's following up shows no sign of bleeding.

CASE REPORT

A 19-year-old man was admitted to hospital due to upper stomachache for 6 d, hematochezia for 3 d and syncope twice. He looked pale and weak when admitted. Blood count reveals RBC 2.44 × 10^{12}/L, Hb 71 g/L, HCT 0.20. There is no sign of abnormal of his colon except retention of fresh blood in the following day's colonoscopy. Tc-99m pertechnetate scan in the third day revealed no positive sign neither. The patient had a third time of hematochezia for about 300 mL. Bleeding from the left hemicolon was highly suspected during the second colonoscopy, but exact bleeding point was not observed. He was treated with hemostasia to stop the bleeding and fluid infusion therapy. A fourth time hematochezia occured in day 5. Digital subtraction angiography supported bleeding from left hemi-colon (Figure 1). He was sent to OR for left hemi-colectomy. Pathology confirmed the diagnosis of dieulafoy-like lension of descending colon (Figure 2). The bleeding ceased for 2 d. On day 3 post colectomy (day 7 after admitted), he had the fifth hematochezia, discharged about 1000 mL of blood. Blood transfusion and blood coagulant were used to stop bleeding. Those treatments did not stop the bleeding. He underwent a second laparotomy united colonoscopy. During the surgery laparotomy united colonoscopy, a 2 cm × 1.5 cm meckel diverticulum in terminal ileum was detected (Figure 3). A wide base, smooth, about 0.6 cm × 0.6 cm hemispherical polyp beside it was observed, resection was performed meanwhile. Pathology revealed meckel diverticulum, atopic gastric mucosa polyp accompany with chronic ulcer. The patient recovered in 20 d with neither bleeding nor other complications and was discharged. There was no more hematochezia in the next year's follow up.

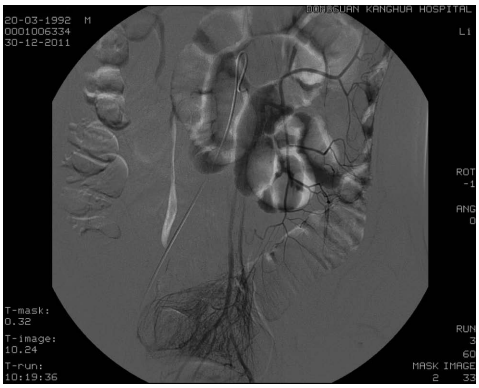

Figure 1 Digital subtraction angiography supported bleeding from left hemi-colon.

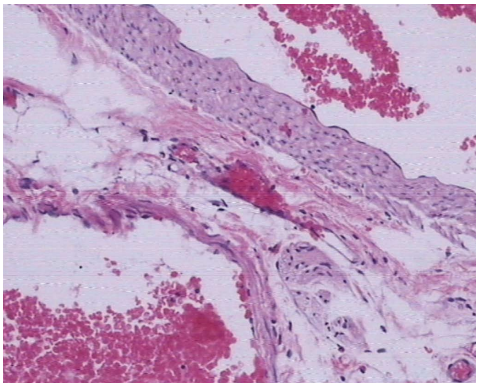

Figure 2 Pathology after left hemi-colectomy confirmed the diagnosis of dieulafoy-like lension of descending colon.

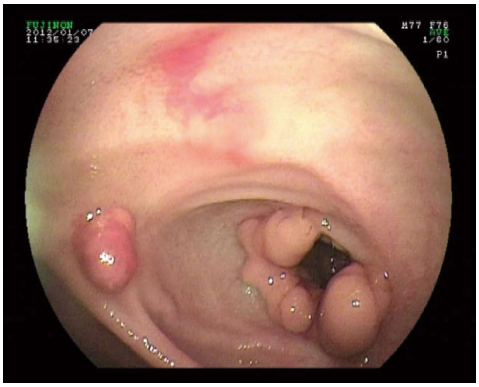

Figure 3 A 2 cm × 1.5 cm meckel diverticulum in terminal ileum was detected by colonoscopy during the second laparotomy which united endoscopy.

DISCUSSION

Dieulafoy lesion/dieulafoy-like lesion is a cause of GI tract bleeding which cannot be ignored, most commonly results the proximal stomach bleeding, but very rare entity that can cause massive lower gastrointestinal track bleeding[1]. Meckel diverticulum is an embryonic remnant of the gastrointestinal duct which is presented in approximately 2% of the population and is estimated to cause symptoms < 5% of the time. It generally results in painless bleeding or abdominal pain[2]. The technetium 99m pertechnetate scan is the best of choice for detecting Meckel diverticulum, with a reported sensitivity of 85% to 90% in the pediatric population[3]. In adults, however, the sensitivity falls on to only 62%[4]. It is an ideal noninvasive and sensitive way to detective meckel diverticulum. We performed surgery though this patient's technetium 99m pertechnetate scan is negative and a meckel diverticulum was found. This case presented of massive lower gastrointestinal bleeding caused by descend colon dieulafoy-like lesion and small bowl meckel diverticulum at same time is a rare condition.

COMMENTS

Case characteristics

A 19-year-old man complained of upper stomachache was admitted to hospital.

Clinical diagnosis

Massive lower gastrointestinal bleeding caused by descend colon dieulafoy-like lesion and small bowl meckel diverticulum at same time.

Differential diagnosis

Tumor of the colon, ischemic colitis, Crohn's disease, Ulcerative colonitis.

Laboratory diagnosis

Blood count reveals RBC 2.44 × 10^{12}/L, Hb 71 g/L, HCT 0.20.

Imaging diagnosis

Tc-99m pertechnetate scan in the third day revealed no positive sign. Digital subtraction angiography supported bleeding from left hemi-colon.

Pathological diagnosis

Pathology confirmed the diagnosis of dieulafoy-like lension of descending colon at the first surgery. Pathology reveals meckel diverticulum, atopic gastric mucosa polyp accompany with chronic ulcer after the second surgery.

Treatment

Left hemi-colectomy and resection of the bowl with meckel diverticulum.

Related reports

Dieulafoy lesion of the colon is reported to be bleeding cause of lower GI tract bleeding, and so does meckel diverticulum.

Experiences and lessons

Massive lower gastrointestinal bleeding caused by descend colon dieulafoy-like lesion and small bowl meckel diverticulum at same time is a rare condition. Both of them may be missed at the first endoscopy examination. Repeated endoscopy examination may be needed when bleeding occurs over and over again.

Peer-review

This case is interesting.

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