Chapter

FEVER OF UNKNOWN ORIGIN IN INTERNAL MEDICINE: A REASONABLE ANALYSIS OF CAUSES AND MISTAKES

Andrea Affronti, Elisa Pollaccia, Marco Affronti, Pasquale Mansueto and Giuseppe Montalto
Department of Internal Medicine and Specialties, University of Palermo, Italy

ABSTRACT

Fever of unknown origin (FUO) is a long-term febrile syndrome whose aetiology remains unknown even after an accurate and appropriate diagnostic procedure is followed either as in hospital or as in out-patient practice.

It is a topic of considerable interest for several reasons:

– The fever alone constitutes the entire clinical picture as other symptoms and signs of localization are absent.
– Particularly if undiagnosed, the fever represents a real issue for both the patient and the doctor, being extremely challenging for the latter.
– It has a high socio-sanitary cost.
– The obscure origin of the fever does not depend on the fact that the diseases involved are rare, but rather on the fact that they are common diseases with uncommon patterns.
– The difficulties met often depend on the very competence of the doctor as well as on the availability of diagnostic tools.

- The technological advances so far obtained at the diagnostic level did not result in a significant reduction in the incidence of FUO, particularly of undiagnosed FUO.
- More than 200 causes were identified, and new, previously unknown ones continue to be discovered.
- Guidelines for an effective and valuable diagnostic procedure were never published.

Through an analysis of some illustrative clinical cases, we will evaluate the different possible causes of FUO (infectious, neo-plastic, autoimmune, non-classifiable, fictitious or simulated, psychogenic, and undiagnosed), the mean time of diagnosis, the relationship between those procedures which successfully result in a diagnosis and those which fail to do so, the errors which determined the appearance of a FUO and, finally the diagnostic and prognostic future of those FUOs which remain undiagnosed despite an accurate and appropriate diagnostic procedure has been done.

Based on the available literature data, we will also discuss the nature of the error according to the case history, the medical examination, the wrong interpretation of a test, the missed assessment of a given symptom and/or of a positive test, the presence of concomitant and misleading pathologies, the atypical nature of the clinical picture and its peculiarity, and the absence of organ involvement. These parameters will enable us to develop a methodological procedure of practical relevance.

INTRODUCTION

It may seem strange to talk about fever of unknown origin (FUO) in 2012, considering the enormous advances in modern diagnostic laboratory tests and imaging techniques and their accuracy. However, the problem of undiagnosed fever remains of great interest, and indeed the most recent studies on this topic indicate that FUO is still undiagnosed in 19% to 30% of cases. Although over 50 years have passed since Petersdorf and Beeson first established the diagnostic criteria for FUO (1), no new definition has been found to substitute them. Even today there are many authors who recommend using the classical principles of the clinical method as the correct diagnostic approach i.e. the physician should:

- compile an extensive medical history (repeating anamnesis on several occasions may provide new elements in the most difficult cases);
- frequently re-evaluate the patient;
- bear in mind the less common manifestations of common diseases;

- perform meticulous physical re-examinations to discover possible new signs.

DEFINITION

The expression "fever of unknown origin" (FUO) (Table 1), indicates a febrile illness, generally of prolonged duration, where the clinical picture is dominated by fever. Other symptoms, signs or further findings which could guide to an early diagnosis are lacking or less evident, or appear only in the later stages of the disease (Scenario 1).

Table. 1 Definitions of temperature.

Normal temperature: temperature preferably measured at the rectum between 37.6 ° C 38.3 ° C in the morning and in the evening. Axillary temperature is in fact unreliable whereas oral and the tympanic are lower than rectal temperatures respectively 0.4 and 0.8 ° C.
Fever: increased body temperature mediated by an altered function of hypothalamic control with an upward shift in the values of the set-point activation of peripheral mechanisms of thermogenesis and inhibition of those of heat dispersion. Pyrogens are involved in this process: they can be exogenous (from sources outside the body) or endogenous (internal ones) the latter being essentially inflammatory cytokines.
Hyperthermia: increased body temperature which prevents the physiological homeostatic mechanisms of control without however increasing the hypothalamic set-point. In other words it occurs due to an alteration in the peripheral mechanisms of thermogenesis and heat dispersion.
Fictitious or self-induced fever: is intermittent daily with no physiological circadian variation is not coupled with heart rate and is usually too high compared to the general health of the patient which remains good.
FUO: fever above 38.3 ° C measured on several occasions during at least three weeks the cause of which remains unknown after 3 days of intensive diagnostic tests out-patient clinic evaluation and hospitalization. Distinctions can be made between i) classical FUO in which the most common causes are infections malignancies and inflammatory diseases ii) iatrogenic FUO: nosocomial FUO which normally appears during hospitalization for other reasons; iii) neutropenic FUO (with values <500 neutrophils/mm3) and iv) FUO associated with HIV infection.
Low-grade fever: refers Commonly to a condition of body temperature continuous or fluctuating between 37.5 and 38.3 ° C (about 101 ° F).
Habitual hyperthermia: a clinical condition characterized by a capricious body temperature as regards the circadian rhythm which can last for years and in which for quite complex reasons the normal temperature of an absolutely healthy subject is set at higher than normal values

Scenario 1: without organic signs

A 14-year-old girl was admitted to hospital for continuous remittent fever of long duration (4 months) , with shivering and sweating, which partially responded to antibiotics. Physical evaluation revealed widespread muscle soreness, slight systolic murmur at the centrum cordis and diffuse micropolyadenopathy. The patient's general health condition was good and there was no weight loss. Laboratory tests showed an ESR of 82 in the first hour and hyposideremia (30 γ%), CRP was positive (1/80). Ultrasonography of the upper and lower abdomen, chest x-ray, barium enema and total body CT scan were all negative. Blood and bone cultures were also negative. Echocardiography, however, showed a holosystolic prolapse of the anterior mitral valve flap.Although there were no specific physical or clinical indications, after 30 days of hospitalization orthopantomography was performed, showing an inflammatory reaction at the apex of the second upper left incisor. The patient was transferred to dentistry and after pus drainage the fever resolved.Diagnosis: FUO diagnosed; apical granuloma of the second upper left incisor. Mitral valve prolapsed

Comment

Periapical dental abscesses are responsible for many episodes of FUO as they often occur with intermittent bouts of fever (2). However, many patients present no symptoms and only a few complain of dental pain or tooth loss. On closer examination of the oral cavity, periodontal diseases and visible and palpable abscesses can be observed. But this is not the rule, and in many cases diagnosis must be made by dental radiography. Antimicrobial therapy alone rarely eliminates the fever since pus drainage and often dental extraction are necessary.Orthopantomography should, therefore, always be performed in cases of long-term FUO before embarking on more complex and invasive examinations, especially when general health is good despite the fever.

One would have thought that with the advances in the field of diagnostic imaging, especially with the advent of CT scan, MRI and other imaging tools, as well as the striking improvement in therapies, FUO would be destined to disappear. This is not the case and FUOs are still far from rare. In fact, a comparison of the various statistics shows that the incidence of FUO has remained essentially unchanged over time, although there have been changes in the spectrum of causes (3) (Table 2).

Table 2. Definitions of fever of unknown origin (FUO) (3).

Classical FUO
• Fever 38.3 °C on several occasions
• Duration 3 weeks
• Diagnosis uncertain after n. days despite appropriate in-hospital investigation or three out-patient visits
Nosocomial FUO
• Hospitalized patients
• Fever 38.3 °C on several occasions
• Infection not present or incubating on admission
• Diagnosis uncertain after 3 days despite appropriate investigations (including at least 48-h incubation of microbiological cultures)
Neutropenic FUO
• Less than 500 neutrophils/ mm^{-3}
• Fever 38.3 °C on several occasions
• Diagnosis uncertain after 3 days despite appropriate investigations (including at least 48-h incubation of microbiological cultures)
HIV-associated FUO
• Confirmed HIV infection
• Fever 38.3 °C on several occasions
• Duration of 4 weeks (outpatients), or n. days in hospitalized patients
• Diagnosis uncertain after n. days despite appropriate investigations (including at least 48-h incubation of microbiological cultures)

FUO has attracted the attention of doctors since 1961, when Petersdorf and Beeson published the results of their study on 100 patients observed between 1950 and 1960 and proposed a definition of FUO based on three criteria: "*febrile illness that lasts for more than three weeks", "ongoing or recurring temperature recorded on several occasions and greater than 38.3°C [101°F] ", "diagnosis is not established after a week of investigation in hospital*." The first of these criteria excluded the vast number of self-limiting febrile illnesses, while the second eliminated habitual hyperthermia; the third, finally, indicated the time limit considered indispensable to complete the appropriate diagnostic tests. This definition has, however, been criticized in subsequent years. First, in relation to the duration of fever, it has been argued that a lack of diagnosis can be dangerous for the patient and represents a great burden of responsibility for the physician, for example, in the course of hyper-acute diseases which last one or two weeks (4).Secondly, there is a close relationship between the magnitude of fever and disease severity. In fact, a persistent low-grade fever may be symptomatic of a serious medical condition, as for example tuberculous infection (Our unpublished

data).Finally, the lack of diagnosis may depend, in some cases, on the degree of clinical experience and skill of the physician (5), as can be seen in Scenario 2. However, despite these limitations the definition of Petersdorf and Beeson has remained the one most followed by practitioners.

Scenario 2 Errors: history, lack of assessment of symptoms and / or a positive test due to the wrong assessment of a test

A shop owner aged 29 was admitted for abdominal pain and fever lasting 18 months, with a history of two previous hospitalizations for the same reason. Anamnesis was: tonsillectomy at 5 years; appendectomy complicated by peritonitis at 12 years. Following this until the age of 18, periodical episodes of abdominal pain accompanied by fever. After this age fever had no longer recurred until recently, when it reappeared, after 11 years, but with the same characteristics as before. At 28 a HP-related duodenal ulcer was found.At first admission white blood cells were 18.000/mm^3. Abdomen X-ray, abdomen ultrasound and colonoscopy were negative. No diagnosis was made (undiagnosed FUO).

At second admission after 3 months, on spiral CT scan of the upper and lower abdomen the only pathologically significant finding was the presence of a discrete distention of the walls of some ileal loops in the left iliac fossa, caused by fluid accumulation, with low hydro-gas levels visible inside them. These loops also showed a slightly thickened wall and marked enhancement consistent with wall inflammation. Double contrast enema showed that the terminal ileum seemed to adhere to the jejunum loops on the mesenteric side, but it appeared regular in size and without mucosa damage.At this point the cause of FUO was diagnosed: Crohn's disease.After 4 months, labeled IgG scintigraphy of the intestine highlighted in the late phase a limited accumulation of activity in the right colic flexure and above right of the urinary bladder.

At third admission: main details from the clinical history:- Periodic fever with abdominal pain originating in the right iliac fossa;- Positive markers of nonspecific inflammation during attacks (ESR, CRP, white blood cells, alpha-2-globulins, fibrinogen);- The tests performed (CT, colonoscopy, intestinal scintigraphy) showed an albeit indirect involvement of the visceral peritoneum;- Good general condition of the patient between episodes and prolonged course of the disease. - Characteristic symptoms : colic-like pain, originating from the right iliac fossa, spreading to the upper abdomen; it was preceded by fever (max temp. 38.5 ° C) and accompanied by nausea and bloating; it was resistant to antispasmodics and after 2-3 days abruptly resolved. These symptoms, always with the same characteristics, had been occurring every 2-3 months and lately approximately every 15 days.A diagnosis was hypothesized: periodic aseptic inflammation of the peritoneal serous.During this hospitalization, at the onset of

the symptoms described colchicine (3 mg) was initiated, which significantly lowered the febrile peak and reduced the abdominal pain.On the basis of this result it was decided to commence colchicine prophylaxis (0.6 mg / day) to prevent the appearance of the symptoms, which recurred on two other occasions after the drug was suspended. Meanwhile, genetic analysis of the genomic DNA extracted from peripheral blood lymphocytes detected the presence of the M694V mutation of the FMF gene (Familial Mediterranean Fever).Therefore, the final diagnosis of this FUO was: Familial Mediterranean Fever

Comment

FMF diagnosis may be difficult in patients who do not have a typical family history (as in our case) or when the symptoms of serositis (pain) are not correctly interpreted or are absent (6). Some indirect signs of peritoneal serous involvement, already present on second admission (spiral CT, double contrast enema), were wrongly interpreted as being compatible with Crohn's disease, while in fact, they were evidence of an aseptic inflammation of the serosa. Moreover, the periodical frequency of these manifestations was clear from the patient’s history.

ETIOLOGY

Infectious diseases, malignancies and autoimmune diseases are considered to be the three leading causes of FUO today.In the 1970s, malignancies exceeded infections as a cause of FUO (31% versus 30%), but in later years and in the most recent case studies infections have re-emerged as the most frequent cause in about one third of cases, followed by malignancies and then autoimmune diseases.

Infections are usually divided into systemic and localized forms. The majority of the latter, with the exception of sinusitis and brain abscesses, develop in the abdomen, either as diffuse or circumscribed peritonitis, or as infections of the individual organs (liver, gallbladder, spleen, kidney, prostate, fallopian tubes, ovaries etc.). Unfortunately, these forms, which are far from rare in the field of infectious causes of FUO, may remain undiagnosed even today in spite of the sophisticated diagnostic tools available.In addition to these three groups a fourth must be added, which consists of various non-classifiable (*miscellaneous*) diseases, which include pulmonary embolism, drug fever, inflammatory bowel disease, familial Mediterranean fever, aortic aneurysm, hypertriglyceridemia,

etc.Finally, there is the already-mentioned high percentage of FUO which remains undiagnosed or is diagnosed only at autopsy (7).

Of special interest are simulated or fictitious, "fevers", obtained by clever manipulation of the thermometer during the recording of body temperature, often caused by true self-harm, the expression of a determination, in some cases highly pathological, to simulate a disease state which does not exist.These "fevers" must be distinguished from psychogenic fevers in which real conversion disorder symptoms may cause FUO, even if the percentage of cases is limited. The pathophysiological mechanisms of this group of fevers have not yet been defined, although the close relationship between emotional distress and fever is well known.

DIAGNOSTIC APPROACH

Despite the extraordinary progress made in recent decades in the field of medicine, FUO continues to pose a diagnostic enigma. Few other syndromes, in fact, have such a wide variety of possible diagnoses and reveal such a high potential misuse of laboratory tests and imaging studies. However, although FUO has aroused interest for a long time and studies are continually being made, the three classic medical procedures are still indispensable in the diagnostic methodology of FUO: compilation of patient history, physical examination (including the observation of the temperature curve) and laboratory investigations. To underline the extraordinary importance of the physical examination, a study by Platt noted that a thorough anamnesis is diagnostic in 2/3 of cases (8). Unfortunately, in patients with FUO there is a significant shortage or lack of data offered by history and physical examination, as Scenario 1 shows. On the other hand, compiling a patient’s medical history is an invaluable tool for generating initial hypotheses and setting up a positive interpersonal relationship between doctor and patient. The hypotheses generated are based on information that the patient tells the doctor and on the connection made by the physician between this information and disease models in his/her memory. An error at this stage would be particularly serious, although probable in cases of FUO where diagnosis is primarily based on symptoms, such as rheumatic polymyalgia for example, and as described in Scenario 3, which is also a clear example of how the onset of FUO can be determined by any number of reasons and/or errors.

In physical examination the most frequent error is that it can be summary, due to lack of time and expertise. On physical examination false negatives are more frequent than false positives, respectively 20.5% and 6.4% in one standardized

study (9). Other notable errors are that no physical signs are completely accurate and reproducible and that a physical sign which has been properly detected may be incorrectly interpreted. Chronological modes of performance have been proposed to make diagnostic tests more effective and efficient: i) a type of "sequential" method, requiring appropriate further tests on the basis of the results obtained from previous investigations; or ii) a "predetermined" method which is based on a set diagnostic protocol that indicates the whole process to be followed from the very beginning to exclude or confirm hypotheses. The sequential method based on the use of diagnostic algorithms (10) will pass on to the next stages of the diagnostic process after a question has been answered with one of only two possible responses: positive or negative. Although an approach of this type allows the number of tests to be reduced, it is very long and too schematic. The default choice is based upon two criteria. The first is to correctly request the initial diagnostic tests which can confirm or rule out the most common causes of FUO. The second is to give preference to those inquiries which, according to the case in hand, are considered more likely to bear fruit. The Hurley list of diagnostic tests for the study of patients with FUO is a clear example (11). The first level consists primarily of bacteriological/serological tests, which are sometimes the very commonly used ones; the second level consists of the more complex but non-invasive investigations, while the third level consists solely of invasive procedures.

Scenario 3 prevalent mistakes: history, correct diagnostic test not requested. Other reasons: characteristics and rarity of the clinical picture

Mauritian illegal immigrant woman aged 26, married with one child, a domestic worker resident in Palermo for 4 years.The onset of the disease (3 months before admission to hospital) was characterized by pain in both the small and large joints with moderate swelling, especially in the morning. NSAID therapy was initiated.

One month after onset: fever associated with headache, asthenia and anorexia.

At this stage the tests showed moderate anemia (Hb = 11.6g /dl) and hyposideremia (14 γ%), ESR in the first hour was 40, ASO 1/300 and PCR 1/40 with positive streptozyme (+ +). RF test was negative but Rose-Waaler was positive (+). Erythromycin therapy was commenced with NSAIDs.

2 months later, a period of hospitalization for a high fever. Laboratory tests showed a worsening of anemia and an increase in inflammatory markers and streptozyme test (+ + +). There was also a modest increase in IgA and IgG with circulating immune complexes slightly increased (31.5ng %). Throat swab was negative, while parasitological examination of the feces showed the presence of eggs of *Trichuris trichura*. Lymphocyte immunophenotyping, autoantibodies

(ANA, AMA, ASMA, C3, C4), serology for brucellosis, salmonellosis, toxoplasmosis, malaria, hydatid disease, mononucleosis, visceral leishmaniasis and HIV were normal.

Chest X-ray with stratigraphy, X-ray of the spine, X-ray of the shoulder and coxal articulations, elbows and knees, X-ray of the hands, pelvis examination, echocardiography and sternal puncture were normal. Corticosteroid therapy was commenced to assess response.

On second hospitalization after 3 months: the patient's clinical condition was poor, she was pale, emaciated and asthenic, with loss of appetite. She had been suffering from diarrhea, albeit modest, for a few days and reported occasional earlier episodes. A careful, sensitive and extensive history revealed that the patient was living in extreme poverty and had a 2 year-old son. Her husband was a drug addict and a pusher, working occasionally as a tailor for infrequent customers. They lived in one room in an apartment with the remaining 3 rooms occupied by other families, located in a poor neighborhood of Palermo (Ballarò) where the roofs of the houses often collapse in the early winter rains. There was only one bathroom, no heating and the house was very damp and unhealthy. The patient was practically forced to work 14 hours a day to support the family on her own, even when she was not well, and like all mothers in this situation she was eating little and badly. It was not easy to obtain this information, not so much due to transculturation problems (she had been in Italy for four years) but rather because she wanted to protect her husband, who she was very attached to and, despite everything, was the only person she could rely on as a sick woman in a foreign country.

An intradermal Mantoux test was performed, yielding an intensely positive wheal and eschar formation. Ultrasound of the abdomen (which had not been previously performed) showed a distended gallbladder with a small calculus 8mm in diameter, while in the pericaval area there were small rounded hypoechoic formations, probably hyperplasic lymph nodes. Enteroclysis was performed, showing a temporary blockage of the barium column at the jejuno-ileal junction with modest and transient ectasia of the loops upstream: at that point there was a constant and acute angulation of the bowel due to mesenteric adhesions. The opacification then extended to the ileum, where the loops were close together but not clearly adhering to each other. The last loop showed signs of edema of the mucosa, but with no organic shrinkage. Biopsy showed a histological picture compatible with a tuberculosis process. TB treatment caused the disappearance of symptoms and today, 5 years later, she is still well.

FUO diagnosis, Articular rheumatism of Grocco-Poncet type in a subject with isolated tuberculous enteritis.

Comment

The forms of tuberculosis that most often cause FUO disease are: the disseminated type, which presents without the characteristic miliary picture on chest radiographs or the extra-pulmonary type without clear signs of foci (12). In this case the rare isolated intestinal location of the tuberculosis was peculiarly preceded by para-infective (immune) polyarthritis in the carpo-metacarpal joints, prevalently in the right index finger, which is known as Poncet's disease (13). The history of diarrhea, albeit mild, together with the report of the unsanitary conditions and poverty in which the patient was forced to live guided us to the diagnosis, which was late but fortunately without serious consequences for the patient. Another mistake was that of not performing an ultrasound scan of the abdomen; in FUO it must never be forgotten even in the absence of physical or clinical indications. The concept of "near misses" or "close calls" can be applied to these diagnostic errors which are also found in other clinical cases, that is, where potential mistakes are corrected before they can cause damage.

In the study of patients with FUO there has also been a great deal of discussion about the possible presence of "potential diagnostic clues" (PDCs), defined as all those symptoms, signs or laboratory abnormalities that can help in making a diagnosis. According to De Kleijn, differential diagnostic protocols should be applied to help identify PDCs, including an extensive medical history and a thorough physical examination (7). While they do not offer excessive hope, because in a high percentage of cases they are completely non-specific and therefore of little diagnostic aid, their presence should not be underestimated.

But going beyond these methodological choices, it must be said that, paradoxically, the greater availability of technological tools sometimes brings with it the risk of confusing the doctor who is trying to solve the intricate puzzle of FUO. There is a diagnostic "weight" to be attributed to the individual examinations, which is expressed not only in terms of the specificity and sensitivity of tests but also in terms of tolerability by the patient and their economic burden.

Current tests have high levels of reproducibility and accuracy, but at least three factors cause frequent misdiagnosis: i) the variability of the dysfunctions and anatomical alterations of diseases, ii) the inappropriate choice of tests and iii) the incorrect interpretation of the results (14) (Scenario 4). Often there is an excessive number of test requests stemming from defensive attitudes in medicine. An excess of requests has two main drawbacks: it increases the probability of false positives as well as the economic burden. In this connection it must be remembered that the frequency of false positives increases with the number of

tests, and the proportion of false positives over the total positive results increases with a decreasing pre-test probability of disease. Avoiding the excessive use of a test does not entail, however, limiting its prescription when it is needed. Failure to prescribe the necessary tests is the second major cause of diagnostic errors in hospitals, after the failure to generate hypotheses or delay in considering the hypothetical correct diagnosis (Scenario 5). False negative errors are more frequent in patients with a disease which is mild or presents in an original form and the probability is higher if the sensitivity of the test is low (for example if a tumor marker is used to rule out a suspected malignant fever at an early stage), or if the anatomic or functional disease is atypical. Overall, failure to request the most suitable laboratory tests or imaging investigations, test request errors and the inappropriate interpretation of results are among the most frequent causes of failure or delay in diagnosis. The availability of multiple test images for the same clinical condition (ultrasound, CT, MRI, etc.) is an advantage, but requires choices that are not always easy to weigh up in terms of accuracy, invasiveness and cost (Scenario 6).

Errors of diagnosis may also be due to cognitive errors in assembling the data, in making assumptions and in verifying the errors in diagnostic reasoning. In the case of FUO, these are due to the tendency to take into account only the typical presentations of a disease, consequently failing to diagnose atypical variants (*representativeness*), as has been repeatedly recalled, and the tendency to remember the most recent and easily memorable cases, for example those with an unexpectedly positive or negative outcome of the disease (*availability bias*).

The problem of the number and invasiveness of diagnostic procedures is particularly acute in elderly patients, who poorly tolerate a long diagnostic process and invasive investigations. Indeed, considering the different etiologic spectrum of FUO in the elderly, more targeted diagnostic procedures have been proposed.

Scenario 4: misinterpretation of false negative test

A 26-year-old man was hospitalized for an irregular fever which had started a month earlier, followed by weight loss and general malaise. Physical examination showed a deterioration in the patient's general health with pale skin and mucosa and hepatosplenomegaly. Laboratory tests showed: Hb = 9.6 g%, RBC 3.100.000/mmc; WBC 2100/mmc with N = 40%, L = 60%; platelets = 56.000/mmc; total proteins = 8.1 g% and gamma-globulin = 3.1 g%.Imaging showed Visceral Leishmaniasis, whereas serology with IF and bone marrow aspiration were negative for VL.The patient was transferred to the Department of infectious diseases where splenic biopsy showed the presence of parasites of the genus *Leishmania*.Diagnosis: FUO diagnosed, Visceral Leishmaniasis.

Comment

Fever caused by visceral leishmaniasis may appear to be of unknown origin especially in the initial stage, which lasts a few weeks, and is characterized by isolated episodes of fever which are not preceded by shivering, but conclude with profuse sweating (15). The febrile periods alternate with periods of apyrexia lasting 4-7 days. At a later stage symptomatology becomes much richer with the addition of the characteristic fever, splenomegaly, hepatomegaly, pancytopenia and hypergammaglobulinemia. In the present case in spite of the negative immunofluorescence and bone marrow aspiration, the clinical presentation strongly suggested visceral leishmaniasis, leading us to transfer the patient to the Department of infectious diseases where splenic biopsy promptly revealed the presence of *L. Donovani*.Laboratory tests are not always easy to interpret. In cases of visceral leishmaniasis, splenic puncture is the gold standard for the isolation of the parasite, while both the serology with the immunofluorescence technique and bone marrow aspiration have a low specificity and therefore negative results are not always reliable.

While the clinical study of a patient with FUO should be individualized and not be restricted by rigid rules to be applied in all situations, it is advisable to follow some precise lines of investigation in any case. Accordingly, when faced with a patient with prolonged fever physicians should ask themselves the following questions: Is the fever *real* or *imaginary*? And if it is real, is it *self-inflicted*? Is the fever due to *therapies*? Is the cause of FUO an *infectious, neoplastic or autoimmune disease*? Is this a *rare* form *and / or difficult to classify*? Is this a *non-diagnosable* form *at the present time*? (Fig. 1)Simulated and self-inflicted fevers are part of the wide category of malingering, sometimes including the not so rare Munchausen syndrome (16), and according to various statistics they can represent 2% - 9% of FUO.As regards the second question, all therapies should be stopped as soon as possible to detect a drug-related fever. The persistence of fever 72 hours after discontinuation of the suspected drug indicates that it cannot be the cause of the fever (17). The drugs most commonly involved are bactericides (especially beta-lactam antibiotics), cardiovascular (quinidine) and antineoplastic drugs and those acting on the central nervous system (phenytoin). All these drugs can cause a true hypersensitive reaction, while occasionally some drugs such as cocaine and its derivatives can induce fever through an alteration of thermoregulation; the exact mechanism by which the majority of the drugs which most frequently or occasionally cause fever (antihistamines, barbiturates, salicylates and antibiotics such as vancomycin) is unknown. Only in 20% of cases does the presence of eosinophilia and the

appearance of a rash offer an important signal for a correct diagnosis. Answering the above two preliminary questions will avoid a long and difficult diagnostic course, thus reducing discomfort to the patient as well as cutting back the social and health costs.Immediately afterwards the physician should consider the other causes of FUO, namely infectious diseases, cancer and autoimmune diseases, which together constitute the most common and frequent forms.At this point, the disease may be considered rare and hard to classify, which accounts for between 5% to 10% of cases, according to the various statistics. The list of these continues to grow, posing many problems for etiology and nosology.After this procedure, some fevers will still remain undiagnosed despite several investigations. Their prevalence varies considerably in the different series, ranging from 10% to 30%, but it is important to underline that this percentage has been steadily increasing in recent years.

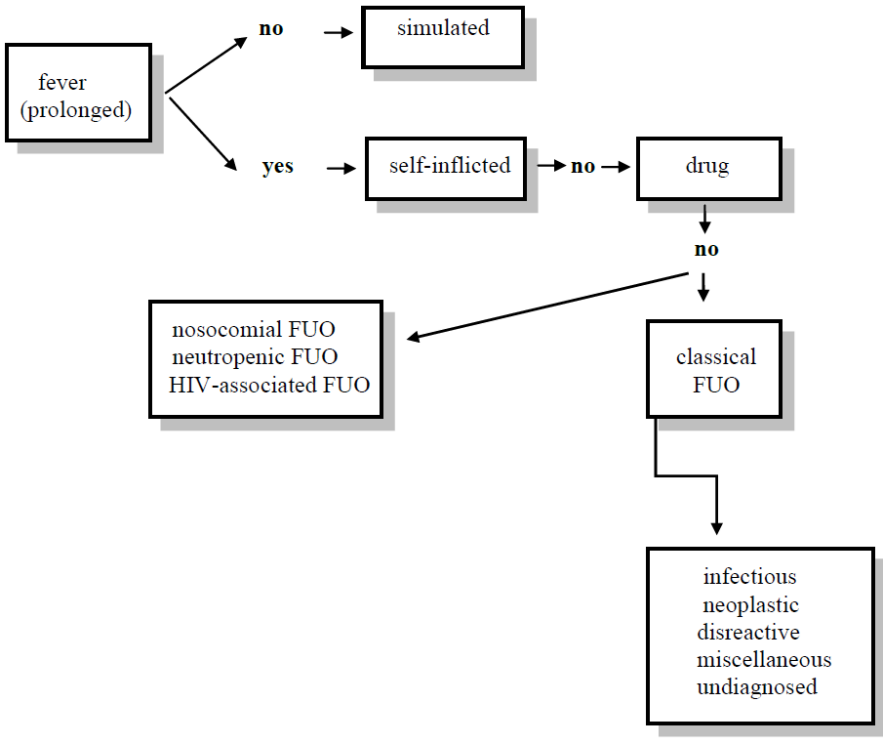

Figure 1. Minimum diagnostic workup to diagnose the prolonged fever.

Scenario 5 Prevalent mistakes: failure to request a test, misinterpretation of tests, other reasons: atypical presentation

G.P. aged 28, a butcher, was referred to us for continuous-remittent fever (up to 38.5 ° C) and sub-continuous abdominal pain (upper quadrants, medium intensity), presenting neutrophilic leukocytosis and increased ESR. After a month, the patient was discharged with a diagnosis of "multiple splenic abscesses and deep-seated lymphadenopathy due to typhoid fever. This diagnosis was based on:

- CT scan = abdominal abscesses of the spleen and the distal part of the third portion of the duodenum and also multiple retroperitoneal lymph nodes at the intestinal loops;
- positive ELISA serology for salmonella = IgG = 1/400, IgM = 1/160;
- good response to therapy with (chloramphenicol) CAF + Ampicillin with improvement in the clinical and biochemical results.

After 4 months a second hospitalization for recurrence of fever, abdominal pain and multiple abscesses of the spleen with neutrophilic leukocytosis and increased ESR. Therapy was commenced with cefotazime, netilmicin, ciprofloxacin and imipenem, but the fever regressed with CAF + ampicillin.

5 months later, 3rd hospitalization for splenectomy + lymph node biopsy due to the reappearance of symptoms on discontinuation of the antibiotic therapy. Histological examination of the spleen showed multiple abscesses with pus, presence of granulomas with central sclerosis and neutrophil hyper-reactivity with no signs of vasculitis. Histological examination of the lymph node showed presence of granulomas with central necrosis and giant cells and moderate eosinophilia.

After a period of apyrexia of about 1 month, renewed fever and emaciation led to the 4th hospitalization. Laboratory tests showed microcytic anemia (Hb = 9.3 g/dl, neutrophilic leukocytosis (24,000 WBC - with N = 80%); reduction in serum iron with normal ferritin and 4% saturation index; aspirate negative. Traces of protein were present in the urine and ESR in the first hour was 60 mm. Numerous blood cultures, urine cultures, sputum examination and stool cultures were negative. Serology for brucella, coxiella, chlamydia, pseudomonas, pseudomallei, yersinia and syphilis was negative. Tests for parasites (toxoplasma, malaria, leishmania, amoeba, toxocara, echinococcus), fungi (coccidia, histoplasma, blastomyces, candida and aspergillus) and viruses (influenza A and B, adenovirus, HIV) were negative.Autoimmune pathology: c-ANCA was strongly positive. Instrumental tests, chest X-ray, orthopantomography and

echocardiogram were normal. Skull X-ray: paranasal sinusitis. CT abdomen: small para-aortic lymph node, splenectomy. CT paranasal sinuses: sinuses opaque, no bone involvement. Consultations: infectious diseases, microbiology, rheumatology, ophthalmology, dentistry, otolaryngology, gastroenterology.The clinical data can be summarized as follows:

- fever, neutrophilic leukocytosis, increased ESR in subject with splenectomy and negative histology
- partial response to CAF in combination with ampicillin;
- lymphadenopathy;
- nasal sinusitis;
- positive for c-ANCA. *autoimmune or other?*

We were guided towards diagnosis when scintigraphy with radio-labeled white blood cells showed accumulation of the tracer in the colon and sinuses. Colonoscopy showed diffuse ulcers in the ascending, transverse, descending and sigmoid colon, as well as in the rectum, while histological examination showed granulomatous aphthous ulcerations.The final diagnosis: FUO diagnosed, Crohn's disease.

Comment

In Crohn's disease the characteristic symptoms are often absent (18), despite the presence of granulomas without caseous necrosis in various tissues such as lymph nodes, bone marrow, kidney, liver and spleen (as in our case). In these rare cases biopsy of the involved tissue and contrastographic tests are essential (19). In our case, in addition to the atypical picture, there were misinterpretations of spleen histology and of the positive c-ANCA autoantibodies, which are often correlated with inflammatory bowel disease (20). Scintigraphy with radio-labeled white blood cells, which would have highlighted a disease of the colon, was not performed immediately.

Scenario 6 prevalent error: physical examination and lack of assessment of a positive test

A 50-year-old man was hospitalized for daily, continuous-remittent fever lasting 4-5 days, followed by a period of 15 days of apyrexia, which had started 8 months earlier.The periods of fever regularly alternated with apyrexia and two days before each bout of fever a dry, hacking cough appeared. The current hospitalization was preceded by a first admission 5 months after onset when the

only physical finding was the presence of a mobile lymph node in the left axillary region modestly increased in volume and not tender. On that occasion, laboratory tests showed elevated ESR (46 in the first hour), while CT scan showed a partial obliteration of the left costo-phrenic angle and absence of pathological deep-seated lymph nodes. Bone marrow biopsy was negative for lymphoma and axillary lymph node biopsy showed a reactive hyperplasia. Diagnosis at discharge: recurrent fever of unknown origin (follow-up required).

At admission to our department the patient's general condition and nutritional and mental status were good. Body weight = 80 kg, height = 175 cm. Mild hepatomegaly was found: liver diameter (LD) = 18 cm, parenchymatous consistency not tender, with smooth surface and rounded margin. There was also bilateral micro-polyadenopathy in the axillary and inguinal lymph nodes and a lymph node increased in volume in the left submandibular region. Laboratory tests showed an increase in ESR in the first hour = 63, an increase in PCR (96 IU), AST /ALT = 63/108 IU/mL, hyperfibrinogenemia = 915 mg/dl and hyper-alpha-2-globulinemia = 0.85 g/dl. Instrumental tests performed (chest X-ray, bronchoscopy, bronchoalveolar lavage, CT scan chest and abdomen, bone marrow analysis, orthopantomography, prostate ultrasound, endoscopy and colonoscopy showed hyperplastic lymph nodes of 2 cm in the left external iliac and inguinal regions and 1 cm lymph node in the para-aortic, infrarenal and interaortocaval regions. There was also hyperdensity of the mesenteric apex and a calcific formation between the head of the pancreas and the vena cava; a further two calcifications were found in correspondence with the right hemidiaphragm.At this point, laparotomy and subsequent biopsy of an abdominal lymph node permitted the diagnosis of FUO: non-Hodgkin's lymphoma.

Comment

Lymphoma is a malignant disease which most commonly causes FUO, including both Hodgkin's and non-Hodgkin's lymphomas (21). Patients usually have a constantly high temperature during the day, but occasionally there is a fever that disappears and reappears at intervals of several days (Pel-Ebstein fever), especially in Hodgkin's disease. Many factors can make diagnosis difficult: superficial lymph nodes may be normal on physical examination, the involvement of retroperitoneal, mesenteric and pelvic lymph nodes (common in most histologic subtypes of non-Hodgkin lymphoma) does not cause the usual symptoms except in the case of very large lymph nodes or those that lead to obstruction, mediastinal lymphadenopathy may not be visible on chest X-ray,

lymph node biopsies are not diagnostic because of the small size of the sample or the location of the lymphoma - in fact, generally speaking non-Hodgkin's lymphoma may involve non-lymphatic structures such as the liver, spleen, bone marrow or the basement membrane of blood vessels (for example: intravascular or angiotropic large cell lymphoma). There are some rare cases of unexplained anemia and thrombocytopenia due to infiltration of the bone marrow, or isolated splenomegaly. In our case the abdominal CT scan was decisive for diagnosis, but only when it was taken adequately into account. In this respect, Mourad asserted that CT scan in FUO has a diagnostic yield of 19% (the diagnostic yield represents the number of patients with a positive test divided by the total number of patients) (22). Clinical follow-up in 32 of 47 cases with normal CT scan of the abdomen identified only one patient with abdominal lymphoma. The diagnostic utility of laparotomy in FUO is uncertain, especially in the post-CT and empiric therapy era.Physical examination guided towards the diagnosis, although in the early stage the superficial lymph nodes involved were small and with physical characteristics suggesting nonspecific reactivity.

CONCLUSIONS

As can be seen from the above, FUO represents a clinical condition in which the etiological diagnosis is often difficult but most of the time possible. A good number of cases of FUO that are not diagnosed in the first instance depend on a sort of refusal by physicians to further analyze the other possible causes of an unusual febrile response.

The best approach is probably to refer the patient to the internal medicine department, as the long list of over 200 causes of FUO affects all fields of human pathology. Both rare and more common diseases are, however, difficult to diagnose because they can evolve in a completely atypical pattern. The most correct line of action is therefore to review every case of fever several times, never underestimating the possibility that clues are present but have not yet been detected, nor losing sight of the basic underlying clinical reasoning, even for a moment.

Although the literature on diagnostic workup is limited there is evidence in favor of adopting a methodology that should, however, be considered as a basis open to modifications. In any case, the diagnostic process must begin with the compilation of an extensive history and a thorough examination.Prognosis depends on the category of FUO etiology, and the undiagnosed forms generally have a good prognosis.Undiagnosed patients should be followed up clinically by

periodically revaluating medical history and physical examinations.Thus, the etiological diagnosis of FUO can be seen as an ongoing effort, implying constant and careful consideration and review of specific clinical questions. This type of procedure is often more useful and decisive than the many sophisticated imaging techniques. There are no alternatives to these fundamental clinical principles.

REFERENCES

[1] Petersdorf RG, Beeson PB (1961) Fever of unexplained origin: report on 100 cases. *Medicine* 40(1):1-30.

[2] Hirschmann JV (1997) Fever of unknown origin in adults. *Clin Inf Dis* 24: 291-302.

[3] Durack DT., Street AC (1997) Fever of unknown origin - reexamined and redefined. *Curr Clin Trop Inf Dis* 10:143-8

[4] Casanova P (1981) Conduite à tenir en présence d'une fiévre prolongée d'étiologie obscure. *Sem.Hôp*. 57, 427.

[5] Iandolo C. Manfellotto D (1987). Le febbri di origine oscura, una guida alla diagnosi. *Roma, Edizioni Luigi Pozzi*. Pag. 28

[6] Simon A, Dodè C, van der Meer JWM, Drenth JPH (2001) Familial periodic fever and amyloidosis due to a new mutation in the TNFRSF1A gene. *Am J Med* 110:313-6.

[7] de Kleijn EM, Vandenbroucke JP, van der Meer JM (1997) Fever of unknown origin (FUO), IA: prospective multicenter study of 167 patients with FUO using fixed epidemiological criteria. *Medicine* (Baltimore) 76:392-400

[8] Platt R (1947) Two essays on the practice of medicine. *Lancet* 2,305

[9] Pagliaro L, Bobbio M, Colli A (2011) La diagnosi in Medicina, storia strumenti scenari e incertezze nell'incontro tra paziente e medico. *Raffaello Cortina Editore*, Milano, 259-266

[10] Vickery DM, Quinnel RK (1977) Fever of unknown origin. An algorithm approach. *JAMA* 238,2183

[11] Hurley DL Fever in adults (1983) What to do when the cause is not obvious. *Post-grad Med* 74, 232

[12] Barbado FJ, Vazquez JJ, Pena JM, Arnalich F, Ortizvazquez J (1992) Pyrexia of unknown origin: changing spectrum of disease in two consecutive series. *Postgrad Med J* 68:884-887

[13] 13) Montuschi E (1944) A case of tuberculous rheumatism (Poncet-Grocco type). *Ann Rheum Dis*, 4:26-28.

[14] 14) Pagliaro L, Bobbio M, Colli A (2011) La diagnosi in Medicina, storia strumenti scenari e incertezze nell'incontro tra paziente e medico. *Raffaello Cortina Editore*, Milano, 259- 266
[15] Iandolo C, Manfellotto D (1987) Le febbri di origine oscura, una guida alla diagnosi, Roma, *Luigi Pozzi Editore*. Pag.80
[16] Asher R (1951) Münchausen's Syndrome. *Lancet*, 260,339
[17] Edwards IR, Aronson JK (2000) Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 356:1255-9
[18] Hirschmann JV (1997) Fever of unknown origin in adults. *Clin Inf Dis* 24:291-302.
[19] Bury B.Technetium-99m HMPAO labelled leucocyte scanning in the initial diagnosis of Crohn's disease. *Brit J Radiol* 1995; 68:437.
[20] Yang P, Jarnerot D, Tysk C, Lindberg E. P-ANCA in monozygotic twins inflammatory bowel disease. *Gut* 1995; 36: 887-890
[21] Knockaert DC, Vanneste LJ, Vanneste SB, Bobbaers HJ (1992) Fever of unknown origin in the 1980s: an update of the diagnostic spectrum. *Arch intern Med*. 152:51-55
[22] Mourad O, Palda V, Detsky AS. A comprehensive evidence – based approach to fever of unknown origin. *Arch Intern Med* 2003; 163: 545-551