Rare disease

A difficult case of fever of unknown origin

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Summary

A 57-year-old holidaymaker in Madeira was airlifted to England with a 4-week history of fever, limb weakness and hypophonia. Having undergone a range of investigations during his hospital admission abroad – including ultrasound, CT, echocardiogram and lumbar puncture – the patient arrived without any explanatory diagnosis. At presentation, the only investigatory positives were raised blood inflammatory markers and a, previously unidentified, ‘old left frontal infarct’ found on head CT. A broad infective and immunological screen proved negative, raising the possibility of vasculitis. Finally, the presence of subacute cerebral and renal infarcts identified on MRI and CT in combination with a negative antineutrophil cytoplasmic antibodies (ANCA) test and distinctive muscle biopsy features confirmed the clinical suspicion of polyarteritis nodosa. An immunosuppressive regime of glucocorticoid therapy and cyclophosphamide were initiated with immediate significant clinical improvement.

BACKGROUND

Polyarteritis nodosa (PAN) is rare. Watts *et al* estimate the annual incidence in three regions of Europe to be between 4.4 and 9.7 per million population.¹ Furthermore, indistinct systemic symptoms predominate on presentation, with virtually any organ potentially affected. Together these make for a particular diagnostic challenge.

CASE PRESENTATION

The previously fit and well 57-year-old man’s first presentation was to his general practitioner, 11 days before his departure for holiday in Madeira, Portugal. The patient experienced a short transient episode of confusion, followed by left-sided shoulder stiffness and bilateral wrist swelling. A diagnosis of frozen shoulder was made and the patient was managed on Naproxen.

On his second day in Madeira, the patient developed significant bilateral leg swelling. On attending the local emergency department, the patient was hypertensive (blood pressure 210/110), had a fever of 38.5°C and had significantly raised inflammatory markers. The patient was admitted and extensive investigations were carried out, including lumbar puncture and whole body CT. Interestingly, the only positive sign identified was what was described as an old left frontal lobe infarct but no obvious source of sepsis was identified. On the eighth day of admission, almost 3 weeks since first symptoms, the patient’s voice became hypophonic, and he developed limbs weakness and experienced intermittent periods of confusion. At this stage the patient was treated with broad-spectrum antibiotics (meropenem, levofloxacin) without any improvement. Five weeks following the onset of symptoms, the patient was airlifted back to England and promptly admitted via air ambulance to his local Medical Admission Unit.

In addition to the history mentioned above, malaise and weight loss of three stones over a 2-month period were

also reported on admission. Otherwise system enquiry was unremarkable, and the understanding that the patient was previously well and took no regular medications corroborated. On examination, the patient was cachexic, lethargic, but rousable and well orientated. He had bilateral peripheral pitting oedema up to knees and a livedo reticularis rash over both anterior shins and thighs. Heart sounds were normal and no murmur or stigmata of endocarditis identified.

Figure 1 MRI brain: T2 turbo spin echo malacic changes in left frontal convexity consistent with an old infarct.

Figure 2 MRI brain: diffused weighted imaging demonstrated hyper-intensity within left posterior medulla, which was not matched on analog-to-digital converter sequence suggesting that the infarct is subacute.

There was reduced air entry to both lungs and some bibasal crackles audible. Neurologically, the patient had dysphonic and dysarthric speech, saccadic eye movements and generalised limb weakness (MRC grade 3 to 4 through both upper and lower limbs). A nasopharyngoscopy confirmed unilateral left focal cord palsy. Observations confirmed a fever of 38.8°, sinus tachycardia at 120 beats per min, otherwise blood pressure and other vital signs were stable.

INVESTIGATIONS

Initial bloods showed a microcytic anaemia (mean corpuscular volume 87.9, haemoglobin 8.4), a leucocytosis (white cell count 22) associated with neutrophilia, raised inflammatory markers (C reactive protein 128, ferritin 965) and deranged liver function (bilirubin 21, alkaline phosphatase 218, alanine transaminase 184) with hypoalbuminaemia (Alb 21), and hyponatraemia (127). Creatine kinase was within normal limits.

There were three sets of negative blood cultures, also one set of negative mid-stream urine associated with mild proteinuria (0.83 g/24 h). Initial chest radiograph was normal and ECG showed only sinus tachycardia. Transoesophageal echocardiogram did not reveal any vegetation. Further infectious disease screen included negative Hep B sAg, Hep C, HIV Ab, cytomegalovirus, West Nile virus, *Borrelia burgdorferi*, toxoplasmosis, leishmania and malaria. Immunology blood tests were negative: antinuclear antibody, antiextractable nuclear antigen/centromere, anti-ribonucleoprotein (RNP) 70, anti-CL1 RNP, anti-SM, anti-Ro, anti-La, anti-Scl-70, anti-Jo-1, ACE and notably ANCA was negative. Protein electrophoresis showed raised α -1 and α -2 globulins and diffusely increased δ globulin, (suggesting non-specific acute on chronic inflammation). No paraprotein was detected and immunoglobulin levels were within normal limits.

Imaging was more enlightening. As well as confirming the old left frontal lobe infarct (figure 1), MRI of the head

Figure 3 CT abdomen with contrast, porto-venous phase showing multiple hypo-attenuation lesions within both kidneys with cortical scarring.

suggested a subacute pontine infarct, potentially within 2 weeks (figure 2). Further, the CT chest/abdomen/pelvis showed multiple segmental renal infarcts (figure 3). Given these findings a CT mesenteric and renal angiography was undertaken which interestingly did not demonstrate the characteristic microaneurysms or abrupt cut off of small arteries seen in PAN.

Nerve conduction studies confirmed a patchy predominantly axonal sensory motor polyneuropathy. There was slowing of both motor and sensory conduction velocities with patchy myopathic changes, these were all suggestive of systemic vasculitis. It was however muscle biopsy that provided a definitive diagnosis. A sample taken from the left quadriceps femoris muscle showed active inflammation of intramuscular arteries, clearly in keeping with vasculitis (figure 4A,B). The likelihood of PAN being indicated by the absence of granulomatous inflammation around small intramuscular arteries which favoured this over Wegener's Granulomatosis or Churg Strauss Vasculitis (figure 5).

DIFFERENTIAL DIAGNOSIS

The differential in this case was broad. Potential infective causes included infective endocarditis, hepatitis B or C virus, as well as HIV infection. There was the possibility of other systemic vasculitides such as Wegener's Granulomatosis, Churg Strauss syndrome, Henoch-Schönlein purpura or vasculitis secondary to connective tissue disease, such as systemic lupus erythematosus or rheumatoid arthritis. Finally, there was the possibility of a range of conditions that could mimic vasculitis including malignancy, simple atherosclerotic disease and thrombotic or embolic disorders, such as antiphospholipid syndrome.

TREATMENT

The patient was started on intravenous methylprednisolone followed by high dose daily oral prednisolone. Twelve days later, a regime of six pulses of cyclophosphamide once every 2 weeks was introduced, with a corresponding reduction in oral prednisolone. Patient's oral prednisolone was eventually tapered down to 10 mg once daily with an increasing dose of oral azathioprine (2.5 mg/kg).

Figure 4 (A, B) Muscle biopsy showing inflammation of intramuscular arteries (x20 and x40 magnification).

OUTCOME AND FOLLOW-UP

The patient clinically improved on the initiation of treatment, with speech and muscle power notably strengthening; progress reflected biochemically in falling inflammatory markers. With continuing remission the patient was discharged to rehabilitation with physiotherapy support and rheumatology outpatient follow-up (supplement, video 1).

Video 1 Patient's perspective.

The patient was re-admitted 3 months later with chest pain and symptoms of congestive cardiac failure. On ECG he had new onset atrial fibrillation, and transthoracic ECHO indicated dilated cardiomyopathy. A coronary angiography was undertaken in order to identify possible ischaemic heart disease, however this was entirely normal. Currently the patient remains under investigation and it is unclear whether this episode was connected to his PAN.

DISCUSSION

PAN is primarily a vasculitis of medium-sized arteries, causing inflammation potentially affecting any organ system. Unlike other systemic vasculitides, PAN does not affect the venous system.²

The pathogenesis of PAN is characterised by transmural arterial inflammation, leading to necrosis and occlusive lesions.² The aetiology of this inflammatory process in PAN is only partially understood. There links to pre-existing conditions such as connective tissue diseases, hairy cell leukaemia and chronic viral infection (such as HIV or hepatitis B, C).^{3–5} This association is most apparent with regard to Hepatitis B, with some older studies identifying up to a 60% of PAN occurring in conjunction with hepatitis B virus (HBV), the HBV-PAN.⁶ More recently however, this HBV-PAN has become less prominent; with falling incidence of hepatitis, occurring on the background of effective vaccination, Guillevin *et al* identified a reduction of HBV-PAN to levels as low as 7.3%.^{6,7} Therefore currently a notable proportion of PAN cases remain idiopathic.

The severity and presentation of the condition is dependent on the degree and pattern of organ involvement. A typical patient would complain of constitutional symptoms such as fever, weight loss and malaise, asymmetric arthralgia or myalgia and abdominal pain. Examination may reveal distinctive skin lesions (palpable purpura or infarcts on digital tips) hypertension or neurological deficits such as peripheral neuropathy. In this case, the patient had constitutional symptoms of

Figure 5 Muscle biopsy. Adenosine triphosphatase 4.6 preparation showing that the atrophy affects mainly the type 2b fibres (intermediate darkness) more than the type 2a (light ones) more than the type 1 (darkest in the preparation): these are indicative of ischaemia secondary to the vasculitis.

myalgia, central and peripheral neurological deficits and a rash in the lower extremity compatible with livedo reticularis. Nevertheless, it should be emphasised that the infarcts, distinct in territory and timing, identified in this case were exceptional, it is rare to see central nervous system involvement in PAN. In addition, the identified proteinuria on urine dipstick was an indicative renal sediment abnormality. PAN can remain isolated and limited to single organ involvement. However, the worsening symptomatology manifest in this case represented multi-organ involvement of severe PAN.

The disparate presentations and nature of PAN raises potential indications for many investigations. The first objective of investigations is to rule out underlying infection or concealed autoimmune diseases. Therefore, a full septic screen and basic autoantibodies screen would be reasonable initial steps towards establishing a diagnosis of PAN. Despite a negative yield of ANCA, it is important to remember that vasculitis is still a possibility, especially in the case of PAN. The second purpose of investigations is to confirm clinical suspicion. The diagnosis should ideally be confirmed by tissue biopsy of a clinically affected organ, classically renal biopsy. Alternatively, the diagnosis of PAN can also be established using conventional angiography or less invasive CT or MRI arteriography techniques.

Focusing on making a diagnosis of PAN involving the kidneys, radiology techniques may be advantageous over renal biopsy because of less bleeding risk and less chance of false-negativity.

Previously, prognosis of untreated PAN was poor, with 1-year and 5-year survival rates as low as 50 and 13 per cent respectively.^{8 9} However, therapy has improved the 5-year survival to almost 80 per cent.¹⁰ Although many treatments have been tried, including plasmapheresis and interferon α , glucocorticoid therapy alone or in combination with cyclophosphamide remains the principal therapeutic approach. It is important to remember that both glucocorticoid and cyclophosphamide have potentially serious adverse effects. We recommend providing prophylactic therapy, such as alendronic acid, for glucocorticoid-induced osteoporosis. For patients on cyclophosphamide, we advocate prophylaxis against *Pneumocystis jirovecii* pneumonia with trimethoprim-sulfamethoxazole. Last, we advise the administration of mercaptoethane sulfonate when patients receive intravenous cyclophosphamide, in order to prevent bladder toxicity. Azathioprine is also commonly used as a immunosuppressive drug to maintain remission. The duration of treatment of PAN remains a subject of debate. Once patients are in remission, some authors claimed that relapses are relatively uncommon.^{11 12} Our authors' view is that patients should stay on treatment for up to 24 months.

Learning points

- ▶ Systemic vasculitis is an important differential diagnosis in patients who present with fever of unknown origin.
- ▶ PAN is a rare systemic necrotising vasculitis, typically affecting medium-sized vessel. It can affect any organ system, resulting in a range of presentations.
- ▶ The differential diagnosis of PAN is broad, including infectious disease, especially infective endocarditis, malignancy, arterial occlusion though thrombosis or embolism, as well as other systemic vasculitides. It is important to exclude infections before initiation of immunosuppressive therapy.
- ▶ A negative yield of ANCA does not exclude the possibility of vasculitis, especially in PAN.
- ▶ Untreated PAN is associated with a poor prognosis. Therefore, it is important to establish the diagnosis early and start immunosuppressive treatment. Glucocorticoid therapy alone or in combination with cyclophosphamide induces remission in most cases.

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