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N2010 Adult-Onset Still's Disease Complicated by Hemophagocytic Syndrome and Catastrophic Antiphospholipid Syndrome Resulting in Four Limb Amputation

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Hemophagocytic syndrome is a potentially fatal hyperinflammatory condition, characterized by aggressive proliferation of activated macrophages and histiocytes that phagocytose other hemopoeitic cells. This overactive immune reaction is responsible for the clinical manifestations of HPS [1], namely prolonged fever, hepatosplenomegaly, lymphadenopathy, skin rash, central nervous system abnormalities, pancytopenia and coagulation disorders. HPS has been classically subdivided into primary or genetic, and secondary or acquired, although more recently this distinction has been thought to be an oversimplification. The secondary type may be associated with autoimmune diseases (when it is sometimes referred to as macrophage-activation syndrome), specifically systemic juvenile idiopathic arthritis and adult-onset Still's disease; viral infection, most commonly Epstein-Barr virus; and underlying malignancy [1].

Catastrophic antiphospholipid syndrome is a potentially life-threatening variant occurring in less than 1% of APS patients. The underlying pathology involves thrombotic microvasculopathy, which can rapidly lead to multiorgan failure and death in 30–50% of patients. Important precipitating factors include infection and preceding surgical procedures [2].

HPS = hemophagocytic syndrome
APS = antiphospholipid syndrome

PATIENT DESCRIPTION

Six months before her admission to our hospital, a 20 year old black female student developed arthritis in her wrists, elbows and knees, and was initially diagnosed with seronegative rheumatoid arthritis and started on a combination of immunosuppressants. She was admitted to her local hospital 4 months after her initial presentation, with chest pain, pyrexia and a rash on her arms and face. In view of the additional findings of splenomegaly, abnormal liver function tests and a markedly elevated ferritin level of 25,913 ng/ml, she was re-diagnosed with adult-onset Still's disease and prednisolone 60 mg daily was began.

She presented again to her local hospital with ongoing pyrexia and clinical deterioration a few days after discharge. *Klebsiella pneumoniae* was cultured in the urine. Chest X-ray revealed a pneumonic process. A computed tomography chest scan showed small bilateral pleural effusions and a small pericardial effusion. She was treated for urosepsis with intravenous amikacin and meropenem. However, she became hemodynamically compromised and a few days later developed generalized tonic-clonic seizures. CT and magnetic resonance imaging of the head and cerebrospinal fluid examination were normal. Bone marrow trephine revealed evidence of hemophagocytosis. Several days later she developed right foot-drop. This evolved into a sensory and motor disturbance in a glove and stocking distribution and severe pain in her limbs, with weakening of her peripheral pulses. Doppler studies confirmed distal vaso-occlusion in all four limbs. In an attempt to restore perfusion, prostacyclin and heparin infusions were administered. Rheumatologists at her local hospital optimized her immunosuppression with intravenous methylprednisolone pulses and initiated intravenous immunoglobulin. At this stage she was transferred to our tertiary center's intensive care unit for specialist input.

On admission to our hospital, the patient was hemodynamically stable. She had cool peripheries with absent peripheral pulses and diminished upper and lower limb reflexes. Blood results [Table 1] revealed anemia and thrombocytopenia in the context of a marked inflammatory response. Liver function tests were abnormal and there was a significant hyperferritinemia. Antiphospholipid screen revealed positive lupus anticoagulant (using Taipan snake venom assay) but negative anti-cardiolipin and β2-GPI antibodies. The coagulation screen and blood film were consistent with disseminated intravascular coagulopathy. Further search for infection demonstrated

Table 1. Blood results on admission to St Thomas' Hospital

Blood test	Result	Normal range
White cell count	15.9 x 10^9/L	4–11 x 10^9/L
Neutrophils	14.9 x 10^9/L	1.5–7 x 10^9/L
Hemoglobin (g/dl)	8.5	12–15
Platelets	36 x 10^9/L	150–400 x 10^9/L
Sodium (mmol/L)	127	135–145
Potassium (mmol/L)	5.3	3.5–5
Creatinine (µmol/L)	47	45–84
Alkaline phosphatase (IU/L)	351	35–129
Alanine aminotransferase (IU/L)	99	4–45
Bilirubin (µmol/L)	16	0–21
Albumin (g/L)	23	40–52
C-reactive protein (mg/L)	204	0–4
Erythrocyte sedimentation rate (mm/hr)	18	0–15
Creatine kinase (IU/L)	21,480	25–195
Ferritin	39,727 ng/ml	22–275 µg/L
Prothrombin time INR	› 10	2–4.5 ratio
Activated partial thromboplastin time	› 10	0.8–1.2 ratio
Fibrinogen (g/L)	0.31	1.67–5.43
D-dimer (µg/ml)	71	‹ 0.25
Lactate dehydrogenase (IU/L)	11,643	0–250

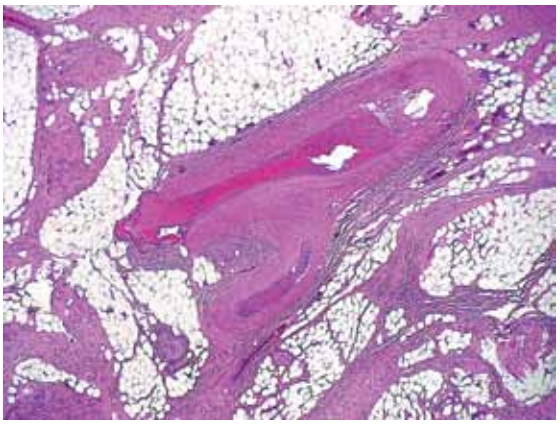
cytomegalovirus viremia. Autoimmune serology (antinuclear antibody, anti-double-stranded DNA, extractable nuclear antigen, anti-neutrophil cytoplasmic antibodies, rheumatoid factor) was negative and complement levels were normal. Urinary examination revealed heavy proteinuria (urinary protein:creatinine ratio 5296), despite normal serum creatinine. Urinary cytology showed granular casts and dysmorphic red cells. Doppler scans confirmed progression of distal limb vaso-occlusion, with arterial thromboses to the level of both forearms and knees.

Medical treatment consisted of antimicrobial agents (meropenem and antiviral drugs) to treat the underlying sepsis; management of DIC with fresh frozen plasma, cryoprecipitate and anticoagulation; and iloprost infusion, plasma exchange, IVIG and high dose steroids. Unfortunately, within 24 hours her condition deteriorated and she developed well-demarcated dry gangrenous limbs. She consequently underwent quadruple amputations in a single-stage operation 3 days after admission to our hospital. Histopathology from specimens of her limb amputations [Figure 1] showed widespread DIC with early ischemic necrosis of the epidermis and skin appendages.

Her postoperative recovery was complicated by neutropenic sepsis, although no source was clearly pinpointed. She suffered from further thrombotic episodes leading to skin necrosis in her proximal limbs, and for this reason her initial anticoagulation with intravenous heparin infusion was switched to lepirudin, a direct thrombin inhibitor. Bleeding complications included a small subarachnoid hemorrhage and upper gastrointestinal bleeding. In total, she underwent a further five operations to revise her amputations. In spite of this, over the next 6 months she made a very promising recovery. The combination of intensive physiotherapy and the fitting of prosthetic limbs enabled her to walk with the use of a crutch by the time of discharge. Her anticoagulation was switched to warfarin (target international normalized ratio 3-4) and her prednisolone dose was tapered down to 7.5 mg daily. The ferritin level dropped to 1327 ng/ml at discharge [Figure 2].

DIC = disseminated intravascular coagulopathy
IVIG = intravenous immunoglobulin

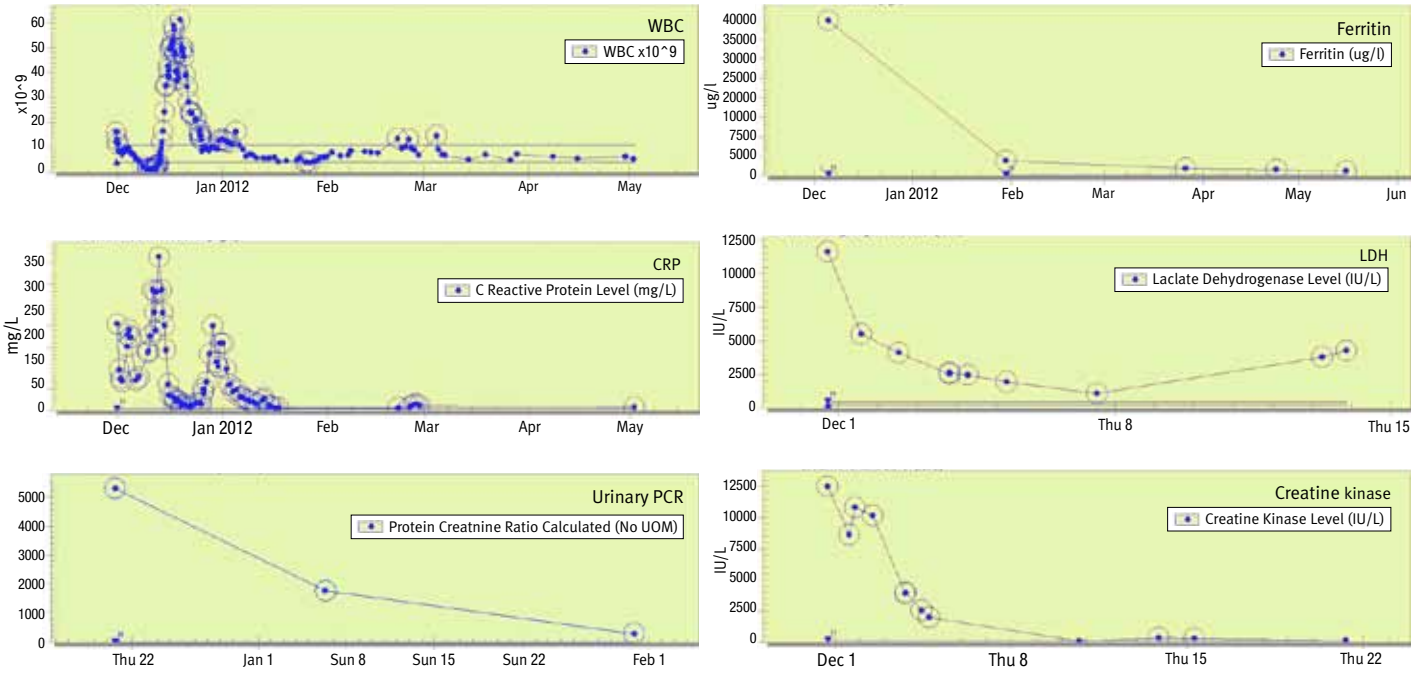
Figure 1. Histopathology from right arm amputation specimen showing acute vascular thrombosis (Courtesy Dr. F. Tungekar)



COMMENT

This is a complex case of a young woman with adult-onset Still's disease, who presented with sepsis, and went on to suffer from widespread DIC resulting in infarction of her limbs. Two main diagnoses were considered. The first was that of catastrophic APS. Indeed, when considering the classification [Table 2] [3], she met all four of the necessary criteria, with affected organs including her arterial circulation, skin and most likely her kidneys. Her antiphospholipid screen was difficult to interpret in the context of sepsis and the concomitant use of anticoagulation; however, lupus anticoagulant remained positive (in compliance with the International Society on Thrombosis and Haemostasis guidelines [4]) 3 months after the initial thrombotic episode. The second diagnosis in question was HPS, and she met six of the eight diagnostic criteria [Table 3] [1]. To further support this diagnosis, she had an underlying diagnosis of a rheumatologic condition that is associated with HPS and infective triggers consisting of

Figure 2. Trend of blood results and disease markers, from December 2011 to May 2012



WBC = white blood cell count, PCR = protein creatinine ratio

Table 2. Diagnostic criteria for catastrophic APS: all four are required for definite diagnosis

a. Evidence of involvement of ≥ 3 organs, systems and/or tissues
b. Development of manifestations simultaneously or in less than a week
c. Confirmation by histopathology of small vessel occlusion in ≥ 1 organ or tissue
d. Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibody)

Table 3. Diagnostic criteria for HPS: criteria A or B must be met for a diagnosis

A. A molecular diagnosis consistent with HPS: pathological mutations of PRF1, UNC, Munc18-2, Rab27a, STX11, SH2D1A or BIRC4
OR
B. 5/8 criteria:
a. Fever 38.3°C
b. Splenomegaly
c. Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood):
- Hemoglobin ‹ 9 g/dl (in infants ‹ 4 weeks: Hb ‹ 10)
- Platelets ‹ 100 x 10^3/ml
- Neutrophils ‹ 1 x 10^3/ml

d. Hypertriglyceridemia (fasting 265 mg/dl) and/or hypofibrinogenemia (≤ 150 mg/dl)
e. Hemophagocytosis in bone marrow or spleen or lymph nodes or liver
f. Low or absent natural killer cell activity
g. Ferritin › 500 ng/ml
h. Elevated soluble CD25 (soluble interleukin-2 receptor alpha)

Criteria fulfilled by our patient are highlighted in green

Klebsiella urosepsis and cytomegalovirus viremia, another recognized trigger of HPS. There is one previous report of APS-related HPS [5].

Ferritin is best known as the cellular storage protein for iron. It is also an acute-phase reactant that coordinates cellular defense against oxidative stress and inflammation. Elevated serum ferritin is one of the hallmarks of HPS; it is also characteristically high in adult-onset Still's disease and often correlates with disease activity [6]. Interestingly, an association has been reported between hyperferritinemia and serologic APS in patients with systemic lupus erythematosus [7]. To our knowledge, this is the first report of HPS in association with adult-onset Still's disease and catastrophic APS.

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