A case of fever of unknown origin

Introduction

Often seen as a mild disease, longstanding fever without foci can mask unexpected disorders. Reports of inflammatory myofibroblastic tumours of the gastric curvature are scarce and evidence-based decisions when these are recognized are few. However, the current patient recovered after surgery and has been asymptomatic afterwards. This article outlines the step-by-step diagnosis of fever of unknown origin. Although self-limited febrile processes commonly end without aetiological diagnosis, further investigations are needed when systemic involvement is detected or they recur.

Discussion

Fever of unknown origin refers to a prolonged febrile illness without an established aetiology despite intensive evaluation and diagnostic testing. This entity, which is often mistaken by clinicians for 'fever without localizing signs', must meet several criteria already accepted in the literature (Petersdorf and Beeson, 1961). Aetiological possibilities are many and a structured approach is necessary (Cunha et al, 2015). Because this patient's general condition was acceptable and investigations were repeatedly normal he was reluctant to undergo further tests. However, the unexplained febrile illness convinced the authors to evaluate further and was the key to reaching an accurate diagnosis.

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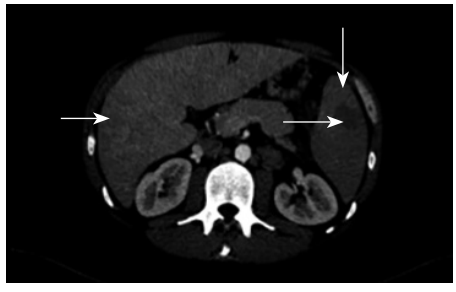
Inflammatory myofibroblastic tumour is a mass lesion of unknown cause. It can be found in numerous sites, such as the orbit, skull base, thyroid, liver, spine and typically in the lung (Melloni et al, 2005). Less common sites are stomach, lymph nodes and spleen. Its appearance is often linked with viral (cytomegalovirus, human herpesvirus 8) reactivation or persistent bacterial infection (Lewis et al, 2003). It is a rare condition.

Over half of patients are less than 40 years old and clinical symptoms depend upon the localization, being able to mimic malignant tumours both clinically and radiologically. Pathogenic mechanisms are debated and still remain unclear, ranging from an inflammatory reaction to an infection or an underlying low grade malignancy. As

Figure 1. Horizontal arrows showing homogeneous hepatosplenomegaly and vertical arrow showing splenic infarction.



CASE REPORT

A 30-year-old man attended the emergency department with a 1-month history of high fever, chills and diffuse abdominal discomfort. He denied weight loss, cutaneous lesions, arthralgia or any epidemiological risk factors for infections. Apart from a similar episode 5 years ago which spontaneously resolved, the patient's past medical history was unremarkable. On physical examination he was feverish and haemodynamically stable. An enlarged liver was found on palpation with no localized abdominal tenderness. Laboratory results showed a hepatic cytolytic pattern with mild normocytic/normochromic anaemia and elevated inflammatory markers.

An ultrasound scan showed features of homogeneous hepatosplenomegaly. Having obtained blood cultures, he was admitted to the ward without antibiotic prescription. Previous findings were confirmed and indicated that this case was a fever of unknown origin. Infectious (including tuberculosis, HIV, hepatitis B and C, Epstein–Barr virus, cytomegalovirus, human herpesvirus 8, parvovirus, enterovirus, rubeola, measles, influenza, adenovirus, respiratory syncytial virus, Borrelia, Brucella, Coxiella, Legionella, Mycoplasma and Chlamydophila) and rheumatic conditions (normal rheumatoid factor, anti-CCP (cyclic citrullinated peptide), antinuclear antibodies, extracted nuclear antibodies, anti-neutrophil cytoplasmic antibodies and complement) were ruled out. Iron profile, vitamins, hormones, serum electrophoresis and immunoglobulins were within normal limits. A computed tomography body scan confirmed the homogeneous hepatic and splenic enlargement, and found a haemorrhagic splenic infarct (*Figure 1*) with retroperitoneal and gastric lymphadenopathy. Liver biopsy showed minimum focus of lobular inflammatory activity with slight sinusoidal congestion.

As the diagnosis remained unclear and the patient was still feverish and anaemic, the differential diagnosis was broadened. A transthoracic echocardiogram, full clotting panel, peripheral blood smear and the paroxysmal nocturnal haemoglobinuria gene test were performed to exclude causes of systemic infarcts. Transthoracic echocardiogram and blood cultures with pan-polymerase chain reaction test excluded culture-negative endocarditis. Angiotensin-converting enzyme, beta-2-microglobulin a, serum free light chain measurement, direct and indirect Coombs test were normal. A positron emission tomography scan showed standardized uptake value 8 in lymph nodes of the lesser gastric curvature and standardized uptake value 6 at the mesentery lymph nodes. Ultrasound-guided biopsy was consistent with an inflammatory myofibroblastic tumour. The patient underwent caudal pancreatectomy, splenectomy and resection of the segmental gastric curvature. He has completely recovered.

inflammatory myofibroblastic tumour might become locally invasive and involve adjacent structures, surgical resection is the treatment of choice (Thistlethwaite et al, 2011). Patients who are unable to have complete surgical resection should receive glucocorticoids, radiotherapy or chemotherapy. Inflammatory myofibroblastic tumour reactivation after initial resection has been reported (Weinberg et al, 1987). **BJHM**

Cunha BA, Lortholary O, Cunha CB (2015) Fever of unknown origin: a clinical approach. *Am J Med* **128**(10): 1138.e1–1138.e15. https://doi.org/10.1016/j.amjmed.2015.06.001

Lewis JT, Gaffney RL, Casey MB, Farrell MA, Morice WG, Macon WR (2003) Inflammatory pseudotumor of the spleen associated with a clonal Epstein-Barr virus genome. Case report and review of the literature. *Am J Clin Pathol* **120**(1): 56–61. https://doi.org/10.1309/BUWNMG5RV4D09YYH

Melloni G, Carretta A, Ciriaco P et al (2005) Inflammatory pseudotumor of the lung in adults. *Ann Thorac Surg* **79**(2): 426–432. https://doi.org/10.1016/j.athoracsur.2004.07.077

Petersdorf RG, Beeson PB (1961) Fever of unexplained origin: report on 100 cases. *Medicine* **40**(1): 1–30. https://doi.org/10.1097/00005792-196102000-00001

Thistlethwaite PA, Renner J, Duhamel D, Makani S, Lin GY, Jamieson SW, Harrell J (2011) Surgical management of endobronchial inflammatory myofibroblastic tumors. *Ann Thoracic Surg* **91**(2): 367–372. https://doi.org/10.1016/j.athoracsur.2010.09.017

Weinberg PB, Bromberg PA, Askin FB (1987) "Recurrence" of a plasma cell granuloma 11 years after initial resection. *South Med J* **80**(5): 519–521.

LEARNING POINTS

- Although self-limited febrile processes commonly end without aetiological diagnosis, further investigation is needed when systemic involvement is detected or they can recur.
- For patients who are able to have complete resection, surgery is the treatment of choice.

Acute dyspnoea in a paraplegic man

A 72-year-old paraplegic man presented with acute dyspnoea (oxygen saturations (in air) of 79%). Examination revealed raised jugular venous pressure and bilateral leg swelling. Initial arterial blood gas measurements indicated type 1 respiratory failure. D-dimer level was elevated at 5.64 ng/ml.

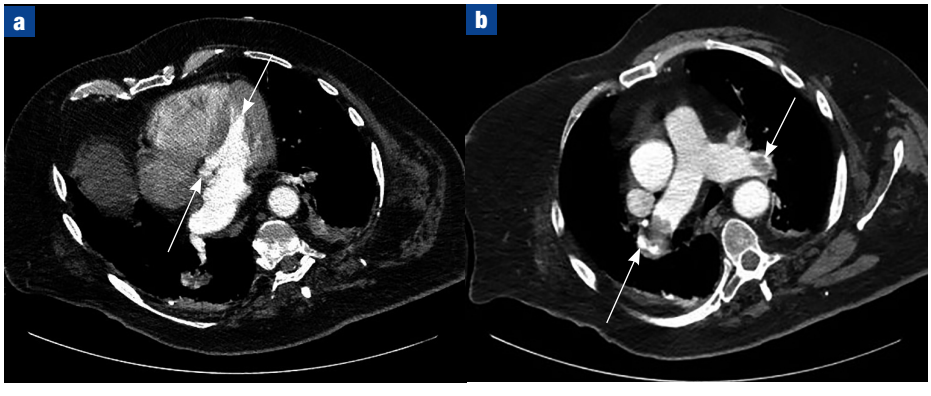
Computed tomography pulmonary angiogram (*Figure 1*) showed right ventricular dilatation and displacement of the interventricular septum, suggesting right heart strain secondary to bilateral large pulmonary emboli. Transthoracic echocardiogram showed severely impaired and dilated right ventricular and pulmonary artery systolic pressure >40 mmHg (i.e. pulmonary hypertension); a unifying diagnosis of cor pulmonale. No regional wall abnormalities were identified and therefore McConnell's sign, i.e. akinesia of the mid-right ventricular wall with apical sparing in a patient with an acute pulmonary emboli (Matthews and McLaughlin, 2008), was not present.

Embolic disease increases pulmonary resistance and right ventricular afterload through obstruction and vasoconstriction. Consequently, the interventricular septum deviates toward the left ventricle in diastole. Right ventricular wall tension increases and may result in myocardial ischaemia. Right ventricular failure in the presence of acute pulmonary emboli carries high mortality (Piazza and Goldhaber, 2005). Hence early recognition is crucial and treatment involves therapeutic anticoagulation and restoring oxygenation. **BJHM**

Matthews JC, McLaughlin V (2008) Acute right ventricular failure in the setting of acute pulmonary embolism or chronic pulmonary hypertension: a detailed review of the pathophysiology, diagnosis, and management. *Curr Cardiol Rev* **4**(1): 49–59. https://doi.org/10.2174/157340308783565384

Piazza G, Goldhaber SZ (2005) The acutely decompensated right ventricle: pathways for diagnosis and management. *Chest* **128**(3): 1836–1852. https://doi.org/10.1378/chest.128.3.1836

Figure 1. a. Computed tomography pulmonary angiogram demonstrating bowing of the cardiac septum (arrows) and a dilated right ventricle suggestive of acute right heart strain. **b.** Bilateral emboli in the left and right pulmonary arteries (arrows) with co-existing pulmonary hypertension.



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