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Severe inflammatory response and vasculitis leading to quadruple limb amputations

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Lesson

A systemic inflammatory response causing multi-organ failure and requiring multiple amputations was refractory to all treatments except Anakinra, and the cause remains unclear.

Case report

A previously fit 33-year-old Somali woman returned from holiday in Canada with an urticarial rash on her upper arms accompanied by fever, dyspnoea, polyarthralgia, fatigue and headache. The rash resolved but the other symptoms continued, and after four weeks she received Clarithromycin for pharyngitis. A week later, she suffered a miscarriage at six weeks' gestation (G4 P3) and was given Trimethoprim for a urinary tract infection. After a further week of persistent symptoms, she was admitted for treatment of pneumonia with IV Meropenem and Clarithromycin but deteriorated and was admitted to the intensive treatment unit (ITU) with type I respiratory failure. She was tachycardic with cool peripheries but normotensive, and all peripheral pulses were palpable. She was pyrexial (38.9°C) and fully alert with no focal neurology. The differential diagnosis on ITU admission was systemic inflammatory response syndrome (SIRS) secondary to sepsis or pulmonary embolism (PE). She continued on IV antibiotics and was commenced on therapeutic low-molecular weight heparin (Clexane) until CT pulmonary angiogram excluded PE. Echocardiogram excluded endocarditis and evacuation of the uterus showed no retained products. All cultures were negative and blood results revealed a white cell count of 25.1×10^9/L, CRP of 197 nmol/L and Ferritin >40,000 ng/mL. All other investigations were unremarkable (Table 1). She soon required intubation and ventilation and the initiation of two vasopressor infusions (dopamine and noradrenaline). After 48 h, she remained pyrexial and active cooling was commenced with haemofiltration; this necessitated anticoagulation with IV unfractionated heparin. Within 24 h, she developed a non-blanching, purpuric rash over her breasts, abdomen and all four limbs which rapidly developed into large, tense bullae and full-thickness necrosis at the fingertips and toes. An abdominal skin biopsy revealed necrotizing small vessel vasculitis. She received a three-day course of 1 g methylprednisolone; however, after 48 h the necrosis had covered the limbs, breasts and abdomen, and peripheral pulses were no longer palpable. After a further week with continued skin loss and minimal response to steroids, it was considered that her condition may be due to adult Still's disease. Other causes had been excluded; she had a raised Ferritin level and met the Yamaguchi criteria. For this reason, she was commenced on Anakinra (100 mg daily), which had shown some benefit in previous case reports of adult Still's disease. She responded rapidly and within a week was extubated with decreasing vasopressor requirements. On further investigation, an angiogram showed asymmetric iliac arteries with no flow beyond the popliteal arteries, and a muscle biopsy revealed non-viable tissue below the knees. She underwent bilateral above-knee and below-elbow amputations and debridement of skin over her abdomen and breasts. Five months later, she has undergone extensive skin grafting and is now receiving rehabilitation with limb prostheses.

Discussion

This patient presented with SIRS and progressive necrotizing vasculitis of unknown cause. Fifty percent of vasculitis cases are idiopathic, but 15–20% are secondary to infection, 15–20% associated with inflammatory disease, 10% due to a drug reaction

Table 1. Investigation results.

Positive results	Negative/normal results
Microcytic anaemia (Hb 7–11) Elevated WCC (50.4), CRP (257), Ferritin (67313) Deranged clotting (elevated APTT and PT) Deranged LFTs (elevated ALT and γ-GT) Bone marrow: increased haemophagocytic activity. Electrophoresis: possible α thalassaemia carrier. Blood film: reactive looking film. Skin biopsy: necrotic small vessel vasculitis.	**Cultures** Blood, urine, sputum, throat swab, vaginal swab, abdominal wound, bone marrow, BAL, abdominal skin biopsy, pleural fluid, CSF, TB quantiFERON test **Serology/infectious diseases** ASOT, *Chlamydia*, *Clostridium difficile*, CMV, Hepatitis, HIV, Rubella, Syphilis, Toxoplasmosis, *Mycoplasma pneumoniae*, Flavivirus, Dengue antibodies, West Nile virus, Alphavirus, strongyloides, Q fever, *Rickettsia*, *Coxiella burnetii*, Meningococcal, *Brucella*, Parvovirus, *Borrelia burgdorferi*, Malaria. Previous EBV but no active infection. **Rheumatology** ANCA, ANA, complement, RF, anti-dsDNA, ENA, anticardiolipin antibody. Immunofluorescence, cryoglobulin, sickle cell negative

and 5% associated with malignancy.[1] Infectious causes were deemed unlikely as extensive cultures showed no growth. A drug reaction was considered as she was exposed to multiple drugs including Clarithromycin, Teicoplanin, Ciprofloxacin, Clindamycin, Rifampicin and Paracetamol which have all been reported to cause vasculitis.[2] Heparin is also known to cause skin necrosis and both subcutaneous and IV routes have been implicated with varying severity; however, the ischaemia is thought to be caused by platelet aggregation and thrombosis rather than a vasculitis.[3,4]

Both adult Still's disease and Takayasu's arteritis were considered as inflammatory causes. Adult Still's disease commonly presents with a triad of fever, salmon pink rash and arthralgia.[5] Inflammatory markers, including ferritin, are usually raised and pancytopenia can occur as a result of haemophagocytosis.[5] Diagnosis is based on the Yamaguchi criteria which requires five criteria to be met (two must be major) along with the exclusion of other causes (Table 2).[6] Our patient met six of the criteria.

Only one case report links this condition with vasculitis; a 43-year-old male with adult Still's disease was found to have leukocytoclastic vasculitis on skin biopsy. His condition improved with corticosteroids.[7] Similarly, only one report describes amputation associated with adult Still's disease; a 23-year-old woman developed disseminated intravascular coagulation (DIC) leading to autoamputation of the distal phalanges of two fingers. She also responded to corticosteroids.[8]

Takayasu's arteritis usually affects women of Asian origin aged 20–40. There is granulomatous inflammation of the aorta and major branches leading to stenosis, thrombosis and aneurysms and it can be associated with fever, arthralgia and malaise.[9] Diagnosis criteria from the American College of Rheumatology requires three of the following six criteria to be met:

1. Age ≤40.
2. Claudication of extremities.
3. Decreased pulsation in one/both brachial arteries.
4. 10 mmHg difference in systolic blood pressure between arms.
5. Bruits over subclavian artery or abdominal aorta.
6. Angiographic narrowing of aorta, primary branches or large arteries in upper or lower extremities.[10]

Our patient met criteria one, two, three and six. Many reports describe skin lesions in association with Takayasu's arteritis, especially pyoderma gangrenosum, livedo reticularis and erythema nodosum. One

Table 2. Yamaguchi criteria for diagnosis of adult Still's disease.[6]

Major criteria	Minor criteria
Fever ≥39 for 1 week*	Sore throat*
Arthralgia for 2 + weeks*	Lymphadenopathy
Typical rash	Abnormal liver function*
Leukocytosis*	Hepatomegaly/splenomegaly
	Negative RF, ANA*

*Criteria exhibited by our patient.

report describes a previously fit woman with leg claudication which progressed to gangrene requiring amputation. She was diagnosed with Takayasu's arteritis following angiogram.[9]

Conclusion

Our patient developed a rapidly deteriorating inflammatory and necrotic condition, which failed to respond to all treatments until the initiation of Anakinra prompted a swift response. Her symptoms were consistent with many disease states making treatment complex, and although a drug reaction and systemic inflammatory diseases have been considered these remain diagnoses of exclusion. Without any conclusive diagnostic test, the cause of her catastrophic condition remains unclear leaving both the patient and her physicians uncertain as to why Anakinra worked and whether she is now cured or if she is at risk of recurrence of her symptoms.

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