Rare disease

Churg–Strauss presenting as acute coronary syndrome: sometimes it's zebras

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A 53-year-old patient presented to our institution with troponin-positive chest pain and new-onset peripheral oedema. A week prior, while abroad, he had developed visual disturbances and fever in conjunction with an elevated troponin. Coronary angiography had revealed minor coronary artery disease and he was treated for acute coronary syndrome and occult infection. On arrival to our coronary care unit, further review elicited a history of recently diagnosed and worsening severity asthma with nasal polyposis. A mononeuritis and a vasculitic rash were noted and blood screen showed hypereosinophilia and immunoglobulin E (IgE) elevation. A clinical diagnosis of Churg–Strauss syndrome was made and the patient was treated urgently and successfully with immunosuppressants.

The case illustrates a fulminant presentation mode of this rare vasculitis and the importance of seeking a unifying diagnosis in cases presenting with apparently disparate symptoms and findings.

BACKGROUND

Churg–Strauss syndrome (CSS) is a necrotising vasculitis of small- and medium-sized vessels characterised by asthma, chronic rhinosinusitis and peripheral eosinophilia.¹ The lung would be almost invariably affected, but extrapulmonary involvement is responsible for much of the morbidity and mortality, approximately half of which is due to the more serious cardiac manifestations of CSS.² These may involve all cardiac layers, causing pericarditis, myocarditis and even endocarditis. We, herein, present a patient with multiorgan CSS involvement who was initially diagnosed and treated for acute coronary syndrome (ACS) and presumed occult infection. We highlight how the identification of additional unaccounted findings can raise the suspicion of the rarer underlying and unifying diagnosis.

CASE PRESENTATION

A 53-year-old male physiotherapist who had previously been 'fit and well', other than being treated for asthma, presented with episodes of chest pain and new-onset peripheral oedema that developed during an air travel into the country. Risk factors for coronary artery disease were that he was hypertensive and was a light tobacco smoker.

An interesting prelude to his presenting complaint was that a week previously he had developed a fever (38.2°C), malaise and transient visual disturbances. He attended another institution in South Africa where funduscopy and visual field confrontational testing were normal. He was noted to have a leukocytosis for which he was treated empirically with oral levofloxacin antibiotic. A troponin elevation was also noted and a coronary angiogram was performed, revealing only minimal luminal irregularities in the coronary tree. He was commenced on dual antiplatelet therapy, statin and diltiazem. Three days prior to this

current presentation, he continued to experience a nocturnal fever and progressive dyspnoea.

On examination, the patient was uncomfortable and restless due to leg pain. He was hypoxic (O₂ saturation on air 93% by pulse oximetry), had a regular tachycardia of 90 beats/min and his blood pressure was 146/92 mm Hg. Cardiovascular and respiratory examinations were otherwise unremarkable. On neurological examination, right foot dorsiflexion was impaired with reduced, MRC grade 4 power. There were no cranial nerve deficits and the funduscopy was normal. Findings were, therefore, consistent with a common peroneal nerve mononeuritis. The patient had no further episodes of chest pain but remained dyspnoeic.

Overnight, the patient showed further deterioration with malaise, calf tenderness and finger arthralgia. On direct questioning the patient endorsed that his asthma was of late onset, predominantly over the previous 2 years and of worsening severity, requiring two courses of oral steroids in the previous year. He had also required a nasal sinus polypectomy 6 months prior. There was no history of leukotriene receptor antagonist use.

A purplish, palpable non-blanching purpuric rash, was noted on the shins, palms and soles of the feet (figure 1). Within hours the skin involvement evolved further to an urticarial rash at venepuncture sites and development of splinter haemorrhages (figure 1). A punch skin biopsy was obtained prior to prompt initiation of treatment.

INVESTIGATIONS

ECG showed mild left atrial enlargement but no ischaemic or pericarditic changes. Arterial blood sampling on room air showed reduced Po₂ of 7.78 kPa with markedly elevated alveolar-arterial gradient of 145 kPa (age-expected 2.3 kPa) suggestive of significantly impaired gas exchange.

Figure 1 Purpuric vasculitic rash on the forearm and palm (patch overlying biopsy site) and subsequent urticarial rash.

Initial laboratory assessment revealed an elevated troponin T (2.63 µg/l, reference <0.05 µg/l) and elevated creatine kinase (CK) to 412 IU/l with creatinine 116 µmol/l (estimated clearance 88 ml/min). The white cell count (WCC) was elevated to $20.4 \times 10^9/l$ with predominant eosinophilia of $10 \times 10^9/l$ (49%).

Urgent bedside transthoracic echocardiography showed normal ventricular function with a small pericardial effusion. A pulmonary CT scan revealed pulmonary nodules and infiltrates.

Later analysis of the skin punch biopsy demonstrated acute and chronic inflammation involving the superficial and deep dermis and including numerous eosinophils and neutrophils. Oedema and haemorrhage was noted in the papillary dermis. There were no granulomata or dysplastic changes (figure 2).

Further lab analytics became later available and showed antinuclear antibodies and antineutrophil cytoplasmic antibodies (ANCA) negative, normal complement and total IgE elevated to 666 kU/l. Urinary microscopy was unremarkable, with only scanty epithelial cells and casts, but a 24-h urine collection revealed significant proteinuria of 0.95 g/24 h.

DIFFERENTIAL DIAGNOSIS

The initial differential was of CSS, eosinophilic myocarditis, hypereosinophilic syndrome, endocarditis or concurrent drug reaction to the newly prescribed medications which were stopped. Coccidioidomycosis would also account for many of the findings though there was no history of travel to endemic areas.

The patient fulfilled the American College of Rheumatology (ARC) criteria for diagnosis of CSS based on the findings of (A) asthma, (B) eosinophilia of >10%

of the WCC, (C) mono or polyneuropathy, (D) migratory or transient pulmonary opacities or infiltrates, (E) paranasal sinus abnormality (recent history of nasal polypectomy) and (F) extravascular eosinophils (noted on the skin biopsy). The ARC recommends the presence of four or more of these six criteria for classification of CSS as this yields 85% sensitivity with 99.7% specificity for the diagnosis.³

TREATMENT

The patient's management was further complicated by his presentation on a Saturday when, a rheumatologist's opinion could not be obtained. An ANCA that, if positive, would have proved reassuring of the diagnosis and the decision to treat with steroids but could also not be emergently obtained.

Nonetheless, CSS cardiac involvement necessitates prompt and aggressive therapy as delay can lead to sudden death.⁴ Consequently, after consultation with the pulmonologist, therapy was immediately commenced with a pulse of methylprednisolone 1 g intravenous daily for 3 days. Following subsequent input by a rheumatologist the pulse was followed by prednisolone 60 mg oral daily and mycophenolate mofetil 500 mg oral twice daily.

The patient made a remarkably prompt clinical response to the steroid with resolution of the myalgia and arthralgia and improvement of the cutaneous manifestations. The eosinophilia, troponin and CK rise also subsided. After 10 days, there was no laboratory evidence of ongoing inflammation and the patient was clinically well. The foot drop persisted and the patient experienced severe bilateral peroneal neuropathic pain. Nerve conduction studies confirmed the peroneal nerve damage with reduced sensory and motor amplitudes.

Figure 2 Skin punch biopsy showing dense eosinophilic and neutrophilic inflammatory infiltrate in the dermis with surrounding oedema.

OUTCOME AND FOLLOW-UP

A year after presentation the patient continued to have a common peroneal nerve palsy causing right foot drop and bilateral loss of sensation with associated neuropathic pain. After 2 years, the foot drop has resolved but bilateral sensory loss persists. Remission is being maintained on methotrexate (MTX) 15 mg weekly and daily steroid inhalers for asthma. Flare ups of asthma have been successfully treated with brief courses of oral prednisone 15 mg daily.

DISCUSSION

We describe a patient who presented with chest pain, fever, troponin elevation and leukocytosis and was initially treated for ACS and presumed occult infection but failed to respond. We describe how the apparently disparate symptoms and the WCC differential led to the diagnosis of CSS.

CSS is a rare necrotising vasculitis of small-and-medium vessels associated with eosinophilia. The ARC criteria for CSS diagnosis have been previously listed (see 'Differential Diagnosis'). Additional diagnostic markers are increased levels of soluble interleukin (IL)-2 receptor, eosinophil cationic protein and soluble thrombomodulin but these are not widely available.⁵ Lanham *et al* described three phases of the disease with prodromal pulmonary involvement and nasal polyposis.⁶ Our patient presented with a fulminant overlap of Lanham Stage 2 and 3 findings.

Cardiac involvement occurs in approximately 40% of patients, often with negative ANCA titres and higher peripheral eosinophilic counts, as in this patient.⁷ It may manifest as pericarditis with constriction, myocarditis with biventricular failure and cardiogenic shock or even eosinophilic endocarditis with endocardial thrombosis.⁸ Transient coronary spasm in patients with CSS has been reported, though recent a MRA study found no structural

coronary involvement.^{9 10} Our patient had only minor coronary irregularities on coronary angiography. As there were sufficient clinical symptoms and findings to secure a diagnosis of CSS, including a skin biopsy, it was not necessary to subject the patient to a myocardial biopsy.

Peripheral neurological involvement with mononeuritis multiplex occurs in 50–80% of CSS cases and often affects the sciatic, tibial or peroneal nerves.^{11 12} The neuropathy is secondary to eosinophilic infiltration and necrotising vasculitis of the vasa nervorum leading to nerve infarction. Consequently, recovery is slow and often incomplete as was noted in our patient's peroneal palsy. Visual disturbances were experienced by our patient during his initial presentation; CSS may have ocular and orbital involvement and a few cases of ischaemic optic neuropathy have been reported.¹³

The prognosis of CSS is dependent on the systems involved and may be predicted using the Five Factor score (FFS) where one point is allocated to each of: (A) cardiovascular involvement, (B) impaired renal function (creatinine >140 µmol/l), (C) proteinuria (>1 g/day), or creatinine >140 µmol/l, (D) gastrointestinal system involvement (infarction, haemorrhage or pancreatitis) or (E) central nervous system manifestation.

Initial treatment with corticosteroids leads to remission in over 90% of patients with FFS of zero, though most patients require low doses of oral corticosteroids for persistent asthma even after the vasculitis has subsided.¹⁴ Adjunctive immunosuppressant therapy is therefore often required. Cyclophosphamide is effective but too toxic for these patients of good prognosis whereas MTX can often maintain remission or at least allow significant corticosteroid sparing.⁷ A clinical trial of azathioprine with corticosteroids as first line therapy with CSS patients of low FFS is ongoing. (clinicaltrials.gov:NCT00647166).

Patients with FFS $\geq$ 0 require more aggressive treatment including combination induction therapy such as steroids with cyclophosphamide then maintenance with azathioprine or MTX with tapering of steroids if possible.^{15–18} The use of biologic agents such as anti-CD20, anti-IL-5, anti-IgE or antitumour necrosis factor antibodies is currently undergoing clinical trials.⁷

CONCLUSION

CSS is a multisystem disorder that may present with symptoms mimicking ACS. Examination of a white cell differential revealing eosinophilia, may raise the suspicion of an alternative underlying diagnosis to coronary instability. If a rash is present, biopsy confirmation of an eosinophilic vasculitis is diagnostically helpful, as is measurement of IgE, and, to a lesser extent, ANCA. Early and aggressive immunosuppressive treatment is warranted in patients with cardiac involvement.

In this case, although ACS is common, it did not provide a unifying diagnosis by failing to account for the visual disturbance and eosinophilic leukocytosis, leading to unnecessary, unhelpful and risky diagnostic procedures and treatments. Although Dr Theodore Woodward's variably paraphrased aphorism 'if you hear hoofbeats, think horses not zebras' is a powerful heuristic it is equally important to remember that zebras do occasionally trot by.

Learning points

- This case highlights the importance of checking the white cell count differential – identification of the leukocytosis as being predominantly eosinophilic in nature would have prompted the correct diagnosis and prevented unnecessary diagnostics and therapy.
- Consider CSS in asthmatic adult patients with eosinophilia presenting with chest pain, dyspnoea or even cardiogenic shock, particularly if there are unexplained findings in other systems (such as rash or mononeuritis).
- Prompt and aggressive immunosuppressive treatment is required for Stage 2/3 cases of CSS.
- When a unifying diagnosis for disparate symptoms is rare, Hickam's dictum may outrank Ockham's razor.

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