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ACUTE AORTIC THROMBOSIS WITH LIMB ISCHEMIA IN A PATIENT WITH INFLUENZA A

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ABSTRACT

Background: Influenza A is associated with venous and, less commonly, arterial thrombosis. Stroke and myocardial infarction comprise most arterial events, with only rare involvement of the aorta and peripheral arteries.

Case report: We report a 61-year-old male hospitalized for influenza A pneumonia and rhabdomyolysis who developed acute right lower limb ischemia on day 7 of his admission. Computed tomography scan of the abdomen revealed acute descending and infrarenal aortic thrombosis with embolic occlusion of the right popliteal artery. He underwent successful embolectomy and fasciotomy with good functional outcome.

Conclusion: This case demonstrates that Influenza A infection may provoke severe and unusual thrombotic events, even during the convalescent phase of illness. Prompt diagnosis and intervention are required to reduce the risk of limb amputation and mortality.

KEYWORDS

Influenza A, thrombosis, limb ischemia

LEARNING POINTS

- While influenza A is a known trigger for major arterial events such as stroke and myocardial infarction, this report demonstrates it may also provoke peripheral arterial thrombosis, resulting in critical limb ischemia.
- The diagnosis of arterial thrombosis requires a high index of suspicion, as it may occur during the convalescent phase of illness and result in loss of limb and death without emergent intervention.
- Although case reports suggest arterial thrombosis may be mediated by disease severity and traditional cardiovascular risk factors, limb ischemia may develop in patients without a prior history of thrombosis or established cardiovascular disease.

INTRODUCTION

Influenza A has been associated with a range of extrapulmonary manifestations, including both venous and arterial thrombosis[1]. Several case series and reviews have demonstrated an association between influenza A infection and stroke and acute myocardial infarction (MI), but aortic

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and peripheral arterial events are less commonly seen[1–4]. We report a case of acute aortic thrombosis with embolic occlusion of the right popliteal artery leading to critical limb ischemia.

CASE DESCRIPTION

A 61-year-old man presented to hospital with severe weakness, cough, and shortness of breath of unclear duration. He reported falling at his home several days before admission, but due to confusion, it was not possible to determine if he had been immobilized. His medical history included bipolar I disorder, chronic obstructive pulmonary disease, hypertension, and dyslipidaemia. There was no history of stroke, MI, venous thromboembolism, or coagulopathy. He reported smoking two packs of cigarettes per day for most of his adult life. He recalled good adherence to his medications, which included amlodipine 5 mg daily, valproic acid 500 mg twice daily, risperidone 4 mg daily, loxapine 50 mg daily, atorvastatin 10 mg daily, paroxetine 40 mg daily, trazodone 50 mg daily, and clonazepam 0.5 mg three times daily. Vaccination history against influenza was unknown.

In the emergency department, he was noted to be alert but mildly confused with a blood pressure of 90/56, heart rate of 120, respiratory rate of 20, oxygen saturation of 90 percent on four litres of oxygen via nasal cannula, and a temperature of 38.6°C. Chest auscultation revealed decreased breath sounds bilaterally and diffuse expiratory wheezes. Cardiac, abdominal, neurological, and musculoskeletal examinations were unremarkable with no evidence of peripheral ischemia, oedema, or compartment syndrome.

Laboratory results *(Table 1)* were notable for a creatinine of 131 µmol/l (prior baseline 48 µmol/l), troponin of 595 ng/l, N-terminal pro-B-type natriuretic peptide (NT-proBNP) of 2360 ng/l, creatine kinase (CK) of >20 000 U/l, and markedly elevated aspartate and alanine transaminases of 1860 U/l and 207 U/l, respectively. Electrocardiogram showed sinus tachycardia at 113 beats per minute without ischemic changes. Chest X-ray was normal. Contrast-enhanced computed tomography (CT) scan of the chest demonstrated multifocal mixed ground glass and dense opacities bilaterally. No pulmonary emboli were seen. Given his transaminase elevations, a contrast-enhanced CT scan of the abdomen was ordered in the emergency department to rule out an intrabdominal source of sepsis and showed only nonspecific perinephric stranding. No vascular abnormalities were seen. A nasopharyngeal swab was positive by polymerase chain reaction (PCR) for influenza A (H1N1, pdm09 subtype). Blood cultures and nasopharyngeal PCR for severe acute respiratory syndrome coronavirus 2 were negative.

The patient was diagnosed with influenza A pneumonia and started on oseltamivir and piperacillin-tazobactam for empiric coverage of superimposed bacterial pneumonia due to concern for sepsis. Given prominent wheezing and his smoking history, he received short-acting bronchodilators for 48 hours and a single dose of methylprednisolone.

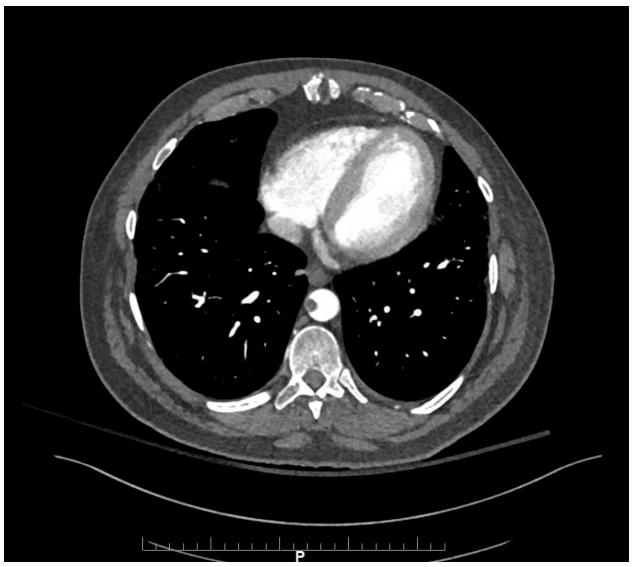


Figure 1. Contrast-enhanced computed tomography angiography of the abdomen demonstrating acute thrombus in the distal descending thoracic aorta.

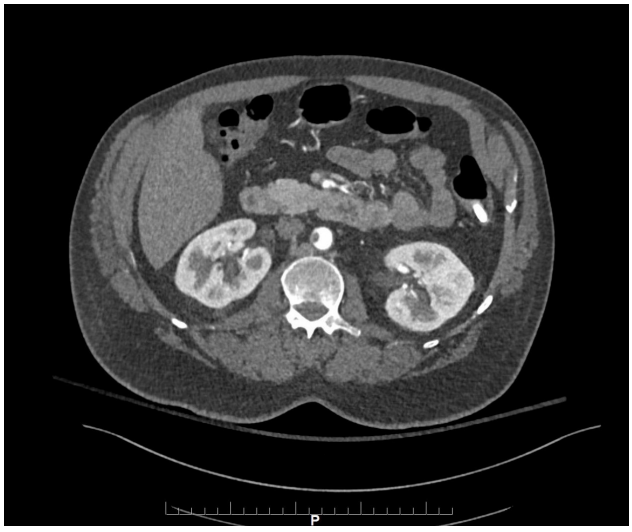


Figure 2. Contrast-enhanced computed tomography angiography of the abdomen demonstrating intraluminal exophytic thrombus in the infrarenal abdominal aorta.

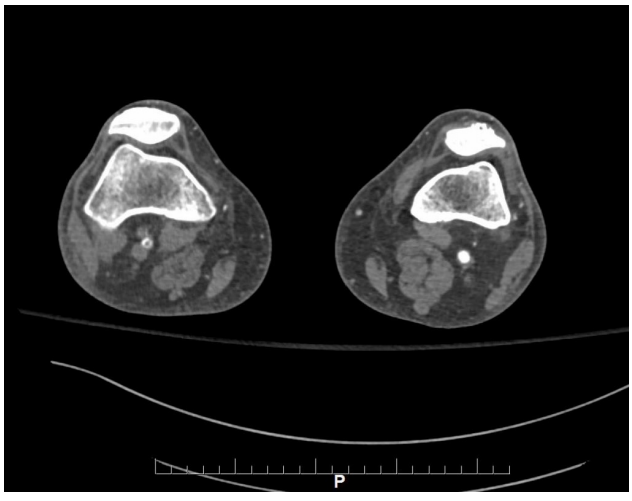


Figure 3. Contrast-enhanced computed tomography angiography of the lower extremities demonstrating acute embolus within the right popliteal artery.

Test result	Day 1	Day 2	Day 3	Day 4	Day 5
Hgb (132-170 g/l)	151	108	129	123	126
WBC (3.5-10 ×10^9/l)	10.6	10.85	9.58	7.61	8.35
Platelets (140-400 ×10^9/l))	120	96	116	122	150
INR (0.9-1.1)	1	*	*	*	*
Glucose (4-8 mmol/l)	6.8	*	*	5.1	*
Sodium (135-145 mmol/l)	133	134	137	135	138
Potassium (3.5-5 mmol/l)	3.8	4.3	4.1	3.9	3.8
Chloride (97-105 mmol/l)	94	100	100	99	97
Bicarbonate (20-30 mmol/l)	24	19	24	23	29
Anion gap (7-18 mmol/l)	15	15	13	13	12
Creatinine (55-105 µmol/l)	131	106	80	62	47
Magnesium (0.74-1 mmol/l)	1.02	0.92	1.02	0.9	0.91
Total bilirubin (3-20 µmol/l)	6	3	*	*	*
Uric acid (180-450 µmol/l)	*	426	*	*	*
VBG: pH (7.32-7.43)	7.45	*	*	7.4	7.44
VBG: pCO_2 (40-50 mmHg)	39	*	*	56	51
VBG: HCO_3 (23-31 mmol/l)	27	*	*	35	35
ALP (40-105 U/l)	48	33	*	*	*
AST (10-50 U/l)	1860	1190	*	*	*
ALT (10-50 U/l)	207	156	*	*	*
CK (0-240 U/l)	>22000	>22000	>22000	20800	8340
LDH (135-225 U/l)	>1800	*	*	*	*
Troponin (0-13 ng/l)	595	242	*	*	*
Lipase (13-60 U/l)	44	*	*	*	*
CRP (<10 mg/l)	86.4	*	*	*	*
Valproic acid (350-700 µmol/l)	380	*	*	*	*
NT-proBNP (<300 ng/l)	2360	*	*	1970	*

* no data point available.
Abbreviations: Hgb, hemoglobin; WBC, white blood cell count; INR, international normalized ratio; VBG, venous blood gas; pCO2, partial pressure of carbon dioxide; HCO3, bicarbonate; ALP, alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; CK, creatine kinase; LDH, lactate dehydrogenase; CRP, C-reactive protein; NT-BNP, N-terminal prohormone of brain natriuretic peptide.

Table 1. Timeline of lab results following admission.

Enoxaparin was started on day 1 of his admission for venous thromboembolism prophylaxis. He received intravenous furosemide on day 2 of his admission due to worsening hypoxia in the context of elevated NT-proBNP and multifocal airspace opacities, but this was discontinued due to evidence of poor intake prior to admission and hypovolemia on exam arguing against pulmonary congestion as the cause for his presentation.

The aetiology of rhabdomyolysis was presumed due to influenza A and potential immobilization. Psychotropic medications were held on admission out of concern for possible neuroleptic malignant syndrome, but our patient

Clinical variable	Bunce et al.[2]	Hüzmeli et al.[7]	Ishiguro et al.[8]	Present case
Age (sex)	50 (female)	28 (male)	58 (male)	61 (male)
Comorbidities	None	Congestive heart failure; permanent pacemaker; protein s deficiency*	MI; hypertension; smoking	Bipolar I disorder; COPD; hypertension; dyslipidaemia; smoking
Site of arterial thrombus	Infrarenal aorta	Infrarenal aorta	Left ventricle	Descending aorta, Infrarenal aorta
Thrombotic manifestations	Bilateral lower extremity ischemia	Bilateral lower extremity ischemia	Right lower extremity ischemia; Bilateral PE; Bilateral lower extremity DVT; Acute MI	Right lower extremity ischemia
Onset of thrombotic symptoms	Not specified**	On presentation to hospital	On presentation to hospital	Day 7 of hospitalization during convalescence
Influenza A subtype (strain)	H1N1 (pdm09)	H1N1 (strain not reported)	Not reported	H1N1 (pdm09)
Vaccination status	Unknown	Unknown	Unvaccinated	Unknown
In-hospital complications	Left AKA; respiratory failure requiring ECMO	Acinetobacter baumannii bacteraemia with sepsis; acute kidney injury	Acute MI; acute DVT and PE; right foot amputation	Acute kidney injury; rhabdomyolysis
Outcome	Survived	Expired	Survived	Survived

*diagnosed during hospitalization.
**thrombosis noted to have developed early in course of admission.
Abbreviations: AKA, above-the-knee amputation; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; ECMO, extracorporeal membrane oxygenation; MI, myocardial infarction; pdm09, pandemic 2009; PE, pulmonary embolism.

Table 2. Comparative clinical characteristics of published cases of influenza-associated limb ischemia.

did not have rigidity or autonomic instability, making this diagnosis unlikely. He was treated with intravenous crystalloid fluid and maintained excellent urine output. On day 4, there was complete renal recovery and improvement in his CK. Intravenous fluids were stopped due to increasing oxygen requirements and evidence of pulmonary oedema on a repeat chest X-ray necessitating an additional dose of intravenous furosemide. An echocardiogram showed normal left ventricular (LV) and valvular function without evidence of LV thrombus.

On day 7, despite improvement in his respiratory symptoms and oxygen requirements, our patient complained of new right ankle pain. Examination revealed a cold, pale limb with absent distal pulses, but normal sensation and power. Urgent contrast-enhanced CT angiography of the abdomen and extremity revealed an acute 1.2 cm thrombus in the distal descending thoracic aorta *(Fig. 1)* and an 8 mm thrombus in the infrarenal abdominal aorta *(Fig. 2)* with embolic occlusion of the p1 and p2 segments *(Fig. 3)* of the right popliteal artery. We started intravenous unfractionated heparin, and the patient underwent emergent right popliteal embolectomy and four compartment fasciotomies. There was excellent vascular recovery post-operatively without ischemic sequalae in the right lower limb. He was discharged on day 18 to an inpatient rehabilitation program on oral anticoagulation with apixaban.

DISCUSSION

Influenza A infection is associated with diverse extrapulmonary manifestations affecting the cardiovascular, musculoskeletal, hematologic, hepatic, and renal systems[1]. Increased rates of both arterial and venous thrombosis have also been reported in hospitalized patients[2–5]. Conversely, vaccination against influenza is associated with a reduced rate of cardiovascular events and death[6]. Existing data from case series and observational studies demonstrate that acute MI and stroke comprise the majority of arterial events, with aortic and peripheral arterial thrombosis only rarely reported[2–5]. In a recent scoping review, Rubino et al. identified 21 cases of influenza-associated arterial thrombosis, including 11 strokes, 5 MIs, and 4 peripheral arterial events, including 2 cases of aortic thrombi[5].

Our patient suffered multiple acute aortic thrombi with embolization to the right popliteal artery despite no history of thrombophilia, though he did have significant cardiovascular risk factors associated with atherosclerotic disease, including hypertension, dyslipidaemia, and smoking. We were only able to identify 3 other case reports of acute

limb ischemia accompanying influenza A infection. Two, like our patient, were diagnosed with infrarenal aortic thrombosis during their hospitalization for viral pneumonia, while the third patient presented with right leg ischemia secondary to an LV thrombus[2,7,8]. Available clinical data for all 4 cases are summarized in *Table 2*.

Despite heterogeneity in patient age and underlying health status, the presence of cardiovascular disease or risk factors in 3 of the 4 cases suggests influenza may precipitate thrombosis or plaque rupture in patients with underlying arterial disease. The pathophysiology underlying this effect is incompletely understood, but the innate cellular response to viremia may lead to endothelial injury with consequent plaque rupture through various mechanisms, including the direct viral activation of platelets, production of pro-inflammatory bone marrow macrophages, and T cell activation within atheroma[9]. Viral subtype may further modify thrombotic risk, as H1N1 was isolated in our patient and most cases identified in the scoping review by Rubino et al, including the 2 patients with de novo aortic thrombosis[5]. Notably, all 4 patients with limb ischemia were seriously or critically ill with viral pneumonia, implying that disease severity also influences thrombotic risk, presumably through a general inflammatory response. This conclusion is supported by observational studies demonstrating an increased incidence of MI after a variety of viral infections[3]. However, incident risk is higher for influenza and severe acute respiratory syndrome coronavirus 2 than other viruses, suggesting pathogen-specific factors remain important, especially in otherwise asymptomatic patients[3,10].

Our patient was unique in that he had no evidence of limb ischemia at presentation to hospital and in fact developed symptoms during the convalescent phase of illness. This permitted early diagnosis of his limb ischemia, which may account for his excellent vascular outcome compared with the remaining cases, two of which required limb amputation with the third dying of septic shock from *Acinetobacter baumannnii* bacteremia.

Future research is needed to delineate the specific mechanisms and epidemiological risk factors underlying influenza-associated arterial thrombosis. Our patient's case demonstrates the importance of vigilance for uncommon, but serious thrombotic complications in patients admitted with severe disease. Early detection and intervention, as in our patient, is essential to prevent limb amputation and death.

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