

CASE REPORT

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Acute adrenal insufficiency following arthroplasty: a case report and review of the literature

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Abstract

Background: Acute adrenal insufficiency is a potentially lethal condition rarely caused by bilateral adrenal haemorrhage due to heparin use. Most of the times, it is difficult to establish the diagnosis, as symptoms are not specific. Few cases have been reported in the literature.

Case presentation: A 52-year-old Caucasian woman presented with abdominal pain, vomiting and weakness nine days after arthroplasty and heparin use. Hyperkalemia, low cortisol and high adrenocorticotropic hormone levels were found, indicating adrenal insufficiency. Magnetic resonance imaging of the upper abdomen was compatible with preceding adrenal haemorrhage. Hydrocortisone and fludrocortisone were administered. Review of the literature revealed 36 cases of postoperative adrenal haemorrhage which are presented briefly.

Conclusion: Postoperative acute adrenal insufficiency due to haemorrhage is a rare condition. If patients are treated based on clinical suspicion, they have good chances to survive. Hydrocortisone is given permanently in the majority of the patients.

Keywords: Adrenal insufficiency, Arthroplasty, Heparin

Background

Acute adrenal failure (AAF) is a potentially life-threatening complication presenting with non-specific symptoms as abdominal pain, nausea, fever, tachycardia, hypotension and lethargy [1]. However, hyponatremia and hyperkalemia as indicators of adrenal insufficiency should be evaluated very thoroughly [2].

AAF may occur in patients with previously undiagnosed primary adrenal insufficiency and sometimes after bilateral adrenal infarction or postoperative haemorrhage in otherwise healthy individuals [1]. The postoperative period carries a high risk for haemorrhage, as platelet consumption may lead to bleeding in vital organs, independently of anticoagulant administration. Additionally, the use of heparin represents an independent risk factor that predisposes to haemorrhage [3]. Injuries during procedures such as extracorporeal shock-wave lithotripsy or electroconvulsive therapy [4,5] or use of certain materials and techniques may also predispose to coagulopathy and haemorrhage [6].

Moreover, hypothermia itself may play an important role in bleeding [6]. As signs and symptoms are not specific, they may easily lead to wrong diagnosis, such as postoperative septic shock or inflammation.

Total hip arthroplasty is a common surgical procedure associated with deep venous thrombosis and pulmonary embolism that are prevented by the use of anticoagulants [7,8]. The extensive use of anticoagulants in these operations explains the fact that bilateral adrenal haemorrhage is more often observed after knee or hip arthroplasty. However, orthopaedic surgery is probably associated with risk factors (other than anticoagulants) which lead to haemorrhage [9].

The use of low molecular weight heparin (LMWH) to avoid postoperative thromboembolic events can induce thrombocytopenia (heparin-induced thrombocytopenia [HIT]) and may lead to bilateral adrenal haemorrhage [2]. A pre-test clinical score (including thrombocytopenia, timing of platelet count fall, thrombosis, presence of other causes for thrombocytopenia, the so-called 4 T's) has been developed to establish the clinical suspicion of HIT [10], while heparin-platelet factor 4-immunoglobulin G (IgG)

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(PF4-IgG) antibodies and 14C-serotonin release assay are useful diagnostic tests [2].

The incidence of bilateral adrenal haemorrhage is estimated to be around 4.7–6.2 cases per million habitants in developed countries, but the prevalence is much higher in hospitalized patients, arising to 1.1% of them [11,12]. There are difficulties in establishing an early diagnosis of the disease [13] and adrenal haemorrhage is usually a post-mortem finding during autopsy performed to unravel the cause of death.

In addition to the elusive clinical presentation, imaging may also be deceiving: the enlarged haemorrhagic adrenals may be misdiagnosed as neoplastic masses, with irregular margins, though maintain their adreniform shape. Acute and subacute adrenal haemorrhage show high attenuation (50–90 HU) at unenhanced computed tomography (CT), without enhancement following intravenous (IV) contrast. In doubtful cases, decreased density and size of the adrenals during follow-up as well as the presence of calcifications may be extremely useful to confirm the diagnosis. Magnetic resonance imaging (MRI) is the most sensitive and specific imaging modality to confirm adrenal haemorrhage. Like CT, the appearance of adrenal haemorrhage on MRI also depends on the progression of the bleeding. The most characteristic sign on MRI is the low signal ring on T2 sequences during the chronic phase [14].

The aim of the present work was a) to present a case of acute adrenal insufficiency caused by bilateral adrenal haemorrhage observed after arthroplasty and b) to summarize the published data regarding this rare and interesting clinical entity.

Computerized literature search was performed in the PubMed electronic database. The original query provided 71 possibly relevant articles. Furthermore, 10 articles were retrieved after searching the “Related Articles” link and the references. Of these, 34 were finally selected (including 36 case reports), whereas the remaining 47 articles were excluded for the following reasons: spontaneous bilateral adrenal haemorrhage without apparent cause (n=9); concurrent diseases (n=7); bilateral adrenal haemorrhage due to heparin for other reason, not postoperatively (n=27); article in Japanese (n=1); reviews and letters to the editor (n=3).

In summary, 36 cases of postoperative bilateral adrenal haemorrhage have been documented. Mean age of patients during haemorrhage was 65.2 years (range 44–83) and there was no particular sex distribution. Abdominal pain, fever, vomiting and hypotension were the main symptoms at presentation, usually occurring between first and second week after surgery. Hyponatremia and hyperkalemia were the most common laboratory findings. In 27 out of 36 patients, diagnosis was made by CT scan, in two by abdominal ultrasound and in one by exploratory laparotomy. In four patients the diagnosis was confirmed after their

death during autopsy and in two cases the imaging was not described. Nine patients succumbed to adrenal insufficiency.

Patients’ clinical characteristics and diagnostic methods are summarized in Tables 1 and 2. Reported cases are divided into two groups: the first includes 21 patients with adrenal insufficiency after orthopaedic surgery (Table 1) and the second reports 15 patients with adrenal insufficiency after any other surgery (Table 2).

Case presentation

Patients’ history

A 52-year-old Caucasian woman, mother of two children, underwent right hip arthroplasty and was administered LMWH (enoxaparin 8,000 IU per day) for seven days in order to prevent thromboembolic events. Arthroplasty was successfully completed without intraoperative or early postoperative complications, except for a fall in platelet count from 214,000/ μ L to 116,000/ μ L. Haemoglobin and white blood cell count were normal. The patient was discharged from the hospital in good condition without any sign or symptom of haemorrhage, thromboembolism or infection.

9th postoperative day, emergency department

On postoperative day 9, she presented in the emergency department complaining of abdominal pain, vomiting and weakness. She was dehydrated and tachycardic (105 beats per minute). Decreased skin turgor and low blood pressure (90/60mm Hg) were observed. Biochemical exams indicated hyponatremia (128mmol/L, normal range 136–145) and hyperkalemia (5.97mmol/L, normal range 3.5–5.1), normal serum glucose levels, as well as normal kidney and liver function. The patient was afebrile and the wound healed satisfactory. The administration of isotonic solutions was decided but the patient responded poorly. Intravenous use of dopamine was added thereafter, resulting in slight improvement of clinical symptoms, mainly vomiting and arterial blood pressure. As the abdominal pain was persistent, the patient underwent abdominal CT which was indicative of “bilateral adrenal adenomas”. Due to this finding, the patient was referred to our department for further evaluation.

Referral to the endocrinology department

Considering the clinical signs of dehydration and the presence of hyperkalemia (5.72mmol/L, normal range 3.5–5.1) and hyponatremia (130mmol/L, normal range 136–145), adrenal insufficiency was suspected. Cortisol levels were measured and found to be very low (cortisol 40nmol/l, normal range 70–250nmol/l). A 250- μ g adrenocorticotrophic hormone (ACTH) stimulation test (Synacthen test) was performed for further evaluation; no increase in cortisol was observed confirming the diagnosis of primary adrenal

Table 1 Adrenal insufficiency after orthopaedic surgery

Cases	Author	Country	Age	Sex	Type of surgery	Diagnosis	Symptoms	Biochemical exams
1	Findling et al., 1987 [15]	USA	44	M	unspecified	CT	abdominal pain, vomiting, hypotension	hyponatremia, hyperkalemia
2	Delhumeau et al., 1989 [16]	France	76	F	total hip arthroplasty	abdominal ultrasound	abdominal pain, fever, hypotension, altered consciousness	hyponatremia, natriuresis, thrombocytopenia
3			74	M	tibial osteosynthesis	not done	abdominal pain, fever, hypotension, shock, altered consciousness	hyponatremia, thrombocytopenia
4			62	M	tibial osteosynthesis	CT	abdominal pain, asthenia, nausea	hyponatremia, thrombocytopenia
5	Ernest and Fischer, 1991 [17]	Australia	68	F	total hip arthroplasty	CT	fever, hypotension	hyponatremia, hyperkalemia
6	Souied et al., 1991 [18]	France	63	F	total hip arthroplasty	CT	fever, hypotension	hyponatremia, hyperkalemia
7	Bleasel et al., 1992 [19]	Australia	69	F	total knee arthroplasty	CT	fever, nausea, vomiting, abdominal pain, hypotension	hyponatremia, hyperkalemia
8	Hardwicke and Kisly, 1992 [20]	USA	63	F	bilateral total knee arthroplasty	CT	fever, nausea, anorexia, vomiting, abdominal pain, confusion, feeling of illness, hypotension	anemia, hyponatremia, hyperkalemia
9	Delhumeau et al., 1993 [21]	France	74	M	total hip arthroplasty, thrombectomy of both limbs due to bilateral arterial thrombosis	CT	abdominal pain, fever, hypotension, abdominal tenderness	hyponatremia, hyperkalemia
10	Santonastaso et al., 1993 [22]	Italy	not reported	F	osteotomy	CT	somnolence, asthenia, hypotension	not reported
11	Ries et al., 1994 [23]	USA	61	F	bilateral total knee arthroplasty	autopsy	abdominal discomfort, nausea, collapse	none
12	Cozzolino et al., 1997 [24]	USA	66	F	total knee arthroplasty	CT	nausea, anorexia, emesis, lethargy	hyponatremia, hyperkalemia, anemia, azotemia
13	Rowland et al., 1999 [25]	Australia	50	M	unspecified	CT	fever, abdominal pain, dizziness, hypotension	hyponatremia
14	Caubet et al., 1999 [26]	France	63	F	tibial osteosynthesis	CT	fever, hypotension, tachypnea	thrombocytopenia, hyponatremia, hyperkalemia, elevated INR
15	Scheffold et al., 2001 [27]	Germany	63	M	intracondylar nail-extension	abdominal ultrasound	abdominal pain, fever	leukocytosis
16	LaBan et al., 2003 [28]	USA	82	F	bilateral knee arthroplasty	CT	abdominal pain, nausea	elevated INR, hyponatremia
17	Schuchmann et al., 2005 [8]	USA	83	F	bilateral total knee arthroplasty	autopsy	anxiety, hypertension, midback pain, shortness of breath, shock	hyponatremia, hypochloremia, leukocytosis, anemia, elevated INR
18	Kurtz and Yang, 2007 [29]	USA	54	F	total hip arthroplasty	CT	fever, abdominal pain, orthostatic syncope	not reported
19	Mongardon et al., 2007 [30]	France	64	M	total hip arthroplasty	CT	fever, abdominal pain, confusion, hypotension	thrombocytopenia, high urinary sodium
20	Thota et al., 2012 [31]	USA	68	M	bilateral total knee arthroplasty	CT	fever, abdominal discomfort, anorexia, fatigue, hypertension, tachycardia, altered mental status	hyperglycemia, leukocytosis, anemia, thrombocytopenia, hyponatremia
21	Chow et al., 2012 [32]	USA	44	M	bilateral total knee arthroplasty	CT	hypotension, abdominal pain, tachycardia, fever	leukocytosis, D-dimers elevation, hyponatremia, thrombocytopenia

Table 2 Adrenal insufficiency after any surgery except for orthopaedic surgery

Cases	Author	Country	Age	Sex	Type of surgery	Diagnosis	Symptoms	Lab results
1	Steer and Fromm, 1980 [33]	USA	71	M	cholecystectomy	not done	abdominal pain, fever, vomiting, anorexia, weakness, hypotension	eosinophilia, hyponatremia, hyperkalemia, prothrombin time elevation
2	Jacobson et al., 1986 [34]	USA	55	M	retropubic prostatectomy	CT	fever, tachycardia, hypotension, dyspnea, abdominal pain, nausea, vomiting, diarrhea, ileus	hyponatremia, hyperkalemia
3	Miller et al., 1986 [35]	USA	81	F	aorto-iliac aneurysmectomy	CT	fever, nausea, vomiting, abdominal pain, lethargy	hyponatremia, hyperkalemia, leukocytosis
4	Homcy and Southern, 1989 [36]	USA	71	M	colectomy	autopsy	confusion, hypotension	hyponatremia
5	Ting et al., 1992 [37]	USA	62	M	coronary bypass grafting	CT	left flank pain, fever, tachypnea, tachycardia, tired, hypotension	leukocytosis, hyponatremia, hyperkalemia
6	Leschi et al., 1994 [38]	France	63	M	aortofemoral bypass graft	autopsy	confusion	hyponatremia, hyperkalemia
7	Belmore and Walters, 1995 [39]	USA	53	M	laparoscopic cholecystectomy	CT	abdominal pain, anorexia, fatigue, hypotension, dehydration	hyponatremia, hyperkalemia, hyperamylasemia, partial thromboplastin time prolonged
8	Scheiwiller et al., 2002 [40]	Switzerland	71	M	low anterior rectum resection	CT	anorexia, abdominal pain, fever, hypotension	hyponatremia
9	Sousa Escandon et al., 2002 [41]	Spain	82	M	partial nephrectomy for renal adenocarcinoma	CT	abdominal pain, nausea, fever, hypotension, severe respiratory distress	hyponatremia, azotemia, anemia, leukocytosis, thrombocytosis
10	Bakaeen et al., 2005 [42]	USA	51	M	coronary artery bypass graft	CT	fever, abdominal pain, diarrhea, orthostatic hypotension, tachycardia	thrombocytopenia
11	Gutenberg et al., 2007 [43]	Germany	69	M	intracranial tumor surgery	exploratory laparotomy	hypotension, abdomen tense	not reported
12	Munoz Corsini et al., 2008 [44]	Spain	63	M	right hemicolectomy	CT	disorientation, difficulty in breathing, tachycardia, fever	leukocytosis, anemia, increase in fibrinogen,
13	Peel and Whitelaw, 2011 [45]	USA	60	M	right hemicolectomy	CT	backache, fever, hypotension, agitation, confusion	hyponatremia, thrombocytopenia, leukocytosis
14	Rosenberger et al., 2011 [2]	USA	69	M	gastrectomy, esophagojejuno-stomy, cholecystectomy	CT	abdominal and flank pain, tachypnea, tachycardia, hypotension, oliguria, myocardial infarction	oliguric renal failure
15	Balsach Sole et al., 2012 [46]	Spain	70	M	cephalic duodenopancreatectomy	CT	lethargy, hypotension	hyponatremia, hypoglycemia

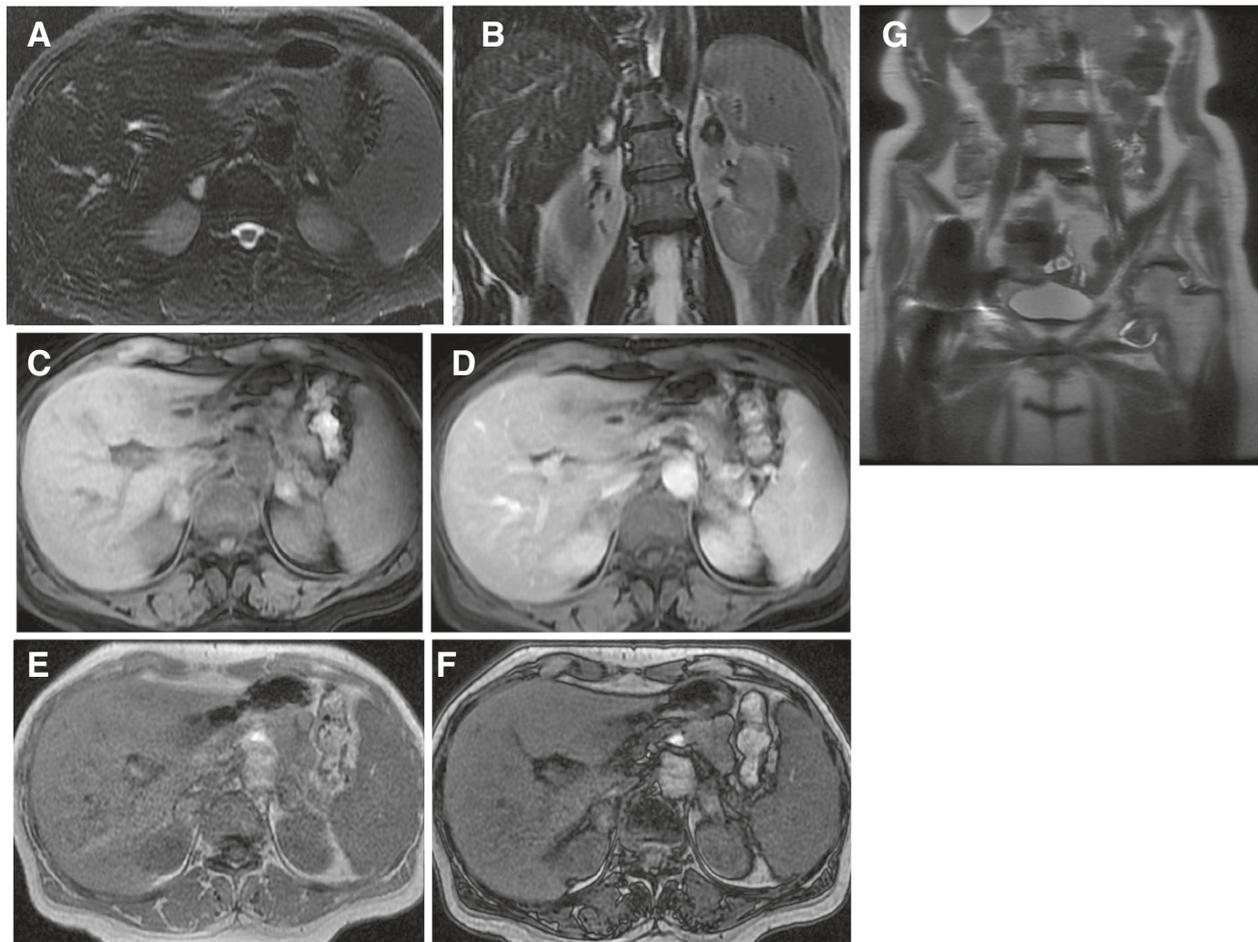


Figure 1 Abdominal magnetic resonance imaging obtained 15 days after surgery. Axial (A) T2 weighted image with fat suppression, coronal (B) T2 weighted image, in and out of phase axial (C, D) T1 images, axial (E, F) T1 weighted images with fat saturation before and after contrast administration, coronal (G) T2-weighted image. Bilateral adrenal lesions showing high signal both on T1-weighted (E) and on T2-weighted images (A, B), and low signal rim on T2-weighted images (A, B), representing haemosiderin. The lesions do not show any signal drop-off on T1 in- (C) and out- of phase images (D). After intravenous contrast administration (F) no enhancement is depicted. These findings are consistent with chronic adrenal hematomas. Note the signal void in the right pelvis due to the presence of a metallic right hip prosthesis.

insufficiency (basal cortisol equal to 32.9nmol/l, 30 and 60 min after Synacthen equal to 34nmol/l and 32.1nmol/l respectively, normal range 70-250nmol/l). ACTH levels were very high (1763.4pg/ml, normal range 9–52). MRI of the upper abdomen showed the presence of bilateral adrenal “lesions” with greatest dimension 2.3cm on the right and 2.5cm on the left. On T2 weighted-images the above mentioned findings had high signal intensity with a low signal intensity ring along the periphery compatible with the presence of haemosiderin consequence of previous haemorrhage and chronic hematomas (Figure 1). No signal drop-off on in- and out- of phase images and no significant enhancement following iv contrast was depicted.

Diagnostic evaluation and therapy

Considering the variety of causes that could trigger bilateral adrenal haemorrhage in accordance with the medical history

of the patient, traumatic injury, burns or pregnancy were ruled out [13]. Furthermore, she was afebrile without any clinical signs of septic shock. Antiphospholipid syndrome was excluded due to the absence of vascular thrombosis and the history of two normal deliveries. Based on the fact that the patient had received LMWH postoperatively, haemorrhage was considered to be the cause of adrenal failure. Heparin-PF4-IgG antibodies (measured by enzyme-linked immunosorbent assay [ELISA]) were negative. Moreover, the low pretest clinical score for HIT (total 2 points, 1 point from thrombocytopenia and 1 point from surgery) in the patient was correlated with high- negative predictive value for heparin induced adrenal haemorrhage [10].

Replacement therapy with hydrocortisone and fludrocortisone was started. Three months later, ACTH levels fell to 397pg/ml. Adrenal MRI showed that the lesions had decreased in size and had homogeneous low

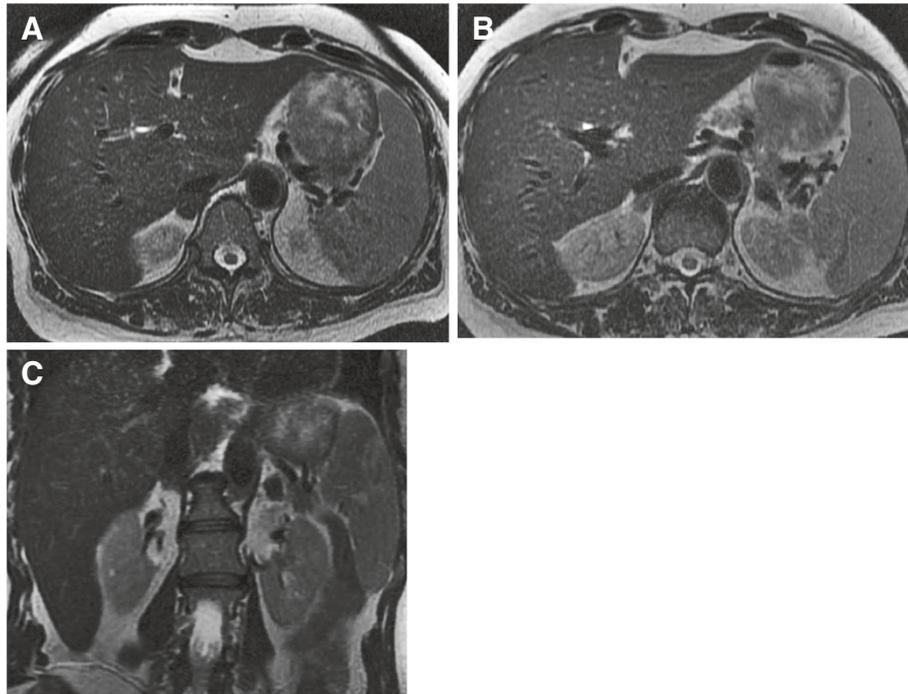


Figure 2 Abdominal magnetic resonance imaging obtained 3.5 months after surgery. Axial (A, B) and coronal (C) T2-weighted images showing a decrease in size and a change of signal of the bilateral adrenal hematomas. The lesions now have homogeneous low signal, due to haemosiderin.

signal on T2 weighted images, findings consistent with the evolution of hematomas (Figure 2). The oral replacement with hydrocortisone and fludrocortisone remains until the present time.

Conclusions

Bilateral adrenal haemorrhage is a rare disease which can follow major surgical operations. It should be suspected in patients presenting with fever, abdominal pain, confusion and hemodynamic collapse not responding to standard medical treatment [31]. The increased incidence after orthopaedic surgery, the association with anticoagulants use and the great mortality in misdiagnosed cases should keep physicians alerted.

Consent

Written informed consent was obtained from the patient 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.

Abbreviations

AAF: Acute adrenal failure; LMWH: Low molecular weight heparin; HIT: Heparin induced thrombocytopenia; IgG: Immunoglobulin G; PF4-IgG: Platelet factor 4- immunoglobulin G; CT: Computed tomography; IV: Intravenous; MRI: Magnetic resonance imaging; ACTH: Adrenocorticotropic hormone; ELISA: Enzyme-linked immunosorbent assay.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SM and MB reviewed the literature and prepared the draft. KX performed and discussed imaging. EM collected patients' clinical data. SG performed the immunoassay. AC and KPP conceived the idea and made the amendments of the manuscript. All authors read and approved the final manuscript.

Disclosure statement

The authors have nothing to disclose.

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