Fever of Unclear Origin and Cytopenia Because of Acute Splenic Sequestration in a Young Immunocompetent Carrier of Beta-Globin Mutation for Hb Valletta

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ABSTRACT: Fever of unclear origin is a clinical challenge in medical practice. Infectious diseases, neoplasms, and collagen vascular illnesses are its main causes in adults and children. Acute splenic sequestration crises, a known potentially fatal complication of sickle cell disease and sickle beta-thalassemia, are uncommon in beta-heterozygosis. We describe a case of prolonged recurrent episodes of fever with spontaneous resolution, commencing at age 10 in a 15-year-old boy with a history of hypochromic microcytic anemia attributed to a thalassemic trait. He was admitted twice to our university hospital for continuous-remittent fever with a pruritic, macular evanescent Still's skin rash, severe splenomegaly, leucopenia, thrombocytopenia, and sudden aggravation of anemia. Infectious, rheumatologic, autoimmune, and hematologic illnesses were excluded. A genetic-based study revealed heterozygosis of the β-globin gene for a A>C (Thr>Pro) substitution at position 87 called Hemoglobin Valletta (alpha 2 beta 2 87 PRO) with a C>G transition in homozygosis in β-globin intronic polymorphism intervening sequence 2 at nucleotide 745. After a follow-up period of 1 year without treatment, the young patient remains apyretic and in good general clinical health with persistent microcythemia and hepatosplenomegaly. Acute splenic sequestration crisis and related cytopenia may be an unusual complication of fever of unclear origin in a beta-thalassemic carrier of a Hemoglobin Valletta mutation and polymorphism in homozygosis of intervening sequence 2 at nucleotide 745. This hemoglobinopathy may predispose to a clinical phenotype of minor or intermediate thalassemia and, during a febrile illness, to hemoglobin instability and splenic sequestration. **KEY INDEXING TERMS:** Fever of unclear origin; Splenomegaly; Still's skin rash; Leucothrombocytopenia; Acute splenic sequestration crises; Beta-thalassemia; Hb Valletta. **[Am J Med Sci 2008; 336(6):508–511.]**

Fever is a common presenting symptom of disease. When prolonged (usually 2–3 weeks in duration) or recurrent, with documented temperatures of >38.3°C, it is a challenging medical problem for the practicing physician, requiring knowledge and experience. Usually 1 week of in-patient investigation serves the dual purpose of documenting the pyrexia and eliminating all readily diagnosable conditions.[1] Thus, frequently, the process of evaluating the fever can prove to be frustrating. The 3 most commonly reported etiologies of fever of unclear origin (FUO) are infections, neoplasms, and collagen vascular diseases, all of which account for about 70% of cases. However, up to 10% of patients with FUO still remain undiagnosed. We present a case, not described in the literature, of prolonged but not regular recurrent FUO, resistant to antibiotics with spontaneous resolution. This person was healthy between febrile episodes except for a mild-moderate degree of hypochromic microcytic anemia and hepatosplenomegaly.

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Case Report

One year ago a 15-year-old obese boy with hypochromic microcytic anemia attributed to a thalassemic trait was admitted twice to our Department of Internal and Specialistic Medicine at the University Hospital of Palermo. He presented with a clinical history of recurrent and prolonged episodes of continuous-remittent pyrexia since he was 10, of 10 days to 1 month in duration, which have resulted in various hospitalizations. These attacks were accompanied by Still's skin rash and an increase in inflammatory markers, and they were treated with numerous antibiotic courses without success. These events remained unclear for about 5 years with recurrences and spontaneous resolutions. The rea-

Table 1. Laboratory Parameters 1 Year before, at First and Second Hospital Admission and at 1 Year Follow-Up

Parameters	One Year Before	First Admission	Second Admission	One Year Later
Red blood cells (μ/L)	4,120,000	4,120,000	3,160,000	4,240,000
Hemoglobin (g/dL)	9.3	9.4	7.1	11.8
Hematocrit (%)	30	29.2	22.1	37
MCV (fl)	72.82	70.9	69.9	73.2
MCH (pg)	22.57	22.8	22.5	24.1
MCHC (g/dL)	31	32.2	32.1	35.2
White blood cells (μ/L)	5300	4100	2330	7800
Lymphocytes (%)	37	39.8	23	39.1
Neutrophils (%)	58	52.3	68	57.2
Platelets (μ/L)	139,000	109,000	59,000	210,000
ESR (mm)	68	50	96	15
CRP (mg/dL)	8.8	12.6	12.8	2.2
AST (U/L)	46	74	56	29
ALT (U/L)	33	52	54	32
Serum iron (μg/mL)	27	12	12	54
Ferritine (ng/mL)	106	268	378	48
LDH (U/L)	370	494	579	180
Total bilirubin (mg/dL)	0.64	0.81	0.76	0.71

MCV indicates mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase.

son for his hospitalization was the onset of another episode of high intermittent pyrexia with a pruritic, salmon pink, macular evanescent skin rash, fatigue and myalgia, which occurred only during the fever spike. On admission, physical examination showed a temperature of 39.3°C, normal vital signs, hepatosplenomegaly with no lymphadenopathy, and cardiac or pulmonary murmurs. Laboratory investigations (Table 1) revealed an aggravation of hypochromic microcytic anemia [with a variable trend of hemoglobin (Hb) from 7.1 to 9.4 g/dL without transfusional support], HbA2 within normal limits and an absence of pathologic Hb at electrophoresis, leucopenia (2330/μL), thrombocytopenia (59,000/μL), an increase in inflammatory markers (C-reactive protein 12.8 mg/dL, erythrocyte sedimentation rate 96 mm/hr), a mild increase in ferritin (378 ng/dL) and lactate dehydrogenase (579 U/L), and low plasma iron levels (12 ng/dL); serum bilirubin levels, rheumatoid factor, antistreptolysin O, and urinalysis were normal. The patient was assessed as having an occult focus of infection or an autoimmune-hematologic illness. Instrumental data collection (echography and computed tomography of the abdomen) demonstrated moderate hepatomegaly and severe splenomegaly (17 cm). Chest radiograms and echocardiogram were normal. After basic and second-line laboratory investigations of FUO (including a peripheral blood examination, antinuclear antibodies, antiextractable nuclear antigens, antineutrophil cytoplasmic antibodies, anti-dsDNA, C3, C4, CH50, chromogranin, blood cultures, fecal occult blood, urine and stool culture, including yersinia research, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, parvovirus, borrellia, rickettsea, mycoplasma pneumoniae, entamoeba histolytica, toxoplasma, malaria, salmonella typhi and paratyphi, toxocara, leishmania, brucella, hepatitis A-B-C serology, Mantoux test, thyroid function, blood folate levels, laboratory examinations for periodic fever as hyper-IgD and familial Mediterranean fever, Gaucher disease test, porphyrias screening, and lymphocytes typization) and excluding odonto-stomatologic diseases (panoramic radiography and dental evaluation were negative), a diagnosis was not made. The hormonal study, performed during hospitalization to investigate the boy's delayed puberty, produced the following results: luteinizing hormone was within the upper limit (1.6 mlU/mL, laboratory range: 1.7–8.6), total testosterone and follicle-stimulating hormone were mildly low but within the normal range (0.48 ng/mL, laboratory range 0.28–11.1 and 3.3 mlU/mL laboratory range 1.5–12.4, respectively) and a reduced free testosterone value (2.2 ng/mL laboratory range 8.7–54.7). Dehydroepiandrosterone sulfate was 143.5 μg/dL (laboratory range for male 100–300) and prolactin, 17-β estradiol, and human growth hormone were within the normal range.

Fever resolved spontaneously during the first hospitalization on the eighth hospital day. The onset of another attack of high fever, which reached 39.6°C and occurred 4 weeks later, was the reason of the second hospitalization. Despite a single course of antibiotic treatment (ampicillin/sulbactam), the persistence of pyrexia lead to a bone marrow aspiration with histologic, microscopic examination and culture excluding hematologic malignancy, Gaucher cells, leishmaniasis and other infections. However, bone marrow hyperplasia without cellular atypia was documented. DNA amplification and Hb gene analysis revealed beta-globin heterozygosis for ACA>CCA transition called Hb Valletta (alpha 2 beta 2 87 PRO)[2] with a C>G transition in homozygosis in β-globin intronic polymorphism intervening sequence 2 (IVS-2) at nucleotide (nt) 745 (IVS-2 nt 745) (normal sequence: AATCCAGCTACCATTC, mutation: GAATGGTACCTGGATTG). Sickle cell disease and spherocytosis were also excluded. A hemotransfusion was necessary during the second hospitalization. Fever disappeared spontaneously in 11 days. The patient was discharged from the hospital without treatment after 14 days with a temperature of 36.6°C. Outpatient follow-up 12 months later disclosed no recurrence of fever and leucothrombocytopenia. The patient is now well with microcythemia and hepatosplenomegaly.

Discussion

Persistent undiagnosed fever remains a common problem in clinical practice. A definitive diagnosis is often difficult despite the recently developed technology usually applied in this situation. In this clinical case, the skin rash had strongly suggested Still's disease. Nevertheless, even if leucopenia had not been considered in excluding it,[3] the absence of arthralgia or arthritis definitively ruled out the diagnosis of Still's disease[4] or juvenile rheumatoid arthritis. Regarding the exclusion of infectious, au-