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CASE REPORT

Pyrexia of Unknown Origin – Differential Diagnosis?

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Abstract

A 68-year-old man presented with a 3-week history of pyrexia of unknown origin. He also suffered from malaise, night sweats, rigors and weight loss but had no localizing symptoms. Pyrexia of unknown origin has a wide array of differential diagnoses and it can be challenging to find the correct diagnosis promptly. Examination of the patient indicated pallor and features of long-standing aortic regurgitation, but was otherwise unremarkable. Due to his history of valvular disease and a recent dental extraction, his investigations were tailored towards infective endocarditis. Blood cultures and echocardiography confirmed this diagnosis by Dukes' criteria. He promptly received antibiotics, made a full recovery and was discharged.

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Background

Pyrexia of unknown origin is defined as a fever of 38.3°C or more lasting at least 3 weeks and for which no cause can be identified after 3 days of investigations in hospital or after 3 or more outpatient visits.¹ There are few other clinical presentations that produce such a wide array of differential diagnoses, including infections, malignancy and connective tissue disorders.² Due to the high mortality rate of many of these conditions, especially if diagnosis is delayed, a high degree of suspicion is imperative. Thorough clinical assessment is vital to provide diagnostic clues and tailor investigations.²

Here, we report a case of pyrexia of unknown origin, which was found to be due to infective endocarditis (IE) in a gentleman with Marfan syndrome. IE is a rare endocardial infection with an annual incidence of 3–10 cases per 100,000 per annum.³ It can be bacterial, viral or fungal, predominately affecting those over age 60 and twice as many men as women.⁴ Over 50% have underlying heart problems (e.g. valvular disease) and intravenous drug use is an important risk factor.³ Unfortunately, diagnosis is commonly delayed as symptoms are often non-specific. Diagnosis is by Dukes' criteria.⁴ Treatment is frequently with antibiotics, but surgery is indicated in uncontrolled infection, heart failure or embolic event.^{3,6} Prompt diagnosis is vital as mortality rates of between 14–46% have been reported and complications include congestive heart failure and stroke.⁷

Marfan syndrome, an additional uncommon condition affecting this patient, is an autosomal dominant disorder affecting fibrillin-1 (an extracellular matrix protein),

which causes weakening of connective tissue. Common features are lens dislocation, skeletal features (e.g. arachnodactyly, scoliosis) and dural ectasia. Cardiac features include valve incompetence, such as in this case, and aortic dissection, which often requires monitoring and medication.⁸

Here, we describe the difficulty in diagnosing IE due to its non-specific presentation. We also aim to highlight how considering a patient's characteristics can aid in the diagnosis of a non-specific complaint such as pyrexia of unknown origin. Finally, we discuss the guidelines for the use of prophylactic antibiotics in high risk individuals.

Case Report

A 68-year-old gentleman with Marfan syndrome presented with a 3-week history of malaise and fever, and a 2-week history of rigors and night sweats. His appetite was poor, he had lost 2 kg of weight and felt slightly nauseated, but denied vomiting. He had no rashes or skin lesions and denied any other symptoms on systemic enquiry. His past medical history included aortic regurgitation (moderate and asymptomatic), essential hypertension, hypercholesterolaemia and benign prostatic hyperplasia (BPH), but he had no history of malignancy or long-standing infections. He is a retired, married, non-smoker and is fully independent. He denied recent foreign travel or intravenous drug use but had a dental extraction the previous month.

On general inspection, conjunctival pallor was present but there was no jaundice, cyanosis or rashes. His temperature was

38.5°C but his other observations were all normal. On cardiovascular examination, he had no splinter haemorrhages, finger clubbing, Osler’s nodes or Janeway lesions. He had a collapsing radial pulse and a visible carotid pulsation (Corrigan’s sign). His dentition was good and his JVP was not elevated. He had no palpable heaves or thrills but his apex beat had a heaving

character in the sixth intercostal space, displaced 2 cm laterally of the midclavicular line. Heart sounds I + II were present with an early diastolic murmur (intensity grade 3), suggestive of aortic regurgitation. Peripheral pulses were normal. Examination of other systems was unremarkable.

Differential Diagnosis of Pyrexia of Unknown Origin:

Differential Diagnosis	Factors Supporting	Factors Against
Infective Endocarditis	Aortic regurgitation. Recent dental extraction.	No features of IE on examination (e.g. Janeway lesions, Osler’s nodes)
Other Infections e.g. abscesses, oral cavity infections or bone infections	Infective symptoms and prolonged pyrexia.	No obvious source of infection or localized symptoms to suggest site (e.g. hepatobiliary, diverticular, urinary)
Haematological malignancy e.g. lymphoma, leukaemia, myeloma	Pyrexia, cachexia, night sweats, weight loss. Many haematological malignancies commonly occur in >60yrs. Anaemic on examination.	No lymphadenopathy, hepatomegaly or splenomegaly. No clinical evidence of thrombocytopenia (e.g. bruising). No compression features typical of lymphoma.
Other Malignancies e.g. lung, colorectal, renal	Rapid weight loss, pallor on examination.	No localizing clinical signs or symptoms. No lymphadenopathy on examination.
Tuberculosis	Pyrexia, rigors, night sweats, weight loss.	No respiratory symptoms. No history of previous TB and no known risk factors.
Connective Tissue Disorders e.g. polymyalgia rheumatica (PMR), systemic lupus erythematosus (SLE), vasculitis	Malaise, pallor on examination.	No proximal muscle features typical of PMR, vasculitic rash or multisystemic features of SLE.

Investigations

The patient was anaemic (Hb 8.6 g/L) with a neutrophilia and raised c-reactive protein. Blood cultures were positive for viridians streptococci. Urinalysis and throat swab showed no organisms. An ECG, chest X-ray and abdominal CT scan were unremarkable. A transoesophageal echocardiogram indicated vegetation attached to the aortic valve and ventricular septum. The diagnosis of IE was made by the modified Duke's Criteria⁴ on the fourth day of admission. No other source of infection was found.

Management, Outcome & Follow up

The patient was promptly prescribed intravenous benzylpenicillin and gentamicin as per BSAC guidelines.⁴ He was also prescribed paracetamol and thromboembolism prophylaxis. His clinical response and observations were monitored closely. A repeat echocardiogram was arranged the following week to assess valve function, vegetation size and if surgical repair was required. The patient responded well to antibiotics and did not require surgery. He continued on benzylpenicillin for 4 weeks and gentamicin for 2 weeks and was discharged home.

Discussion

Pyrexia of unknown origin has a wide range of differential diagnoses and requires prompt and appropriate investigations. IE is an important differential diagnosis and, due to its often non-specific presentation, it requires a high degree of suspicion. It has been reported that around 25% of those with IE have clinical signs for over one

month before admission to hospital.⁹ Delay can lead to devastating and even multiple complications, for example cases of multiple embolic events and renal failure or splenic rupture and fatal intra-abdominal haemorrhage have been reported.^{10,11}

Prompt blood cultures and transoesophageal echocardiography are necessary to confirm the diagnosis of IE. Clinical examination is essential for excluding other causes and aiding diagnosis. Signs on examination include cardiac murmurs (which are present in around 50%) and vasculitic rashes.³ However, classical signs including Janeway lesions or subconjunctival haemorrhages are only present in a minority and, therefore, their absence does not exclude the diagnosis, as illustrated by this case.⁹

In this case, acknowledging the patient's risk factors aided the prognosis, which included his valvular heart disease related to Marfan syndrome and a recent dental extraction. This indicates the importance of taking a thorough history and having an awareness of risk factors. Between 1955 and 2008, prophylactic antibiotics were prescribed as a preventative measure to those undergoing interventional procedures who were deemed to have a high risk of IE (e.g. those with valvular diseases). However, new guidelines published by NICE in 2008 stated it was no longer recommended to offer antibiotic prophylaxis as the potential benefits are minimal.¹² It is possible that prophylactic antibiotics in this case could have prevented the development of IE. A similar case in 2011 was reported, where a patient with a congenital heart defect developed IE after a dental procedure, and the authors speculated whether the new guidelines were wise.¹³ This was reiterated by another case describing a previously independent 69-year-old man with a prosthetic aortic valve and known

poor dentition, who developed IE 10 days after a dental procedure.¹⁴ He unfortunately developed a cerebrovascular complication and died. The authors questioned whether strict adherence to the new guidelines is appropriate and suggested the decision should be made by case by case decisions.¹⁴ Interestingly, the American Heart Association and the European Society for Cardiology both recommend prophylaxis for high risk individuals.^{15,16} From these cases it is clear that clinicians should be aware that a history of a recent interventional procedure, especially in susceptible individuals, is an important risk factor in the context of IE.

Key Learning Points

- Pyrexia of unknown origin has a wide range of differential diagnoses including infections, malignancies and connective tissue disorders.
- Infective endocarditis is a rare infection which can present with non-specific complaints, such as pyrexia and malaise.
- It generally affects elderly patients and other risk factors include intravenous drug use, valvular disease, prosthetic valves and cyanotic congenital heart disease.
- Having a high degree of suspicion of endocarditis is necessary for prompt diagnosis and management as mortality is high.
- NICE guidelines state that prophylactic antibiotics are no longer recommended as a preventative measure in those who are deemed to have a high risk of infective endocarditis undergoing interventional procedures.

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