CASE REPORT

Catastrophic antiphospholipid syndrome (CAPS) induced by influenza A virus subtype H1N1

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SUMMARY

Catastrophic antiphospholipid syndrome (CAPS) has been associated with several bacterial and viral infections. We presented a case report of a woman who presented to the emergency room, with influenza A virus subtype H1N1 which progressed to CAPS in the course of 17 days. We believe this is the first case that links CAPS with H1N1.

BACKGROUND

Catastrophic antiphospholipid syndrome (CAPS) is a severe autoimmune condition accompanied by rapid multiorgan failure. It is characterised by antibodies against phospholipids in vascular cell membranes and is a much more fulminant form of antiphospholipid antibody syndrome (APS) typically seen in patients with systemic lupus erythematosus. Even though catastrophic APS has a devastating 30–50% mortality rate, it represents less than 1% of all cases of APS, making it extremely difficult to study.^{1–2}

CAPS is diagnosed by following the Asherson criteria: (1) evidence of involvement of ≥ 3 organs/systems/tissues; (2) confirmation of small vessel occlusion in ≥ 1 organ/tissue by histopathology; and (3) laboratory confirmation of antiphospholipid antibodies (aPL) which includes anticardiolipin antibodies as well as lupus anticoagulants.^{1–3}

Patients typically present with small vessel thromboses that lead to complications within cardiac, pulmonary and renal systems.^{3–4} CAPS is most often seen in patients following bacterial and/or viral infections, including *Salmonella typhi*, HIV, parvovirus B19 and hepatitis C.^{4–6}

The exact mechanism of developing CAPS after an infection is unknown, although it has been speculated to involve molecular mimicry by the invading organism.^{3–5} This conclusion has been hard to support because these infections have no known common antigen and the presence of aPL increase the risk for CAPS but do not predict the progression to CAPS.⁵

To our knowledge, there has been no case of catastrophic APS induced by an influenza strain reported in the medical literature. We presented a case of catastrophic APS in a woman who presented to the emergency room (ER) with symptoms of the flu that was confirmed as the H1N1 strain.

CASE PRESENTATION

A 50-year-old woman presented to the ER with cough, congestion, fatigue, memory lapses, myalgias and dysphagia for 1 week. She had self-medicated

with an antihistamine. Her medical history was insignificant except for a chronic obstructive pulmonary disease from a 34 pack-year history of smoking. A chest X-ray revealed bilateral infiltrates with labs showing white cell count $2600/\text{mm}^3$, platelets $100\,000/\text{mm}^3$ and elevated liver function tests (LFTs). Significant vital signs included a temperature 100.4°F and room air saturations of 89%. She was admitted and started on ceftriaxone, azithromycin, methylprednisolone, nebulised bronchodilators and fluids. She tested negative for HIV, antinuclear antibody, *Legionella*, *Mycoplasma*, *Aspergillus* and an H1N1 nasal swab. Her dysphagia was attributed to oral candidiasis and her elevated LFTs to antihistamine ingestion. Acetylcysteine was administered.

Within 5 days she developed respiratory distress requiring intubation. A CT scan of her chest revealed diffuse ground glass infiltrates bilaterally. She progressed into acute respiratory syndrome (ARDS) with septic shock, requiring a triple lumen catheter and a right radial arterial line. She experienced, refractory hypoxia with saturations of 40% requiring an inverse ratio on her ventilator, high levels of positive end-expiratory pressure and fraction of inspired oxygen. A bronchoscopy was non-diagnostic. Her LFTs remained elevated despite a normal abdominal ultrasound. Blood cultures were negative. She received broad spectrum antibiotics and voriconazole. Endotracheal sputum for H1N1 PCR was obtained. Her serum lactate dehydrogenase (LDH) level returned at 1586 IU/L ($\text{nl}=105\text{--}333\text{ IU/L}$). Empirical Oseltamivir Phosphate (Tamiflu) was started and her LDH (1352 IU/L) as well as C reactive protein (CRP) improved.

Her right hand became cool and discoloured with cyanotic nail beds (figure 1). An angiogram of the right arm revealed occlusion of the right radial

Figure 1 Cyanosis and ischaemia of right fingers.

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artery. She underwent thrombectomy which reoccluded. She was anticoagulated. Heparin-induced thrombocytopenia antibody was negative. Her PCR for H1N1 came back positive. A repeat CT scan of the chest revealed improving bilateral infiltrates but new evidence of multiple splenic infarctions, a left renal infarction and hepatomegaly. A transesophageal echocardiogram was negative for thrombus or vegetation. Carotid angiogram was negative.

OUTCOME AND FOLLOW-UP

Her last week of hospitalisation included failed attempts at ventilator weaning and a decompensated mental status. She had hemiplegia of the right upper and lower extremities with gaze paresis. Lumbar puncture was unremarkable. An MRI of the brain revealed multiple lesions of the right frontal, occipital, cerebellar and left temporoparietal cortex. Results were positive for lupus anticoagulant and cardiolipin IgM. High-dose steroids were initiated for probable vasculitis. LDH levels continued to decrease (1051–644 IU/L).

On the basis of having a positive cardiolipin IgM, lupus anticoagulant, vascular events involving multiple organs and a positive real-time reverse transcriptase PCR (rRT-PCR) for H1N1 she was diagnosed with CAPS induced by influenza A virus subtype H1N1.

She was transferred to a tertiary care centre for 3 weeks of plasmapheresis after which she improved and was discharged to a rehabilitation centre.

DISCUSSION

Patients who present with influenza A subtype H1N1 may develop catastrophic APS. This patient presented with flu-like symptoms and tested negative for influenza A virus subtype H1N1 by nasal swab. Antiviral therapy was started on the rationale of an evolving viral process, limited reliability of the H1N1 nasal swab testing and the presence of an elevated LDH level. A positive rRT-PCR confirmed influenza A subtype H1N1.

The H1N1 influenza was first detected in the USA in April 2009.⁷ Laboratory testing by the Centers for disease control (CDC) confirmed that this virus was new to humans and involved person-to-person transmission. The CDC outlines ideal methods for collecting, storing and shipping nasopharyngeal swab specimens.⁷ Although, our nasal swab was negative, it may have been a function of timing or handling of the specimen. The definitive test for H1N1 remains the rRT-PCR assay or viral cultures.^{7 8}

H1N1 is resistant to two antiviral drugs, amantadine and rimantadine, but susceptible to the antiviral drugs oseltamivir and zanamivir.⁷ Typically, antiviral treatment is started immediately for any patient with confirmed or suspected influenza who is hospitalised, severely ill or at high risk for complications, (ie, >65 years, immunosuppressed, pregnant).^{7 8} Our patient was hospitalised with pneumonia; in addition, her clinical picture was suspicious and improved on medication initiation, shown by a decrease in her LDH and CRP levels. Clinical recognition that nasal swabs can be negative with a positive rRT-PCR, especially in the presence of pulmonary infiltrates.

Mortality in the USA with '2009 H1N1' occurred in people ranging in age from 22 months to 57 years.⁷ A retrospective study by Xiuming *et al*, examined the independent risk factors for mortality in 155 hospitalised adults infected by H1N1 in Beijing, China. Comorbidity existed in 81 patients (52.3%). The most common symptoms were fever (93.5%), cough (91.6%), and dyspnoea (47.1%). Pneumonia was diagnosed in 129 patients (83.2%). Elevated LDH was seen in 58% of patients,

and was the only laboratory value associated with an increased risk of mortality ($p=0.027$). Twenty-seven patients (17.4%) died within 28 days of hospitalisation. Oseltamivir was initiated in 125 patients but only 16 patients received it within 48 h of symptom onset. Diabetes, septic shock, altered mental status and treatment with corticosteroids were also associated with higher mortality rates ($p=0.052$).⁹ Our patient survived even though she had an elevated LDH level of 1586 IU/L and received corticosteroids.

Mortality rates with CAPS were first reported to be approximately 50%^{1 2} but with early diagnosis and aggressive treatment, it has now fallen to 30%.¹⁰ The main cause of death (33.3%) was cerebral involvement (stroke, hemorrhage, encephalopathy), followed by cardiopathology and infection. Our patient survived despite the mortality rates associated with H1N1 as well as CAPS independently.

The limitations of this case rest in the difficulty in diagnosing CAPS. The CAPS Registry Project Group has correlated over 400 patient's case report worldwide, reviewing their clinical, laboratory and therapeutic data.¹¹ Women represent 72% of all reported cases (age range 11–60) with a mean age of 37 years.^{3 11} There are two distinct clinical features, organs affected by a thrombotic event and a systemic inflammatory response syndrome. Renal disease (71%) is the most frequent presentation, followed by pulmonary complications (64%) with ARDS the most common pulmonary manifestation. Dyspnoea is a common symptom; cerebral manifestations are frequent (62%), and small vessel cerebrovascular occlusive disease is seen. Skin complications, *livedo reticularis*, purpura and skin necrosis occur in 50% of cases.^{3 11} Our patient presented with ARDS, dyspnoea, cerebral infarct, small vessel occlusions and skin necrosis as seen in figure 1.

Twenty years after CAPS was originally described in 1992, we believe this is the first case of CAPS induced by the influenza A virus subtype H1N1 virus.

Learning points

- ▶ H1N1 presented with extremely high lactate dehydrogenase level.
- ▶ H1N1 presented with severe vasculitis symptoms (probable catastrophic antiphospholipid syndrome).
- ▶ Empiric antivirals should be started empirically with suspicion of H1N1 in severely ill patients.

Contributors All authors contributed in the preparation of this manuscript and in patient care.

Competing interests None.

Patient consent Obtained.

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