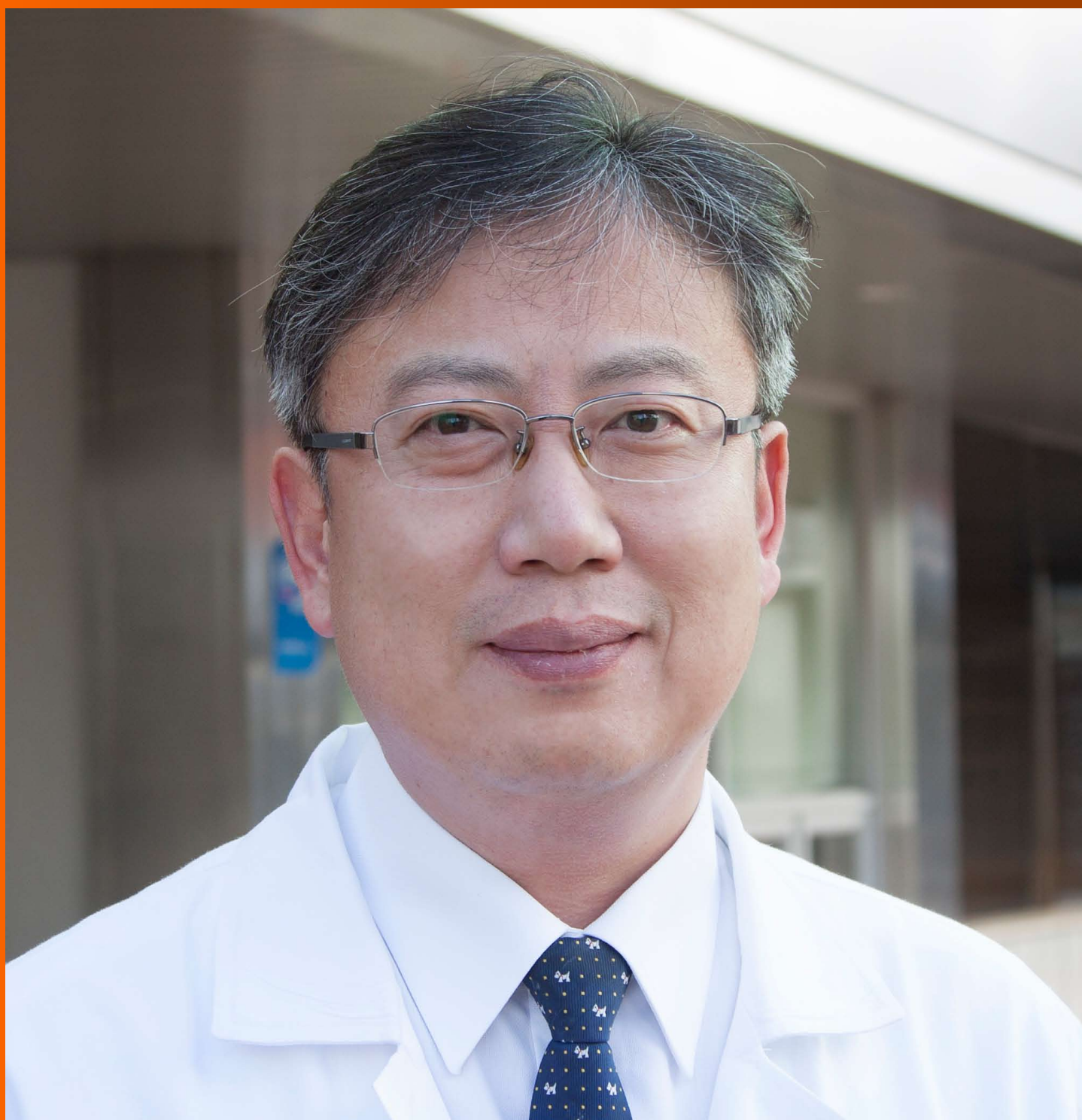


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Externalized conductors and insulation failure in Biotronik defibrillator leads: History repeating or a false alarm?

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Abstract

Conductor externalization and insulation failure are frequent complications with the recalled St. Jude Medical Riata implantable cardioverter-defibrillator (ICD) leads. Conductor externalization is a "unique" failure

mechanism: Cables externalize through the insulation ("inside-out" abrasion) and appear outside the lead body. Recently, single reports described a similar failure also for Biotronik leads. Moreover, some studies reported a high rate of electrical dysfunction (not only insulation failure) with Biotronik Linx leads and a reduced survival rate in comparison with the competitors. In this paper we describe the case of a patient with a Biotronik Kentrox ICD lead presenting with signs of insulation failure and conductor externalization at fluoroscopy. Due to the high risk of extraction we decided to implant a new lead, abandoning the damaged one; lead reimplant was uneventful. Subsequently, we review currently available literature about Biotronik Kentrox and Linx ICD lead failure and in particular externalized conductors. Some single-center studies and a non-prospective registry reported a survival rate between 88% and 91% at 5 years for Linx leads, significantly worse than that of other manufacturers. However, the preliminary results of two ongoing multicenter, prospective registries (GALAXY and CELESTIAL) showed 96% survival rate at 5 years after implant, well within industry standards. Ongoing data collection is needed to confirm longer-term performance of this family of ICD leads.

Key words: Implantable cardioverter defibrillator; Biotronik implantable cardioverter defibrillator lead; Externalized conductors; Insulation failure

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Core tip: Conductor externalization and insulation failure are frequent complications with the recalled St. Jude Medical Riata implantable cardioverter-defibrillator leads. Cables can externalize through the insulation ("inside-out" abrasion) and appear outside the lead body. Recently similar failure mechanisms have also been described for Biotronik leads. Some studies reported a high rate of electrical dysfunction (including insulation

failure) with Biotronik Linx leads and a survival rate between 88% and 91% at 5 years, significantly worse than that of other manufacturers. However, the preliminary results of two ongoing multicenter, prospective registries showed 96% survival rate at 5 years, well within industry standards.

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INTRODUCTION

Implantable cardioverter-defibrillator (ICD) is a well established life-saving therapy for patients at risk of sudden cardiac death from ventricular arrhythmias. "Achille's heel" of the ICD system is the lead, because of its susceptibility to mechanical and electrical defects^[1]. Incidence of lead failure can be as high as 0.58%/year, increasing with time (up to 10%-15% at 10 years of follow up)^[2,3]. Lead failure has a broad range of clinical presentations and outcomes, the most dreaded being potentially lethal proarrhythmia and inability to interrupt spontaneous ventricular arrhythmias.

Conductors fracture and insulation failure are the main mechanisms responsible for lead failure^[1-3]: Two classical examples are the recalled Medtronic Sprint Fidelis leads and the St. Jude Riata leads family.

Sprint Fidelis leads (Medtronic Inc., St. Paul, Minnesota, United States) were recalled from the market, in October 2007, because of a high failure rate due to conductor fracture. On the other side, Riata family of ICD silicone leads (St. Jude Medical, Sylmar, California, United States) underwent class I recall by the Food and Drug Administration, in December 2011, because of insulation failure. In particular, Riata leads are susceptible to a unique failure mechanism: The conductor cables can externalize through the silicone insulation ("inside-out" abrasion) and appear outside the lead body^[3].

Recently, single case reports described a "Riata like" insulation failure mechanism also for Biotronik Kentrox and Linx ICD leads (Biotronik, Berlin, Germany)^[4-9]. Moreover, some single-center studies and a non-prospective registry reported a high rate of electrical dysfunction (including but not limited to insulation failure) with Biotronik Linx leads and a reduced survival rate in comparison with the competitors^[10-12]. Nevertheless, the preliminary results of two ongoing multicenter, prospective registries (GALAXY and CELESTIAL) showed 96% survival rate at 5 years after implant, well within industry standards and not different from that of other manufacturers^[13].

In this paper, we describe (beyond the already published case reports) a patient, managed at our institution, with a Biotronik Kentrox ICD lead presenting with signs of insulation failure and conductor externalization at fluoroscopy. Subsequently, we review currently available literature about Biotronik ICD lead failure and in particular insulation failure with externalized conductors.

ANATOMY OF A DEFIBRILLATOR LEAD

General concepts

Each ICD lead has several components^[3]: Conductor, insulation material, defibrillation coil, electrode, fixation mechanism to myocardium, division point of single conductors and connector. Most manufacturers use similar materials, even if assembled in different ways. All modern ICD leads have a multi-lumen design. High-voltage shock conductors include a low-resistance core of silver-platinum and are coated with polytetrafluoroethylene and ethylenetetrafluoroethylene (ETFE); they lie in a silicone cylinder with 3-6 lumens. Low-voltage conductors are made of alloy of cobalt, nickel, chromium silver and molybdenum. A central coil conductor used for the pacing-sensing cathode (tip) allows for stylet insertion and extension/retraction of the fixation helix. Conductors for the pacing-sensing anode (ring) and high voltage coils are built in parallel cables around the central coil (Figure 1). Lead design may vary among manufacturers: Coils can be placed in symmetric or asymmetric manner; compression lumens can be present or not, etc. All leads, anyway, will have minimum one distal right ventricular (RV) shock coil, necessary for the delivery of high-voltage shock therapy. Dual-coil leads have another shock coil, usually located in the superior vena cava (SVC). Dual-coil leads may ensure greater defibrillation efficacy, especially in right-sided implants, but they involve greater procedural difficulties and risks, when extraction is required, due to fibrotic tissue around the proximal coil (Figure 2).

Last generation ICD leads use a DF-4 connection, that has replaced the old, multicomponent yokes (DF-1/IS-1). DF-4 connection has the pace-sense conductors and the defibrillation conductor(s) connected to a single pin. The new connection has the advantage of a reduced pocket bulk and prevents the accidental reversal of high-voltage connections during implantation or replacement procedures.

ICD leads always have bipolar sensing and the tip electrode is always used as a cathode. However two types of sensing design exist. The dedicated bipolar lead has a ring electrode as sensing dedicated anode. On the other side, the integrated bipolar lead has the RV defibrillation coil, integrated within the shock circuit, as the anode. Therefore, a dedicated bipolar lead is more complex because it requires two conductors, versus one in an integrated bipolar lead. Dedicated and integrated leads show no difference regarding

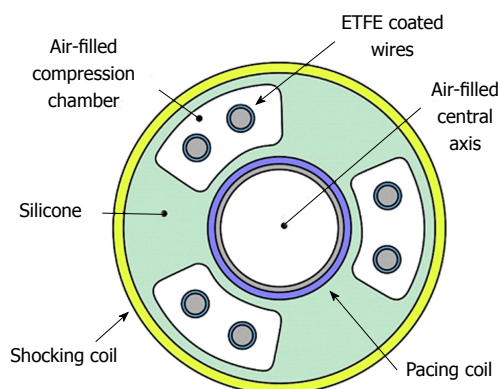


Figure 1 Cross-section design of a modern implantable cardioverter-defibrillator lead. ETFE: Ethylenetetrafluoroethylene.

sensing of ventricular fibrillation (VF). However, an integrated bipolar lead has a larger “antenna”, more prone to oversensing of diaphragmatic myopotentials, electromagnetic interference (EMI) and atrial “far field” signals. Dedicated bipolar leads are more prone to oversense the T wave. Current ICD leads diameters vary from 6.3 to 8.6 French.

Biotronik Kentrox and Linx leads

Kentrox SL (marketed from 2001 to 2005) is a 9.3 French, passive fixation ICD lead with an isodiametric design, coated with fractal iridium. The sensing is dedicated bipolar. The lead is insulated with silicone rubber similar to first generation Riata leads insulation. In contrast to Riata lead, Kentrox does not present a “redundant” design that can facilitate the movement of the cables within the lumen (and was supposed to be implied in “inside-out” abrasion)^[6]. Nevertheless, the mechanism of Kentrox externalization described in literature (see next paragraphs) seems to be very similar to that of Riata leads: “Inside-out” abrasion (movement of the conductors within the insulation, leading to cable externalization through the outer layer) rather than “outside-in” (contact with another lead or anatomic structures, *e.g.*, tricuspid valve).

Linx family leads (marketed in 2005) are 7.8 French with an isodiametric design and dedicated bipolar sensing. The cross-section of Linx lead is comparable to that of Kentrox and, although having a smaller diameter, the thickness of the silicone layer is equal. Moreover, Linx is equipped with integrated flat-wire shock coil (Protek®) which reduces fibrotic tissue ingrowth.

Linx^{Smart} lead (marketed in 2009, from 2012 proMRI model) is additionally treated with Silglide®, a surface treatment which ensures lubricious coating, improved gliding, low friction and reduces the risk of abrasion (Figure 3). In a similar manner, Riata ST and Durata St. Jude Medical models were provided with an additional abrasion-resistant silicone-polyurethane co-polymer (Optim™). Silicone rubber is inert and more biostable compared to polyurethane, but has a higher coefficient

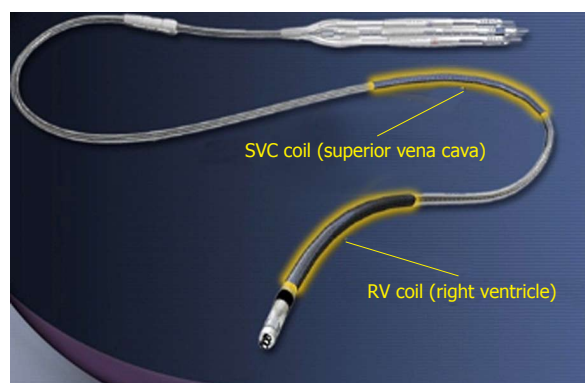


Figure 2 A typical transvenous implantable cardioverter-defibrillator lead with DF-1 connection and dual-coil design. SVC: Superior vena cava.

of friction and is more vulnerable to abrasion and breaches. On the other side, polyurethane is too stiff to be used as the only insulation material in ICD leads. That is why each manufacturer attempted to “reinforce” silicone with different proprietary solutions.

Finally, Protego family leads (marketed in 2013) are almost identical to Linx, their new feature is the introduction of a DF-4 connection.

CASE REPORTS

The case managed in our center

A 71-year-old man, with ischemic dilated cardiomyopathy, was evaluated in our center for a suspect ICD malfunction. He had been implanted, 10 years before, with a Biotronik defibrillator and a Kentrox dual-coil lead as primary prevention. In 2013 the device was replaced (normal battery depletion) and an Ellipse St. Jude defibrillator was implanted and connected to the old Kentrox lead. Early in 2016 at device interrogation we found abnormally low pacing impedance values (< 200 Ohm) and repetitive nonphysiological high-rate sensed events on sensing channels (both near and far field), suggesting an insulation defect. These episodes were of brief duration, therefore they did not trigger inappropriate shocks (Figure 4). At fluoroscopy conductor externalization was evident just proximal to the ventricular coil (Figure 5). Due to a deemed high risk of extraction we decided to implant a new lead, abandoning the damaged one; reimplant was uneventful. Subsequent defibrillation testing on induced VF was performed successfully.

In our center we have followed a total of 35 patients with Biotronik ICD leads: 5 Kentrox, 27 Linx and 3 Protego models, implanted between 2005 and 2016. The above-mentioned case is the only failure we had to face so far.

Published case reports of Biotronik ICD leads (insulation) failure

Shoemaker *et al.*^[4] was the first to report the phenomenon of conductor externalization in a Linx lead.

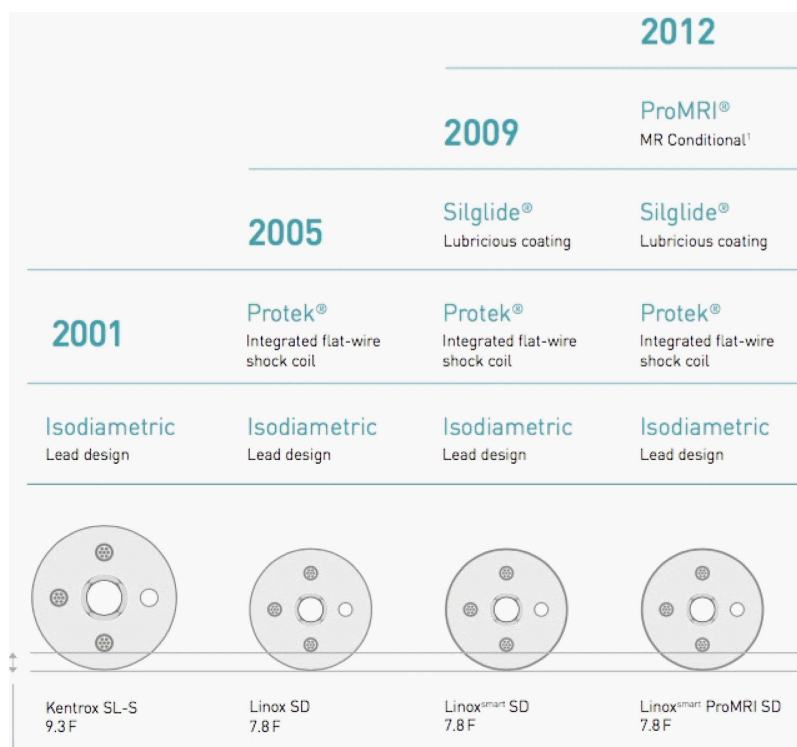


Figure 3 Overview of Kentrox and Linux Biotronik leads. Courtesy of Biotronik Italia.

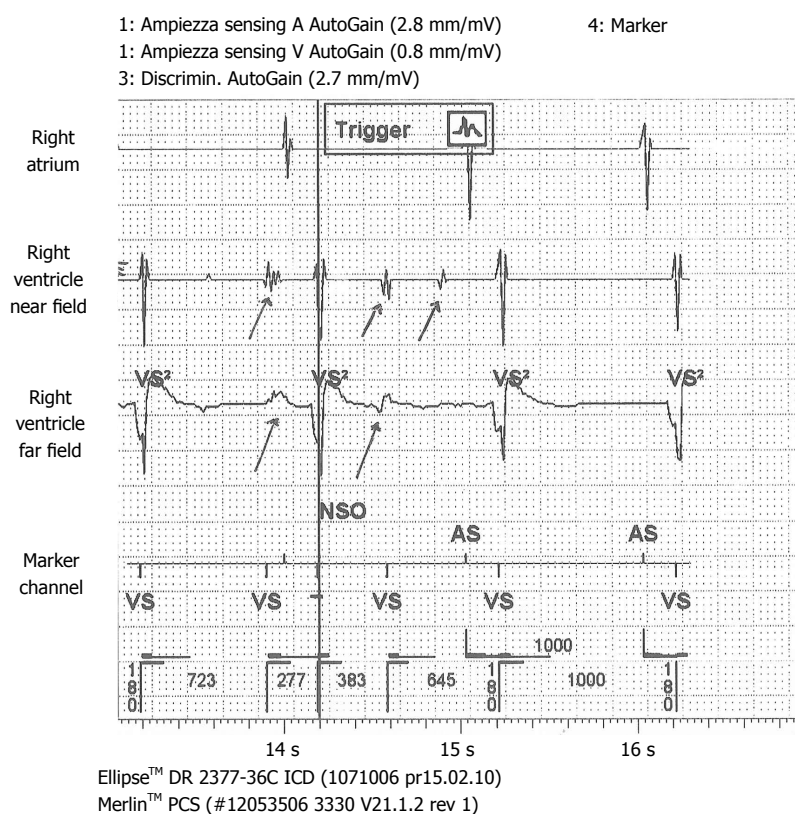


Figure 4 Intracardiac electrogram recording of non-physiological sensed events due to insulation failure in the patient managed in our center. NSO: Non sustained oversensing; AS: Atrial sensing; VS: Ventricular sensing.

The lead was dual-coil, implanted 4 years before, in a patient with a persistent left and absent right SVC. The externalized conductors, proximal to the caval coil, were incidentally discovered during a coronary angiogram. There was no change in baseline electrical performance of the lead which was, however, extracted. It is noteworthy that a lead with externalized conductors

may still function normally because high-voltage and pace-sense ring cables are covered with ETFE, which serves as a second insulation. However, if ETFE abrades, electrical short circuits can occur during shock delivery with inability to defibrillate and catastrophic consequences.

In a successive paper, Manfredi *et al.*^[5] described

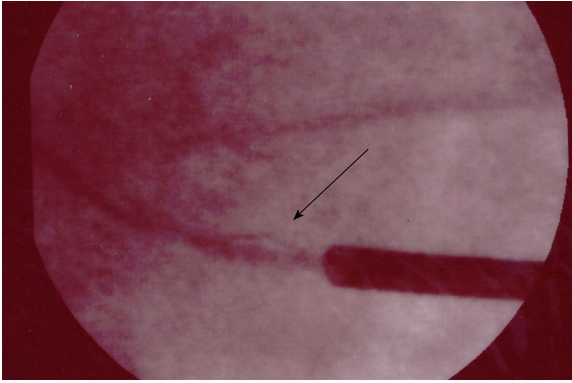


Figure 5 Fluoroscopy image of Kentrox conductor externalization just proximal to the ventricular coil in the patient managed in our center.

a dual-coil Linx lead, implanted 8 years before, in a 53-year-old man with ischemic dilated cardiomyopathy for primary prevention. During an electrophysiological study, the lead had conductor wires protruding outside the body lead, between caval and ventricular coil. Also in this case, device interrogation revealed normal baseline electrical values. The patient was not pacing dependent and had never received appropriate or inappropriate ICD therapy; therefore, it was decided to follow the lead closely without extracting or replacing it.

Abi-Saleh *et al*^[6] were the first to describe externalized conductor in a Kentrox lead. The dual-coil lead had been implanted, 7 years before, in a 38-year-old man with Brugada syndrome after cardiac arrest from VF. The patient presented with multiple inappropriate shocks due to noise which was evident on intracardiac electrogram (suggesting insulation failure); moreover, device check also revealed high pacing and shock impedance (suggesting concomitant conductors fracture). Fluoroscopy showed externalized conductors at the level of tricuspid valve. The patient underwent Kentrox extraction and reimplantation of a new ICD lead.

Another case of Kentrox failure was described by Bogossian *et al*^[7]. The paper reports the first evidence of conductor externalization in a single-coil Biotronik lead, which had been implanted, 11 years before, in a 14-year-old boy after cardiac arrest from idiopathic VF. The lead presented externalized conductors at the region of tricuspid valve. Electrical measurements of the lead showed a significant decrease of sensing values, as well as a high-voltage shock impedance > 300 Ohm (suggesting both insulation failure and conductor fracture). The malfunctioning lead was explanted and a subcutaneous ICD was implanted.

In the case report by Reichlin *et al*^[8], a Linx dual-coil lead presented with multiple inappropriate shocks due to noise on the sensing channel, suggesting insulation failure. Baseline electrical parameters (sensing values, pacing threshold and impedances) were normal. The lead had been implanted, 8 years before,

in a 54-year-old man with non-ischemic dilated cardiomyopathy. At fluoroscopy externalized conductor cables were seen just proximal to the ventricular coil. The lead was extracted and visual inspection confirmed the externalization of pace-sense cables, putative source of noise.

Finally, Wutzler *et al*^[9] described the case of a 31-year-old man with VF which was not interrupted by his ICD. The device was explanted: An area of burn marks on the surface with a small hole in the titanium can was found. Further analysis by the manufacturer showed a defect of the defibrillator output stage, indicating shock delivery via a low impedance shock path and premature battery discharge. These findings suggest an isolation defect of the ICD lead (Biotronik Linx^{Smart}).

SINGLE-CENTER STUDIES AND A NON-PROSPECTIVE REGISTRY

Given this background and the published case reports, some centers started to systematically review all Biotronik leads implanted in their institutions.

Howe *et al*^[10] reviewed all Biotronik ICD leads implanted in Royal Victoria Hospital, Belfast, United Kingdom, between 2006 and 2014. They included Vigila and Volta ICD leads marketed by Sorin (Sorin Group, Milan, Italy) but produced by Biotronik and identical to Linx. A total of 98 leads were included in their retrospective analysis (86 Linx and 12 Vigila/Volta). The authors identified a total of 4 lead failures, corresponding to 4% of all Biotronik leads. The failed leads presented with signs of insulation failure: 3 cases of nonphysiological high rate noise sensing leading to VF detection; 1 case with a significant decrease in pacing lead impedance. Only 1 case of externalized conductors was evident at fluoroscopy. All malfunctional leads were subsequently replaced.

Noti *et al*^[11] reported their experience with Biotronik ICD leads, implanted in their center (University Hospital of Bern, Switzerland) between 2006 and 2014. They retrospectively compared performance of all Linx/Vigila leads ($n = 93$) with that of all Boston Scientific Endotak Reliance integrated bipolar leads ($n = 190$) and Medtronic Sprint Quattro dedicated bipolar lead ($n = 202$), implanted during the same period. Moreover, all Linx/Vigila leads were screened with fluoroscopy for conductor externalization. Lead failure was defined as follows: Recurrent nonphysiological high-rate sensing unrelated to EMI or T-wave oversensing; a sudden rise in pacing or shock impedance unrelated to perforation or dislodgment; sudden increase in pacing threshold and/or sudden decrease in R-wave sensing; visual evidence of fracture or insulation failure or externalization. The authors identified 9 cases of lead failure in Biotronik leads (9.7%): 2 cases of externalization, 6 cases of nonphysiological high rate noise sensing (5 cases with

inappropriate shocks), 1 case of high-voltage conductor fracture. All failures concerned Linux leads (not Vigila). Lead failure was about 1% for Boston and Medtronic leads. Notably, lead survival at 5 years was 88% for Biotronik, 97.5% for Boston, 100% for Medtronic leads. Moreover, the median time from implant to failure was shorter with Biotronik leads (46 mo) compared with Boston and Medtronic (60 mo). A total of 10 patients died during the study period but circumstances of death were not systematically evaluated. The authors concluded that survival of Biotronik ICD leads was significantly worse than that of other leads; insulation failure was the most common presentation even if conductor externalization was seen only in a minority of failed leads. Younger age was found to be an independent predictor of failure.

In 2015, Padfield *et al.*^[12] published the results of a multicenter retrospective ICD registry, performed in British Columbia (BC) region of Canada. Following the introduction of Linux leads the authors began to observe cases of early failure, some of which associated with conductors externalization. Therefore, they systematically evaluated the long term performance of all Linux leads implanted in BC, using St. Jude Medical Durata ICD leads (implanted during the same period) as comparator. This retrospective analysis included a total of 477 Linux and 838 Durata leads, implanted between 2008 and 2014. Definition of lead failure was almost identical to the above-mentioned paper of Noti *et al.*^[11]. Over a median of 39 (27-50) mo Linux leads had a higher failure rate than the Durata: 16/477 cases of Linux failure vs 4/838 for Durata (3.4% vs 0.4%). Linux failure type in detail was as follows: 11 cases of recurrent nonphysiological high-rate sensing; 7 cases of sudden impedance rise consistent with lead fracture; insulation failure was confirmed in 6 cases (exposed conductors in the pocket, insulation abrasion, "outside-in" abrasion, etc). Notably, no clear case of "Riata like" externalized conductor was evident at fluoroscopy, but systematic radiographic analysis was not performed. Survival rate at 5 years was 91.6% for Linux vs 99.4% for Durata ($P < 0.0001$). Failure occurred earlier with Biotronik leads compared to Durata. Female sex was the only independent risk factor for Linux failure in this study ($P = 0.004$). Patient survival analysis was not an end-point of the study and not reported.

Taken together these 3 studies^[10-12] (with the limitations that we will discuss thereafter) analyzed 668 Biotronik ICD leads and showed a worrisome incidence of Linux leads failure, ranging from 3.4% to 9.7% (vs 1% of Endotak Reliance and Sprint Quattro leads and 0.4% of Durata). Survival rate at 5 years (88%-91%) was significantly lower in comparison with the competitors. Failure occurred earlier with Biotronik leads compared to the others. Insulation defect was the main mechanism of failure, while conductor fracture was less frequent but not negligible. Conductor externalization was present only in a minority of cases but fluoroscopic screening was not performed systematically in all studies.

BIOTRONIK PRODUCT PERFORMANCE REPORT

In contrast to the above-mentioned studies, Linux survival rate was 96%-97% at 5 years of follow-up in a product performance report published by Biotronik in July 2015 ([http://www.biotronik.com/files/38E6-CFB4E275DE2CC1257EC800531F89/\\$FILE/Product_Performance_Report_July_2015.pdf](http://www.biotronik.com/files/38E6-CFB4E275DE2CC1257EC800531F89/$FILE/Product_Performance_Report_July_2015.pdf)), well within industry standards. Anyway, it is well known that reported failure rates from manufacturers are frequently based on voluntary product return and not on systematic data collection, so they are prone to under-reporting bias.

ONGOING PROSPECTIVE REGISTRIES

Conflicting results of spontaneous studies vs Biotronik report prompted to evaluate post-market, long-term performance of Linux leads in 2 ongoing large, multicenter, *prospective*, non-randomized, independent registries GALAXY (NCT00836589) and CELESTIAL (NCT00810264)^[13].

GALAXY registry was designed to obtain long-term safety and reliability data on Linux family leads implanted in 98 United States sites. Enrollment started in 2009 and was completed in 2011, a total of 1997 patients being included. CELESTIAL post-approval registry was originally designed to evaluate long-term performance of Biotronik Corox family of bipolar left ventricular leads. However many Linux were implanted and included in the study of this ICD lead. The enrollment (2499 patients in 97 United States sites) started in 2008 and was completed in 2013.

A total of 3,933 Linux leads were implanted for both registries and included in the analysis. All patients were implanted with a Biotronik ICD or biventricular defibrillator. The GALAXY and CELESTIAL registry protocols collected adverse events (AEs) related to the implanted system or procedure. A "system-related" AE was defined as follows: (1) an event related to the implanted system occurred; and (2) an action was taken to address the event, or lead use was continued despite a known performance issue, which would have otherwise implicated an action to be taken (e.g., patient too ill for extraction).

The median follow-up was 3.6 years for Linux models and 2.3 years for Linux^{Smart}. The analysis of Linux leads showed an excellent performance over time: The estimated cumulative survival rate probability was 96.3% at 5 years after implant for Linux models and 96.6% at 4 years for Linux^{Smart} leads. A relatively low rate of chronic AEs was observed (2.31%). The most common AEs were: Oversensing (23, 0.58%); conductor fracture (14, 0.36%); failure to capture (13, 0.33%); insulation breach (10, 0.25%); high pacing impedance (8, 0.20%).

The authors concluded that Linux leads are safe, reliable and rarely associated with lead-related adverse events, with a clinically acceptable estimated survival

probability that is well within industry standards. Data collection is still ongoing and will be updated in the near future.

DISCUSSION AND CONCLUSION

Transvenous ICD leads are prone to failure over time, representing the weakest link of a defibrillation system. Lead models from various manufacturers have different performance records. Endotak Reliance (Boston), Sprint Quattro (Medtronic) and Durata (St. Jude Medical) have a very low incidence of failure (between 0.4% and 1%); this is especially true for the leads marketed from a longer time and with longer follow-up duration (Endotak and Sprint Quattro). On the opposite side, other leads have been withdrawn from the market because of a very high rate of failure, and this is the case of Medtronic Sprint Fidelis (over 268000 leads implanted worldwide) and St. Jude Riata (over 227000 implants worldwide).

Recent case reports^[4-9] and some studies^[10-12] have raised doubts about the performance of Biotronik ICD leads too. Over 140.000 Biotronik ICD leads have been marketed worldwide (including Kentrox, Linx and Vigila/Volta) so it is of utmost importance to have a high level of awareness and attention when following patients with these leads. For this reason expert consensus exists that systematic post-market surveillance of (all) ICD leads is essential to evaluate their long-term performance.

Linx and Riata leads share some structural similarities: Silicone insulation without outer coating, a coaxial lead design, a rather small diameter. The unique insulation defect described for Riata leads ("inside-out" abrasion) has been consistently reported also for Kentrox and Linx leads. The exact failure mechanism of Biotronik lead is not fully clear, but it is plausible that it is very similar to Riata. While case reports focused the attention on conductors externalization, other studies have shown that this phenomenon was present only in a minority of cases, even if fluoroscopic screening was not always performed systematically. More importantly, insulation defect was the main mechanism of failure for Biotronik leads (independently from conductor externalization). Conductor fracture was less frequent but (differently from Riata) not negligible.

A very important point is to explain the discrepancies existing between single-center studies plus the Canadian retrospective registry^[10-12] on one side, and the results of the United States prospective registries (CELESTIAL and GALAXY)^[13] on the other side. The former showed a worrisome incidence of Linx leads failure (from 3.4% to 9.7% vs 0.4%-1% of competitors) with a significantly lower lead survival rate at 5 years (88%-91%). The latter (CELESTIAL and GALAXY registries) substantially confirm the results of product performance report published by Biotronik, with a 96% survival rate at 5 years and a relatively low rate of chronic adverse events (2.3%). First of all, single-center and retrospective

studies have a relatively small sample size (a total of 668 leads) compared to the 2 United States prospective registries (3.933 leads), so it is harder to draw conclusions with smaller numbers. Secondly, the 2 United States registries^[13] have a prospective design and a more complete protocol which are best suited to address the question of lead performance. Finally, in the BC Canadian registry Linx leads were predominately connected to a Medtronic device, while most Durata leads were connected to a St. Jude Medical ICD. This is important because each manufacturer has its own proprietary sensing filters and algorithms. Medtronic devices have a proprietary Lead Integrity Alert (LIATM) which is sensitive to nonphysiological short V-V sensing intervals: this algorithm can be useful to assess lead performance, including Linx^[14], but when used with non-Medtronic leads it can potentially overestimate the incidence of failure.

In conclusion CELESTIAL and GALAXY registries are quite reassuring, even if Linx performance seems to be slightly inferior to Endotak Reliance, Durata and Sprint Quattro. Data collection from the registries is still ongoing and will be updated in the near future to confirm longer-term performance of this family of ICD leads. Meantime, Biotronik leads can be managed according to usual clinical practice. Literature data do not support the need for a routine fluoroscopic screening, but (in our opinion) it is reasonable to have the lead connected to a Biotronik device whenever possible. Finally, remote monitoring should be activated for early detection of potential nonphysiological high-rate sensing before the occurrence of inappropriate shocks.

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This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the Journal. We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals will require the submission of a new author agreement form approved and signed by all the original and added submitting authors. Patient's consent was obtained. The authors report no relationships that could be construed as a conflict of interest.

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Fatality in Kikuchi-Fujimoto disease: A rare phenomenon

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Abstract

Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is an uncommon

condition, typically characterized by lymphadenopathy and fevers. It usually has a benign course; however, it may progress to fatality in extremely rare occasions. The diagnosis is made *via* lymph node biopsy and histopathology. Our patient was a young female who presented with shortness of breath, fever, and malaise. Physical examination revealed significant cervical and axillary lymphadenopathy. Chest X-ray displayed multilobar pneumonia. She required intubation and mechanical ventilation for progressive respiratory distress. Histopathology of lymph nodes demonstrated variable involvement of patchy areas of necrosis within the paracortex composed of karyorrhectic debris with abundant histiocytes consistent with KFD. After initial stabilization, the patient's condition quickly deteriorated with acute anemia, thrombocytopenia and elevated prothrombin time, partial prothrombin time, and D-dimer levels. Disseminated intravascular coagulopathy (DIC) ensued resulting in the patient's fatality. DIC in KFD is not well understood, but it is an important cause of mortality in patients with aggressive disease.

Key words: Kikuchi-Fujimoto disease; Disseminated intravascular coagulopathy; Histiocytic necrotizing lymphadenitis; Lymphadenopathy; Fatality

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Core tip: Kikuchi-Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is an uncommon condition, typically characterized by lymphadenopathy and fevers. KFD is an extremely rare disease. With this case we wish to highlight that KFD carries a risk of mortality in the setting of acute, aggressive disease, which is in contrast to the benign, self-limiting condition that has been classically documented in literature. The patient emphasizes the importance of recognizing this as we present the fourth case of disseminated intravascular coagulopathy as a cause of fatality in these patients.

Barbat B, Jhaj R, Khurram D. Fatality in Kikuchi-Fujimoto

disease: A rare phenomenon. *World J Clin Cases* 2017; 5(2): 35-39 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v5/i2/35.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v5.i2.35>

INTRODUCTION

Kikuchi-Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is a rare, self-limiting condition characterized by regional lymphadenopathy, fevers, night sweats, and upper respiratory symptoms. Although a viral or autoimmune pathogenesis has been suggested, the etiology continues to remain unknown. Diagnosis is based on histologic features noted on excisional biopsy. A majority of cases have a benign course; rarely does KFD result in death. After performing a wide literature search, we only found three other documented cases that resulted in death from disseminated intravascular coagulopathy (DIC). This disease was initially thought to have a predilection for Asian women between the ages of 20 and 35 years. However, new cases of KFD have also been described in non-Asian ethnicity and young age groups in the United States^[1]. Recognition of KFD is essential because it can easily be mistaken for lymphoma, tuberculosis, or carcinoma^[2]. Here we report a case of a patient with KFD who died secondary to DIC.

CASE REPORT

The patient was a previously healthy, 21-year-old female who presented with a two-day history of dyspnea, fever, and malaise. Initial set of vitals revealed a blood pressure of 109/57 mmHg, temperature of 38.2 °C, heart rate of 118 bpm, respiratory rate of 24 breaths/min, and oxygen saturation of 78% on room air. On 4 liters of nasal cannula, her oxygen saturation improved to 97%. A chest X-ray demonstrated multifocal pneumonia. Treatment for community-acquired pneumonia was initiated with ceftriaxone and azithromycin. On physical examination, she was noted to have significant axillary, cervical and inguinal lymphadenopathy. Her respiratory status continued to decline despite supplemental oxygen therapy and antibiotics, requiring emergent endotracheal intubation with mechanical ventilation. A computerized tomography (CT) chest, abdomen, and pelvis was performed, which revealed significant cervical and axillary lymphadenopathy, bilateral lung consolidation, and a moderate pericardial effusion (Figure 1).

As the patient's presentation was very severe, a comprehensive differential was considered. Among the entire laboratory data that was performed HIV, streptococcus pneumonia, legionella, histoplasma, brucella, aspergillus, tuberculosis, influenza, respiratory syncytial virus were negative. There was a mild elevation in mycoplasma IgM and chlamydia antibody titer. The patient's antibiotic therapy was tailored to include a broader spectrum of organisms. Bronchoscopy with

bronchoalveolar lavage was performed given the above CT findings. There was no evidence of mucus plugs, active bleeding, endobronchial lesions or anatomical abnormalities. Pathology of the fluid revealed presence of acute inflammatory cells. A transthoracic echocardiogram revealed normal systolic function with a moderate pericardial effusion without tamponade physiology.

Due to the significant lymphadenopathy, pericardial effusion, and an elevated LDH of 2319 unit/L, a concern for lymphoma was raised. Therefore, a cervical lymph node biopsy was performed. Histopathology demonstrated variable involvement of patchy small to large areas of necrosis within the paracortex. The necrotic areas were composed of karyorrhectic debris with abundant histiocytes consistent with KFD (Figure 2).

Septic work up consisting of blood, sputum and urine cultures remained negative throughout her admission. Despite aggressive antibiotic therapy, high dose steroids, and supportive care, the patient's condition continued to decline. She required increasing pressure support to maintain oxygenation. Intravenous immune globulin (IVIG) was given without any improvement in the patient's symptoms. The hemoglobin level began to precipitately decrease without any active sites of bleeding. A hemolytic work up was initiated, which revealed a haptoglobin < 10 mg/dL and schistocytes on peripheral smear. She then developed significant thrombocytopenia with platelet level recorded as low as 26 K/mcL. Partial thromboplastin time, prothrombin time levels and D-dimer levels started to rise. Fresh frozen plasma was transfused for impending DIC. The patient's clinical condition and laboratory parameters continued to deteriorate despite resuscitative efforts in the intensive care unit. Unfortunately, she expired secondary to development of DIC.

DISCUSSION

KFD, or histiocytic necrotizing lymphadenitis, is rare and usually has a benign self-limiting course. The etiology of this disease has not been established yet, but there are viral origins including HHV-6, HHV-8, and EBV that have been theorized^[3]. One study found that apoptotic cell death plays a role in the pathogenesis of KFD^[4]. The most common symptoms include, but are not limited to lymphadenopathy, fatigue, fevers, night sweats and weight loss.

There are no specific laboratory values that are pathognomonic for this disease. A case review of 244 patients with KFD revealed laboratory values that were unremarkable except for an elevated ESR, mild neutropenia, and lymphocytosis in some cases^[5]. Imaging can aid in limiting the differential diagnosis. CT and magnetic resonance imaging can be useful for evaluating patients with cervical lymphadenopathy. CT features may mimic those of lymphoma; however, lymph nodes in KFD are not as large as those in

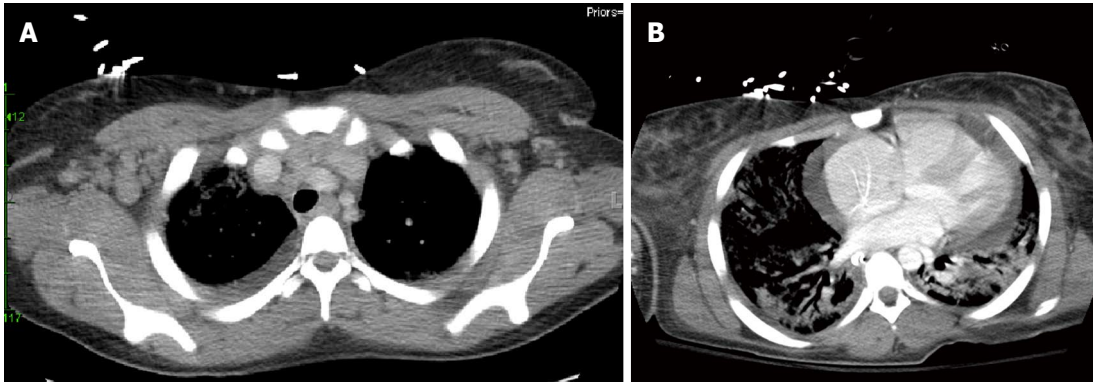


Figure 1 Computerized tomography chest. A: Computerized tomography (CT) chest demonstrating significant axillary lymphadenopathy; B: CT chest revealing bilateral lung consolidation, and a moderate pericardial effusion.

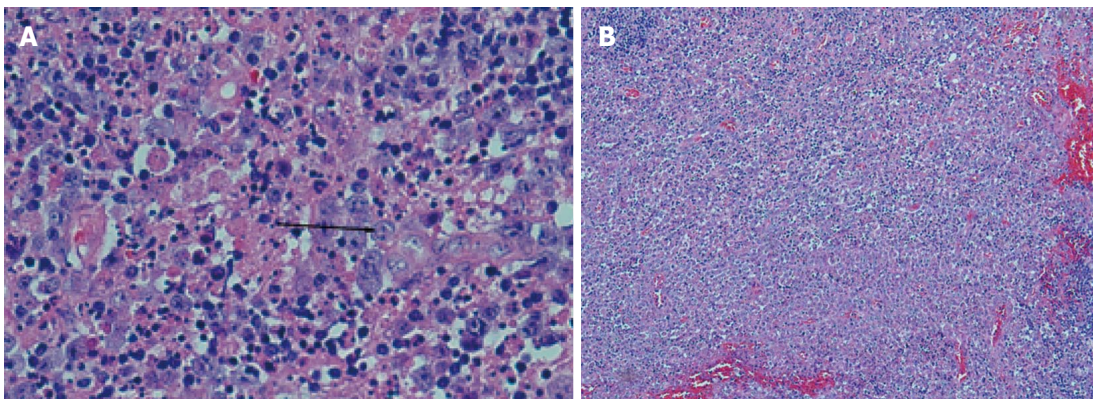


Figure 2 Histopathology. A: High magnification view with arrow revealing histiocyte. Histiocytes are derived from blood monocytes and digest debris; B: Sample of a cervical node biopsy revealing multiple areas showing necrotic foci.

lymphoma^[6].

A definite diagnosis of KFD is made by biopsy, typically excisional, but fine needle aspiration has also been used. There are some characteristic histologic features of KFD including patchy necrotizing areas primarily in the paracortical regions that contain fibrinous material with karyorrhexis. A distinctive mottled appearance may be noted, as immunoblasts tend to border necrotic zones^[7]. Early diagnosis is important as the clinical and laboratory presentations can imitate situations needing time-consuming and expensive interventions^[5]. KFD can be easily misdiagnosed; literature estimates as high as 40% of the time with lymphoma being the most commonly mistaken diagnosis^[8].

Once the diagnosis is made, symptomatic and supportive treatment is usually adequate. When symptomatology requires treatment, a short course of corticosteroids is preferred. Currently, there are no recommendations on exact dosage or route of administration^[9]. In severe cases, high dose intravenous steroids have been shown to be effective and aid in symptom reduction^[10]. IVIG has been shown to be successful in several, critical cases. Once again, no formal recommendations on dosing and duration exist.

IVIG has been routinely implemented as empiric therapy in autoimmune and inflammatory processes secondary to its immunomodulatory properties^[11]. In individuals with a benign hospital course, it is important to have adequate follow up as patients have an increased risk of relapse. One study showed that hydroxychloroquine could be used in the treatment of relapsed KFD^[12]. On rare instances, despite these treatment modalities, KFD may progress to mortality such as the patient we presented.

Our patient is unique as she had an extremely progressive course of Kikuchi lymphadenitis with subsequent multiorgan failure and death from DIC. In our review of literature, we found three other documented cases of death in KFD as a result of DIC (Table 1)^[13,14]. Other causes of death included hemophagocytic syndrome and severe infection^[15], pulmonary hemorrhage^[16] and acute heart failure^[17].

The precise mechanism of DIC in KFD is unknown. A proposed mechanism involves a massive cytokine release during the acute phase of the disease, mainly consisting of tumor necrosis factor- α , interleukin-1, and interleukin-6. These cytokines result in significant endothelial damage and activation of the thrombosis and anticoagulation cascade pathognomonic for DIC^[13].

Table 1 Fatalities in Kikuchi-Fujimoto disease

| Ref. | Presentation | Presence of autoantibodies | Cause of death |
|--|--|-----------------------------|----------------------|
| Uslu <i>et al</i> ^[13] , 2014 | A 32-year-old female with fever, fatigue, chest and abdominal pain for 15 d | Not mentioned | DIC |
| Sharma <i>et al</i> ^[14] , 2015 | A 57-year-old fever with fever and UTI | Yes: ANA, anti-La, anti-RNP | Septic shock and DIC |
| Sharma <i>et al</i> ^[14] , 2015 | A 55-year-old female with fever, dizziness, loss of balance, decreased hearing, diarrhea, vomiting and a non-blanching rash over the upper arms and thighs | Yes: Anti-Ro and anti-La | DIC |

DIC: Disseminated intravascular coagulopathy; UTI: Urinary tract infection; ANA: Antinuclear antibody; anti-RNP: Anti-ribonucleoprotein.

In our patient, all other potential causes of DIC including sepsis and acute myeloid leukemia were negative, supporting the association of DIC and KFD.

KFD is an extremely rare disease. With this case we wish to highlight that KFD carries a risk of mortality in the setting of acute, aggressive disease, which is in contrast to the benign, self-limiting condition that has classically been documented in literature. Our patient emphasizes the importance of recognizing this fact as we present the fourth case of DIC as a cause of fatality in these patients.

COMMENTS

Case characteristics

The patient is a 21-year-old female who presented with symptoms of malaise and fevers.

Clinical diagnosis

The main clinical findings included cervical and axillary lymphadenopathy.

Differential diagnosis

Differential diagnosis included lymphoma, viral syndrome and bacterial infections. Computerized tomography scan findings confirmed the lymphadenopathy as well as bilateral lung consolidation, and a moderate pericardial effusion. Histopathology of the lymph node biopsy revealed findings consistent with Kikuchi-Fujimoto disease (KFD).

Treatment

In most cases, supportive treatment is adequate. In severe cases and relapsing cases, intravenous immune globulin and hydroxychloroquine have been used, respectively.

Related reports

Unfortunately, our patient expired secondary to disseminated intravascular coagulopathy (DIC). The exact mechanism of how DIC occurs in KFD is unknown; however, it has been proposed that cytokine release plays a role. With this case we wish to highlight that KFD carries a risk of mortality in the setting of acute, aggressive disease, which is in contrast to the benign, self-limiting condition that has classically been documented in literature.

Term explanation

KFD: Kikuchi-Fujimoto disease.

Peer-review

KFD is an extremely rare disease. The authors highlighted that KFD carries a risk of mortality in the setting of acute, aggressive disease, which is in contrast to the benign, self-limiting condition that has been classically documented in literature. This set of cases emphasizes the importance of recognizing the fact of DIC as a cause of fatality in these patients.

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Aggressive restenosis after percutaneous intervention in two coronary loci in a patient with human immunodeficiency virus infection

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Abstract

A 54-year-old black African woman, 22 years human immunodeficiency virus (HIV)-positive, presented with an acute coronary syndrome. She was taking two nucleoside reverse transcriptase inhibitors and two protease inhibitors. Viral load and CD4 count were stable. Angiography revealed a right coronary artery lesion, which was treated with everolimus eluting stent. She also underwent balloon angioplasty to the first diagonal. She re-presented on three different occasions and technically successful coronary intervention was performed. The patient has reported satisfactory compliance with dual anti platelet therapy throughout. She was successfully treated with surgical revascularisation. The patient did not experience any clinical recurrence on follow up. This case demonstrates exceptionally aggressive multifocal and recurrent in-stent restenosis in a patient treated for HIV infection, raising the possibility of an association with HIV infection or potentially components of retro viral therapy.

Key words: Coronary artery disease; Restenosis; Human immunodeficiency virus

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Core tip: With an increasing burden of cardiovascular disease in patients with human immunodeficiency virus (HIV), a subgroup of patients may emerge in whom this represents a significant clinical challenge. Better understanding of the responsible mechanisms may allow more tailored pharmacotherapy for susceptible individuals. We report an exceptionally aggressive and recurrent case of coronary stent restenosis in HIV positive patient. Numerous percutaneous interventions were performed but eventually patient was treated successfully with surgical revascularisation.

Alkhalil M, Conlon CP, Ashrafian H, Choudhury RP. Aggressive restenosis after percutaneous intervention in two coronary loci in a patient with human immunodeficiency virus infection. *World J Clin Cases* 2017; 5(2): 40-45 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v5/i2/40.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v5.i2.40>

INTRODUCTION

Restenosis is encountered after coronary revascularisation and it is attributed as part of the arterial healing process in response to stents^[1]. It had been a major drawback when using balloon angioplasty and bare metal stents but was reduced using drug eluting stents^[2]. Procedural-related factors, such as stent malposition, coronary anatomy (e.g., ostial disease) and patient-specific considerations (e.g., diabetes) increase risk of instant restenosis (ISR)^[1].

Human immunodeficiency virus (HIV) has been linked to increase risk of future cardiovascular events^[3,4]. Contrary to earlier reports^[5], restenosis was found to be comparable between patients with and without HIV infection^[3,4]. The increase use of drug eluting stents may have contributed to the reduction in ISR in HIV population^[6].

We have encountered a case of aggressive and recurrent restenosis in HIV patient despite using second-generation drug eluting stent. Below we described the details of this case with brief review of the literature.

CASE REPORT

A 54-year-old black African female was diagnosed HIV-positive 22 years prior to presentation with an acute coronary syndrome (ACS). She had been managed with combination of two nucleoside reverse transcriptase inhibitors (Lamivudine and Abacavir) in addition to two protease inhibitors (Lopinavir and Ritonavir). The CD4 count had been stable of 250 cells/mm³ with a viral load of 150-250 copies/mL. There was a history of treated hypertension and treated hypercholesterolemia.

Her cardiac history (below) spans 20 mo. Initial presentation was with an episode of chest pain at rest associated with inferolateral ST segment depression on

the ECG. Angiography revealed a 70% right coronary artery (RCA) lesion, which was treated with a 3.0 mm × 23 mm Xience (Abbott Vascular) Everolimus drug eluting stent (DES), post dilated with a 3.0 Quantum non-compliant balloon (Boston Scientific) (Figure 1A and B). In addition, she underwent balloon angioplasty to the first diagonal branch with 3.0 × 12 Maverick balloon (Boston Scientific) (Figure 1C and D).

She represented 7 mo later with stable angina and was found to have a *de novo* lesion in the mid left anterior descending artery (LAD) with satisfactory result to the diagonal branch but severe in stent restenosis (ISR) in the previously stented RCA. The ISR segment was predilated with Maverick balloon (Boston Scientific) and a paclitaxel-eluting balloon was inflated to 18 atmosphere for 45 s (Figure 2A and B). The LAD lesion was stented with 3.5 mm × 23 mm Xience stent and post dilated with 3.5 × 12 Quantum non-complaint balloon (Figure 2C and D).

Eight months later, she presented again with an acute coronary syndrome. Repeat angiography demonstrated severe ISR in both the RCA and LAD stents. Following lesion preparation with a 3.0 cutting balloon, both RCA and LAD were stented - with 3.0 mm × 28 mm and 3.5 mm × 28 mm Xience stents respectively (Figure 3). Stents were post dilated to high pressure with 3.5 Quantum balloon. The end angiographic result was excellent in both arteries.

Yet, within 4 mo she was experiencing recurrent exertional chest discomfort. A further coronary angiogram showed subtotal occlusion of the LAD with TIMI2 flow and both antegrade and retrograde filling, from RCA. The occluded segment was within the distal portion of the stent. The RCA was sub totally occluded by severe ISR in the stented segment (Figure 4). It is worth noting that patient has reported satisfactory compliance with her dual anti platelets therapy throughout her multiple interventional procedures. She was referred for surgical revascularisation.

DISCUSSION

This case demonstrates exceptionally aggressive multifocal and recurrent instant restenosis in a patient treated for HIV infection. Restenosis can occur as part of an arterial healing response after injury following coronary stenting^[1]. Neointimal hyperplasia occurs due to proliferation of smooth muscle cells and has been successfully ameliorated by the use of drug-eluting stents^[2]. In contemporary series, the restenosis rate in first generation DES ranged between 0% and 16% depending on complexity of targeted lesions^[7], while the rate of recurrent restenosis was 11%^[8]. Factors associated with increased risk of ISR include: Diabetes mellitus, small calibre vessel disease, ostial disease and vein graft stenosis^[1].

Treatment options are balloon catheter angioplasty, implantation of a second, coated or uncoated stent,

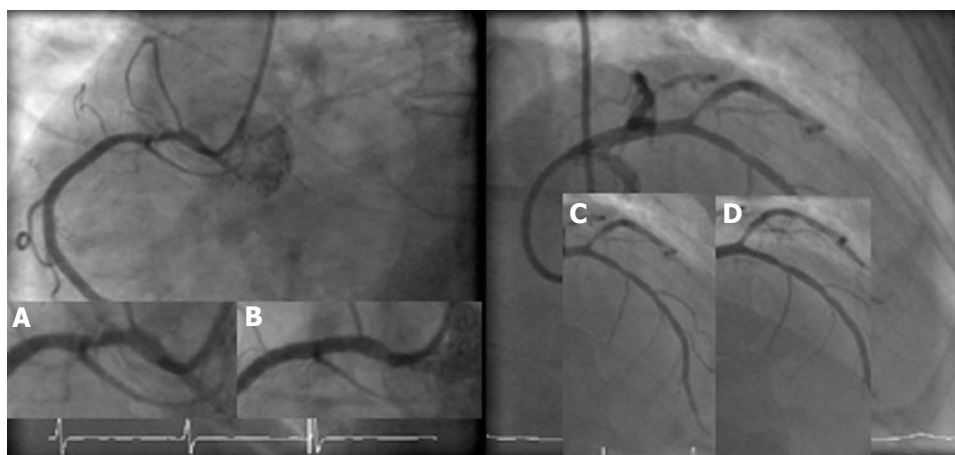


Figure 1 Initial coronary angiogram showing proximal right coronary and first diagonal stenoses. A, B: Right coronary artery pre- and post-stenting with 3.0 Xience Everolimus drug eluting stent, respectively; C, D: Pre- and post-balloon angioplasty to first diagonal, respectively.

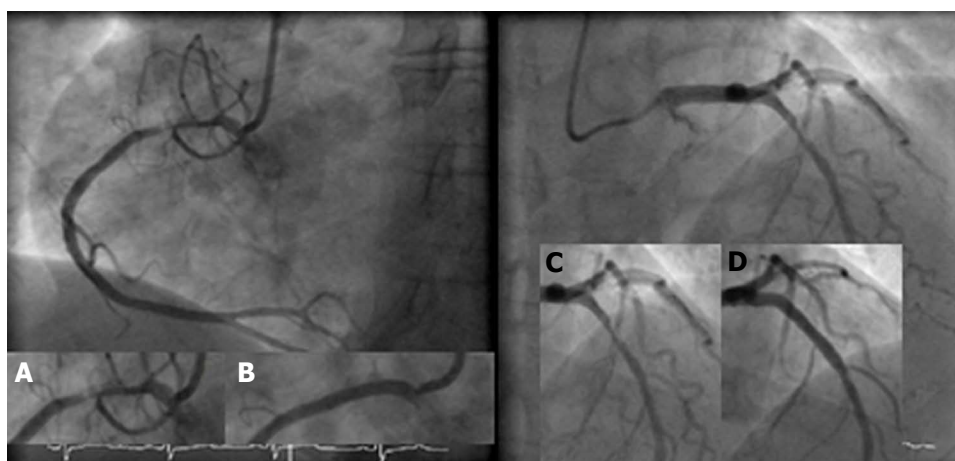


Figure 2 Second coronary angiogram following presentation with stable angina. A, B: Severe instent restenosis in the proximal segment of RCA and result post-Paclitaxel drug eluting balloon; C, D: Severe stenosis in mid LAD segment stented and subsequently stented with 3.5 Xience Everolimus drug eluting stent. LAD: Left anterior descending artery; RCA: Right coronary artery.

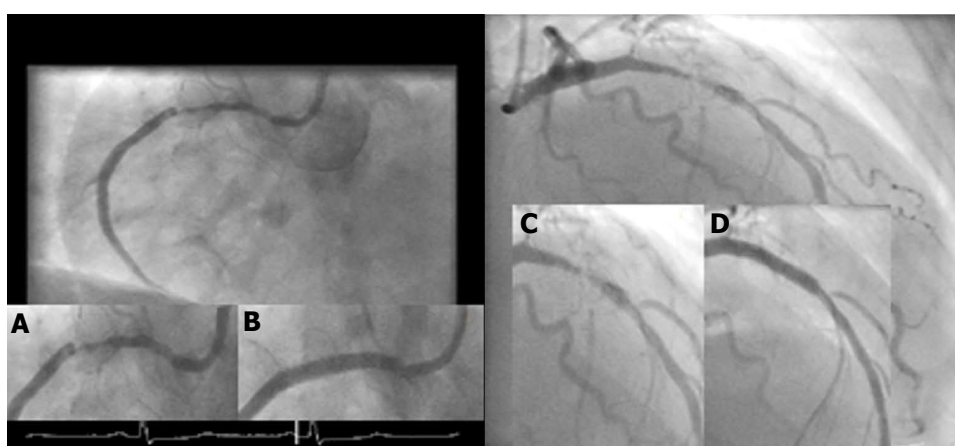


Figure 3 Coronary angiogram performed following second acute coronary syndrome event. A, B: Severe recurrent instent restenosis within the proximal segment of RCA and subsequent Xience stent; C, D: Severe ISR within mid LAD stented segment and subsequent Xience stent. LAD: Left anterior descending artery; RCA: Right coronary artery; ISR: In stent restenosis.

mechanical debulking (e.g., rotablation), intracoronary irradiation (brachytherapy) and drug eluting balloon.

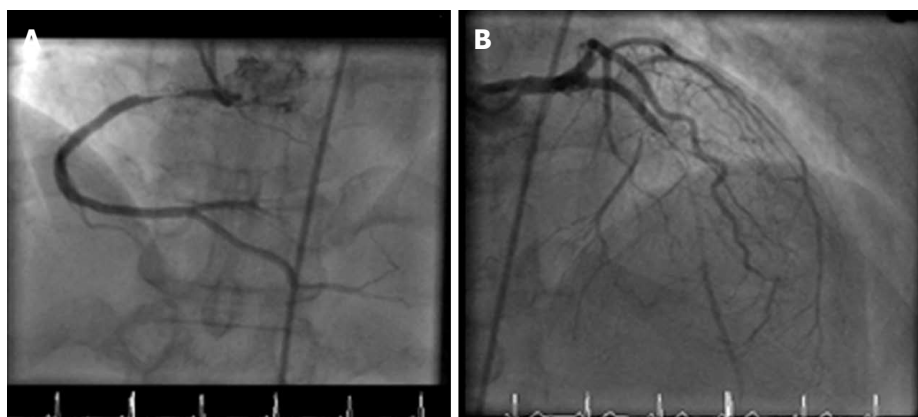


Figure 4 Further coronary angiogram following intractable angina symptoms. A: Sub totally occluded proximal RCA within stented segment; B: Sub totally occluded LAD with antegrade filling. LAD: Left anterior descending artery; RCA: Right coronary artery.

These approaches have various rates of success^[9].

In an HIV-positive population, a higher rate of ischemic heart disease compared to general population has been reported^[10]. Although there was no difference in morbidity or mortality during hospital admission between HIV and general population, it was noted that on long term follow up there was an increased risk of recurrent ischemic events in HIV compared to non HIV presenting with ACS^[3,4]. There was no difference in the rate of clinical restenosis between two groups^[4]. Although it has previously been reported that target vessel revascularization and ISR were higher in HIV population^[5], this trend was diminished in more contemporary studies^[3,4]. This may be explained by the high rate of stenting in the latter studies with drug eluting stents leading to 60% fewer major adverse cardiovascular events in HIV population^[6].

Antiretroviral therapy (ART) is a potential atherosclerotic risk in HIV patients^[11]. Although this therapy has improved the care of HIV infection, metabolic side effects have been observed, including dyslipidaemia and insulin resistance^[11]. The combination therapy was independently associated with increased rate of myocardial infarction^[11]. Moreover, the incidence of myocardial infarction rose after the introduction of protease inhibitors^[12]. This risk was still significant for protease inhibitor after adjustment for lipid concentration^[10].

Nucleoside reverse transcriptase inhibitors did not show similar cardiovascular risk profile as protease inhibitors^[13]. No associations between the rate of myocardial infarction and cumulative or recent use of zidovudine, stavudine, or lamivudine. On the other hand, recent, but not cumulative, use of Abacavir or Didanosine was associated with increase rate of myocardial infarction^[14]. Interestingly, neither drug is thought to have substantial effect on metabolic profile^[14].

In this case, patient was non-diabetic and both LAD and RCA stents were deployed at high pressure with satisfactory angiographic results. Everolimus eluting

stents were persistently used to treat the restenosis in this case. It is unlikely that using another stent with different drug such as zotarolimus or biolimus may have changed the outcome. Recent meta-analysis demonstrated that although second generation stents carry lower risk of target vessel revascularisation compared to first generation stents (which eluted sirolimus or paclitaxel), there was no difference among everolimus, zotarolimus or biolimus drug eluting stents^[15]. Whether HIV status may have influence on drug eluting stent outcome is not well documented and further research is warranted.

In this case, the HIV therapy had been stable and has not changed over the period of coronary intervention, and nor had the viral load or CD4 count. Yet, we observed aggressive restenosis raising the possibility of an association with her HIV infection or potentially components of her ART therapy. Although HIV infection causes attenuated inflammatory response to infections, it causes profound functional alterations of the endothelium, resembling the subclinical inflammation in atherosclerosis^[16]. Leukocyte adherence to endothelium is enhanced as the expression of cell adhesion molecules increases^[16]. Higher levels of soluble adhesion molecules have been found before the introduction of ART^[17]. Moreover, ART has a stimulator effect on some of these molecules, enhancing HIV effect on endothelial function^[17]. Furthermore, HIV infection can stimulate proliferation of human vascular smooth muscle cells and therefore promote atherosclerosis^[10]. Although it has been reported that risk of restenosis in HIV corresponds to level of viral load^[18], it is not clear whether smooth muscle cell proliferation and the accumulation of extracellular matrix, which are the main processes involved in in-stent restenosis, may be induced by protease inhibitors or by the HIV itself^[19]. The chronic low-level inflammation in HIV patients may also contribute to their high rate of restenosis^[5]. HIV patients have higher levels of C-reactive protein than their age and sex-matched controls^[5].

This case shows exceptionally aggressive restenosis after PCI. As cardiovascular disease becomes more prevalent in patients with HIV, a subgroup of patients may emerge in whom this represents a significant clinical challenge. Better understanding of the responsible mechanisms may allow more tailored pharmacotherapy for susceptible individuals.

COMMENTS

Case characteristics

A 54-year-old lady with 22 years history of human immunodeficiency virus (HIV) on antiretroviral therapy.

Clinical diagnosis

Coronary artery disease with recurrent in-stent restenosis.

Differential diagnosis

Stent thrombosis.

Laboratory diagnosis

Rise in cardiac enzymes, including troponin.

Imaging diagnosis

Diagnostic angiogram confirming restenosis of coronary stents.

Treatment

Despite attempts with percutaneous revascularisation, patient was eventually and successfully treated with surgical revascularisation.

Term explanation

ISR: In-stent restenosis.

Peer-review

The authors report a clinical case of a patient with HIV infection on antiretroviral therapy with recurrent in-stent restenosis requiring several percutaneous intervention and finally coronary artery bypass graft. The case is interesting and well written.

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Unexpected challenging case of coronary sinus lead extraction

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Abstract

An 84-year-old woman implanted with cardiac resynchronization therapy defibrillator underwent transvenous lead extraction 4 mo after the implant due to pocket infection. Atrial and right ventricular leads were easily extracted, while the attempt to remove the coronary sinus (CS) lead was unsuccessful. A few weeks later a new extraction procedure was performed in our center. A stepwise approach was used. Firstly, manual traction was unsuccessfully attempted, even with proper-sized locking stylet. Secondly, mechanical dilatation was used with a single inner sheath placed close to the CS ostium. Finally, a modified sub-selector sheath was successfully advanced over the electrode until it was free of the binding tissue. The post-extraction lead examination showed an unexpected fibrosis around the tip. No complications occurred during the postoperative course. Fibrous adhesions could be found in CS leads recently implanted requiring non-standard techniques for its transvenous extraction.

Key words: Cardiac resynchronization therapy; Coronary sinus lead; Transvenous lead extraction; Cardiac pacing; Fibrosis

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Core tip: Coronary sinus lead extraction is a safe procedure with complication rates comparable to those of the extraction of other leads in experienced centers. The main difficulties may be related to the thickness of the coronary sinus structure and the fibrotic adhesions along it. In this case report we describe an unusual case of persistent fibrosis at the tip of a coronary sinus lead only 4 mo after implantation and the non-standard techniques adopted to achieve successful extraction.

Bontempi L, Tempio D, De Vito R, Cerini M, Salghetti F, Dasseni N, Villa C, Raweh A, Inama L, Vassanelli F, Luzi M, Curnis A. Unexpected challenging case of coronary sinus lead extraction. *World J Clin Cases* 2017; 5(2): 46-49 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v5/i2/46.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v5.i2.46>

INTRODUCTION

As the number of cardiac resynchronization therapy (CRT) devices increases, so does the need for coronary sinus (CS) lead extraction, especially because patients with CRT are among those with the highest risk of device related complications^[1]. Although there are potential risks of complications associated with the thin wall of the CS and of the afferent branches, CS lead extraction is a safe procedure when performed by experienced professionals due to the generally low rate of adhesions along the coronary vein^[2]. We shall describe an uncommon case of fibrotic adhesions at the tip of the CS lead a few months after the implant and the transvenous techniques adopted to successfully extract the lead.

CASE REPORT

An 84-year-old woman implanted with CRT defibrillator for idiopathic cardiomyopathy underwent a transvenous lead extraction (TLE) 4 mo after the implant due to a local pocket infection with chronic positive blood culture of *Staphylococcus Pseudintermedius*. Atrial and right ventricular leads were easily extracted, while the attempt to remove the CS lead (Attain® Performa™ Model 4298, Medtronic, Minneapolis, MN, United States) was unsuccessful in the referral center. The patient was then brought to our attention to complete the extraction of the CS lead, in accordance with the current guidelines which set a class I indication to complete system removal in case of device-related infection^[3]. The procedure was carried out, under local anesthesia, in our laboratory by two expert interventional electrophysiologists and

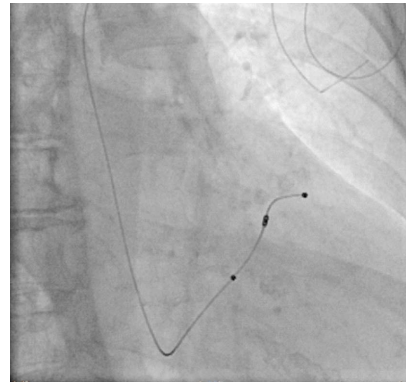


Figure 1 Coronary sinus lead position before cardiac lead extraction.

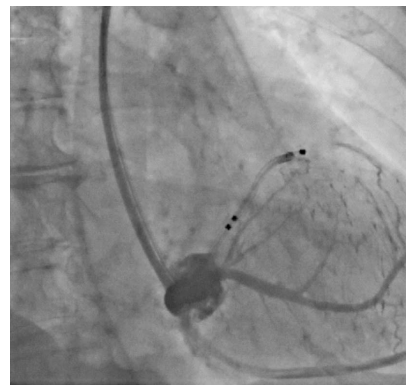


Figure 2 Coronary sinus angiography, by Attain Command™ Delivery system.

a cardiac surgeon on standby. Before the procedure, contrast material was administered through the intravenous line, ipsilateral to the site of placement to assess the patency of the subclavian vein. The CS lead was visually examined by fluoroscopy (Figure 1). Two unsuccessful attempts of gentle manual traction (MT) were subsequently performed: The first after the introduction of an Attain Hybrid guidewire (Medtronic) and the second with a locking stylet LLD E (Lead Lock Device Spectranetics, Colorado, United States or Cook Intravascular Inc, IN, United States) advanced as distal as possible. Mechanical dilatation (MD) was then used through a single polypropylene inner sheath with an internal diameter of 8.5 Fr (Cook Intravascular Inc.) advanced up to the CS ostium. Stable traction of the locking stylet still failed to detach the lead; all movements were carefully coordinated in order to avoid injury to the vessel, and especially to the superior vena cava.

Afterwards, CS was cannulated using an Attain Command™ Delivery System (Medtronic), but due to the inability to reach the tip of the lead, an Attain Select™ sub-selector (Medtronic) was added and advanced inside the CS branch. After both sheaths were successfully inserted, angiographies were performed to verify the integrity of the vascular system (Figure 2). At the sub-selective CS venography, the vessel of the electrode was not visualized. A distal branch occlusion



Figure 3 Coronary sinus subselective angiography by Attain Select™ sub-selection catheter.

was present, probably due to the development of fibrotic processes (Figure 3).

In order to give more cutting force and increase the shear strength, we decided to cut the sub-selector sheath 1.5 cm from the distal part. With the modified delivery system, the lead was disengaged and pulled back into the sheath.

Despite the short implantation period, the post-extraction examination showed an extended fibrosis on the surface of the lead body (Figure 4). No CS dissection was observed and the postoperative course was uneventful.

DISCUSSION

We are reporting a difficult CS TLE a few months after the implant, which required challenging MD up to the distal tip of CS lead using both conventional sheaths and modified CS lead delivery due to fibrotic adherence.

Recently, HRS published an expert consensus statement^[3] which asserts that the infection of the pocket, device, and/or lead is the most frequent Class I indication for lead removal.

Lead extraction is still a challenging procedure requiring specific expertise. HRS recommends at least 40 cases experience for the physician acting as first operators, whereas a minimum number of 20 annual extractions should be requested^[4,5].

A frequent issue found during the lead extraction is the presence of fibrotic processes on body leads, both in vascular and endocardial side. This problem is much more sporadic in the CS, where the only region easily affected by fibrosis is the ostium. However, there is still a great concern about CS extraction because of the potential risk of cardiac tamponade due to CS dissection.

CS leads can be often successfully extracted with direct traction only, as reported by a recent study on 125 leads^[6], but literature is not exhaustive.

Nevertheless, in a small percentage of cases, major and possibly life-threatening complications are related to the extraction tools used in the weak CS structure in unfavourable anatomical positions, raising questions regarding the possible need of tools specifically designed

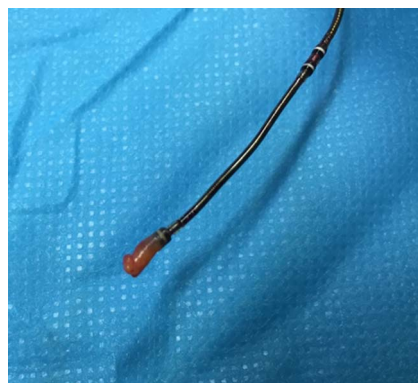


Figure 4 Extracted electrode with fibrotic adhesions at the distal tip.

for this structure.

In addition, CS leads have different designs, having a smaller body diameter than atrial or ventricular leads with less physical resistance to traction and a higher risk of rupture. In order to avoid lead damage the counter pressure or countertraction maneuvers have to be applied with special care.

Our procedure consisted in the following phases: (1) manual traction was attempted; (2) a locking stylet (LLD E) was put forward along the lumen and locked at the distal part of the lead, then MT was attempted again; (3) as traction was unsuccessful due to unexpected fibrosis, a modified delivery sheath was advanced over the lead until the lead was disengaged from all the tissue at the distal tip of CS lead. Despite our experience in lead extraction^[7], in this case removing a CS lead was unexpectedly difficult, not only by MT but also performing MD.

To date, there are no tools specifically designed for CS lead extraction. In order to complete the procedure successfully we had to directly modify a standard CS delivery system to obtain a non-traumatic dissection of local fibrosis.

This case highlights the importance of approaching each single procedure with caution as even a potentially simple case may be challenging for an expert operator.

In conclusion, persistent fibrosis at the tip of a CS lead was found during the extraction procedure 4 mo after implant. A tailored technique consistent of locking stylet MT with a modified sub-selector delivery sheath advanced over the lead in the CS branch was successful.

COMMENTS

Case characteristics

An 84-year-old woman implanted with cardiac resynchronization therapy defibrillator had persistent fevers.

Clinical diagnosis

The patient presented a pocket infection.

Differential diagnosis

The patient underwent transvenous lead extraction 4 mo after the implant, but difficulties were found in the coronary sinus lead extraction.

Laboratory diagnosis

The infection presented persistent positive blood culture of *Staphylococcus Pseudintermedius*.

Imaging diagnosis

At the sub-selective coronary sinus venography, the vessel of the electrode was not visualized; a distal branch occlusion was present, probably due to the development of fibrotic processes.

Pathological diagnosis

The post-extraction examination showed an extended fibrosis on the surface of the lead body.

Treatment

A modified sub-selector sheath was successfully advanced over the electrode until it was free of the binding tissue.

Related reports

Coronary sinus leads can be often successfully extracted with direct traction only, the presence of fibrotic processes on body leads is uncommon in the coronary sinus, in particular after few months from the implant.

Term explanation

A sub-selector sheath is a tool used during resynchronization therapy defibrillator implant to reach and deliver the electrode in the target vessel of the coronary venous system.

Experiences and lessons

Persistent fibrosis at the tip of a coronary sinus lead might be found also few months after implant, a tailored technique with a modified sub-selector delivery sheath advanced over the lead in the coronary sinus branch allowed to complete the extraction procedure.

Peer-review

This is a rare case report about coronary sinus lead extraction using new

techniques. This manuscript is nicely structured and well written.

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Rapunzel syndrome is not just a mere surgical problem: A case report and review of current management

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Abstract

Recurrent Rapunzel syndrome (RRS) is a rare clinical presentation with fewer than six cases reported in the PubMed literature. A report of RRS and literature review is presented. A 25-year-old female was admitted to hospital with a 4-wk history of epigastric pain and swelling. She had a known history of trichophagia with a previous admission for Rapunzel syndrome requiring a laparotomy nine years earlier, aged 16. Psychological treatment had been successfully achieved for nine years with outpatient hypnotherapy sessions only, but she defaulted on her last session due to stressors at home. The abdominal examination demonstrated an epigastric mass. Computer tomography scan revealed a large gastric bezoar and features of aspiration pneumonia. The patient underwent emergency open surgical laparotomy for removal as the bezoar could not be removed endoscopically. The bezoar was cast in a shape that mimicked the contours of the stomach and proximal small bowel, hence the diagnosis of RRS. The patient was seen by a psychiatrist and was commenced on Quetiapine before discharge. She continues to attend follow-up.

Key words: Trichobezoars; Rapunzel syndrome; Recurrence; Obsessive compulsive disorders; Case report

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Core tip: There remain to be clear guidelines on the management of trichotillomania associated disorders. Here we report that Rapunzel syndrome requires a comprehensive and long-term psychiatric follow-up as it is not a primary surgical condition. A late relapse of the condition is possible and recognizing this as a clinical possibility can intensify efforts in relapse prevention during the follow-up period. This approach is important in eliminating the need for recurrent surgical

interventions and associated morbidity. Multidisciplinary health care teams headed by a psychiatrist as well as family support play a key role in the prevention of recurrence.

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INTRODUCTION

A bezoar is a collection of foreign material in the gastrointestinal tract. A trichobezoar is a bezoar formed by the ingestion of hair and occurs typically in patients with trichotillomania. The latter is defined as an irresistible desire to pull out one’s hair and it has been included in the 2013 Diagnostic Statistical Manual (DSM-5) of the American Psychiatry Association as an obsessive compulsive disorder^[1].

Rapunzel syndrome is a rare manifestation of a trichobezoar, which occurs when strands of swallowed hair extend beyond the pylorus of the stomach, into the intestine as a tail^[2]. It was first described by Vaughan *et al*^[3] in 1968. Primary or recurrent cases of trichobezoars may lead to complications such as intussusception^[4,5], pancreatitis^[6] and bile duct dilatation^[4]. Significant other complications such as gastric perforation^[7,8], peritonitis^[9], and even death^[10] have also been reported. Despite the potential for significant complications and mortality, there is still a lack of any specific and comprehensive guidelines on appropriate postoperative follow-up for patients with Rapunzel syndrome to reduce the risk of recurrence^[11].

In this case report, we present a rare case in which Rapunzel syndrome represented nine years following an initial laparotomy. This manuscript is written in accordance with the case report (CARE) guidelines^[12]. The clinical management dilemmas in this case, including those accounting for the recurrent Rapunzel syndrome (RRS), have been reported to inform guidelines on appropriate postoperative follow-up of patients with Rapunzel syndrome.

CASE REPORT

A 25-year-old female was admitted to hospital with a 4-wk history of epigastric pain, swelling and early satiety. The symptoms, while initially intermittent, had become more constant and severe over the four days prior to admission. She denied any nausea, vomiting, weight loss or change in bowel habit. She had a known history of trichophagia (compulsive ingestion of hair) with a previous admission for Rapunzel syndrome requiring an anterior gastrotomy nine years earlier,

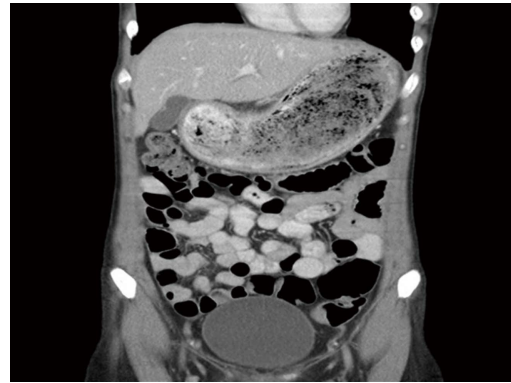


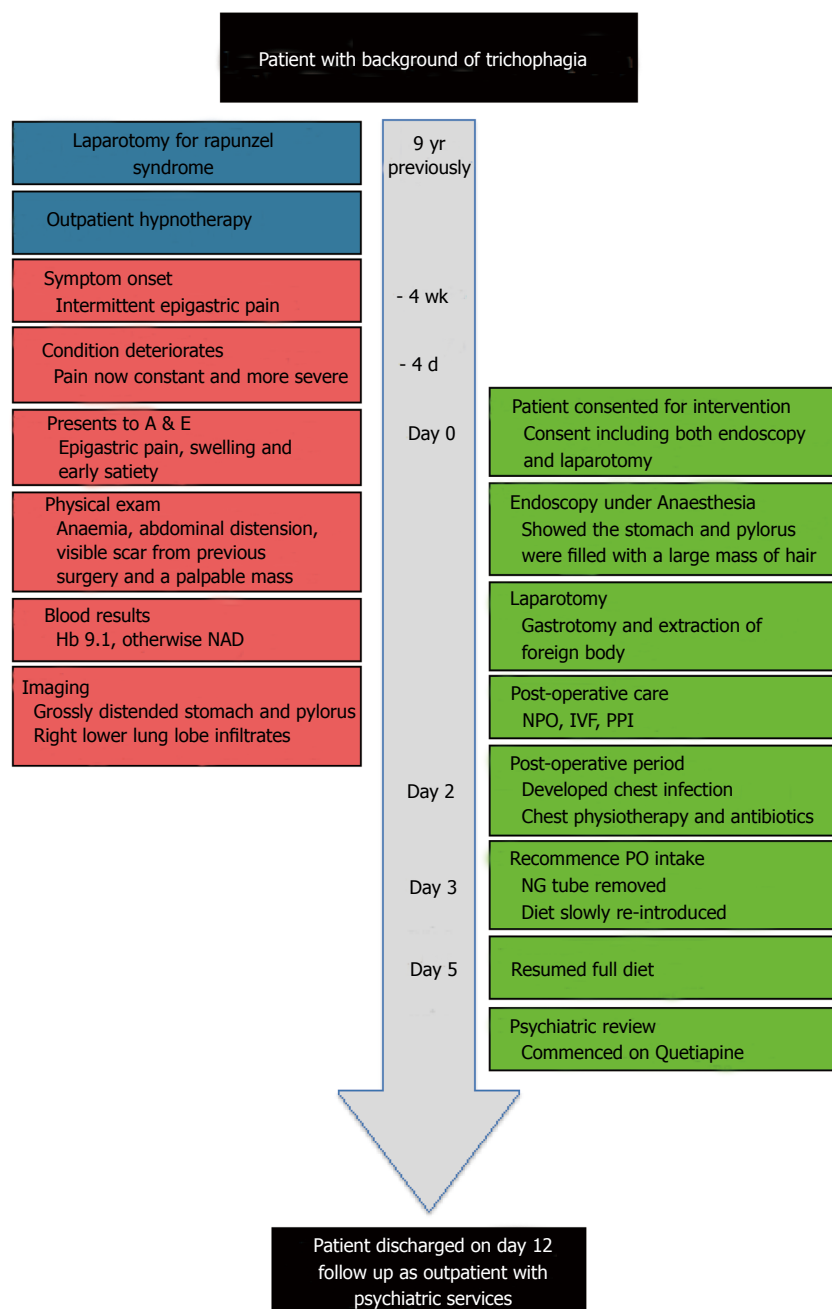
Figure 1 Computed tomographyscan of the abdomen revealing a large gastric bezoar.

aged 16. She had been referred to a psychiatry service following this episode and was successfully managed with a non-pharmacological treatment strategy in the form of behavioural therapy for nine years. The patient reported finding initial outpatient hypnotherapy sessions very beneficial, however, she admitted to later defaulting on follow-up appointments due to stressors at home.

On examination, she was anaemic, and her abdomen was distended with an upper midline laparotomy scar visible, consistent with her previous surgery. A firm abdominal mass, which extended from her left subcostal region to her umbilicus, was palpable. At this point, the differential diagnosis included an enlarged spleen, recurrence of the trichobezoar or Rapunzel syndrome. Her blood work revealed a microcytic hypochromic anaemia with a haemoglobin level of 9.1 g/dL. Blood urea, creatinine, electrolytes, blood glucose, serum amylase and liver function tests were normal. An abdominal CT showed a grossly distended stomach and pylorus filled with debris (Figure 1), with infiltrates within the right lower lung lobe. Following this, the patient consented to the removal of the foreign body under general anaesthesia (Figure 2).

The patient was brought to the theatre, intubated, and under general anaesthesia, a diagnostic upper gastrointestinal endoscopy was performed. The endoscopy showed that the stomach and pylorus were filled with a large mass of hair (Figure 3). The greater curvature of the stomach was also ulcerated. The high density of the hair conglomerate precluded successful endoscopic extraction, and surgical exploration was performed through a 7-cm upper midline incision. The adhesions from her previous surgery were divided and an Alexis® O Wound Protector (Applied Medical, United States) was used to protect the wound. A gastrotomy (5 cm) was made in the anterior stomach away from the pylorus. The foreign body was visualised, grasped, and carefully extracted from the stomach. The trichobezoar weighed 850 g and was cast in a shape that mimicked the contours of the stomach and proximal small bowel, hence the diagnosis of RRS (Figure 4). The gastrotomy was closed in two layers, and this was followed by

Figure 2 Timeline.



fascial and skin closure.

Postoperatively, the patient received analgesia and was kept nil by mouth for three days. She received intravenous fluids and proton pump inhibitors during this period. The postoperative period was complicated by a chest infection on day 2. The infection necessitated chest physiotherapy and an extended duration of prophylactic antibiotics to a full 7-d course. Of note, the chest infection was apparent at the time of pre-operative diagnosis. The nasogastric tube was removed on day 3, and her diet was slowly re-introduced. She had resumed full diet by day 5 and was also commenced on haematinics. She was reviewed by a psychiatrist and was started on Quetiapine 25 mg daily before discharge on day 12. Outpatient follow-up for further management of her mood symptoms and

cognitive behavioural therapy was arranged.

DISCUSSION

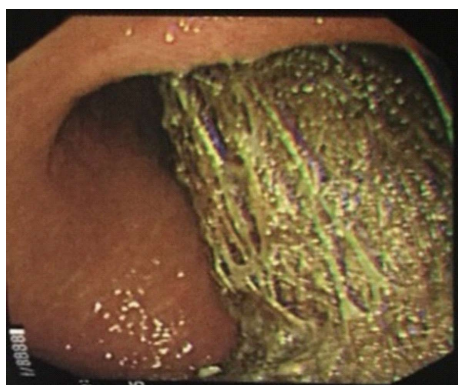
Rapunzel syndrome is not a primary surgical condition. Treating the underlying trichotillomania is critical in preventing a relapse, but this can be challenging in clinical practice. Clinical dilemmas and valuable lessons learned from the management of this rare case of recurrence are described herein.

Firstly, laparotomy is the recommended approach of choice for removal of the trichobezoar in Rapunzel syndrome^[11,13]. Enzymatic degradation, pharmacotherapy, endoscopic fragmentation and laparoscopy have been shown to be ineffective in these cases as the tail often extends into the jejunum^[13,14]. The

Table 1 Management of cases of recurrent Rapunzel syndrome in the literature¹

| Ref. | Year published | Age (S1) | Psychiatric management | Age (S2) | Psychiatric management | Interval (recurrence) | Reason for recurrence |
|--|----------------|----------|--|----------|--|-----------------------|--|
| Memon <i>et al</i> ^[2] | 2003 | 10 | Advised treatment of her emotional disturbances | 12 | Supervised psychiatric treatment ² | 2 yr | Unresolved emotional stress factor (ignored psychiatric treatment, continued to eat hairs of females neighbours) |
| Eryilmaz <i>et al</i> ^[23] | 2004 | 12 | Psychiatric treatment ² | 19 | Supervised treatment with family counselling | 7 yr | Underlying depressive personality disorder |
| Morales-Fuentes <i>et al</i> ^[22] | 2010 | 16 | No treatment mentioned | 22 | Psychiatric treatment ² | 6 yr | Inadequate initial treatment Obsessive disorder Pleasure feeling of how the hair scrapped the throat |
| Jones <i>et al</i> ^[6] | 2010 | 35 | No treatment mentioned | 37 | Quetiapine Habit reversal training with family and neighbours involvement | 2 yr | Inadequate initial treatment |
| Tiwary <i>et al</i> ^[18] | 2011 | 10 | Behavioural therapy Clomipramine after 1 mo Follow-up × 6/12 | 15 | Supervised psychiatric treatment ² | 5 yr | Lack of psych follow-up Defaulted after 6/12 |
| Current study | 2016 | 16 | Behavioural therapy | 25 | Supervised behavioural therapy Quetiapine 25 mg | 9 yr | Defaulted follow-up due to stressors at home |

¹All cases involved female patients; ²Details not specified. S1: First surgical intervention; S2: Second surgical intervention.

**Figure 3** Gastroscopy showing the obstructing trichobezoar.**Figure 4** The fully extracted giant gastric trichobezoar with a tail.

major drawback of the open surgical technique is the high incidence of postoperative infection^[13]. However, the chest infection in this case report was arguably present due to aspiration at the time of diagnosis and was evident on the preoperative CT imaging. The site of incision, the wound protection technique, and the outlined postoperative care all limited the morbidities in this case. The pre-morbid anaemia and gastric ulceration were also well managed using haematinics and proton pump inhibitors.

Secondly, this case showed that cognitive behaviour therapy in the form of exposure and response prevention, although useful in the initial management may become limited in the long-term prevention of relapse of trichotillomania. For this behavioural therapy to be effective, there needs to be a comprehensive home support network with family or friends also monitoring treatment compliance at home^[6,15]. Randomised

control trials have shown that patients who respond to psychotherapy might still be stigmatized or be socially rejected^[16]. Such stigmatization and rejection may lead to depression, the latter has been described as an independent predictor of quality of life deficits in patients with trichotillomania^[17]. The involvement by the family helps to reinforce treatment and facilitates early detection of relapse. Despite these efforts in the management of our case, the presence of home stressors was subtle and was undetected in the outpatient setting. The result was a delay in diagnosis of a relapse, an emergency presentation and morbidity at presentation.

Thirdly, a comprehensive and long-term psychiatric follow-up is needed in all cases as late relapse is possible. An ideal psychiatric follow-up approach is one which can early detect relapse, or highlight those who require closer monitoring and more aggressive treatment.

Furthermore, patients who are on pharmacological therapy should be monitored by a psychiatrist. Continued surveillance by carers for adverse events while on medication is also advisable. Close monitoring is especially important during the times of adjustment of dosage regimens. Adjunctive investigations such as biannual abdominal imaging during the follow-up period has been proposed by some authors^[6], while others advocate routine ultrasound^[11] or upper GI endoscopy at 6, 12 and 24 mo^[18]. The use of trichotillomania severity scales as a way of assessing treatment response may prove useful in the future^[19]. All these proposals are however yet to be universally adopted in clinical practice.

Currently, there are no Food and Drug Administration approved treatments for trichotillomania, which makes it difficult for clinicians to select an appropriate therapeutic plan^[20]. When effective, long-term treatment with an SSRI may be a reasonable first-line option to prevent relapse^[21]. Clomipramine, quetiapine or augmenting an SSRI with an atypical antipsychotic have been used for treatment-resistant cases^[6,21]. However, all cases in which a drug treatment is considered should be referred to a psychiatrist who then makes a decision on the appropriate therapy^[21]. In this case report, quetiapine was recommended. Furthermore, patients on drug treatment should be carefully monitored as treatment may be associated with psychiatric comorbidity and suicidal ideation in later life^[21]. It is clear that new targets are warranted to ensure a clinically supported effective pharmacological approach to treat this condition^[20].

Recurrence of Rapunzel syndrome is extremely rare and fewer than six cases have been reported in the PubMed database^[2,6,18,22,23]. Management of the condition can be challenging even in experienced hands. Our patient did well on cognitive therapy alone for nine years without any issues, and this justified the continued non-pharmacological management in the first instance. As mentioned earlier, pharmacological treatment may be limited and is not without risks, but this had to be instituted following the relapse. So far, the cases of recurrence have been recorded in females with variable times of between two and nine years between the initial surgical treatment and presentation with relapse (Table 1). Our review of the management also showed that RRS occurs when the underlying psychological trigger is under-diagnosed or treated. With specific reference to the index case report, it was principally due to an inadequate supervision by carers and subsequent failure of the patient to attend follow-up sessions.

In conclusion, this case report is relevant as it clearly describes important clinical lessons learned from the psychological and surgical management of a case of RRS which, to our knowledge, represents the longest published interval between initial treatment and presentation with relapse of the condition. The key message is that although surgery is the initial treatment, a comprehensive and long-term postoperative psychiatric follow-up is needed in patients with Rapunzel

Syndrome as a late relapse is possible. Multidisciplinary health care teams headed by a psychiatrist as well as family support play a key role in the prevention of recurrence. It is hoped that our shared experience will inform the management of similar cases.

COMMENTS

Case characteristics

A 25-year-old lady with a previous history of gastrotomy for Rapunzel syndrome presented with a 4 wk history of epigastric pain, swelling and early satiety.

Clinical diagnosis

Trichophagia and finding of a firm abdominal mass, which extended from her left subcostal region to her umbilicus.

Differential diagnosis

Recurrent Rapunzel syndrome (RRS), gastric trichobezoar; also consider an enlarged spleen (splenomegaly) if the history of trichophagia is not apparent.

Laboratory diagnosis

The only abnormal laboratory finding was microcytic hypochromic anaemia.

Imaging diagnosis

Computed tomography showed a grossly distended stomach and pylorus filled with debris.

Pathological diagnosis

RRS.

Treatment

Gastrotomy with complete removal of the trichobezoar, psychotherapy, pharmacological treatment and long-term psychiatric follow-up.

Related reports

Relapse of Rapunzel syndrome following initial surgery classically occur within the first seven years of initial treatment and have very rarely been reported beyond this time frame. Stigmatization or social rejection of patients who respond to psychotherapy can lead to depression and relapse.

Term explanation

Rapunzel syndrome is a benign entity that classically occurs when strands of swallowed hair extend beyond the pylorus of the stomach, into the intestine as a tail. It is known to be difficult to remove with pharmacotherapy or endoscopic fragmentation and requires a gastrotomy for removal.

Experiences and lessons

Rapunzel syndrome requires a comprehensive and long-term psychiatric follow-up as it is not a primary surgical condition. A late relapse of the condition is possible and recognizing this as a clinical possibility can intensify efforts in relapse prevention during the follow-up period, thereby eliminating the need for multiple surgical interventions and morbidity. Multidisciplinary health care teams headed by a psychiatrist as well as family support play a key role in the prevention of recurrence.

Peer-review

An interesting case, focusing on surgical as well as psychiatric treatment of RRS. Albeit a rare condition, the paper provides a thorough review of the literature and adequate advice on the management.

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Rhabdomyolysis following severe hypokalemia caused by familial hypokalemic periodic paralysis

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Abstract

Rhabdomyolysis continues to appear with increasing frequency and represents a medical emergency requiring rapid appropriate treatment. One of the unusual causes of nontraumatic rhabdomyolysis is hypokalemic periodic paralysis without secondary causes. Primary hypokalemic periodic paralysis is a rare genetic disease characterized by episodic attacks of muscle weakness due to decreases in serum potassium. A 30-year-old woman who had 3 episodic attacks of hypokalemic periodic paralysis was admitted in emergency room with sudden onset symmetrical muscle weakness. After several hours, she started to complain myalgia and severe ache in both calves without any changes. Laboratory test showed markedly elevated creatine phosphokinase, lactic dehydrogenase levels with hypokalemia, rhabdomyolysis resulting from hypokalemia was diagnosed. Here, we report an unusual case of rhabdomyolysis caused by severe hypokalemia, which was suggested a result of familial hypokalemic periodic paralysis.

Key words: Rhabdomyolysis; Hypokalemia; Familial hypokalemic periodic paralysis

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Core tip: Familial hypokalemic periodic paralysis is characterized by periodic attacks of muscle weakness due to decreases in serum potassium, caused by genetic defect of potassium-sensitive muscle membrane excitability with familial occurrence. Rhabdomyolysis following severe hypokalemia as the manifestation of familial hypokalemic periodic paralysis is rare, but it occasionally develops acute kidney injury, disseminated intravascular coagulation, arrhythmia as a potentially life threatening complication promptly recognized by the treating physician. The authors pointed to early detection of rhabdomyolysis as a serious complication of severe

hypokalemia, and ruling out other causes of hypokalemia by step-wise approach, finally reached the diagnosis with the familial hypokalemic periodic paralysis.

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INTRODUCTION

Nontraumatic rhabdomyolysis is a polyetiological disease that continues to appear with increasing frequency and represents a medical emergency, that it occasionally develops acute kidney injury, disseminated intravascular coagulation and cardiac arrhythmia as a potentially life threatening complication^[1,2]. One of the most interesting causes of nontraumatic rhabdomyolysis is potassium deficiency caused by a variety of reasons. Familial hypokalemic periodic paralysis is a rare genetic disease characterized by periodic attacks of muscle weakness due to decreases in serum potassium without other detectable causes^[3]. Rhabdomyolysis following severe hypokalemia as the manifestation of primary hypokalemic periodic paralysis is extremely rare^[4]. Here, we report an unusual case of rhabdomyolysis caused by severe hypokalemia, which in turn was the result of primary hypokalemic periodic paralysis.

CASE REPORT

A 30-year-old woman was brought to the emergency room with sudden-onset, rapidly symmetrical flaccid weakness in the proximal lower extremity muscles after excessive intake of carbohydrates. She did not complain of nausea, vomiting, diarrhea, fever or rash, and there was no history of medication use, nor had she experienced any trauma or vigorous exercise. Her menstrual cycle was regular and she was married and nulliparous. The patient reported a history of 3 similar episodes of weakness in the past year. All episodes occurred after consuming excessive carbohydrates and drinking alcohol. Each time she was admitted to a hospital emergency room and muscle weakness improved after intravenous potassium administration. There was no detectable reason for her hypokalemia whenever she did it. Unusual point was her family history that included the sudden cardiac death of her father, paternal uncle and brother without determination of the exact cause. On physical examination, her blood pressure was 120/80 mmHg, heart rate was 78 beats/min and body temperature was 36.4 °C. Cardiopulmonary examination was unremarkable. Neurological examination revealed symmetrical flaccid muscle paralysis involving predominantly the thighs and calves, areflexia without sensory involvement and

positive Trousseau sign. Initial laboratory investigations demonstrated markedly severe hypokalemia (K 1.6 mEq/L) with hypophosphatemia (phosphorus 0.8 mg/dL), while other routine chemistry including total calcium level, liver function and hematological laboratory values were normal. Plasma renin activity, aldosterone and thyroid hormone levels were within normal range (Table 1). ABG analysis revealed the following: pH 7.48, PaCO₂ 29 mmHg, PaO₂ 106 mmHg, bicarbonate 22.3 mEq/L and oxygen saturation 98.8%. This respiratory alkalosis was considered as results of hyperventilation due to her complaints. Urinary excretion of potassium was 2.5 mmol/L and urinary osmolality was 326 mOsm/kg; the transtubular potassium gradient was 1.67. Blood and urine cultures were all negative, and serology for viruses including hepatitis B virus, hepatitis C virus, human immunodeficiency virus and resilient packet ring was also negative, so no recent infections were suspected. Electrocardiogram revealed a Q-T interval elongation pattern corresponding to hypokalemia-related changes (Figure 1). After 6 h of potassium administration, the patient suddenly developed tetany and a severe ache in both calves without corresponding physical exertion. Initially she complained only of weakness without pain, but she began to show new symptoms including severe muscle tenderness, myalgia. Also, her urine color changed to dark-brown, described as "tea-colored" and the amount of urine decreased. We suspected rhabdomyolysis and laboratory tests showed elevated creatine phosphokinase (45720 IU/L) and lactic acid dehydrogenase (LDH 1686 U/L) and low serum potassium (2.2 mmol/L) (Table 1). We sought to determine the cause of hypokalemic rhabdomyolysis using a step-wise approach. Rhabdomyolysis was accompanied by episodic muscle weakness with severe hypokalemia and no other causes, including thyrotoxicosis, hyperaldosteronism, renal loss or gastrointestinal loss. Based upon these clinical features, a diagnosis of primary hypokalemic periodic paralysis was made due to a positive family history of unexpected sudden cardiac death and hypokalemia during paralytic attacks without other detectable causes. We diagnosed the patient with rhabdomyolysis following severe hypokalemia caused by familial hypokalemic periodic paralysis. DNA analysis and muscle biopsy was planned for exact diagnosis (sporadic or familial), but we could not perform, because she refused further tests. After treatment *via* hydration, potassium replacement and medication with spironolactone, the patient's creatine phosphokinase and potassium levels normalized and her symptoms improved. The patient described in the case report exhibited characteristic clinical features of rhabdomyolysis caused by profound potassium deficiency associated with primary hypokalemic periodic paralysis.

DISCUSSION

Rhabdomyolysis is a pathological condition involving

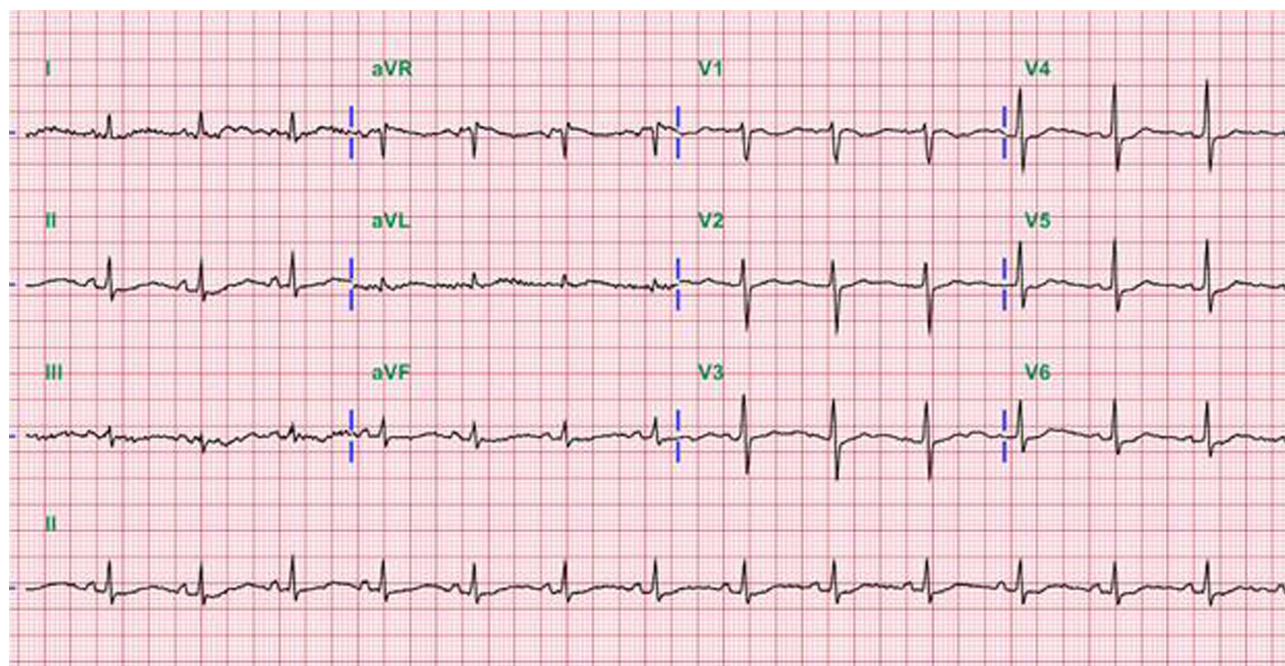


Figure 1 Q-T interval elongation.

Table 1 Clinical course of the patient

| HD | #1 | #2 | #3 | #4 | #5 | #6 |
|--------------------|-----|-------|-------|-------|-------|------|
| Potassium (mmol/L) | 1.9 | 2.2 | 3.7 | 3.2 | 3.9 | 4.6 |
| Na (mmol/L) | 143 | 146 | 145 | 146 | 144 | 145 |
| CPK (U/L) | 110 | 45720 | 41200 | 37700 | 10899 | 1933 |
| LDH (U/L) | | 1686 | 496 | 342 | 242 | 186 |

CPK: Creatine phosphokinase; LDH: Lactic dehydrogenase.

skeletal muscle cell damage leading to the release of toxic intracellular material into the blood circulation. It ranges from an asymptomatic illness to a life-threatening condition associated with acute kidney failure, disseminated intravascular coagulation, and critical arrhythmia as complications of rhabdomyolysis^[1]. There are multiple causes of rhabdomyolysis, which can be classified as physical (traumatic) and non-physical (nontraumatic) causes. One major cause of rhabdomyolysis is muscular trauma, and less common causes include muscle enzyme deficiency, electrolyte abnormality, infection, toxins, endocrinopathy, and drugs including β -mimetics, insulin, laxatives or diuretics such as thiazides. One of the most interesting causes of non-traumatic rhabdomyolysis is electrolyte abnormalities including potassium deficiency^[2]. The mechanism of the hypokalemia-induced rhabdomyolysis is still not clear, but it may be related to the fact that hypokalemia may induce muscle injury or frank necrosis as a consequence of relative ischemia^[4].

Potassium plays an important role in regulating muscle blood flow, and local potassium levels in capillaries are essential regulators of vascular tension.

Changes in potassium distribution across the cellular membrane might affect excitability and contractile force of muscle tissue^[3]. Normally during exercise, muscles release intracellular potassium, causing local pockets of hyperkalemia, which in turn trigger vasodilation and increase perfusion to active myocytes^[3]. Effect of total body potassium depletion decreases local hyperkalemia preventing vasodilation and leads to tissue hypoxia. Severe hypokalemia contracts capillaries, reduces muscle blood supply and results in muscle cell damage^[3,5]. The clinical manifestations of potassium depletion vary, because hypokalemia affects the function of several organs including cardiovascular system, neurologic system, muscles, and kidneys. The severity of the clinical symptom depends on the degree of hypokalemia, more severe hypokalemia may lead to progressive weakness, hypoventilation and even complete paralysis. Also, the occurrence of side effect (or complication) of hypokalemia, for example like rhabdomyolysis, is related to the severity of pre-existing potassium deficiency and the underlying disease state^[5,6]. For the accurate treatment of these symptoms of hypokalemia, it requires correct identification of the cause. Among the various causes of hypokalemia, drugs such as diuretics, laxatives or insulin are the most common cause of potassium depletion, which induced by abnormal losses of potassium, or redistribution within cells. Thus, the first step in the management of hypokalemia is to review the patient's drug record. In the absence of an inciting drug, hypokalemia can result from an acute shift of potassium from the extracellular compartment to cells, from inadequate intake, or from abnormal losses through the kidney and intestinal losses by diarrhea^[3]. This diagnosis is readily made from the

history under most conditions. In situations where the cause of hypokalemia is not obvious, measurement of urinary potassium excretion and blood pressure as well as assessment of acid-base balance are often helpful. In the presence of hypertension, Cushing syndrome or aldosteronism should be suspected in any patient with the triad of hypertension, hypokalemia and metabolic alkalosis^[6]. Rare hereditary defects in renal salt transport, such as Bartter syndrome or Gitelman syndrome, can cause hypokalemia without hypertension in a manner similar to that of diuretics. Potassium loss can also occur due to diabetic ketoacidosis and renal tubular acidosis^[7]. Severe hypokalemia can occur, although rarely, in association with thyrotoxicosis, resulting in a clinical syndrome characterized by the sudden onset of severe muscle weakness and paralysis^[3]. Signs and symptoms of thyrotoxic periodic paralysis usually accompany acute episodic attacks of muscle weakness and paralysis, and it is clinically identical to hypokalemic periodic paralysis, so the misdiagnosis may be made^[8,9].

Hypokalemic periodic paralysis leads to randomly-spaced attacks or episodes of weakness that range from mild to flaccid paralysis triggered by falls in serum potassium, and involve several or all of the skeletal muscles with complete recovery between attacks^[8,9]. It is categorized as primary, due to a genetic defect with familial or sporadic occurrence or as secondary, due to drugs, suprarenal gland disease^[9]. Primary hypokalemic periodic paralysis can be associated with mutations in genes encoding for subunits of the muscular sodium channel, calcium channel and potassium channel^[8,10]. Diagnosis is based on patient history and can be confirmed by evaluation of serum electrolytes and trans-tubular potassium concentration gradient during an attack using the CMAP amplitude test (Exercise EMG) or by DNA analysis and muscle biopsy^[9]. Negative DNA test results are not conclusive^[10]. Triggers for paralysis may be a carbohydrate-rich diet such as consumption of sweet and starchy, alcohol or strenuous physical activity. Other precipitating factors include stress related to infections, menstruation, lack of sleep or certain drugs such as β -mimetics, insulin or corticosteroids^[9]. Appropriate management includes a diet low in sodium and simple carbohydrates. Patients should avoid over-exertion and becoming chilled, and should take supplemental potassium. Acetazolamide is highly effective for prevention of paralytic attacks and some patients require potassium supplementation in order to achieve complete control of episodes. Acetazolamide is a carbonic anhydrase inhibitor, causing the accumulation of carbonic acid, however the mechanism of the therapeutic effects of the drug in hypokalemic periodic paralysis is not clear and appears to be independent of carbonic anhydrase inhibition. It is reported that acetazolamide is expected to trigger calcium-activated potassium channels on skeletal muscle and make sarcolemma channel activity intense, and restore the serum K^+ levels to control values^[11-14]. Patients who fail to respond to acetazolamide, may respond well to

potassium sparing diuretics including spironolactone.

This case report has two limitations. First, genetic analysis and muscle biopsy for diagnostic confirmation was not done because of patient's reluctance. However, it is known that negative result of genetic analysis and muscle biopsy are not conclusive, we could approach the final diagnosis based on the clinical course and family history of patient. Second, on the suspicious of rhabdomyolysis, myoglobin levels as a sensitive marker of muscle damage was not measured. However, tea-colored urine showed myoglobinuria, and it suggested that myoglobin was released into the circulation.

In summary, primary hypokalemic periodic paralysis is a rare genetic muscle disease leading to periodic muscle weakness and hypokalemia without other detectable causes. Rhabdomyolysis presenting with severe hypokalemia as the first manifestation of primary hypokalemic periodic paralysis is extremely rare and represents a medical emergency requiring rapid diagnosis and appropriate treatment. We report a case of rhabdomyolysis following severe hypokalemia caused by familial hypokalemic periodic paralysis. This case acts as a reminder of the risk of rhabdomyolysis among patients with familial hypokalemic periodic paralysis.

COMMENTS

Case characteristics

A 30-year-old woman, who had 3 episodic attacks of hypokalemic periodic paralysis was admitted in emergency room with sudden onset symmetrical muscle weakness. After several hours, she started to complain myalgia and severe ache in both calves without any changes.

Clinical diagnosis

Initial symptoms included episodic attacks of muscle weakness due to decreases in serum potassium. Later she complained myalgia and severe ache in both calves, and her urine color was changed to dark-brown.

Differential diagnosis

Drug-induced hypokalemia, thyrotoxic periodic paralysis, Cushing syndrome, hyperaldosteronism, Conn syndrome, Bartter syndrome, Gitelman syndrome, Liddle syndrome, diabetic ketoacidosis, renal tubular acidosis.

Laboratory diagnosis

Laboratory examinations showed markedly decreased in serum potassium, elevated creatine phosphokinase, lactic dehydrogenase levels.

Treatment

Intravenous hydration, potassium replacement and medication with spironolactone.

Related reports

Nontraumatic rhabdomyolysis is a polyetiological disease, and one of the most interesting causes of nontraumatic rhabdomyolysis is potassium deficiency. Hypokalemia is resulted in the various causes such as thyrotoxicosis, cushing syndrome, hyperaldosteronism, Conn syndrome.

Term explanation

Familial hypokalemic periodic paralysis is characterized by periodic attacks of muscle weakness due to decreases in serum potassium, caused by genetic defect of potassium-sensitive muscle membrane excitability with familial occurrence. Nontraumatic rhabdomyolysis is a polyetiological disease, and one of the most interesting causes is severe hypokalemia.

Experiences and lessons

Rhabdomyolysis following severe hypokalemia as the manifestation of familial hypokalemic periodic paralysis is rare, but it occasionally develops a potentially life threatening complication. The authors pointed to early detection of rhabdomyolysis as a serious complication of hypokalemia, and ruling out other causes of hypokalemia by step-wise approach, finally reached the diagnosis with the familial hypokalemic periodic paralysis.

Peer-review

The paper is well-written.

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Indolent lung opacity: Ten years follow-up of pulmonary inflammatory pseudo-tumor

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Abstract

Inflammatory pseudotumor (IPT) has always been considered a diagnostic challenge. Its rarity and resemblance to other more common pathological entities imposes that neither clinical nor radiological characteristics can lead to a definitive diagnosis. The surgical excision of the lesion is the ultimate approach for accurate diagnosis and cure. Moreover the true nature of IPT, its origin as a neoplastic entity or an over-reactive inflammatory reaction to an unknown trigger, has been a long debated matter. Surgery remains the treatment of choice. IPT is mostly an indolent disease with minimal morbidity and mortality. Local invasion and metastasis predict a poor prognosis. We hereby present a unique case of pulmonary IPT that was surgically excised, but recurred contralaterally, shortly thereafter. Despite no medical or surgical treatment for ten years, the lesion has remained stable in size, with neither symptoms nor extra-pulmonary manifestations.

Key words: Inflammatory pseudotumor; Anaplastic lymphoma kinase; Inflammatory myofibroblastic tumor; Plasma cells granuloma; IgG4-related sclerosing disease

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Core tip: Inflammatory pseudotumor is considered a diagnostic challenge, with no one-self explained pathophysiology. Over-reactive inflammatory response to various triggering agents or even an entity with malignant potentials represents the two-sided pendulum. Accurate pathological identification lies on adequate tissue acquisition, which often occurs during surgical resection; the preferred treatment approach. Even though both local recurrence and metastasis represent a poor prognosis, its indolent course is not a well-known property, which we do here highlight in our patient with a 10-year follow up, possessing a stable and indolent disease.

Degheili JA, Kanj NA, Koubaissi SA, Nasser MJ. Indolent lung opacity: Ten years follow-up of pulmonary inflammatory pseudotumor. *World J Clin Cases* 2017; 5(2): 61-66 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v5/i2/61.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v5.i2.61>

INTRODUCTION

Inflammatory pseudotumor (IPT) of the lung had been first described by Brunn^[1] in 1939 and the term had been coined by Umiker *et al*^[2] in 1954. Most commonly IPT presents in the lung and orbit. Other less common locations include: Liver, spleen, stomach^[3], breast, esophagus, salivary glands^[4], and the central nervous system^[5]. It accounts for less than 1% of all lung specimens' pathologies^[6].

Given the heterogeneity in its true pathogenesis, several interchangeable terms have been linked to IPT such as: Plasma cell granuloma, inflammatory myofibroblastic tumor (IMT), xanthoma, fibroxanthoma, and histiocytoma^[7]. This resulted in some confusion among the medical societies regarding IPT true definition and description. A simple and clear classification has been reported which divided the spectrum of IPT into non-neoplastic versus neoplastic variants, the latter including IMT^[8].

CASE REPORT

A 43-year-old female, smoker with a history of left tuberculous pleuritis treated in 1997, presented 6 years later to our clinic complaining of exertional shortness of breath of one year duration.

Computed tomography (CT) of the chest revealed the presence of a left upper lobe mass 3.0 cm × 3.0 cm, along with prominent bilateral hilar and mediastinal lymph nodes. Pulmonary function tests showed mild restrictive disease. She underwent left lateral mini-thoracotomy followed by wedge resection of the lesion with mediastinal lymph node biopsy. Grossly, no parietal pleural involvement was noted, and no frozen section

was sent, at that time, for intra-op identification. Pathology came out to be acute and chronic non-specific inflammation along with fibrosis (Figure 1). No treatment was initiated, and the patient was discharged home, advising close follow-up.

Ten years following her thoracotomy, the patient presented back for asymptomatic right middle lobe opacity, not resolving on several antibiotic regimens.

CT chest revealed a right middle lobe mass extending to the right lower lobe, with mediastinal and hilar lymphadenopathy (Figure 2).

A CT-guided core biopsy of the middle lobe mass was performed. Histopathological examination revealed a matrix of spindle cells consistent of fibroblasts and myofibroblasts, intermixed with inflammatory cells including leukocytes, plasma cells, and histiocytes (Figure 3). A low mitotic activity was noted among cells, with no dysplasia. These findings highly suggest a pulmonary IPT of the lymphoplasmacytic subtype. Anaplastic lymphoma kinase (*ALK*) gene mutation was absent on the tissues, and serum IgG4 level was 0.279 g/L (0.052-1.25 g/L). Pathologic reexamination of the previously resected left upper lobe lesion confirmed similar histopathological findings. Given the indolent course of the disease and the asymptomatic status, along with a financial burden on the patient, a watchful waiting approach was elected, instead of surgical resection, with CT of the chest, to be done, every 2 to 3 years.

DISCUSSION

Pulmonary IPT represents a distinct group of pathologies ranging from benign lesions as plasma cell granuloma to lesions with more malignant potentials as IMTs^[9]. IPT of the lung is a rare entity, constituting around 0.7% of all lung tumors, and approximately 0.04% to 1.2% of all thoracotomies^[10]. Most of IPT lesions occur in younger age groups, with no sex predilection^[11]. In fact, IPT in the pediatric age group is mostly of neoplastic form (IMT). The more benign forms of IPT usually occur in the adult population^[8].

Pathogenesis

The predominant infectious/inflammatory etiology: The pathogenesis of IPT is elusive. Inflammation in IPT has been attributed to a metabolic disturbance, pulmonary infection, and/or antigen-antibody interaction to an unknown agent^[7]. Thirty percent of IPT cases are reported to be preceded by recurrent respiratory tract infections. Isolated pathogens include: Human Herpes Virus, Epstein Barr Virus, *Nocardia*, *Mycoplasma*, and *Actinomyces*^[4,12]. Repetitive respiratory insults will call for inflammatory cells to migrate to the insult site. Subsequently over-reactive inflammation results in proliferation and infiltration of inflammatory cells, including lymphocytes, plasma cells, and histiocytes. This could explain the persistent elevation in serum

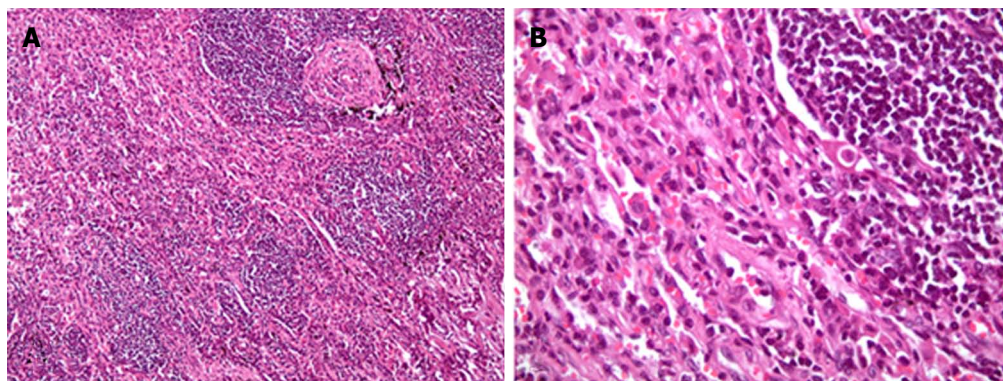


Figure 1 Initial lung resection revealing diffuse infiltration of inflammatory cells and undifferentiated fibroblasts, representing acute and chronic non-specific inflammation, along with fibrosis (A: 10 \times ; B: 40 \times magnification).



Figure 2 Computed tomography of the chest revealing a right middle lobe mass (arrow), with multiple calcified hilar and mediastinal lymph nodes (arrow heads).

inflammatory biomarkers, as C-reactive protein and erythrocytes sedimentation rate^[10].

The genetic postulate: *ALK* gene has been used as a molecular surrogate to differentiate benign IPT from malignant IMT. *ALK* gene is present on chromosome 2p2. The gene encodes for tyrosine kinase receptors, and the resultant derangement will cause *ALK* protein over-expression and cell proliferation^[4]. *ALK* positivity is only observed in IMT patients. Approximately half of IMT patients stain positive for *ALK*; yet show a great variation with age^[8]. In contrast to other tumors that stain positive for *ALK*, *ALK*-positive IMT is associated with better prognosis than *ALK*-negative IMT, as the latter is associated with higher rate of metastasis^[13].

Malignant potentials of IMT have been attributed to the derangement of *ALK*^[14]. This proves to be pivotal in the medical treatment of IPT, as certain drugs can competitively inhibit such receptors and prohibit proliferation^[15].

IPT vs IgG4-related diseases: A subset of IPT has been correlated with IgG4-related diseases^[16]. "IgG4-related" sclerosing disease, a new disease entity, reflects the presence of abundant IgG4-plasma cells in

the tissues^[17,18]. IgG4 is the least abundant of all IgG subclasses, and accounts for less than 6% of the total IgG subclasses in the serum^[19]. Serum IgG4 is elevated in certain pathological entities such as atopic dermatitis, pemphigus vulgaris, and sclerosing pancreatitis^[10]. The IgG4-related IPT behaves differently than isolated IPT, as it responds greatly to steroids, precluding the need for surgical resection^[8]. To confirm the diagnosis of IgG4-related pulmonary IPT, histological analysis is needed. A recent study reported the presence of IgG4-positive plasma cells in Plasma Cell Granuloma, a type of Pulmonary IPT^[20]. This is contrary to serum IgG4 which is not always elevated^[17]. Obliterative vasculitis also raises the probability of IPT over IMT^[18]. The ratio of IgG4 over IgG-positive plasma cells, within tissue specimens, acts as a surrogate for diagnosis of IgG4-related IPT. A ratio greater than 50% is usually diagnostic^[13].

Histopathology

Histologically, IPT consists of proliferation of fibroblasts and myofibroblasts intermingled with varying numbers of inflammatory cells including: Lymphocytes, polyclonal plasma cells, macrophages, and histiocytes^[8]. Various histological classifications have been inaugurated, describing IPT. The most commonly used is that of Matsubara *et al.*^[21], and that of the World Health Organization (WHO)^[22]. The former classifies IPT, according to dominant component cells and main histological characteristics, into 3 subtypes: Organizing Pneumonia, Fibrohistiocytoma, and Lymphoplasmacytic type; each constituting 44%, 44% and 12%, respectively. The WHO classification, on the other hand, divides IPT into compact spindle cell and hypocellular fibrous patterns^[22].

Clinical presentation

Almost 70% of IPT cases are discovered incidentally. Such patients are either asymptomatic or complain of symptoms of other diseases^[12]. Symptoms such as cough, hemoptysis, shortness of breath, and chest pain occur in 25% to 50% of patients^[11]. Fever is not

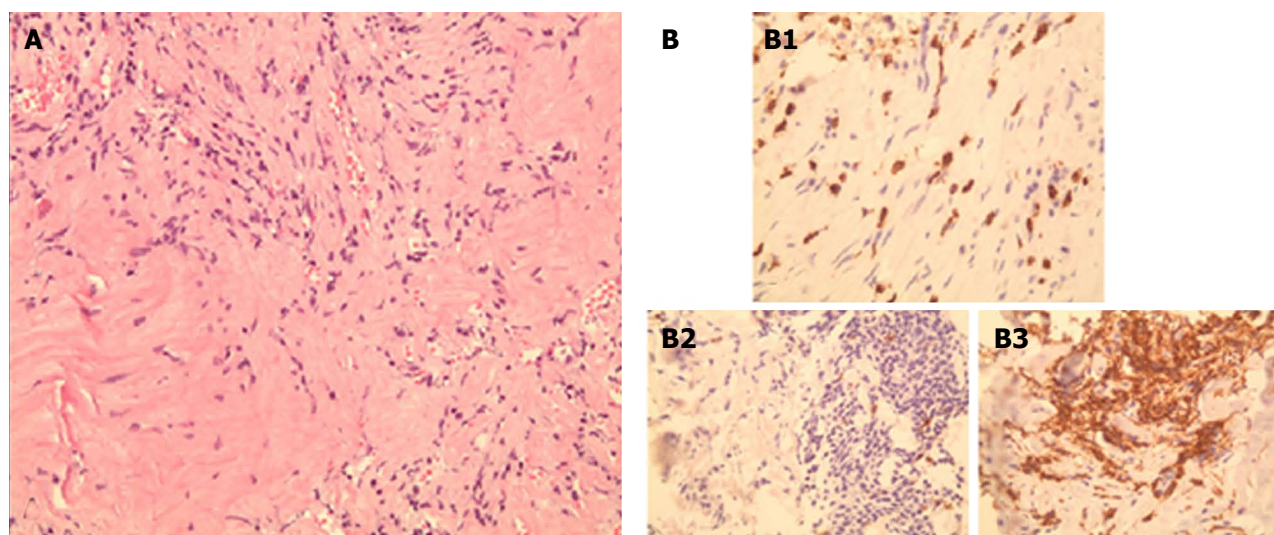


Figure 3 (A) Heavy infiltration of lymphocytes, plasma cells, and histiocytes, within a background of spindle-shaped fibroblasts and myofibroblasts, arrayed in fascicles (B). Immunostaining of tissues showing positivity for CD3 (B1), negativity for CD20 (B2), and positivity for CD138 (B3), respectively.

uncommon^[22], mainly due to interleukins' production (e.g., IL-1 β , IL-6)^[23].

Radiologic manifestations

Well-circumscribed solitary nodules, with peripheral lower lobar predilection, constitute the usual radiologic manifestation of IPT. In one study, this has been reported to occur in 87% of patients^[24]. Multiple nodules do present in only 5% of cases^[25]. Calcifications and lymphadenopathy are seen in 15% and 7% of cases, respectively^[26]. Cavitary lesions and pleural effusions are quite rare findings^[4]. Based on the radiological mode of presentation, it is difficult to differentiate IPT from other entities such as lung tumor or pulmonary tuberculosis; thus rendering IPT a clinical and a radiological challenge^[11].

Diagnosis

Transbronchial lung biopsy (TBLB) is not a favored diagnostic tool in IPT due to the small size of pieces, taken during the procedure, which renders the diagnosis a difficult call^[11]. In fact, only 6.3% of IMT or IPT cases are diagnosed using TBLB^[27]. Moreover, not uncommonly, lung tumors are surrounded by chronic inflammation because of the resulting insult to normal tissue, thus rendering diagnosis even more staggering. Definitive diagnosis of IPT is mainly achieved by surgical resection, which if complete, will lead to definitive cure in most cases.

Prognosis

The prognosis of IPT/IMT is variable. It usually depends on the tumor size and the magnitude of surgical resection^[27]. Tumors greater than 3 cm are usually not amenable to complete resection. This implies a drop in long-term survival to less than 50%^[12]. After complete resection, prognosis is favorable, with 5- and 10-year

survival of 91% and 77%, respectively^[28]. Metastatic lesions of IPT have approximately a 30-fold increase in recurrence rate, and are associated with a poor prognosis^[12]. Positive margins after incomplete resection result in recurrence rate from 5% to 25%^[10,13]. Pulmonary IMT, when not excised, shows continuum growth in approximately 8% of cases with a 5% risk of distant metastasis^[13].

Treatment

As previously stated, complete resection represents the most favorable and recommended diagnostic and therapeutic approach for pulmonary IPT. Patients who witness disease recurrence or those who do not fit for surgery may rarely benefit from other approaches including corticosteroids, chemo, and/or radiotherapy. Those modalities can also be used as adjuncts to suspected incomplete resection^[29]. Radiotherapy has little to offer for these slow-growing lesions; hence radiation may cause more damage than cure. Corticosteroids' use has shown contradictory results, though certain case reports showed complete regression after prolonged treatment^[12]. Interestingly, many IPT lesions resolve completely after core biopsy. Such paradoxical behavior termed "spontaneous resolution", is not a well understood phenomenon^[13]. Methotrexate was used in some cases with modest results^[30]. Crizotinib, a newly synthesized ALK inhibitor, has been used on a patient with pulmonary IMT, and showed sustained partial response^[31].

In conclusion, this case, to the best of our knowledge, represents the longest reported follow up in an IPT patient. The absence of symptoms and the relative stability of the lesion, after 10 years, stipulate the natural and the benign behavior of this slowly-growing entity. The true outcome of IPT clearly requires further investigation. Greater capabilities in deciphering the

diagnosis and approach to this disease, without relying on *en bloc* excision, lie on top of these investigations.

COMMENTS

Case characteristics

A 43-year-old woman, smoker, with history of left upper lobe mass resection, discovered after investigation for one year history of exertional dyspnea. Pathology back then showed acute and chronic non-specific inflammation with fibrosis. Ten years later, follow up on non-resolving right middle lobe opacity, despite multiple antibiotic regimens, resulted in a computed tomography (CT)-guided biopsy to be performed. Matrix of spindle cells intermixed with inflammatory cells was noticed.

Clinical diagnosis

Diagnosis of pulmonary inflammatory pseudotumor (IPT) was established from the core-guided biopsy.

Differential diagnosis

Differential diagnosis of pulmonary IPT includes lung carcinoma and pulmonary tuberculoma; two entities that needed to be taken into consideration while suspecting pulmonary IPT.

Laboratory diagnosis

In most isolated cases, laboratory data is normal except, in some cases, where pulmonary IPT is associated with IgG4 disease, for which the serum IgG4 subclass would be elevated.

Imaging diagnosis

Pulmonary IPT is difficult to diagnose, based on different radiological modalities alone. Its radiological resemblance with other entities, such as pulmonary tumor and tuberculosis, renders IPT a radiological challenge.

Pathological diagnosis

Histological examination of the CT-guided core biopsy revealed a matrix of spindle cells consistent with fibroblasts and myofibroblasts, intermixed with inflammatory cells, composed of lymphocytes, plasma cells, and histiocytes.

Treatment

En-bloc surgical resection with negative margins represents the core treatment for pulmonary IPT. Patients, who are ineligible for surgical intervention, can benefit from other suboptimal modalities including corticosteroids and chemotherapy. The novel use of Crizotinib has proven its efficacy in IPT patients possessing anaplastic lymphoma kinase-positivity.

Related reports

The present case report represents the longest follow-up, extending over a decade period, in a patient with pulmonary IPT, with no current or previous treatment. This highlights the indolent course of this disease entity, despite some other data reports evidence of local invasion or metastasis, even.

Term explanation

Pulmonary IPT constitutes less than 1% of all lung malignancies, and involves a spectrum of diseases, exhibiting benign behavior to more malignant potentials, as described by the inflammatory myofibroblastic tumors (IMT). Histologically, IPT constitutes of spindle cells intermingled with inflammatory cells, which are arrayed in fascicles.

Experiences and lessons

IPT of the lung is a rare disease entity, for which observation is regarded as a valid option, to be taken, but closely, into consideration.

Peer-review

The review is well structured and current enough. The article provides informa-

tion that is useful for application to clinical practice.

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Multiple perforations and fistula formation following corticosteroid administration: A case report

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Institutional review board statement: The subject gave written informed consent to the study protocol, which was approved by the ethics committee of Shengjing Hospital.

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Abstract

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic small- and medium-sized-vessel vasculitis. The literature contains only a few reports of gastrointestinal perforation with this condition. We report a patient with EGPA treated with high-dose steroid who underwent emergency surgery for intestinal perforations. We performed a simple repair of the 11 perforations. Intestinal fistulas developed 8 d postoperatively; they healed well after 60 d of continuous washing and negative pressure suction. The clinical data of 14 additional patients with EGPA or Churg-Strauss syndrome complicated with gastrointestinal perforation, which were reported from 1996 to 2014, were also collected and compared. The formation of multiple perforations and fistulas following high dosage steroid administration can have a good outcome with appropriate management. Meticulous attention to abdominal symptoms and appropriate interventions can result in timely management. Corticosteroid administration remains a very important perioperative procedure for EGPA.

Key words: Vasculitis; Eosinophilic granulomatosis with polyangiitis; Churg-Strauss syndrome; Gastrointestinal perforation; Surgery

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Core tip: Eosinophilic granulomatosis with polyangiitis (EGPA) complicated with intestinal perforation is very rare. It needs urgent surgical intervention but hormone administration usually covers up the situation and

delays the prognosis. We report a 43-year-old male diagnosed with EGPA by biopsy who experienced high-dose hormone administration, 11 intestinal perforations, postoperative intestinal fistula, and eventually recovered. This article aims to share the treatment course and experience.

He JN, Tian Z, Yao X, Li HY, Yu Y, Liu Y, Liu JG. Multiple perforations and fistula formation following corticosteroid administration: A case report. *World J Clin Cases* 2017; 5(2): 67-72 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v5/i2/67.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v5.i2.67>

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare type of necrotizing vasculitis affecting small to medium-sized vessels. It is typically characterized by asthma, lung infiltrates, necrotizing granulomas, and hypereosinophilia. It is an uncommon form of vasculitis with a prevalence that ranges from 10.7 to 13 cases/million^[1]. Gastrointestinal involvement has been reported to occur in approximately 50% of EGPA patients. Symptoms include abdominal pain, vomiting and diarrhea^[2]. Although EGPA very easily involves the digestive system, the chance of digestive tract perforation is very low and only a handful of cases have been reported. We report a case of EGPA with 11 intestinal perforations, and discuss the subsequent treatment.

CASE REPORT

A 43-year-old male with a 3-mo history of asthma was admitted to the Rheumatoid Immune Department of Shengjing Hospital in July 2013. The patient complained of a cough of one-month duration, blood-stained sputum, 14-d peripheral purpura, 3-d diarrhea, and an oral ulcer. His height was 176 cm and weight was 72 kg when admission. His temperature was 37.2 °C, his pulse was 78 per minute, and his blood pressure was 128/78 mmHg. Multiple skin purpura was found in the physical examination. Heart sounds were clear and regular with no murmur. A few moist rales were heard with lung auscultation. Abdominal examination was unremarkable. Laboratory studies revealed leukocytosis (15600/mm³) with eosinophilia (20.3%), a marked increase in inflammatory indices (ESR: 69 mm at the first hour; CRP: 176 mg/L), rheumatoid factor (656 UI/mL), and positive pANCA antibody. A pulmonary computed tomography (CT) scan revealed multiple low-density oval shadows, with the largest one measuring about 3.2 cm × 2.6 cm (Figure 1). A diagnosis of vasculitis was made. A biopsy of the nasal mucosa revealed an eosinophilic infiltration. We diagnosed EGPA according to the revised international Chapel Hill nomenclature. The patient received methylprednisolone

(120 mg intravenously daily) and ifosfamide for the treatment of the pulmonary lesions. The patient's condition exacerbated during the first three days following admission; the methylprednisolone dose was increased to 500 mg (intravenously daily × 2) and then was gradually tapered. On the 13th day after admission (160 mg methylprednisolone intravenously daily), he experienced a sudden onset of fever and abdominal pain. The physical examination revealed generalized abdominal tenderness without apparent rebound tenderness, and muscle tension. No specific treatment was given. After 11 h, the abdominal pain exacerbated and peritonitis developed. An abdominal CT scan showed an amount of free gas in the abdominal cavity (Figure 2). A laparotomy was performed immediately, which revealed scattered eleven perforations in the intestine. The proximal one was located approximately 150 cm distal from the ligament of Treitz ligament, and the distal one located approximately 50 cm from the ileocecal valve, with the largest measuring about 3 cm × 3 cm (Figure 3). Considering the high risk of short bowel syndrome, we made a simple repair of the intestinal perforations. Histopathological examination did not reveal either eosinophilic infiltration or granuloma formation of the vessels (Figure 4).

Continued intravenous therapy with intermittent ifosfamide as well as somatostatin and esomeprazole was administered postoperatively. The hormone dosage was tapered from 160 mg downward. On postoperative day 6, when the steroid was reduced to 80 mg, the patient's vasculitis exacerbated and he developed fever and new purpura on the entire body. Eight days postoperatively, an intestinal fistula developed, which was confirmed by fistulography (Figure 5). With continuous saline washing through a double-lumen cannula connected to a negative pressure suction apparatus, the drainage was about 300 mL intestinal fluid daily; the fistula slowly healed. The patient began eating on postoperative day 45. Gastric retention occurred after eating; it was treated with decompression *via* a nasogastric tube, total parenteral nutrition, and a gastric motility stimulating agent. The patient resumed eating about two months postoperatively, and the drainage was minimal. When the steroid dosage was reduced to 60 mg intravenously, the fistula healed and the patient was discharged.

Unfortunately, four months later, an intestinal fistula and vasculitis recurred. Although the amount was 5 mL daily, he was readmitted and underwent continuous washing and negative pressure suction. The fistula healed slowly during one month. When last seen in the outpatient clinic in March 2014, he was in good health without any symptoms or eosinophilia. Laboratory analysis revealed 0.1% eosinophils and negative pANCA antibodies.

DISCUSSION

EGPA, formerly named churg-strauss syndrome (CSS),

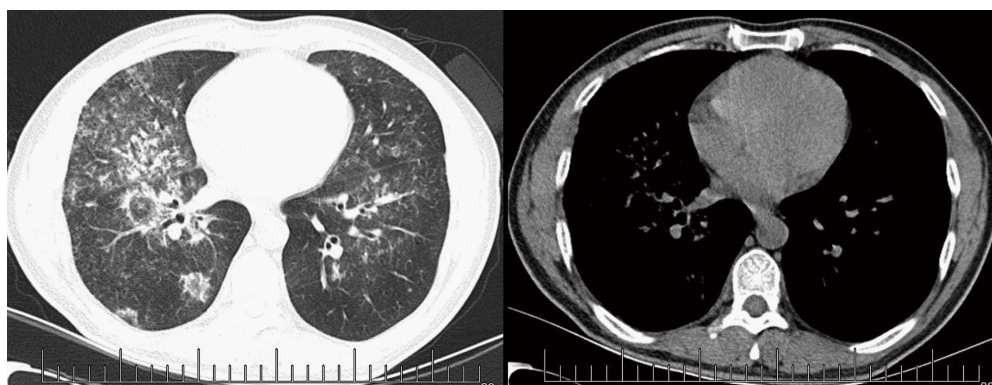


Figure 1 Pulmonary computed tomography images showing bilateral consolidation with air-bronchogram, especially in the right lung with multiple ground glass low-density shadows.

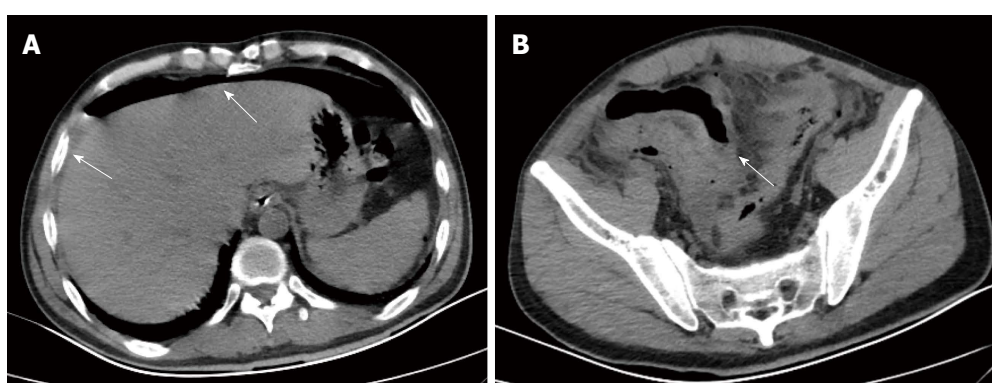


Figure 2 Abdominal transverse computed tomography images. A: Free air in the abdomen and fluid around the liver; B: Intestinal wall thickening in the right lower quadrant and seepage, scattered with free air.

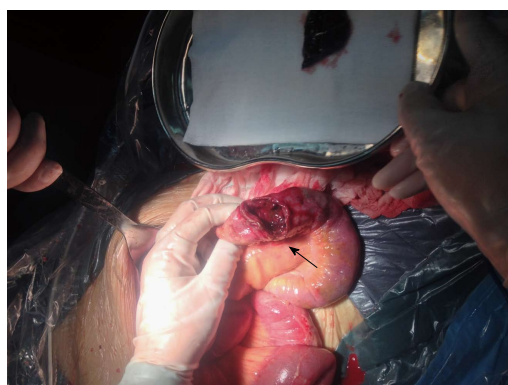


Figure 3 Intraoperative findings. There were 11 perforations in the intestine. The arrow points to the bigger one measuring about 3 cm × 3 cm.

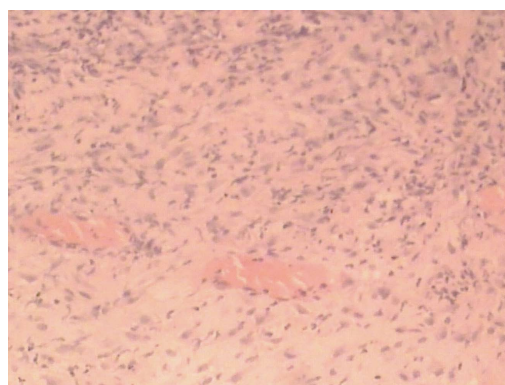


Figure 4 Histopathological examination showing a large number of infiltrated inflammatory cells (HE staining, × 100).

is characterized by the presence of severe asthma as well as blood and tissue eosinophilia. It is an uncommon form of vasculitis, with a prevalence that ranges from 10.7 to 13 cases/million. Although it is classified as vasculitis, the affected tissue usually does not show necrotizing vasculitis or granulomata, rather an apparently nondestructive infiltration of the vessel walls by eosinophils; in fact, only 40%-60% of patients with CSS have anti-neutrophil cytoplasmic antibodies (ANCA)s^[3]. For this reason the diagnostic criteria remain clinical.

Gastrointestinal involvement is present in 32.6% of CSS patients. In 29.11% of the cases, the large bowel is involved, in 53.5%, the small bowel is involved, in 16.6%, the gastroduodenal region is involved, and in 6.3%, pancreatitis and cholecystitis occur. The mortality rate is 11.9%^[4-6]. Although gastrointestinal symptoms are common, perforated ulcers are relatively uncommon and only a small number of cases have been documented in the literature^[7]. Because multiple organs are involved and peritonitis symptoms are not typical, complicated clinical manifestations occur, which delays

Table 1 Summary of cases of Churg-Strauss syndrome/eosinophilic granulomatosis with polyangiitis with digestive perforation in the English literature

| Ref. | year | Age/ sex | Initial symptoms | WBC (/mm ³) | Eosino (%) | Hormone | Perforation | treatment | Histology | Second perforation | Pro- gnosis |
|--|------|---------------|---|----------------------------|---------------|------------------------|----------------------------|-------------|--|-----------------------|----------------|
| Ikoma <i>et al</i> ^[10] | 2014 | 19/ female | Asthma | 24700 | 39 | Yes | Ileum | Anastomosis | Transmural infiltration of numerous eosinophils with thrombosis and extensive involvement of small arteries | No | Alive |
| Kaul <i>et al</i> ^[11] | 2014 | 58/ male | Low-grade fever | 94000 | 42 | Yes | Ileo-caecal junction | Ileostomy | Transmural inflammation of sub-mucosal and serosal vessels with perivascular infiltrate comprising of lymphomononuclear cells and eosinophils | No | Alive |
| Assmann <i>et al</i> ^[12] | 2014 | 32/ male | Dyspnea, fatigue, fever and chest pain | - | 5500/1 | Yes + cyclophosphamide | Middle part of jejunum | Anastomosis | - | No | Alive |
| Assmann <i>et al</i> ^[12] | 2014 | 36/ male | Dyspnea, fatigue, fever and chest pain | - | 4900/1 | Yes + cyclophosphamide | Colon transversum | Anastomosis | Eosinophilic infiltration and thrombotic vessel occlusion | No | Alive |
| Çiledağ <i>et al</i> ^[8] | 2012 | 35/ male | Anorexia | - | 35 | Yes | Small intestine | Repair | - | No | Died |
| Venditti <i>et al</i> ^[13] | 2011 | 69/ male | Abdominal pain | - | - | Yes | Right and transverse colon | Ileostomy | Multiple ulcers, extravasal granulomas and mucosal pseudopolyps | No | Alive |
| Zanaboni <i>et al</i> ^[14] | 2008 | 43/ male | Asthma | 32000 | 65 | Yes | Small intestine | Anastomosis | Necrotizing ischemic vasculitis with inflammatory granulomatous infiltrates of lymphocytes, polymorphonuclear cells and eosinophils | Yes | Alive |
| Rolla <i>et al</i> ^[15] | 2007 | 55/ male | Asthma | 15500 | 21 | Yes | Ileum | Anastomosis | Granulomatous vasculitis with eosinophilic infiltration | No | Alive |
| Murakami <i>et al</i> ^[5] | 2004 | 51/ female | Asthma | 27650 | 62 | Yes | Ileum | Anastomosis | Angiitis of small vessels surrounded by eosinophilic infiltration and granuloma of the vessels | No | Died |
| Nagashima <i>et al</i> ^[16] | 2002 | 67/ male | Asthma | 18500 | 65 | Yes | Intestine | Anastomosis | Vasculitis in the small arteries and arterioles characterized by thrombotic occlusion with fibrinoid necrosis of the vascular wall and prominent inflammatory cell infiltration in the perivascular region | No | Alive |
| Nakamura <i>et al</i> ^[17] | 2002 | 31/ male | Epigastralgia | 19700 | 40 | Yes | Jejunum and ileum | Anastomosis | Multiple ulcerative lesions with remarkable eosinophilic infiltration and thrombosis obstruction of small vessels | No | Alive |
| Alvarez <i>et al</i> ^[18] | 2002 | 64/ female | Urticaria, recurrent rhinitis, and asthma | 10000 | 34 | Yes | Intestine | Anastomosis | Wall ulcerations, vascular thrombosis with fibrinoid necrosis, and eosinophilic infiltrates | Yes | Died |
| Kim <i>et al</i> ^[4] | 2000 | 72/ female | Asthma | 6600 | 14 | Yes | Sigmoid colon | Anastomosis | Ulceration with heavy infiltrations of eosinophils, neutrophils and lymphoplasmic cells | - | - |

| | | | | | | | | | | | |
|-------------------------------------|------|-------------|--|-------|----|-----|---------|-------------|---|----|------|
| Sharma <i>et al</i> ^[19] | 1996 | 16/ male | Low-grade, continuous fever and wheezing sounds in the chest | 12600 | 70 | Yes | Jejunum | Anastomosis | Necrotizing vasculitis with marked eosinophilic infiltration of medium-to- small blood vessels and extravascular granulomas | No | Died |
|-------------------------------------|------|-------------|--|-------|----|-----|---------|-------------|---|----|------|



Figure 5 Fistulography showing that after injection of contrast agents, the intestine of the right lower quadrant abdomen developed a fistula.

treatment and results in a poor prognosis.

A systematic review of the literature was performed using the keywords “Churg-Strauss syndrome/eosinophilic granulomatosis with polyangiitis” and “gastrointestinal perforation” in PubMed to search articles from 1951 to December 2014. In China, CSS/EGPA with gastrointestinal perforation is very rare, and there is no relevant report. The articles were restricted to English language only. Duplicate reports and papers with important data missing were excluded. We included the papers on digestive tract perforation with CSS/EGPA, and compared the characteristics (Table 1). The average patient age was 46.3 years (range: 16–72 years; males: 10; females: 4). A half of the patients were complicated with the symptom of asthma, and all of them had received corticosteroid treatment. Their prognosis was poor, with 4/13 (30.77%; case 13 was unknown) dying during hospitalization, although the causes of death were very different. A second perforation of the digestive system occurred in 2 (15.38%) of 13 patients (case 13 was unknown).

Ulceration, perforation, and stenosis of the gastrointestinal tract are assumed to be the results of ischemia caused by vasculitis. The small intestine is the most commonly affected site^[8]. Immunosuppressive therapy, especially large-dosage corticosteroids, may play an important role in the development of an intestinal perforation. However, sometimes, it is difficult to distinguish clinically whether the intestinal perforation is due to vasculitis itself or immunosuppression^[9].

Treatment of a gastrointestinal perforation in patients with active vasculitis can be challenging. A delayed diagnosis may lead to a delayed cure, as in our patient. First, we did not pay adequate attention to the digestive symptoms: Sour regurgitation, heartburn,

and abdominal pain. Second, the symptoms of peritonitis are often atypical in patients receiving long-term administration of glucocorticoids. Third, when the digestive tract perforation occurred, the patient was in the rheumatic ward. As a result of consultation, diagnosis, and department transference, treatment delay can occur. Fourth, the gastrointestinal perforation may occur during a clinical remission. The perforation of this case occurred during the process of steroid tapering. Pathologic examination of the perforated bowel revealed no significant eosinophil infiltration.

In conclusion, improved awareness of gastrointestinal symptoms may allow for timely management of a perforation. Multiple perforations and fistulas caused by high dosage steroids can have a good outcome with appropriate management. Prompt surgical treatment is necessary. The choice of the appropriate surgical approach should be based on the time the perforations occurred, their size, numbers, and sites. Adequate steroid administration and intensive care play an important role during perioperative treatment.

COMMENTS

Case characteristics

A 43-year-old male with a 3-mo history of asthma, a cough of one-month duration, blood-stained sputum, 14 d of peripheral purpura, 3 d of diarrhea, and an oral ulcer. On the 13th day after admission, the patient experienced a sudden onset of fever and abdominal pain. And the abdominal pain exacerbated and peritonitis developed rapidly.

Clinical diagnosis

History of asthma, peripheral purpura, and peritonitis.

Differential diagnosis

Granulomatosis with polyangiitis, microscopic polyangiitis, and polyarteritis nodosa.

Laboratory diagnosis

Laboratory studies revealed leukocytosis (15600/mm³) with eosinophilia (20.3%), a marked increase in inflammatory indices (ESR: 69 mm at the first hour; CRP: 176 mg/L), rheumatoid factor (656 UI/mL), and positive pANCA antibody.

Imaging diagnosis

A pulmonary computed tomography (CT) scan revealed multiple low-density oval shadows, with the largest one measuring about 3.2 cm × 2.6 cm. An abdominal CT scan showed free air in the abdomen.

Pathological diagnosis

A biopsy of the nasal mucosa revealed an eosinophilic infiltration.

Treatment

Continued intravenous hormone therapy with intermittent ifosfamide

perioperatively, and intestinal perforation repair.

Related reports

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare type of necrotizing vasculitis affecting small to medium-sized vessels; it is typically characterized by asthma, lung infiltrates, necrotizing granulomas, and hypereosinophilia. Gastrointestinal involvement even perforation is more unusual and results in a poor prognosis.

Term explanation

EGPA with multiple intestinal perforations is very rare. Prompt surgical treatment is necessary. Adequate steroid administration and intensive care play an important role during perioperative treatment.

Experiences and lessons

Reasonable amount of hormone administration is the key point during the treatment. Excess hormone may induce intestinal perforation while insufficient amount could induce disease relapse and intestinal fistula postoperatively.

Peer-review

This is an interesting case report and the paper is well written.

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