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Influenza A(H1N1) Infection Complicated by Hemolytic Uremic Syndrome in an Older Adult: A Case Report

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Abstract

Influenza A(H1N1) is a rare trigger for thrombotic microangiopathy (TMA), most often presenting as hemolytic uremic syndrome (HUS). HUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Some cases of influenza-associated HUS are thought to result from direct viral injury to the vascular endothelium, while others may reflect influenza triggering complement activation in individuals with an underlying complement regulatory defect. We report a case of an 80-year-old woman admitted with influenza A(H1N1) pneumonia who developed HUS. Thrombotic thrombocytopenic purpura was considered unlikely, as the activity of ADAMTS13 was not severely reduced. She recovered without dialysis or disease-specific treatment such as plasma therapy or complement inhibition. This case highlights the diagnostic challenges of TMA in the setting of influenza infection and the importance of early expert input in management. It also illustrates that recovery from influenza-associated HUS with best supportive care is possible, although an underlying complement predisposition cannot be excluded without further testing.

Categories: Hematology, Nephrology, Infectious Disease
Keywords: adamts13, atypical hemolytic-uremic syndrome (ahus), drug-induced immune hemolytic anemia, hemolytic uremic syndrome (hus), influenza a(h1n1), thrombotic microangiopathy (tma)

Introduction

Influenza A(H1N1) is associated with a broad spectrum of complications, with older adults at disproportionately increased risk of severe disease and mortality [1-3]. Pulmonary complications include severe pneumonia, acute respiratory distress syndrome, and exacerbation of underlying chronic lung disease [1], while extrapulmonary manifestations may involve the cardiovascular, neurological, renal, and other organ systems [2].

Thrombotic microangiopathy (TMA) describes a pathological process characterized by endothelial injury and vascular occlusion, resulting in microangiopathic hemolytic anemia, thrombocytopenia, and organ injury [4]. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) have traditionally been regarded as the primary TMA syndromes [4]. TTP is driven by severe deficiency of ADAMTS13, the enzyme that cleaves von Willebrand factor multimers, whereas HUS includes Shiga toxin-associated HUS and complement-mediated HUS (CM-HUS), the latter driven by dysregulation of the alternative complement pathway [4]. Both TTP and CM-HUS may be inherited or acquired, with acquired forms typically caused by autoantibodies against ADAMTS13 or complement factor H, respectively [4]. TMA may also arise in the context of a coexisting condition, such as infection, pregnancy, or malignant hypertension [4].

TMA associated with influenza A(H1N1) is rare and has been predominantly linked to HUS and, less commonly, TTP [5]. Whether influenza A(H1N1) carries a higher propensity for HUS than other influenza subtypes remains uncertain [5]. Proposed mechanisms of influenza-associated TMA are varied and include unmasking of an underlying complement regulatory defect, development of ADAMTS13 inhibitors, direct viral injury to the endothelium, neuraminidase activity, and platelet and thrombin activation [5,6].

Case Presentation

An 80-year-old woman presented to the emergency department with a four-day history of nonproductive cough, fatigue, reduced oral intake, and watery diarrhea. She had recently been exposed to a viral illness within her household. Her past medical history included stage 3 chronic kidney disease, atrial fibrillation, and ischemic heart disease. On admission, she was febrile (38.2°C), tachypneic (respiratory rate 28/min), and hypoxemic (oxygen saturation 80% on room air), with clinical signs of dehydration and right-sided mid-to-

lower zone crackles on auscultation. Chest radiography demonstrated patchy opacification in the right lower zone consistent with infective consolidation (Figure *1*). Initial laboratory investigations showed a normal white blood cell count (5.2 × 10^9/L) with lymphopenia (0.21 × 10^9/L) and an elevated C-reactive protein (CRP) level of 392 mg/L. Hemoglobin and platelet counts were within normal limits (126 g/L and 191 × 10^9/L, respectively), and renal function was at baseline, with a creatinine level of 96 µmol/L and an estimated glomerular filtration rate of 48 mL/min/1.73 m^2. She was started on supplemental oxygen (12 L/min via a non-rebreather mask), intravenous fluids, and empiric antibiotics (amoxicillin-clavulanate and doxycycline). A respiratory viral polymerase chain reaction panel was positive for influenza A(H1N1) on day one of admission. Her white blood cell count gradually increased over the following days, peaking at 18.4 × 10^9/L on day four.

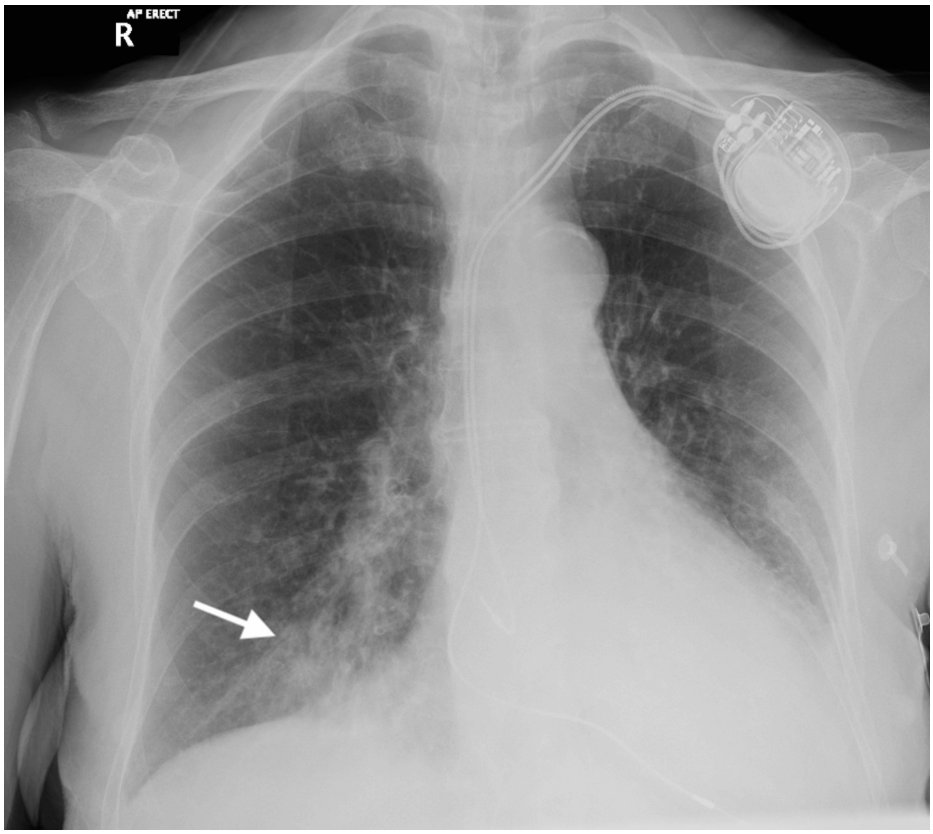


FIGURE 1: Anteroposterior chest radiograph on admission

Patchy opacification in the right lower zone (arrow), consistent with infective consolidation. A cardiac pacemaker is noted.

On day six, the patient deteriorated clinically, developing macroscopic hematuria and jaundice. Her diarrhea had resolved by this time. Repeat laboratory testing revealed a fall in hemoglobin to 102 g/L (mean corpuscular volume 92 fL) and thrombocytopenia (92 × 10^9/L), alongside a rise in total bilirubin to 102 µmol/L (predominantly unconjugated), undetectable haptoglobin (<0.1 g/L), and worsening renal function, with creatinine rising to 130 µmol/L. Coagulation studies demonstrated a mildly prolonged prothrombin time (14 seconds), with a normal activated partial thromboplastin time (22.8 seconds) and elevated fibrinogen (5.01 g/L). The absolute reticulocyte count at this stage was normal at 32 × 10^9/L. Serial peripheral blood films demonstrated red cell fragments (schistocytes) accompanied by spherocytes and polychromasia, with occasional burr cells and nucleated red blood cells. Genuine thrombocytopenia was confirmed on blood film review. The combination of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury raised suspicion of TMA, specifically HUS. The hematology and nephrology teams were consulted, and TTP and CM-HUS were identified as the leading diagnostic considerations. An urgent workup for TTP was initiated. The PLASMIC score was five, indicating intermediate risk [7], and ADAMTS13 activity was sent for analysis. The sample was taken before any blood transfusion. Stool cultures were also sent. Following specialist discussion, including advice from the national specialist center for atypical HUS, the TMA was considered most likely related to her underlying infection, and plasma exchange was therefore not pursued. Anticomplement therapy was similarly deferred, with a plan to reconsider it if renal function or hemolysis failed to improve following resolution of the infection. Oseltamivir was started, antibiotic therapy was escalated to piperacillin-tazobactam, and supportive management with supplemental oxygen and intravenous fluids was continued.

ADAMTS13 activity, available on day seven, was mildly reduced at 37.9 IU/dL. Lactate dehydrogenase, initially unreportable because of sample hemolysis, was markedly elevated at 2,261 U/L on day eight. Stool cultures were negative for enteric bacterial pathogens, including *Campylobacter*, *Salmonella*, *Shigella*, and *Escherichia coli* O157:H7, although specific Shiga toxin testing was not performed. The Epstein-Barr virus (EBV) DNA viral load was elevated at 9,346 IU/mL and was managed with clinical monitoring without specific antiviral therapy. Testing for cytomegalovirus, human immunodeficiency virus, and pneumococcal antigen was negative, as were multiple blood and urine cultures. Abdominal ultrasound demonstrated no organomegaly. A direct antiglobulin test (DAT) was weakly positive (1+) for immunoglobulin G (IgG) and negative for C3d. Serum complement C3 was normal (1.29 g/L), and C4 was low (0.08 g/L). Antiphospholipid testing revealed an elevated anticardiolipin IgG level (257 GPL U/mL) and a positive lupus anticoagulant, with normal anti-beta-2-glycoprotein I antibodies (Tables *1*, *2*). She had no previous history of thrombosis.

Parameter	Results (day)	Reference range
Hemoglobin (g/L)	126 (0), 102 (6), nadir 51 (9), 109 (discharge), 117 (follow-up)	115–148
Platelet count (× 10^9/L)	191 (0), 92 (6), nadir 44 (7), 283 (discharge), 313 (follow-up)	140–400
White blood cell count (× 10^9/L)	5.2 (0), peak 18.4 (4)	2.9–9.6
Lymphocyte count (× 10^9/L)	0.21 (0)	0.80–3.50
MCV (fL)	92 (6)	81–100
Reticulocyte count (× 10^9/L)	32 (6), 202 (12)	25–105
Total bilirubin (µmol/L)	102 (6)	<21
LDH (U/L)	2,261 (8)	≤240
Haptoglobin (g/L)	<0.1 (6)	0.3–2.0

TABLE 1: Hematological and hemolysis parameters

Day of measurement shown in parentheses (day 0: day of admission). Follow-up: one month after discharge. MCV: mean corpuscular volume; LDH: lactate dehydrogenase.

Parameter	Results (day)	Reference range
Creatinine (µmol/L)	96 (0), 130 (6), peak 487 (12), 160 (discharge), 110 (follow-up)	47–99
CRP (mg/L)	392 (0)	<5
PT (seconds)	14 (6)	9.7–12.0
APTT (seconds)	22.8 (6)	20.0–29.0
Fibrinogen (g/L)	5.01 (6)	1.70–4.90
ADAMTS13 activity (IU/dL)	37.9 (7)	60–146
Complement C4 (g/L)	0.08 (6)	0.10–0.40
Anticardiolipin IgG (GPL U/mL)	257 (8)	<10

TABLE 2: Renal, inflammatory, coagulation, and immunological parameters

Day of measurement shown in parentheses (day 0: day of admission). Follow-up: one month after discharge. CRP: C-reactive protein; PT: prothrombin time; APTT: activated partial thromboplastin time; IgG: immunoglobulin G; GPL: IgG phospholipid units.

The patient required multiple red blood cell transfusions, with hemoglobin reaching a nadir of 51 g/L. The platelet count fell to a nadir of 44 × 10^9/L, although platelet transfusion was not required. She was transferred to a nephrology unit on day 10 for monitoring and renal supportive care. Creatinine continued to rise, peaking at 487 µmol/L on day 12 before improving. Hemodialysis was considered but ultimately not required, as serum potassium remained normal, there was no metabolic acidosis, and renal function gradually recovered with supportive care alone. The absolute reticulocyte count increased to 202 × 10^9/L by

day 12 (reticulocyte percentage 8.77%). Weekly erythropoietin was started on day 14 as supportive treatment for ongoing anemia. The patient gradually improved and was discharged on day 28. At discharge, creatinine was 160 µmol/L, hemoglobin was 109 g/L, and the platelet count was 283 × 10^9/L (Figure 2). The white blood cell count and CRP had normalized. At one-month follow-up, creatinine had further improved to 110 µmol/L and hemoglobin to 117 g/L, with a platelet count of 313 × 10^9/L, and erythropoietin was discontinued. Repeat lupus anticoagulant testing at 12 weeks was planned, with ongoing follow-up through her local nephrology team.

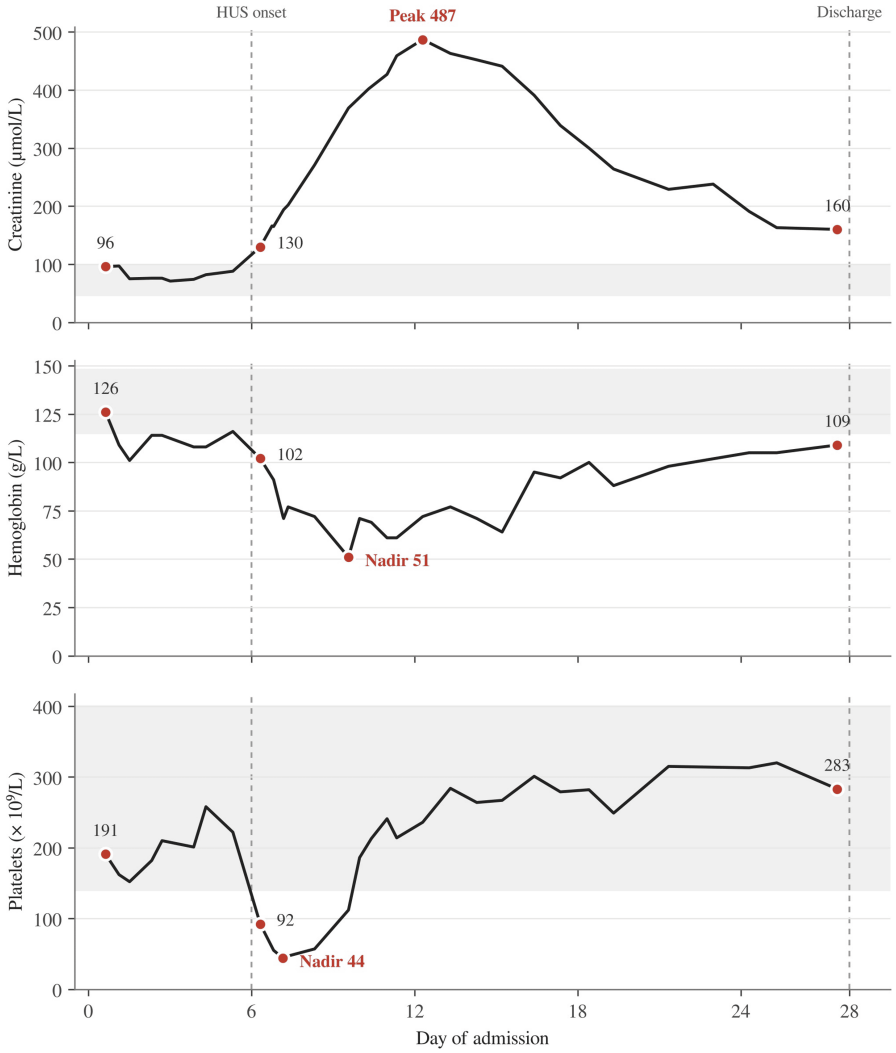


FIGURE 2: Serial creatinine, hemoglobin, and platelet count during admission

Shaded areas indicate reference ranges. HUS: hemolytic uremic syndrome.

Discussion

Identifying the specific form of TMA is essential, as each form carries distinct management implications and may require time-sensitive treatment [4,8]. However, this can be challenging for several reasons [4,5]. Clinical features overlap between different forms of TMA. For example, diarrhea and neurological symptoms lack diagnostic specificity, as either may occur irrespective of the underlying cause [4]. Key investigations, such as ADAMTS13 activity and complement studies, are also limited by long turnaround times [4]. Furthermore, a trigger such as influenza does not map onto a single underlying mechanism, so the differential diagnosis should remain broad [5]. Given this diagnostic complexity, early involvement of specialists with expertise in TMA, including hematologists and nephrologists, is important [4,8].

A detailed discussion of the assessment of TMA is beyond the scope of this report, but it broadly begins with a thorough history and examination, including a review of drug exposures and coexisting conditions [4]. TTP should be suspected in patients with severe thrombocytopenia (platelet count <30 × 10^9/L) and relatively

mild kidney dysfunction (serum creatinine <200 µmol/L) [4]. Tools such as the PLASMIC score can help estimate the probability of TTP [4,7]. CM-HUS should be suspected in patients with a relevant family history, severe kidney dysfunction, or TMA that fails to improve rapidly following treatment of the suspected underlying cause [4]. In influenza-associated TMA, recommended investigations include ADAMTS13 activity, complement studies, and genetic screening for complement and coagulation factor variants [5]. Complement studies in this setting comprise plasma C3, total and alternative pathway hemolytic activity (CH50 and AH50), soluble C5b-9, and anti-factor H antibodies [5]. Concurrent invasive pneumococcal disease should also be excluded, as influenza transiently increases susceptibility to pneumococcal infection, which can itself cause HUS [5].

General principles of TMA management recommend starting empiric treatment without waiting for the results of further testing [4]. Therapeutic plasma exchange and high-dose corticosteroids are considered when TTP is suspected, whereas C5 inhibition is considered when CM-HUS is suspected [4]. There are no established treatment recommendations specific to influenza-associated HUS or TTP, and the evidence base remains limited by small patient numbers [5]. In their review of 25 reported cases of influenza-associated TMA, Bitzan and Zieg emphasized the benefit of best supportive care, including blood product transfusion, management of respiratory and renal complications, and treatment of the underlying influenza infection and any concurrent bacterial infection [5]. Most patients received plasma therapy, two received anticomplement therapy, and outcomes were generally favorable [5]. Notably, the median age of patients in the review was 15 years, and the oldest was 68 years, so evidence in older adults remains particularly limited [5].

The clinical and laboratory findings in our patient were most consistent with influenza A(H1N1)-associated HUS, based on its onset during confirmed influenza infection and the absence of a clear alternative cause. Although the PLASMIC score indicated only an intermediate probability of severe ADAMTS13 deficiency, the score has reduced sensitivity for TTP in older adults and may therefore be less reliable in this population [9]. The subsequent ADAMTS13 result excluded severe deficiency, making TTP unlikely [4]. Shiga toxin-associated HUS appears less likely given the overall clinical context and negative stool cultures. The EBV DNAemia most likely represents viral reactivation secondary to severe illness rather than primary infection [10]. Similarly, the positive antiphospholipid antibodies may reflect transient positivity, which is well described during acute infection and does not in itself indicate antiphospholipid syndrome [11].

The weakly positive IgG DAT and persistent spherocytes suggest that an immune mechanism may also have contributed to hemolysis, although DAT positivity is not by itself diagnostic of immune hemolysis [12]. Exposure to amoxicillin-clavulanate before hemolysis raises the possibility of drug-induced immune hemolysis or a positive DAT through nonimmunologic protein adsorption [13,14]. Without elution or drug-dependent antibody testing, neither could be confirmed [15]. Warm autoimmune hemolytic anemia appears less likely, given that hemolysis resolved without the immunosuppressive therapy usually required in this condition [16]. A drug-related immune component to the hemolysis therefore remains possible but unproven.

Our patient's recovery without targeted therapy is consistent with the generally favorable outcomes reported in influenza-associated HUS [5]. However, this alone does not rule out a complement-mediated process, as spontaneous recovery has been described in patients with suspected or confirmed complement gene mutations, including one who subsequently relapsed and required complement inhibition [5,17]. This is particularly relevant given that seven of the eight patients in the review by Bitzan and Zieg who underwent genetic testing had complement gene mutations [5]. Taken together, and in the absence of complement studies beyond C3 and C4 levels or genetic screening, an underlying complement-mediated predisposition unmasked by infection cannot be excluded in our patient.

The timing of antiviral therapy in this patient also merits consideration. A multicenter study of intensive care unit patients aged 65 years and older with influenza A(H1N1) found that oseltamivir initiated more than 48 hours after symptom onset was independently associated with higher mortality [18]. Our patient had already presented beyond this window, and oseltamivir was started once features of HUS became apparent. It remains uncertain whether earlier antiviral therapy would have prevented or attenuated TMA in this patient, as current evidence does not establish whether neuraminidase inhibitors prevent or ameliorate influenza-associated TMA [5].

Conclusions

Although rare, HUS should be considered a potential complication of influenza A(H1N1), including in older adults. Multidisciplinary input remains integral to investigation and management in such cases, given the complexity of distinguishing between forms of TMA. Current knowledge of influenza-associated TMA relies largely on isolated case reports with limited diagnostic workup, including the present case. Wider reporting of complement studies, genetic screening, and treatment outcomes may help to clarify the mechanisms of this condition and guide future treatment.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Qasim Alhaj Ali

Acquisition, analysis, or interpretation of data: Qasim Alhaj Ali, Aya Gendeel, Yosra Taha, Ella Fernandes, Dimitra Stathi

Drafting of the manuscript: Qasim Alhaj Ali, Aya Gendeel, Yosra Taha, Ella Fernandes

Critical review of the manuscript for important intellectual content: Qasim Alhaj Ali, Dimitra Stathi

Supervision: Qasim Alhaj Ali, Dimitra Stathi

Disclosures

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