CASE REPORT

PAN's labyrinth: a multidisciplinary delayed diagnosis and patient's perspective

Emma Louise Barlow,^{1,2} Owen Seddon,³ Brendan Healy³¹Cardiff University, Cardiff, UK²Greater Manchester, UK³Department of Microbiology, University Hospital of Wales, Cardiff, UK**Correspondence to**Emma Louise Barlow
barlowel1@cardiff.ac.uk

Accepted 12 December 2015

SUMMARY

Polyarteritis nodosa (PAN) is a rare, severe form of vasculitis affecting medium-sized vessels. It manifests as a multisystem syndrome, and may be associated with hepatitis B virus-associated PAN (HBV-PAN) although the incidence of this is declining with better vaccination strategies and awareness of bloodborne virus screening. We report a case in which a patient displayed many classical features of the disease, occurring separately over a period of months and leading to contact with various medical specialties. Managing each symptom in isolation led to a number of misdiagnoses (including testicular cancer) and the patient experienced considerable psychological stress and morbidity as a result. The case was complicated by acute pancreatitis developing after an initial treatment response. This may have been iatrogenic (as a consequence of either entecavir or steroids) or secondary to PAN. For our patient, this led to a protracted clinical course but eventual complete resolution of both pathologies.

BACKGROUND

Polyarteritis nodosa (PAN) is a rare condition (annual incidence 4.6 cases per 1 000 000 in the UK) and centres may have limited experience in managing these cases. Owing to a paucity of trial data optimal treatment is uncertain. There is no single diagnostic test so a clinical index of suspicion is required. This multisystem disease therefore presents a significant diagnostic challenge even in cases with typical features.

This case highlights potential pitfalls in the diagnosis, namely that the symptoms may be temporally dissociated, and fall under the remit of different specialties. It also highlights a potential treatment complication (pancreatitis) of which clinicians should be mindful, and our patient's perspective demonstrates the impact of the delayed diagnosis from a physical and psychological perspective.

CASE PRESENTATION

A 54-year-old man with no significant medical history presented to his general practitioner reporting gradually worsening abdominal and testicular pain. There was no history of altered bowel habit, weight loss or vomiting. There was no haematospermia and no penile discharge. Systemic review was otherwise unremarkable. Examination demonstrated a normal abdomen with mild tenderness but no peritonism. Examination of the testicles and hernial orifices was normal.

Initial investigations revealed raised inflammatory markers (C reactive protein, CRP 128 mg/L) and

deranged liver function tests (alanine transaminase, ALT 336 IU/L, alkaline phosphatase (Alk Phos) 275 IU/L, albumin (Alb) 27 g/L, bilirubin 8 µmol/L). Metabolic and autoimmune liver screens were normal as was ultrasonography of the liver and biliary tree. Screening for viral hepatitis showed evidence of recently acquired hepatitis B infection (core antibody (IgM) positive, surface antigen positive, 'e' antigen positive). The patient disclosed an episode of unprotected sexual intercourse with a new partner 3 months prior to presentation, which was the likely route of acquisition. A diagnosis was made of acute hepatitis B accompanied by a presumptive diagnosis of sexually transmitted orchitis for which he received antibiotics while urinary testing for chlamydia/gonorrhoea was carried out. He was referred to the infectious disease clinic for monitoring of his hepatitis.

Tests for chlamydia and gonorrhoea infection were negative and the patient continued to experience testicular pain after antibiotic treatment. The infectious disease team arranged an ultrasound examination of the testes. This showed multiple stromal abnormalities and solid lesions within the left testicle, with a differential diagnosis that included testicular lymphoma. He was referred to the urologists, who arranged a staging CT and listed him for a left-sided orchidectomy to obtain a histological diagnosis. He was counselled that he would likely require bilateral orchidectomies.

Four weeks after his initial presentation, the patient developed bilateral atraumatic ulnar nerve palsies. He self-presented to accident and emergency and was seen by the trauma and orthopaedic team, who diagnosed bilateral compressive ulnar neuropathies. This was a clinical diagnosis, made without imaging or nerve conduction studies. He was managed conservatively with analgaesics and referred for physiotherapy.

The patient attended his follow-up with infectious diseases. He had ongoing abdominal pain, particularly after food, and had lost 5 kg in weight. His inflammatory markers continued to be raised and he had become anaemic (CRP 104, haemoglobin 108 g/dL). Taken alongside his new neuropathy and testicular stromal abnormalities this suggested a systemic vasculitis; abdominal angiography was performed. This demonstrated multiple microaneurysms throughout his abdominal vasculature (figure 1), strongly suggesting the diagnosis of hepatitis B virus-associated PAN (HBV-PAN). He met 7 of 10 American College of Rheumatology (ACR) criteria (figure 2),¹ having no evidence of livedo reticularis, hypertension or abnormal renal

CrossMark

To cite: Barlow EL, Seddon O, Healy B. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-213495

Figure 1 Abdominal angiography results showing multiple microaneurysms throughout the patient's abdominal vasculature. (A) Renal vasculature. (B) Hepatic vasculature.

function. He had all three of the positive discriminators suggested by the French Vasculitis Study Group (FVSG) (figure 3). Autoantibody screening was negative for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides. A biopsy was deemed unnecessary given the characteristic angiography findings.

The patient was treated with entecavir at a dose of 500 µg daily and prednisolone at a dose of 1 mg/kg daily, and received three cycles of plasma exchange at weekly intervals. After 1 month, he had responded well to treatment with normalisation of his CRP to 2, and a decline in his viral load from 10⁸ to 10⁵ IU/mL. His abdominal and testicular pain resolved. His liver function tests improved (ALT 73, Alb 30) and he had otherwise normal parameters on discharge.

After a 5-week interval, he was readmitted with a recurrence of his acute upper abdominal pain. His blood parameters had deteriorated (CRP 200, ALT 90, Alk Phos 150). His amylase was also raised at 281 IU/mL. He had frank peritonism and urgent CT of the upper abdomen was in keeping with acute pancreatitis, showing inflammatory change and fat stranding adjacent to the head of the pancreas, along with a cystic fluid collection in the pancreatic head, which had partially decompressed into the small bowel.

The patient was managed with radiological and then open drainage of his pancreatic collections, and recovered well with normalisation of his blood parameters and physiology. He required pancreatic enzyme supplementation as a consequence of significant pancreatic necrosis, but had no associated vascular or

1990 criteria for the classification of polyarteritis nodosa

1. Weight loss >4 kg

Loss of 4 kg or more of body weight since illness began, not due to dieting or other factors

2. Livedo reticularis

Mottled reticular pattern over the skin of portions of the extremities or torso

3. Testicular pain or tenderness

Pain or tenderness of the testicles, not due to infection, trauma, or other causes

4. Myalgias, weakness, or leg tenderness

Diffuse myalgias (excluding shoulder and hip girdle) or weakness of muscles or tenderness

5. Mononeuropathy or polyneuropathy

Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy

6. Diastolic BP >90 mm Hg

Development of hypertension with the diastolic BP higher than 90 mm Hg

7. Elevated BUN or creatinine

Elevation of BUN >40 mg/dl or creatinine >1.5 mg/dl, not due to dehydration or

8. Hepatitis B virus

Presence of hepatitis B surface antigen or antibody in serum

9. Arteriographic abnormality

Arteriogram showing aneurysms or occlusions of the visceral arteries not due to obstruction of leg muscles, arteriosclerosis, fibromuscular dysplasia, or other noninflammatory causes

10. Biopsy of small or medium-sized artery showing PMN

Histologic changes showing the presence of granulocytes or granulocytes and mononuclear leukocytes in the artery wall

* For classification purposes, a patient shall be said to have polyarteritis nodosa if at least 3 of these 10 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 82.2% and a specificity of 86.6%. BP = blood pressure; BUN = blood urea nitrogen; PMN = polymorphonuclear neutrophils.

Figure 2 The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa.¹

French Vasculitis Study Group (FVSG) proposal for diagnostic criteria for polyarteritis nodosa (1996)

Positive predictive items:

Positivity for hepatitis B virus infection
Arteriographic abnormalities
Mononeuropathy or polyneuropathy.

Negative predictive items:

Presence of anti-neutrophil cytoplasmic antibodies (ANCA)
Asthma
Ear, nose, or throat signs
Glomerulopathy
Cryoglobulinaemia.

Figure 3 French Vasculitis Study Group (FVSG) proposal for diagnostic criteria for polyarteritis nodosa (1996).¹⁰

bowel injury. As possible precipitants included steroid treatment and entecavir, he underwent an accelerated weaning off of his steroids and his entecavir was switched to an alternative nucleoside analogue, tenofovir. With physiotherapy, ulnar nerve function improved and under follow-up, his hepatitis was virologically suppressed. He remains surface and 'e' antigen-positive.

DISCUSSION

PAN is a rare systemic inflammatory disease caused by a necrotising vasculitis that targets medium-sized vessels, sparing microscopic vasculature.^{2 3} There are no specific laboratory findings or biomarkers that confirm a diagnosis of PAN. Criteria have been developed, such as the 1990 ACR criteria described in the case history (figure 2), and those proposed by the FVSG in 1996 (figure 3).^{4 5} These criteria are for classification rather than diagnostic purposes and are currently under revision. They have been criticised for being insufficiently discriminatory between PAN and microscopic polyangiitis. The Chapel Hill Consensus Conference (CHCC) definition is more discriminatory, defining PAN as "Necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with antineutrophil cytoplasmic antibodies (ANCA)."⁶ Application of the CHCC definition suggests that PAN is increasingly rare in the UK, but this may reflect better exclusion of other vasculitides rather than a true decline in incidence.⁵

When diagnosing systemic vasculitides, a biopsy sample of involved, accessible tissue should be collected wherever practical to allow sampling of medium-sized arteries and aid in the diagnosis. The most accessible tissue sites for biopsy include the skin, peripheral nerve, testes and skeletal muscle. Kidney biopsy may be diagnostic but carries a significant risk of aneurysmal rupture and bleeding. A biopsy at the time of this patient's presentation with either stromal abnormalities in his testes or with bilateral ulnar nerve palsies would have resulted in an earlier diagnosis in this case. Ultimately, multidisciplinary discussion concluded that his presentation and angiography findings were sufficient to make a diagnosis, that a tissue diagnosis would not contribute to his management and that the risk associated with biopsy, particularly kidney biopsy, was not warranted.

Clinically, HBV-PAN is thought to be responsible for almost a third of PAN cases worldwide,⁷ although its incidence in the West is declining in parallel with that of hepatitis B.⁸ This extra-hepatic, vascular manifestation is thought to be immune-mediated through immune complex formation.⁸ PAN usually presents with constitutional symptoms such as fever, malaise, weight loss, abdominal pain, arthritis, myalgia, peripheral

neuropathy, rash, and gastrointestinal (GI) and renal impairment.^{3 9} The signs and symptoms observed in cases of HBV-PAN are similar; however, GI manifestations, malignant hypertension, renal infarcts and epididymo-orchitis are seen more frequently and the severity of disease may be increased.⁷

Treatment of idiopathic PAN consists of immune suppression, for which corticosteroids and steroid sparing agents, such as cyclophosphamide, have been used. In HBV-PAN, virological suppression with a nucleoside analogue (entecavir and then tenofovir in this case) along with clearance of the circulating immune complexes through plasma exchange is the mainstay of treatment. Optimal treatment remains uncertain due to a paucity of trial data.¹⁰ Corticosteroids may have a deleterious effect on viral clearance and there are case reports of immunological rebound on steroid withdrawal, which worsens the associated vasculitides. Therefore, steroids are only recommended in moderate/severe cases.^{10 11}

A delayed diagnosis

Our patient had contact with the urology, orthopaedic and infectious diseases teams as well as with his general practitioner and emergency physicians. At each point, the differential diagnosis for the acute presentation was considered but the teams failed to take account of the patient's broader symptoms and consider a multisystem pathology. The diagnosis of an entrapment neuropathy, for example, was made with an atypical presentation and without nerve conduction studies. This led to a delay in our patient receiving appropriate treatment for a condition associated with significant pain, and could potentially have led to considerable morbidity if orchidectomy had been performed as planned by the urologist. The patient experienced considerable psychological stress as a result of receiving a diagnosis of testicular cancer. The case serves to highlight the need for cooperation between teams when assessing a patient and a holistic approach to assessment, and neatly demonstrates a case where Occam's Razor holds true, that is, several seemingly unrelated pathologies explained by a single diagnosis.

PAN is rare, and HBV-PAN is declining in incidence, and this case report therefore serves to highlight a case in which several of the classical manifestations were present, in the hope that similar presentations may be diagnosed more quickly in future.

Patient's perspective

- ▶ "The whole experience was very frightening for me. Because I was seeing lots of different doctors and specialists it sometimes felt like no one had an overall picture of what was going on and no one could take charge. I realised that no one really knew what the diagnosis was and there were lots of serious possibilities mentioned like cancer and HIV. I genuinely wasn't sure if I was ever going to get better and leave hospital.
- ▶ Having reached the diagnosis I hoped things would get better but I then found the treatment very difficult. The steroids led to vivid nightmares, I've never experienced anything like it, and the plasma exchange was extremely draining.
- ▶ Eventually though things did start to improve and I'm really happy with how things have progressed. I'm independent, back in full employment and enjoying my recreational time."

Pancreatitis—an uncommon complication

Despite the fact that GI disturbances are common in PAN, acute pancreatitis has only been reported in a small number of clinical cases—and always as the initial presentation—in which a number of complications occurred: pancreatic insufficiency with malabsorption, infected pancreatic necrosis and pseudocyst development.³ However, in this case, the pancreatitis occurred both after treatment, and after clinical and biochemical improvement. The possibilities therefore include delayed pancreatitis secondary to PAN, or, more likely, pancreatitis as a consequence of treatment with either entecavir, steroid or plasma exchange.^{12–17}

Learning points

- ▶ Polyarteritis nodosa (PAN) is rare and hepatitis B virus-related PAN (HBV-PAN) increasingly so. However, the diagnosis of HBV-PAN should be considered in anyone presenting with constitutional symptoms in the context of a transaminitis, relevant exposure history or known infection with hepatitis B.
- ▶ In HBV-PAN, gastrointestinal manifestations are common and may include pancreatitis, bowel ischaemia, features of malabsorption and pain. Testicular pain, in particular, appears to be more common in HBV-induced PAN.
- ▶ In the setting of a recently acquired sexually transmitted infection, testicular pain can be misinterpreted as an orchitis. ultrasound scan findings of the testes are also non-specific and can mimic cancer.
- ▶ Pancreatitis may be the acute presentation, but may also be a side effect of treatment with nucleoside analogues or steroids. Deterioration of the abdominal symptoms during treatment should prompt investigation for alternative causes, especially if there was initial clinical response. This case may be a presentation of delayed onset pancreatitis secondary to PAN, which, to the best of our knowledge, has not been previously described.
- ▶ When diagnosing systemic vasculitides, a biopsy sample of involved, accessible tissue should be collected wherever practical.

Contributors This article has been written, contributed to and edited by all the authors. OS and BH were involved with patient care in the clinical setting.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Lightfoot RW Jr, Michel BA, Bloch DA, *et al*. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum* 1990;33:1088–93.
- 2 Hernández-Rodríguez J, Alba MA, Prieto-González S, *et al*. Diagnosis and classification of polyarteritis nodosa. *J Autoimmun* 2014;48:49:84–9.
- 3 Suresh E, Beadles W, Welsby P, *et al*. Acute pancreatitis with pseudocyst formation in a patient with polyarteritis nodosa. *J Rheumatol* 2005;32:386–8.
- 4 Guillemin L, Pagnoux C, Seror R, *et al*. French Vasculitis Study Group (FVSG). The Five Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine (Baltimore)* 2011;90:19–27.
- 5 Waits R, Jolliffe V, Carruthers D, *et al*. Effect of classification on the incidence of polyarteritis nodosa and microscopic polyangiitis. *Arthritis Rheum* 1996;39:1208–12.
- 6 Jennette J, Falk R, Bacon PA, *et al*. 2012 Revised international Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013;65:1–11.
- 7 Ghorbani GA, Alishiri GH, Fau-Pour HK, *et al*. High hepatitis B virus load in a patient with severe polyarthritis nodosa. *Hep Mon* 2010;10:306–9.
- 8 Lane SE, Watts R, Scott DG. Epidemiology of systemic vasculitis. *Curr Rheumatol Rep* 2005;7:270–5.
- 9 Janssen HL, van Zonneveld M, van Nunen AB, *et al*. Polyarteritis nodosa associated with hepatitis B virus infection. The role of antiviral treatment and mutations in the hepatitis B virus genome. *Eur J Gastroenterol Hepatol* 2004;16:801–7.
- 10 Deeren DH, De Backer AL, Malbrain ML, *et al*. Treatment of hepatitis B virus-related polyarteritis nodosa: two case reports and a review of the literature. *Clin Rheumatol* 2004;23:172–6.
- 11 Madachian D, Battegay M, Jacob AL, *et al*. Successful treatment of hepatitis B-associated polyarteritis nodosa with a combination of lamivudine and conventional immunosuppressive therapy: a case report. *Rheumatology (Oxford)* 2000;39:106–8.
- 12 Kaurich T. Drug-induced acute pancreatitis. *Proc (Bayl Univ Med Cent)* 2008;21:77–81.
- 13 Badalov N, Baradaran R, Iswara K, *et al*. Drug-induced acute pancreatitis: an evidence-based review. *Clin Gastroenterol Hepatol* 2007;5:648–61.
- 14 Nitsche CJ, Jamieson N, Lerch MM, *et al*. Drug induced pancreatitis. *Best Pract Res Clin Gastroenterol* 2010;24:143–55.
- 15 Chaudhari S, Park J, Anand BS, *et al*. Acute pancreatitis associated with interferon and ribavirin therapy in patients with chronic hepatitis C. *Dig Dis Sci* 2004;49:1000–6.
- 16 Soyulu AR, Dokmeci G, Tezel A, *et al*. Lamivudine-induced acute pancreatitis in a patient with decompensated Hbv-related chronic liver disease. *J Clin Gastroenterol* 2004;38:134.
- 17 Gubensek J, Buturovic-Ponikvar J, Marn-Pernat A, *et al*. Treatment of hyperlipidemic acute pancreatitis with plasma exchange: a single-center experience. *Ther Apher Dial* 2009;13:314–17.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow