Reminder of important clinical lesson

Churg–Strauss syndrome in a patient previously diagnosed with multiple sclerosis

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Summary

A lady in her 70s with a background of multiple sclerosis (MS) and late-onset asthma was admitted with a 2-week history of cough and shortness of breath, progressive right-sided weakness and functional decline. Investigation revealed eosinophilia, elevated myeloperoxidase antineutrophil cytoplasmic antibody, CT sinuses showed long-standing inflammatory changes consistent with sinonasal polyposis and MRI head showed lesions consistent with vasculitis. She then developed left-sided weakness and increased wheeze. Review of her case notes demonstrated that, the eosinophilia was long-standing, her asthma was severe and steroid-dependent, and her neurologic syndrome was atypical for MS. Intravenous methylprednisolone then cyclophosphamide were administered. She demonstrated remarkable improvement, becoming more alert, with improvement in left-sided weakness. A diagnosis of Churg–Strauss syndrome was established. She was discharged to a nursing home with outpatient rheumatology follow-up. The diagnosis of MS was revisited.

BACKGROUND

Through this report, we highlight how a systemic vasculitis such as Churg–Strauss syndrome (CSS) can clinically be missed due to insidious onset, vague symptoms, and masking of disease by steroid treatment. Clinical presentation may be atypical (*forme fruste*), and when dealing with intractable symptoms such as ‘difficult-to-treat’ asthma, or facing a diagnostic challenge, it is important to keep an open mind and question previous formal diagnoses.

CASE PRESENTATION

Referral and presenting complaint

Our patient was admitted to a district general hospital in the UK with a 2-week history of cough with shortness of breath.

Medical history

Multiple sclerosis (MS) was diagnosed in her 50s after referral to neurologists with a 5-year history of right leg weakness (grade 4) and burning sensation. Examination revealed pyramidal weakness (grade 4) in the right leg, brisk reflexes throughout both lower limbs and bilateral up-going plantars. Vibration sensory loss was noted bilaterally at the ankles. Visual acuity was 6/6 and funduscopy was normal.

Full blood count, B12 and folate were normal. Protein electrophoresis, autoantibodies and venereal disease research laboratory serology were negative. Antinuclear factor (ANF) was positive at 1 in 10 dilution. Cerebrospinal fluid (CSF) cytology and biochemistry were within normal limits. CSF oligoclonal bands were positive and were not matched with serum. CT head and myelogram were normal. Nerve conduction study showed slight reduction in motor amplitudes and normal sensory studies. She was treated with methylprednisolone; her weakness improved as did her dysaesthesia. In her 60s, right arm weakness

was evident. She was treated with further courses of methylprednisolone.

Also at this stage, asthma was diagnosed which was refractory to corticosteroid and antibiotic treatment. She also complained of purulent nasal discharge and frontal headache suggestive of sinus disease.

Transient eosinophilia ($1.30 \times 10^9/l$) was noted. *Aspergillus* radioallergosorbent test (RAST) was negative. Chest x-ray (CXR) showed minimal left basal shadowing. Spirometry results were: forced vital capacity (FVC) of 1.88 l (68.1% predicted), forced expiratory volume in 1 s (FEV1)/FVC ratio of 66.0%, transfer factor (KCO) was normal. There was no significant reversibility to bronchodilators.

Medication

On admission, her medication included salbutamol, seretide (500 Accuhaler, two puffs once nightly, equivalent to 2000 mcg beclomethasone daily), paracetamol and zolpidem. In the months prior to admission, she was maintained on 10 mg prednisolone once daily and her history revealed earlier maintenance on oral steroids; this had been stopped prior to admission.

Social and family history

She was a life-long non-smoker with no animal pets. She had previously lived in a property lined with asbestos. There was no significant family history.

Examination

Vital signs on admission were: temperature 37.1°C, pulse 120/min regular, respiratory rate 22/min, blood pressure 120/69 mm Hg and pulse oximetry 96% saturation on air. She was alert and coherent. Examination of respiratory systems revealed widespread wheeze.

Examination of cardiovascular systems revealed bilateral ankle oedema. Gastrointestinal systems examination was

Figure 1 Chest x-ray on admission: heart moderately enlarged with prominent pulmonary vessels. Lungs generally clear.

unremarkable. Neurological examination demonstrated right-sided arm and leg weakness.

INVESTIGATIONS

Electrocardiography showed sinus tachycardia, rate 120/min with no evidence of ischaemia.

Urinalysis revealed +++ blood and + protein. Full blood count (FBC) identified eosinophilia ($2.9 \times 10^9/l$). Serum biochemistry showed raised alkaline phosphatase with her remaining liver function tests (LFTs) within normal range. C reactive protein was raised at 117 mg/l. Total serum immunoglobulin E (IgE) was raised at 233 U/ml. *Aspergillus* RAST was negative. Vasculitic screen demonstrated positive myeloperoxidase anti-neutrophil cytoplasmic antibody (103 U/l), raised rheumatoid factor (43), raised C3 (1662 mg/l) and C4 (478 mg/l) (figure 1). CXR revealed that, the heart was moderately enlarged with prominent pulmonary vessels. Lung fields were generally clear. Transthoracic echocardiography showed good systolic left ventricular function (figure 2). High-resolution CT thorax showed a tiny left pleural effusion, no evidence of bronchiectasis and no other significant lung disease (figure 3). CT sinuses showed long-standing inflammatory changes likely to be sino-nasal polyposis.

TREATMENT

The initial impression was lower respiratory tract infection and possible bronchiectasis. Oral coamoxiclav was commenced.

She developed new left-sided weakness (grade 3) with reduced level of consciousness and meningism. Upper limb oedema and intermitted diarrhoea (type 7 stool) were

noted. CT head showed no significant abnormality. CSF analysis was normal. IV methylprednisolone was administered. A diagnosis of vasculitis was considered. She was observed to be less drowsy and there was improvement in her left-sided weakness (figure 4). In addition her eosinophilia resolved. MRI head showed multiple areas of increased signal intensity on the diffusion-weighted imaging (DWI) sequence in the occipital lobe, left temporal lobe and the centrum semi ovale bilaterally. These were also seen in the T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences. The distribution was symmetrical. This was considered consistent with vasculitis. Peripheral nerve conduction study showed evidence of a right deep peroneal nerve lesion with evidence of more generalised axonal loss.

Cyclophosphamide therapy was started (10–15 mg/kg, 750 mg); a second dose was given 2 weeks later.

OUTCOME AND FOLLOW-UP

She was discharged to a nursing home. She was tested for thiopurine methyltransferase activity which was normal; immunosuppressant therapy was changed to oral azathioprine (100 mg once daily) and prednisolone (15 mg once daily). Outpatient follow-up with rheumatology was arranged; regular monitoring of FBC and LFTs was also arranged. She died 1 month after discharge.

DISCUSSION

Churg–Strauss syndrome

CSS is a clinical syndrome associated with an uncommon autoimmune disease, defined pathologically by allergic pulmonary and systemic angiitis with granulomatosis. This

Figure 2 High resolution CT thorax: tiny left pleural effusion. No evidence of bronchiectasis or other significant lung disease.

Figure 3 CT sinuses: postsurgical changes are noted in both nasal fossae/maxillary sinuses. Long-standing inflammatory changes are noted in the nasal fossa, maxillary, ethmoid and frontal sinuses, likely to be sino-nasal polyposis.

was first described by Churg and Strauss in 1951.¹ The condition most commonly affects persons between 40 and 70 years of age and is more common in females. Incidence is approximately 2.4 – 6.8 per million person years.^{2–3} The natural history can be described in three phases, usually but not always in order, with a mean latency between first and last stage of 8 years.⁴ Lanham *et al* described: (1) allergic rhinitis and asthma, (2) blood and tissue eosinophilia and (3) systemic vasculitis.

Asthma is found in almost all cases. This tends to be late-onset, progressive and steroid-dependent.

Allergic rhinosinusitis is seen in most, is recurrent and is associated with nasal polyposis. Blood eosinophilia correlates with disease activity and reduces in corticosteroid-induced remission.^{5–6}

Systemic vasculitis predominantly leads to cardiovascular, neurologic, renal, gastrointestinal, cutaneous and rheumatologic disease. Cardiovascular disease is the major cause of death, often a result of heart failure. This results from eosinophilic infiltration of myocardium and coronary vessels.^{5–6} In particular, neurologic disease occurs in most

and often manifests as peripheral neuropathy. Central nervous system involvement is less common and is usually in the form of cerebral infarction, cerebral haemorrhage and myelopathy.

Diagnosis is often made late in the course of disease once systemic vasculitis is evident – characterised by fatigue, malaise, weight loss and specific organ system involvement. This is partly due to high general population prevalence of asthma and rhinitis, which are also associated with eosinophilia. In addition, corticosteroid therapy for asthma can induce steroid-dependent remission and thus mask eosinophilia and vasculitis.

Various definitions of CSS exist. For example, the American college of rheumatology in 1990⁷ established criteria for use in research: (1) confirmed vasculitis, (2) asthma, eosinophilia more than 10%, neuropathy (mono- or poly-), pulmonary infiltrates (non-fixed), paranasal sinus abnormality and extravascular eosinophils (biopsy including vessels). Four or more of features listed in two demonstrated good sensitivity and specificity for CSS. Lanham *et al* (1984)⁴ proposed clinical criteria: asthma, eosinophilia

Figure 4 MRI head: some movement artefact. There are multiple areas of increased signal intensity seen on the diffusion-weighted imaging sequence in the occipital cortex and the centrum semi ovale bilaterally and the left temporal lobe. These are also seen on the T2-weighted and fluid-attenuated inversion recovery sequences. The distribution is symmetrical. There is no haemorrhage.

(more than 1.5) and systemic vasculitis of two or more extrapulmonary organs.

Prognosis is good with corticosteroid and other immunosuppressant (eg, azathioprine or cyclophosphamide) treatment. A 6.5 year actuarial survival rate of 72% with initial clinical remission achieved in 91% of patients has been reported.⁸

Similar published cases

A general search and brief literature review for similar case reports found a report by Scolding *et al* (1997)⁹ of eight cases of cerebral vasculitis. They describe a relapsing-remitting 'MS-plus' syndrome in three patients later confirmed to have cerebral vasculitis. Of note, intrathecal Igs were found in 2/3. Unusual features such as encephalopathic episodes (2/3) and hemispheric stroke-like events (1/3) were described. Our patient demonstrated these features in during her admission. No other sufficiently similar case reports were found.

Case discussion

In her fifties, she presented to neurology clinic. Features of her initial neurologic presentation which favour a diagnosis of MS are: acute neurologic syndrome with upper and lower motor neurone features, unmatched oligoclonal CSF bands and bilateral delayed visual evoked potentials. Against the diagnosis were: the clinical suspicion of peripheral neuropathy, peripheral nerve conduction study with reduced motor amplitudes but normal velocity, suggesting axonal loss but not demyelination, positive ANF and normal CSF white cell counts. Unmatched intrathecal Ig G synthesis has been described in many syndromes aside from MS.^{9 10} Given the absence of documented diagnoses of asthma, allergic rhinitis or eosinophilia at this initial stage, a diagnosis of CSS could not be retrospectively justified.

In her sixties, she was diagnosed with asthma. Certainly the features of her asthma and allergic rhinosinusitis – late-onset, severe, relapsing and steroid-dependent are suspicious of CSS. We could speculate that, further investigation of the eosinophilia, or investigative re-appraisal of her continued neurologic symptoms may have established CSS as the diagnosis at that stage.

During her inpatient stay, evidence for peripheral neuropathy as shown by the latest peripheral nerve conduction study is incompatible with MS. If the peripheral

neuropathy always accounted for her right leg symptoms, any case for MS is further weakened.

CSS emerges as a potential unifying diagnosis in this case. Vasculitis may have thus underlain the chronic neurologic deterioration.

Learning points

- ▶ CSS is often diagnosed late – limitations of definitions and criteria and difficulty obtaining appropriate histologic samples are key underlying reasons.
- ▶ The presence of severe asthma, allergic rhinosinusitis and eosinophilia should lead to the consideration of CSS as a differential diagnosis.
- ▶ Neurologic sequelae of CSS can be misdiagnosed as MS.

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Competing interests None.

Patient consent Not obtained.

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