

An unusual cause for PUO

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Keywords

Rheumatic fever, streptococcus, Jones criteria

Teaching Points

1. Rheumatic fever should be considered in the differential diagnosis of pyrexia of unknown origin (PUO) particularly if there is a preceding history of sore throat.
2. Incidence of rheumatic fever may be increasing due to reduced antibiotic prescription in patients with sore throat.
3. If the condition is diagnosed, bed rest and high dose aspirin are the treatments of choice.

Case report

A 22 year old woman presented with a seven week history of arthralgia, intermittent fever, fatigue, and sore throat. In the week prior to hospital referral she had become more unwell, with painful swelling of her left knee and a non-pruritic, erythematous rash over her forearms. Prior to this illness she had been fit and well with no previous medical or drug history.

On examination she appeared pale, but not significantly unwell, with a low-grade pyrexia of 37.5°C. The rash was confined to the forearms, pale red in colour with an irregular outline (see figure 1). The left knee was minimally tender with no significant effusion or erythema. Her ears, nose and throat were normal, as was respiratory examination. Cardiovascular examination revealed slight tachycardia and a soft ejection systolic murmur, loudest over the aortic area. There was no pericardial rub. Initial investigation revealed a c-reactive protein (CRP) of 63, haemoglobin 101g/l, with a normal white cell (WCC) and platelet count. Blood and urine cultures, viral serology, autoimmune profile and immunoglobulins were negative. Anti-streptolysin-O (ASO) titre was at the upper end of the normal range at 200iu/l. ECG showed a right bundle branch block with anterior T wave inversion; chest X-ray and transthoracic echocardiogram were normal. She was allowed home pending the results of further cultures and serological tests.

At review, one week later, her condition had

deteriorated. The rash persisted and she had become breathless with marked fatigue. She appeared paler and a pericardial rub was now apparent. Repeat blood tests revealed a haemoglobin 74, WCC 22 (neutrophils 19.7), a CRP 130 and ASO titre 400. DNaseB titre was also elevated (1:960). Further investigation with abdominal and pelvic ultrasound, followed by abdominal CT scan showed hepatomegaly, but no other abnormality. Repeat echocardiography showed marked pericardial thickening and bilateral pleural effusions.

Her rash was reviewed by an experienced consultant dermatologist, who diagnosed erythema marginatum. On the basis of this, her persistently elevated CRP, rising ASO and DNaseB titre, fever, arthralgia, and pericarditis, a diagnosis of acute rheumatic fever was made. She was admitted to hospital for bed rest and treated with a single 1.2g intravenous dose of benzylpenicillin, followed by oral amoxicillin 500mg tds. She was treated with aspirin 900mg qds, combined with a proton pump inhibitor as prophylaxis against gastric mucosal damage.

Her condition improved steadily over the next week, after which her inflammatory markers had returned to normal. At follow-up 3 months later she remained well after discontinuation of the aspirin, and she has been advised to continue with treatment with prophylactic doses of penicillin V for at least 10 years.



Figure 1. Photograph of forearm rash, showing features of erythema marginatum

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Discussion

Pyrexia of Unknown Origin is a term applied to patients whose fever has persisted for more than 3 weeks, and whose initial investigations have failed to identify a cause. Although such patients represent a small proportion of emergency medical admissions (approx. 3% of admissions to our unit) they can create diagnostic difficulties which frequently require prolonged hospital admission to resolve.

Rheumatic Fever is a disease which affects predominantly children and young adults as a complication of infection by a group A beta-haemolytic streptococcus. The criteria for diagnosis of rheumatic fever were first published in 1944 by Jones¹ and were most recently updated in 1992 (Figure 2).² As many of these criteria are non-specific, the diagnosis relies on a combination of clinical acumen, along with a high index of suspicion where there is evidence recent group A streptococcal (GAS) infection.³

Although our patient had complained of sore throat, her initial ASO titre was not significantly elevated. Her admission ECG was consistent with a 'carditis', but it was not until our dermatologist identified her rash as erythema marginatum that the diagnosis was made. This rash, which will be unfamiliar to many clinicians, is pale red in colour and distributed in rings or partial rings. Characteristically, new lesions can occur each day for several days, each lasting for only a few hours at a time, leading to its being described historically as the '4 o'clock rash': it came on in the afternoon and if you didn't go and look at it immediately, it would be gone.

Once diagnosed, our patient settled quickly with a combination of high dose aspirin and bed rest. A recent literature review in the British Medical Journal concluded that corticosteroids conferred no additional short or long-term benefit over aspirin.⁴ Penicillin ensures eradication of

the causative organism; prophylaxis with penicillin-V is recommended for 10 years to prevent recurrence.

Although the incidence of acute rheumatic fever had declined since the 1950s in developed countries,⁵ there has been a recent resurgence with new epidemics being reported in the United States.⁶ This may relate to the reduction in antibiotic prescription for the common sore throat. Distinction between a viral and streptococcal cause is notoriously difficult. This was recently illustrated in a study looking at the variability in assessment of sore throats by primary care practitioners in Germany, despite the use of clinical predictor scores.^{7,8} The Infectious Diseases Society of America has advocated the use of rapid antigen diagnostic testing to confirm the diagnosis of GAS pharyngitis. It is hoped that more targeted antibiotic use in the future will reduce the incidence of rheumatic heart disease.⁹

Major Criteria	Minor Criteria
Carditis	fever
Polyarthritits	arthralgia
Chorea	raised ESR
Erythema marginatum	raised CRP
Subcutaneous nodules	prolonged P-R interval
Diagnosis – 2 major criteria or 1 major plus 2 minor criteria together with evidence of streptococcal infection (+ve throat culture, raised ASO titre)	

Figure 2. Jones Criteria 1992

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