Case Reports

An Uncommon Cause of Pyrexia of Unknown Origin

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Learning Points

- An elevated CRP of >200mg/dl usually implies an infective cause for pyrexia, but vasculitides and malignancy should also be considered.
- ANCA can be negative in up to 80% of patients with PAN and hence a tissue biopsy is essential to confirm the diagnosis.
- Vasculitis (usually temporal arteritis) is the underlying cause of PUO in approximately 15% of patients above the age of 60.
- Tumour marker assays (including Ca125) are often unhelpful in the evaluation of patients with PUO, due to their low sensitivity and specificity.
- Careful follow-up of patients with an unidentified source of PUO is invaluable, as new clinical features may appear that allow targeted tissue biopsy.

Keywords
PUO, Vasculitis, Polyarteritis nodosa, Ca125

Introduction

Prolonged unexplained fever is one of the most challenging problems encountered in clinical medicine. We report the case of a patient with an uncommon cause of Pyrexia of Unknown Origin (PUO).

Case report

A 63-year-old lady was admitted under the acute medical team with a fever, associated with a 3-week history of feeling non-specifically unwell, generalised aches & pains, night sweats and a dry cough. She was normally fit and well, with no other significant past medical history and took no regular medications. The only positive finding on examination at this time was mild tenderness over the left loin. Blood results showed a raised white cell count at 17.4×10^9 /l (neutrophils 15.0×10^9/l), a raised C – reactive protein at 220 mg/dl and an elevated alkaline phosphatase at 166 IU/l. An infective source was presumed and the patient commenced empirically on antibiotics. Despite this, the patient persistently spiked temperatures of up to 38.8 degrees Centigrade (°C) at night.

Mid stream urine samples revealed a sterile pyuria only. Abdominal CT scan identified soft tissue thickening around the upper and mid left ureter, which was mildly dilated. Further investigation with an intravenous urogram (IVU) revealed a duplex system on the left. Retroperitoneal fibrosis was also excluded, following discussion of CT findings with radiologists. Serial blood cultures and serological tests to identify an infectious cause were all within normal limits.

Serum Immunoglobulins, complement, autoimmune profile including ANCA were negative.

The tumour markers AFP and CEA were within normal limits, however, CA125 was approximately 3 times the upper limit of normal. This was considered not to warrant further investigation in the setting of a normal abdominal CT scan, following discussion at the gynaecology MDT meeting.

One month following admission, whilst continuing to spike nightly temperatures, the patient developed multiple erythematous, tender, nodular lesions on both breasts. A breast biopsy was performed. In addition to this, a temporal artery biopsy was also requested following rheumatological review, to exclude the possibility of giant cell arteritis . Histology of the breast lump demonstrated transmural inflammation and disruption of elastic lamina within a small/ medium-sized artery in the subcutaneous fat. The infiltrate comprised lymphocytes, histiocytes and eosinophils and was indicative of a vasculitis (Figures 1 and 2). Temporal artery biopsy showed a thickened atherosclerotic artery without any evidence of arteritis. These findings were consistent with a histological diagnosis of classical polyarteritis

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An Uncommon Cause of Pyrexia of Unknown Origin

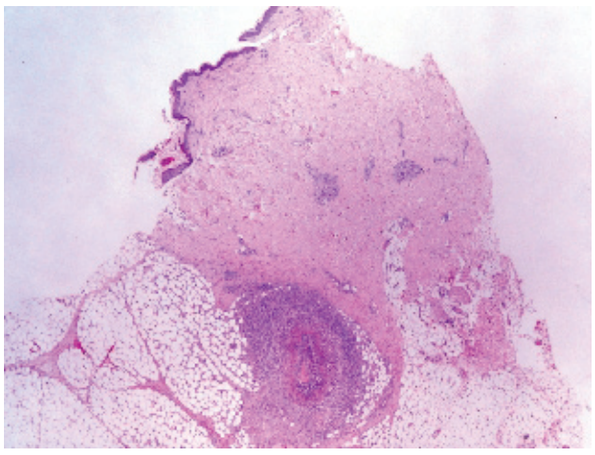

Figure 1.

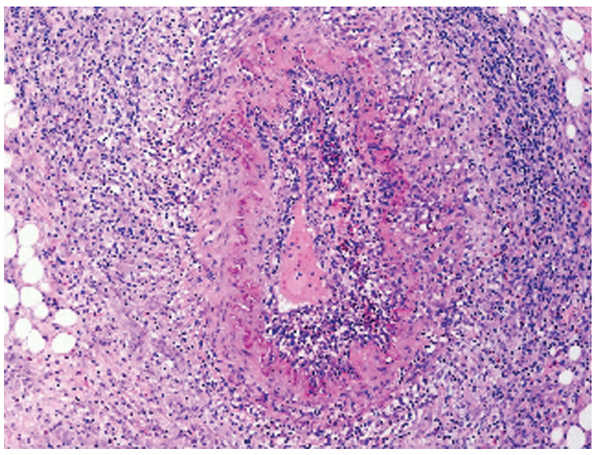

Figure 2.

nodosa. Symptoms and temperature resolved with the commencement of oral prednisolone 30mg once daily. She was discharged home with planned outpatient follow up under the rheumatologists.

Discussion

Pyrexia of Unknown Origin (PUO) is defined as (1) temperatures >38.3°C on several occasions; (2) a duration of >3 weeks; and (3) failure to reach a diagnosis despite 1 week of inpatient investigation.[1] In the western world, infections remain the commonest cause (22–26%), followed by non-infectious inflammatory conditions (22–24%) and malignancies (7–12.5%).[2] Around 20–30% of PUOs defy diagnosis even with the availability of current diagnostic technologies. The usual non-infectious inflammatory conditions causing PUO are systemic vasculitis, Still's disease and systemic lupus erythematosus (SLE).[3]

Systemic vasculitis is an uncommon cause of PUO as the combined incidence of all the vasculitides is less than 100 per million per year. Among the vasculitides, temporal arteritis (also known as giant cell arteritis) is the commonest type seen in patients over the age of 60.[4] It is also the commonest type presenting with fever as the sole symptom. A review of the literature showed that up to 15% of patients over the age of 60 presenting with PUO have temporal arteritis. Following the Chapel Hill Conference on the Nomenclature of Systemic Vasculitis in 1992[5] the term "polyarteritis nodosa(PAN)" or alternatively"classic polyarteritis nodosa," is restricted to disease in which there is arteritis in medium-sized and small arteries without involvement of smaller vessels. Therefore, patients with vasculitis affecting arterioles, venules, or capillaries, including glomerular capillaries (i.e., with glomerulonephritis), are excluded from this diagnostic category. Our patient has classic polyarteritis according to this classification.

It is difficult to establish an accurate picture of the incidence and clinical features of this condition as most of the literature on PAN has included classical PAN and microscopic polyangiitis as well as other small vessel vasculitis. Classical PAN is felt to be more uncommon than microscopic polyangiitis and 20 to 30% of cases are associated with hepatitis B antigenemia, with a further 5% associated with hepatitis C infection. Hairy cell leukemia can also be associated with PAN but there was no evidence of any of these diseases in this patient. Case series and comparisons between patients with classical PAN and microscopic polyangiitis have shown that the presence of renal involvement, pulmonary involvement and positive p-ANCA antibodies are common in microscopic polyangiitis while ANCA positivity. Renal involvement in classical PAN is due to involvement of renal arteries, while in microscopic polyangiitis this is due to a glomerulonephritis. Pulmonary involvement is rare in classical PAN.

Treatment of PAN consists of steroids and other immunosuppressants such as cyclophosphamide. Current opinion is that steroid treatment alone is sufficient for patients who present without any major organ involvement and cyclophosphamide is added if the disease affects any major organ (lung, kidney, gut, brain or heart)[6]. Immunosuppressants are also used for flare-ups uncontrolled by steroids and in patients who become steroid dependant. However, the chance of relapse is higher in patients treated with steroids alone. We decided to treat this patient with steroids alone, as she did not have evidence of any major organ involvement. The fever resolved and inflammatory markers normalised on steroid therapy.

This case highlights the importance of careful clinical observation in evaluation of patients with PUO, and prompt biopsy of any potentially diagnostic skin lesions. This case also highlights the non-specific nature of elevated CA125, and the need for correlation of this serological tumour marker with clinical and radiological findings. CA125 is not a good screening test for ovarian cancer and the positive predictive value in normal individuals is around 3%. Ascites of any cause, arthritis and other abdominal cancers can all cause a rise in CA125. If a malignancy is suspected, a CT scan of the chest, abdomen and pelvis has the advantage of excluding other possibilities such as abscess or spinal pathology.

References

1. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. *Medicine* 1961; **40**: 1–30.
2. De Kleijn EM, Vandenbroucke JP, van der Meer JW. Fever of unknown origin (FUO). I. A prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. The Netherlands FUO Study Group. *Medicine Baltimore* 1997; **76**: 392–400.
3. Knockaert DC, Vanneste LJ, Bobbaers HJ. Fever of unknown origin in elderly patients. *J Am Geriatr Soc* 1993; **41**: 1187–92.
4. Watts RA, Scott DGI: Epidemiology of vasculitis. In Vasculitis. Edited by Ball GV, Bridges SL. London: *Oxford University Press*; 2002: 211–226.
5. Jennete JC, Falk RJ, Andrassy K, *et al*. Nomenclature of systemic vasculitides: Proposal of an international consensus conference. *Arthritis Rheum* 1994; **37**: 187–92.
6. Guillevin L, Lhote F: Treatment of polyarteritis nodosa and microscopic polyangiitis. *Arthritis Rheum* 1998 Dec; **41(12)**: 2100–5.