G.F. Stefanini, O. Quercia , F. Emiliani, N. Stefanini, A.C. Dall'Aglio, A. Lanzi, F.G. Foschi

Fever of unknown origin as unique symptom of an indolent mastocytosis

Department of Internal Medicine I Ospedale di Faenza AUSL Ravenna - E-mail: gf.stefanini@ausl.ra.it

Key words

Indolent mastocytosis, fever of unknown origin

Corresponding author
Giuseppe Francesco Stefanini, MD
Head of Internal Medicine Unit
Faenza Hospital, V.le Stradone 9,
48018 Faenza (Ravenna), Italy
E-mail: gf.stefanini@ausl.ra.it

Summary

A 39-years-old man afferred to our hospital for a fever lasting for more than 6 months, without abnormalities at physical examination (in particular no skin alterations); a recent laboratory and instrumental investigation was ineffective and so a fever of unknown origin (FUO) was diagnosed. Since he reported an history of infantile mastocytosis (usually auto-resolving) we evaluated his serum-tryptase levels that resulted of 49 ug/L (normal value <20 ug/L), raising the doubt of the presence of an active mastocytosis. The following bone marrow evaluation showed aggregates of CD117 positive cells and a c-Kit point mutation at codon D 816V, confirming the diagnosis of indolent mastocytosis. The present case confirm that FUO can be caused by an otherwise asymptomatic indolent mastocytosis, thus suggesting to include the serum-tryptase level measurement in the diagnostic approach to this pathological condition, at least in selected cases.

Introduction

Since its definition from Pedersdorf and Beeson (1) the fever of unknown origin (FUO) remains a diagnostic challenge requiring an investigation that in some cases, despite the involvement of several noninvasive and invasive procedures, fails to explain the cause of the fever.
Mastocytosis is an heterogeneous disorder characterized by accumulation and proliferation of mastocytes in the skin, bone marrow and other tissues, due to mutations in the c-Kit gene (2). The degree of symptoms range from mild to severe and in some patients fever can be the unique finding of the disease (1-4).

Case report

A 39-years-old man underwent to our observation because of a fever lasting for more than 6 months; the fever usually ranged between 37.6 to 38°C, but in several and unpredictable occasions raised till 39°C; several empiric antibiotic therapeutic trials have been ineffective.
The physical inspection did not show any significant information and the subject appeared in perfect shape (due to a regular physical exercise) and with a normal skin.
Clinical, instrumental and laboratory investigations performed in our and in another hospital were unsuccessful, leading to a FUO diagnosis.

In detail, normal results were obtained from laboratory routine tests and protein electrophoresis, serum immunoglobulins IgG, IgM and IgA, beta 2 microglobulin, lactate dehydrogenase, liver and tyroid function tests, erythrocyte sedimentation rate, fibrinogenaemia, C reactive protein, complement C3 and C4 fractions, urinary levels of porphyrines, autoimmune and neoplastic marker. Blood and urine cultures were negative.
Serological investigations about Cytomegalovirus, Herpes simplex, Varicella/Herpes zoster, Epstein-Barr viruses *Borrelia burgdorferi*, Chlamydia, anti-HIV and the markers of hepatitis virus B and C were negative as far as breath test for *Helicobacter pylori*.
Thoracic-abdominal CT, ultrasonography of heart, abdomen and neck were normal; scintigraphy with 99-mTc labeled autologous leucocytes injection did not show any alteration.
At a further anamnestic investigation the patient reported a diagnosis of cutaneous mastocytosis in his childreness completely resolved as usual; so far we evaluated his tryptase serum levels that resulted of 49 ug/L (normal value <20 ug/L) raising the doubt of the actual presence of mastocytosis.
Therefore we submitted the patient to an allergologic workup against common inhalant and alimentary allergens (including skin prick test and specific IgE serum levels) that was completely normal but a very low level (0.13 U/ml; normal range <0.10 U/ml) of IgE specific for *Vespa crabro* in absence of cutaneous reaction was detected.
Although in absence of cutaneous symptom, we submitted the patient to bone marrow evaluation that showed the presence of aggregates of CD117 positive cells and a c-Kit point mutation at codon D 816V using PCR-RLFP (Polymerase Chain Reaction-Restriction Fragment Length Polymorphism) analysis, confirming the diagnosis of indolent mastocytosis following the WHO guideline (4).
The fever disappeared during cetirizine (10 mg/day) and ranitidine (150 mg/day) treatment and relapsed in two different episodes of cetirizine discontinuation.

Discussion

Mastocytosis, characterized by mast cells accumulation and proliferation in the bone marrow, and several other tissues, is due to c-Kit gene mutation (2-5).
The c-Kit ligand act as receptor for stem cell-factor, a growth factor for mast cells; therefore this mutation can result in a ligand independent proliferation/activation of mast cells (5).
When the mast cells infiltration is limited to the skin it can lead to "urticaria pigmentosa" (diffuse cutaneous mastocytosis) and, mainly in children, "solitary cutaneous mastocytoma" that usually remits by adolescence (1, 6).
In adults cutaneous lesions are associated with bone marrow involvement in more than 80% of cases (1, 6); sistemic mastocytosis is in the majority of cases of indolent type but in few occasions can assume an aggressive behaviour, sometime in association with clonal haematologic mast cell disease such as mast cell leukaemia, mast cell sarcoma and extracutaneous mastocytoma (7).
Despite the fact that in indolent mastocytosis, mainly characterized by flushing and hypotension, urticaria pigmentosa (usually the most diagnostic sign) is present in more than 80% of cases (2), we recalled the Hot et al. observation of 2 cases out of 130 FUO, that underwent bone marrow biopsy examination, with "de novo" diagnosis of mastocytosis (3).
Inappropriate release of mast cell mediators results in symptoms of various degree of severity in a large part of patients including itch, abdominal pain, diarrhoea, flushing, headache and syncope (2, 5, 7) but FUO can be the only clinical expression of indolent systemic mastocytosis (3).
It is generally accepted that fever is mainly due to secretion of various Interleukins released by mastocytes; among them interleukin 1 (IL1) is the most conceivable responsible; in our patient the disappearing of the fever after antihistamine administration suggest a role for histamine as pyrogen.
It has been demonstrated an interaction between IL1 and histamine showing that central administration of IL1 in rats may stimulate the synthesis and release of hypothalamic histamine in presynaptic terminals by activation of histidine decarboxylase (8).
The present case confirm that FUO can by caused by an otherwise asymptomatic indolent mastocytosis, suggesting to include the tryptase serum level measurement in the diagnostic approach of this pathological condition, at least in the cases with a positive anamnesis for cutaneous lesions recalling mastocytosis. Moreover the relative low cost of this test and the heaviness of the price in terms of safety and finances, makes this marker a candidate for early test in the work-up of FUO.
Finally, the complete resolution of infantile cutaneous mastocytosis do not seems to be an absolute paradigm.

References

1. Pedersdorf RG, Beeson PB. Fever of unexplained origin: report of 100 cases. Medicine (Baltimore) 1961; 40: 1-30.

2. Murali MR, Castells MC, et al. Case 9-2011: a 37-year-old man with flushing and hypotension. N Engl J Med 2011; 364: 1155-65.
3. Hot A, Jaisson I, Girard C, et al. Yield of bone marrow examination in diagnosing the source of fever of unknown origin. Arch Intern Med 2009; 169: 2018-23.
4. Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leuk Res 2001; 25: 603-25.
5. Piao X, Bernstein A. A point mutation in the catalitic domain of c-Kit induces growth factor independence, tumorigeicity and differentiation of mast cells. Blood 1996; 87: 3117-23.
6. Valent P, Akin C, Escribano L. et al. Standards and standardisation in mastocytosis: consensus statements on diagnostics, treatment recomandations and response criteria. Eur J Clin Invest 2007; 37: 435-53.
7. Klion AD, Noel P, Akin C, et al. Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. Blood 2003; 101: 4660-6.
8. Takano T, Sakaue Y, Sokoda T, et al. Seizure susceptibility due to antihistamines in febrile seizures. Y Pediatr Neurol 2010; 42: 277-9.