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Rheumatologic diseases as the cause of fever of unknown origin

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A B S T R A C T

In 30% of patients with fever or inflammation of unknown origin (FUO/IUO), the cause is eventually found to be a rheumatologic disease such as autoimmune or granulomatous disease or vasculitis. Most of these patients suffer from an uncommon presentation of a common disease, instead of an uncommon disease. We demonstrate the diagnostic challenge with several cases. The workup of FUO is based on the identification of potential diagnostic clues (PDCs). In the absence of PDCs, a standardized diagnostic protocol should be followed, including early FDG–PET/CT. Other imaging techniques or invasive diagnostic techniques should be reserved for those in whom PDCs are present.

Introduction

Although approximately 30% of patients with long-term unexplained fever (fever of unknown origin (FUO), see Table 1 for definition) are eventually diagnosed with rheumatologic diseases such as autoimmune disease, vasculitis, or granulomatous disease [1], these kinds of diseases are often not the first considered in the differential diagnosis by physicians.

Other patients present with long-term unexplained inflammation (inflammation of unknown origin (IUO), see Table 2 for definition) in the absence of fever. Underlying causes, workup, and prognosis are the same for FUO and IUO [2].

It should be kept in mind that most patients with FUO suffer from an uncommon presentation of a common disease instead of an uncommon disease. This makes FUO a diagnostic challenge. We present

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Table 1
Definition of fever of unknown origin (FUO).

1. Fever ≥38.3 °C (≥101 °F) on ≥3 occasions
2. Duration of illness ≥3 weeks
3. No diagnosis despite extensive evaluation including (but not limited to):
- Extensive medical history and physical examination.
- Laboratory: erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), hemoglobin, platelet count, leukocyte count including differentiation, sodium, potassium, calcium, creatinine, total serum protein in protein electrophoresis, alkaline phosphatase (AF), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), lactate dehydrogenase (LDH), creatine kinase (CK), antinuclear antibodies (ANAs), rheumatoid factor (RF), microscopic urinalysis, ferritin.
- Microbiology: blood cultures (minimal 3), urine culture, tuberculin skin test, or interferon-gamma release assay.
- Imaging: chest X-ray, abdominal ultrasound, or chest and abdominal CT scans.
4. No known immunocompromised state:
- Neutropenia (leukocyte count $<1.0 \times 10^9$/L and/or granulocyte count $<0.5 \times 10^9$/L during at least 1 week within the 3 months before the start of the fever.
- Known human immunodeficiency virus (HIV) infection.
- Known hypogammaglobulinemia (IgG <50% of normal value).
- Use of 10 mg prednisone or equivalent dose of steroids during at least 2 weeks in the 3 months before the start of the fever.

Table 2
Definition of inflammation of unknown origin (IUO).

1. Elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) or serum amyloid A (SAA) on ≥ 3 separate occasions
2. Duration of illness ≥3 weeks
3. No diagnosis despite:
-Extensive medical history taking and physical examination.
-Laboratory: hemoglobin, platelet count, leukocyte count including differentiation, sodium, potassium, calcium, creatinine, total serum protein in protein electrophoresis, alkaline phosphatase (AF), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), lactate dehydrogenase (LDH), creatine kinase (CK), antinuclear antibodies (ANAs), rheumatoid factor (RF), microscopic urinalysis, ferritin.
-Microbiology: blood cultures (minimal 3), urine culture, tuberculin skin test, or interferon-gamma release assay.
-Imaging: chest X-ray, abdominal ultrasound, or chest and abdominal CT scans.
4. No known immunocompromised state:
-Neutropenia (leukocyte count $<1.0 \times 10^9$/L and/or granulocyte count $<0.5 \times 10^9$/L during at least 1 week within the 3 months before the start of the fever.
-Known human immunodeficiency virus (HIV) infection.
-Known hypogammaglobulinemia (IgG <50% of normal value).
-Use of 10 mg prednisone or equivalent dose of steroids during at least 2 weeks in the 3 months before the start of the fever.

a case series of four patients with FUO because of a rheumatologic disease who were treated at our university expertise FUO center in the past years.

Case 1. Polymyalgia rheumatica

A 70-year-old woman was referred to our outpatient department after three previous admissions in a Dutch community hospital because of episodes of fever that had been present for 5 months and were accompanied by rigors, night sweats, 17 kg weight loss, fatigue, chest and abdominal pain, myalgia, arthralgia, muscle weakness, and arthritis. Laboratory evaluation showed microcytic anemia, elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and elevated liver enzymes. Antinuclear antibodies (ANAs) were positive at multiple occasions, with repeatedly negative extractable nuclear antibodies (ENAs) and anti-double stranded DNA (anti-dsDNA) antibodies. Antineutrophil cytoplasmic antibodies (ANCAs) were negative. Extensive microbiological investigation, including 19 blood cultures and serology for different pathogens, was negative. PET/CT scan had shown high FDG-uptake in the right hip compatible with large-joint arthritis. A culture of the synovial fluid of the hip had remained sterile. Bone marrow biopsy had shown anemia of chronic disease. She had been treated with multiple courses of broad-spectrum antibiotics, which had resulted in normalization of body temperature. However, fever and inflammation reappeared quickly after each course.

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