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Review

G-CSF-induced aortitis: Two cases and review of the literature

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ABSTRACT

Background: Febrile neutropenia is generally recognised as a complication of myelosuppressive chemotherapy. Recombinant human granulocyte colony stimulating factor (G-CSF) is commonly used as a primary or secondary prophylaxis to reduce the degree and duration of neutropenia in patients at risk of developing chemotherapy-induced neutropenic fever and infectious complications. G-CSF is known to decrease mortality and increase the possibility of maintaining adequate chemotherapy dose intensity and density, which is essential in curable malignancies. Common side effects are generally mild. However, potentially fatal adverse events have also been reported.

Case presentation: Herein, we summarise previously reported and report two new independent cases of G-CSF-induced aortitis, both in patients treated with chemotherapy for breast cancer. The two cases, identified only a few months apart, share several common characteristics including type of cancer, gender, age, chemotherapy, G-CSF treatment regimen, and time span from G-CSF initiation to aortitis manifestation. The two cases were both diagnosed by CT scan and successfully treated with corticosteroids along with discontinuation of G-CSF.

Conclusion: This case report highlights that although aortitis is a rare adverse event of G-CSF treatment, it should be considered in cases of unexplained fever and/or clinical and laboratory findings that do not respond to antibiotics.

1. Introduction

Myelosuppressive cytotoxic chemotherapy may cause severe neutropenia, which increases the risk for potentially fatal infections associated with neutropenic fever [1]. Recombinant human granulocyte colony stimulating factors (G-CSF; filgrastim and PEGylated filgrastim) have been rigorously evaluated and are widely used as primary or secondary prophylaxis to reduce the degree and duration of neutropenia in patients at risk (> 20% anticipated risk) of developing chemotherapy-induced neutropenic fever and infectious complications [1–6]. Granulocyte-macrophage colony-stimulating factor (GM-CSF), which is also approved for this indication, and G-CSF are cytokines reported to have both pro- and anti-inflammatory properties [7–10]. Their use has proven relatively safe in both animal and human studies [11,12]. Despite potential adverse events, G-CSF decreases all-cause mortality [13]. Common side effects are rather mild and include bone pain, headache, and fatigue [14]. However, rare yet serious adverse advents have also been reported, such as pulmonary dysfunction including two cases of fatal lung injury [15,16], haematological adverse events including splenic rupture following splenomegaly due to

Abbreviations: AC, adenocarcinoma; CRP, C-reactive protein; CT scan, computed tomography scan; ER, estrogen receptor; GCA, giant-cell arteritis; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HER2, human epidermal growth factor receptor 2; LVV, large vessel vasculitis; MRA, Magnetic resonance angiography; PET-CT, positron emission tomography–computed tomography; PR, progesterone receptor; SCCA, squamous cell carcinoma; TAK, Takayasu arteritis

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stimulation of myelopoiesis [17], G-CSF-induced haematological malignancies (although this remains a controversial issue [18]), cardiovascular adverse events including arterial thrombosis [19,20] and aortitis have also been reported. There are, to our knowledge, three previously published cases of filgrastim-associated [21–23] and one case of pegfilgrastim-associated aortitis [24]. Herein, we report two independent cases of G-CSF-induced aortitis in patients treated for breast cancer.

2. Case 1

A 70-year old female sought emergency care three days after her first adjuvant chemotherapy cycle with docetaxel, trastuzumab and pertuzumab due to syncope, diarrhoea and dehydration. Her medical history included levothyroxine-substituted hypothyroidism, left-sided breast cancer diagnosed in 2005 and treated with post-operative radiotherapy and tamoxifen, and malignant melanoma of the left leg (Clark stage III) surgically removed in 2006. In 2018, she was diagnosed with a right-side breast cancer (estrogen receptor positive (ER+), progesterone receptor negative (PR-), human epidermal growth factor receptor 2 positive (HER2+)).

The clinical examination revealed no abnormalities, but the patient was admitted to the hospital for observation. CT scan of the brain was normal. She developed fever on the second day of hospital care that advanced into neutropenic fever the following day despite primary prophylaxis with G-CSF, which was continued during the neutropenic fever episode. In addition, the patient was treated with intravenous antibiotics (piperacillin/tazobactam), which were discontinued four days later following improved C-reactive protein (CRP) levels, normalization of neutrophil counts and negative blood cultures. Her hospitalization was complicated by an episode of melena and haematemesis, attributed to gastric ulcers and treated with eradication therapy. On the tenth day of inward care, she developed recurring high-grade fever with greatly increased CRP-levels (Fig. 1). New blood cultures were taken, and she restarted treatment with piperacillin/tazobactam. Two days later, a CT scan was conducted due to further increased CRP levels and no apparent infection focus. The CT scan, which was compared with a CT scan conducted 2 years earlier and a PET-CT scan conducted eight days before the start of G-CSF (Fig. 2A–C) revealed a newly established thickening of the tunica of the thoracic aorta and brachiocephalic trunk, consistent with vasculitis/aortitis; this was not present in the previous scans (Fig. 2D–E). Piperacillin/tazobactam was discontinued following negative cultures, and treatment with a daily prednisone equivalent (prednisolone) dose of 60 mg was initiated the following day. The CRP levels decreased rapidly (Fig. 1) and the patient was discharged a few days later following a quick clinical improvement. A follow-up PET-CT scan conducted 22 days following admission showed no increased FDG-uptake in the aortic wall and no remaining signs of aortitis were observed (Fig. 2F).

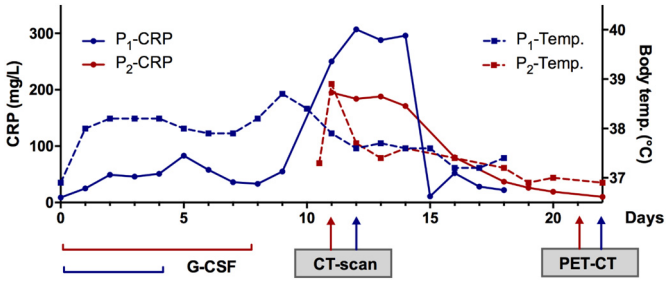

Fig. 1. CRP levels and body temperature over time for case 1 and 2. P1: Patient 1; P2: Patient 2; G-CSF: granulocyte colony stimulating factor; CRP: C-reactive protein.

3. Case 2

A 60-year old female was planned to be treated with adjuvant chemotherapy consisting of three cycles of epirubicin and cyclophosphamide followed by three cycles of docexatel in combination with trastuzumab following a sector resection with sentinel lymph node biopsy for a left-sided breast cancer (ER+, PR-, HER2+). Her medical history included an appendectomy and two right-breast surgeries with benign findings in histology. The patient sought emergency care 15 days after her fourth adjuvant chemotherapy cycle, first cycle with docexatel, due to abdominal pain. G-CSF (filgrastim) had been administered as primary prophylaxis.

The clinical examination revealed no abnormalities other than abdominal tenderness on palpation. The CRP level was highly elevated (Fig. 1) and the patient developed fever after several hours at the emergency department. She was admitted to an inpatient unit with the suspicion of infection. A CT scan of the thorax and the abdomen was performed but no infection focus was ascertained; the patient was however treated with intravenous antibiotics (piperacillin/tazobactam). The CT scan showed minimal amounts of left-side pleural fluid and a sparse infiltrate in the lower lobe of the left lung, a finding of uncertain significance, as well as a halo surrounding the aortic arch by the left subclavian artery and at the lower part of the thoracic/upper part of the abdominal aorta, at the level of the visceral branches. No lumen stenosis or dilatation was seen. The latter findings gave rise to the suspicion of Takayasu arteritis (TAK). After re-examination, the halo was attributed to thickening of the vessel walls, which was apparent in the aortic arch and the crossover between the thoracic and abdominal aorta, as well as the contiguous efferent abdominal vessels (Fig. 3B–C). The findings were consistent with large vessel vasculitis (LVV), and a PET-CT 10 days later (Fig. 3D–E) confirmed the diagnosis. However, a spontaneous partial regress of the thickening was seen compared with the CT scan.

The antibiotics were discontinued and the patient was initiated at high-dose glucocorticoids, with a daily prednisone equivalent (prednisolone) dose of 60 mg with a subsequent quick tapering. The CRP levels were also improved as illustrated in Fig. 1. Total radiological regress was confirmed by follow-up CT scans two months after the first examination (Fig. 3F–G). Docexatel and filgrastim were discontinued following the LVV episode, and the patient continued with trastuzumab monotherapy.

4. Discussion

G-CSF decreases all-cause mortality and increases the possibility of maintaining chemotherapy dose, intensity and density, an absolute prerequisite in curable malignancies [13]. Common side effects are generally mild. The occasional serious adverse advents, such as aortitis, should however not be underestimated. Vasculitides causing inflammation of the aorta, its major branches and the arteries of the extremities more often than other vasculitides constitute the LVV family, which mainly comprises the giant-cell arteritis (GCA) and TAK [25]. As opposed to TAK that occurs in younger adults (before their 40s) [26], GCA generally occurs in adults older than 50 years with a female-to-male ratio of 3:1 [27]. Symptoms of LVV may vary depending on the time from disease onset and the extent of organ or system involvement. Initial symptoms are commonly non-specific, reflecting constitutional symptoms caused by systemic inflammation, such as fatigue, fever or subfebrility, weakness, and muscle and/or joint ache. Intimal hyperplasia and vessel occlusion are consequences of transmural, often granulomatous, inflammatory activity within the arterial wall, resulting in ischemia and organ damage. Headaches, visual symptoms including vision loss, and claudication of the jaw, arms and/or legs are common clinical manifestations. However, destruction of the large elastic arteries may cause dilatation, formation of aneurysms, and potentially fatal dissection or rupture [28,29].

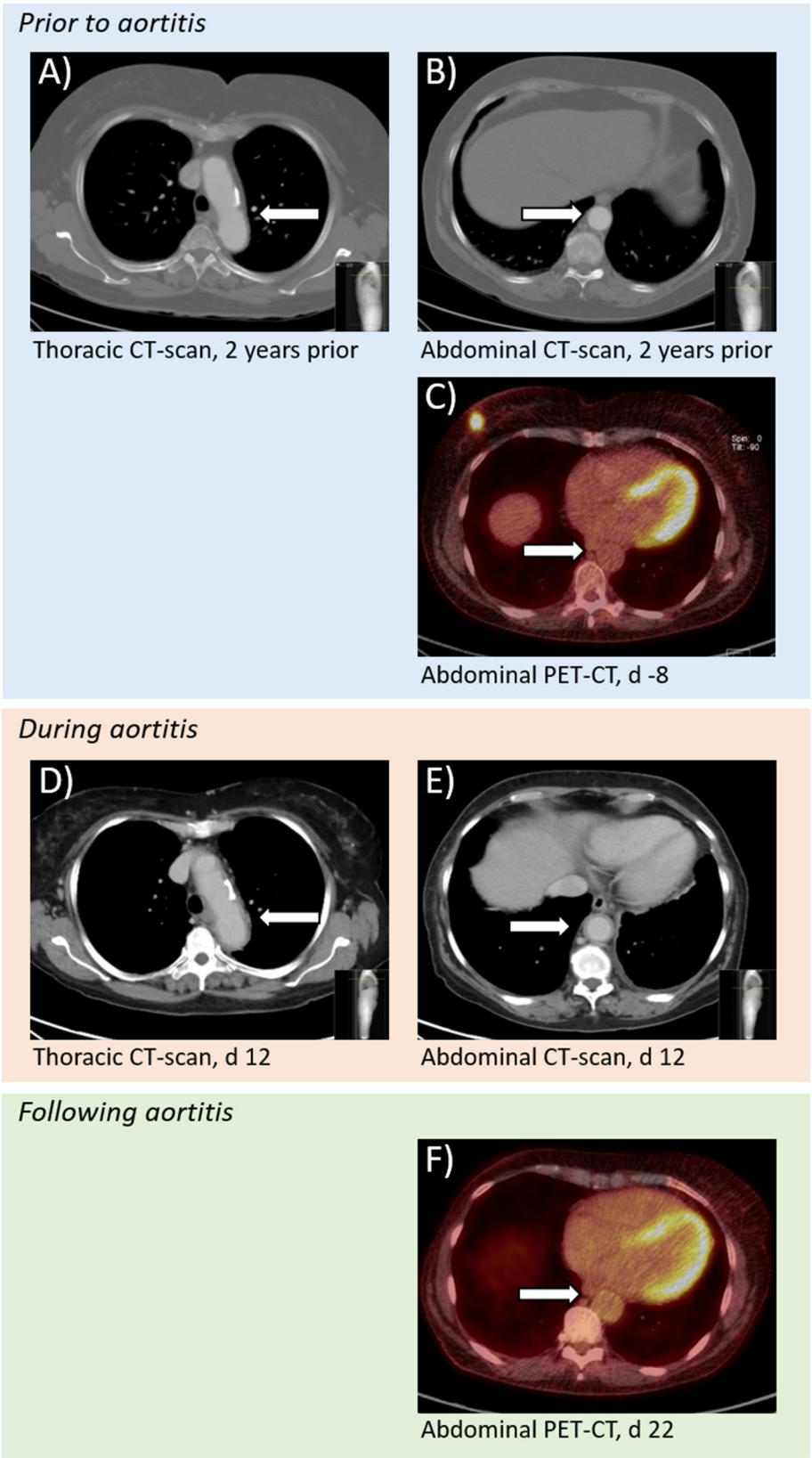

Fig. 2. Radiology over time for case 1. CT and PET-CT scans prior to (A–C), during (D-E) and post-aortitis (F) for case 1. A–B) Prior CT without aortic wall thickening at the level of the aortic arch and diaphragm, respectively. C) Prior F18-FDG PET-CT showing no FDG uptake in the aortic wall at the level of the diaphragm. D–E) CT showing circumferential aortic wall thickening at the level of the aortic arch and diaphragm, respectively. F) Follow-up F18-FDG PET-CT showing no FDG uptake in the aortic wall at the level of the diaphragm.

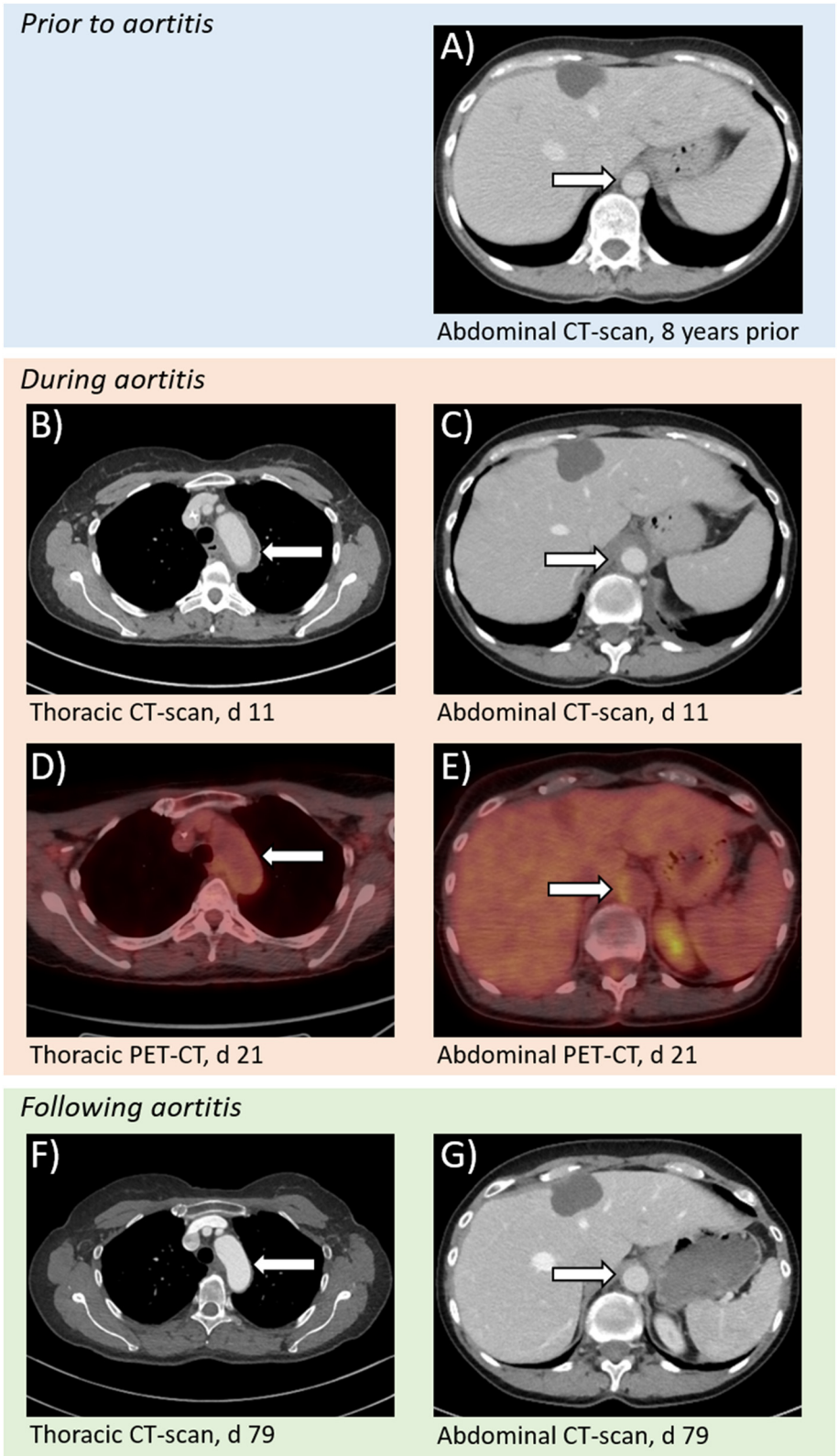

Fig. 3. Radiology over time for case 2. CT and PET-CT scans prior to (A), during (B–E) and post-aortitis (F–G) for case 2. A) Prior CT without aortic wall thickening at the level of the diaphragm. B–C) CT showing circumferential aortic wall thickening at the level of the aortic arch and diaphragm, respectively. D–E) F18-FDG PET-CT showing mild FDG uptake in the aortic wall at the level of the aortic arch and diaphragm, respectively. F–G) Follow-up CT showing decreased aortic wall thickening at the level of the aortic arch and diaphragm, respectively.

Selection of appropriate imaging modalities is essential for the diagnosis of LVV. As a result of technological advances, conventional angiography is no longer considered the gold standard for the diagnosis of LVV. Magnetic resonance angiography (MRA) or CT scan are preferred options by the majority of physicians. The use of PET-CT is preferred in selected cases; this modality may be useful when

Table 1
Reported cases of G-CSF-associated aortitis.

	Ref 21	Ref 22	Ref 23	Ref 24	Case 1	Case 2
Gender	Female	Male	Male	Female	Female	Female
Age	55	54	52	67	70	60
Underlying disease	no (stem cell mobilization, donor)	SCCA lung	no (stem cell mobilization, donor)	AC lung	Breast cancer	Breast cancer
G-CSF	Filgrastim	Filgrastim	Filgrastim	Pegfilgrastim	Filgrastim	Filgrastim
Aortitis	Abdominal	Abdominal	Abdominal	Thoracic	Thoracic	Thoracic
Cancer treatment	n/a	Carboplatin	n/a	Unknown Chemo-therapy	Docetaxel Trastuzumab Pertuzumab	Docetaxel
Onset from G-CSF initiation	2 days	8 days	6 months	8 days	9 days	11 days
Detection	CT/MRI	CT/MRI	CT	CT/US	CT	CT
Steroid response	Rapid, complete	Rapid, complete	Rapid, complete	Rapid, complete	Rapid, complete	Rapid, complete

SCCA: squamous cell carcinoma; AC: adenocarcinoma.

malignancy also is suspected [30]. The two cases reported here, as well as the previously reported G-CSF-associated aortitis cases, were in fact diagnosed by CT scan (Table 1).

The very limited number of reported cases of G-CSF-induced aortitis does not allow for any detailed analysis; thus, risk assessment or identification of potential causes would be highly speculative. However, the two cases described herein share several common characteristics including type of cancer, gender, chemotherapy, G-CSF treatment regimen, and similar age. Moreover, both cases responded well to corticosteroid treatment; however, the contribution of the corticosteroids remains unclear and the spontaneous partial regress from the CT scan to the PET-CT scan in the second case indicates that discontinuation of the chemotherapy and G-CSF treatment might be sufficient. It is noteworthy that both cases had received identical chemotherapy (docetaxel for breast cancer treatment) prior to developing the aortitis. This may of course be circumstantial, but one could speculate that it might imply an increased susceptibility. When comparing all the reported cases (Table 1), there are in fact some common features that could be important for the diagnosis and management of aortitis as an adverse advent following G-CSF therapy. In all reported cases, no common underlying cause of aortitis other than G-CSF treatment was found. The patients were all between 52 and 70 years of age, which may reflect an increased risk of aortitis as a manifestation of giant cell arteritis in patients over the age of 50. However, since G-CSF treatment is also commonly given to patients over the age of 50 who are undergoing chemotherapy, a rare adverse event such as the one described herein (aortitis) is reasonably more likely to be seen in this age group. Furthermore, the onset of aortitis as early as 2–11 days after G-CSF initiation in all but one cases reported in the literature argues for a G-CSF-mediated adverse event rather than an unrelated disease. This short-time span from G-CSF initiation to aortitis manifestation may guide physicians as for when aortitis could be considered a differential diagnosis in patients receiving or patients who recently have received G-CSF therapy and present with signs of systemic inflammation. In the cases reported to date, the female-to-male ratio is 2:1, which is consistent with the increased risk of GCA in females [27]. All reported cases presented with signs of systemic inflammation, including elevated inflammatory markers (CRP and/or erythrocyte sedimentation rate, ESR) and were diagnosed by CT scan. In addition, aortitis was successfully treated with corticosteroid treatment in all reported cases, including the cases described in the present report.

It is worth noting that the two cases reported here occurred only a few months apart. Although this proximity may be coincidental given the very few cases previously reported, it might also indicate that aortitis is an underdiagnosed adverse event of G-CSF treatment.

5. Conclusion

We herein report two independent cases of G-CSF-induced aortitis. This potentially fatal adverse event seems to be very rare, but should be considered in cases of unexplained fever and/or clinical and laboratory findings that do not respond to antibiotics. Along with discontinuation of G-CSF therapy, the response to corticosteroid treatment was in both cases rapid and complete in conformity with the cases previously reported. Although the contribution of corticosteroids remains unclear, the cases presented herein and in previous literature suggest that moderate to high doses of corticosteroids should be initiated promptly upon diagnosis.

Consent for publication

Written informed consent was obtained from the patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Ethics approval and consent to participate

Both cases were observed by the authors in their role as physicians during the patients' routine care and these cases were thus not subjected to ethical board assessment.

Competing interest

The authors declare that they have no competing interests

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Authors' contributions

Conception and design: IP, AM and OW. Manuscript draft: IP, AM and OW. All authors were involved in the identification of the cases and care of the patients, and read and approved the final version of the manuscript prior to submission.

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