Case Reports and Literature Review
Volume 2
Article ID: 100011

Case Report

Still's Disease as a Differential Diagnosis: The Importance of Hyperferritinemia in Cases of Fever of Unknown Origin

Milena C. Iwazaki[1], Igor S. Schleich[1], Lilian Q. Negri[1], Felipe M. Grizzo[2], and Simone Bonafe[3*]

[1]Department of Medicine, Unicesumar, Brazil

[2]Department of Rheumatology, State University of Maringá, Brazil

[3]Department of Infectious Diseases, Unicesumar, Brazil

***Corresponding author**: Simone Bonafe, Department of Infectious Diseases, Unicesumar, 1610 Guedner Avenue 87050-390, Maringá, Brazil, Tel: +554430276360; E-mail: drasimonebonafe@hotmail.com

Received: April 04, 2018; **Accepted**: May 05, 2018; **Published**: May 12, 2018

Citation: Iwazaki MC, Schleich IS, Negri LQ, Grizzo FM, Bonafe S (2018) Still's Disease as a Differential Diagnosis: The Importance of Hyperferritinemia in Cases of Fever of Unknown Origin. Case Rep Lit Rev 2(1): 100011.

Abstract

To report the cases of two male patients presenting with high and long-term fever, arthralgia, weight loss and significantly increased ferritin. After seeing other physicians over a few-months period, both were finally diagnosed by an infectologist. Detailed clinical history and complementary diagnostic exams were performed to rule out neoplastic, infectious and rheumatologic diseases. Before a therapeutic test with corticosteroid, ferritin levels were excessively high. After initiating prednisone patients recovered quickly and ferritin levels decreased. Still's disease must be always considered as a differential diagnosis in patients with fever of unknown origin and high ferritin, mainly when ferritin is 5 times above the upper limit of normality, in order to avoid misdiagnosis of the disease. Early treatment and rheumatology follow-up are important to improve patients' quality of life.

Keywords: still's disease, ferritin, fever, diagnosis of exclusion, underdiagnosed

Introduction

In 1971 Bywaters described Still's disease in adults, already identified by George Still in 1897 in children that presented juvenile idiopathic arthritis, as an inflammatory systemic disease. It is more frequently identified in young male adults without distinction of ethnicity or localization [1].

Still's disease presents non-specific signs and symptoms, predominantly evening fever with peaks over 39°C (60 to 100% of cases), followed by other manifestations such as joint pain (70 to 100%) mainly in wrists, knees and ankles; skin rash (60 to 80%); lymphadenopathy (50%); myalgia (45%); hepatosplenomegaly (30 to 40%); and weight loss (27%). Laboratory confirmed, there is increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in almost all patients, leukocytosis with neutrophilia (80%), increased hepatic transaminases (65%) and hyperferritinemia (70%) [1].

Hyperferritinemia is useful in the diagnosis and very important as a parameter of treatment in patients with Still's disease. An increase 5 times above the upper limit of normality, in presence of signs and symptoms, is highly suggestive of Still's disease [2]. Once the treatment is established, its levels tend to decrease [3].

Case Report 1

A 38-year-old male patient presenting with daily fever (>38°C) for six months, followed by daily sweating, skin rash in upper body and desquamation on lower limbs, intermittent pain in knees, inguinal lymphonodomegaly and loss of 15kg in weight. Laboratory findings revealed C-reactive protein (CRP) 27 mg/dl (reference < 1), erythrocyte sedimentation rate (ESR) 31 mm (reference < 15) and ferritin 1879.40 ng/ml (22-322). Complete blood count, aspartate-aminotransferase (AST) and alanine-aminotransferase (ALT) without changes. Antinuclear factor, rheumatoid factor, antineutrophil cytoplasmic autoantibody (ANCA) and serological tests for infectious diseases were negative. Abdominal ultrasound showing mild hepatic steatosis; chest and abdomen CT scan without significant changes. Neoplastic, infectious and inflammatory diseases were ruled out. Considering the hypothesis of Still's Disease in adult, prednisone was initiated at a dose of 60mg per day. There was complete remission of symptoms and laboratory improvement of ferritin (379.4 ng/dl) within 30 days. It was decided to initiate methotrexate as a corticosteroid sparer. The patient is currently asymptomatic and in quarterly follow-up.

Case Report 2

A 32-year-old male patient presenting with fever for 40 days, sweating, pain in knees and loss of 4 kg in weight in that period. Previous history of endocarditis treated 17 years ago. Patient takes propranolol and hydrochlorothiazide 80/25 mg to treat systemic arterial hypertension. Laboratory findings revealed anaemia (Hb 11.4), leukocytosis of 15,300 cells with 84% of segmented neutrophils, thrombocytosis of 553,000/mm^3, CRP 20.5 mg/dl (reference <1), ESR 120 mm (reference <15), AST 50 U/L (5-40), ALT 68 U/L (7-56), gamma-glutamyl transferase 154 U/L (8-61) and ferritin 1650 ng/ml (22-322). Transesophageal echo-doppler ultrasound with mild mitral regurgitation; normal chest and abdomen CT scan. Antinuclear factor, rheumatoid factor, ANCA and serological tests for infectious diseases were negative. Prednisone 60mg per day was initiated with complete remission of symptoms and laboratory improvement of ferritin (545.2 ng/dl) within 30 days. During the treatment, arterial hypertension became worse, requiring the addition of amlodipine. After methotrexate was initiated and the corticosteroid was suspended, blood pressure improved, and amlodipine could be suspended. The patient is currently asymptomatic and in quarterly follow-up.

Discussion

Still's disease is classified as one of the causes of fever of unknown origin, however difficult to be diagnosed because it is a diagnosis of exclusion [3]. It is considered an autoinflammatory disease presenting abnormality in the innate immune system what requires different strategies until diagnosis and treatment are determined [4]. Serum ferritin in high levels may help to guide the diagnosis and as a therapeutic parameter. Hyperferritinemia in autoimmune diseases, like Still's disease, creates a systemic inflammatory disorder followed by fever and rash in 89% of cases [5], as well as other typical symptoms such as myalgia and arthralgia [6]. It is related to inflammatory and oxidative stress mechanisms and its increased synthesis is related to the histiocytes-macrophages system. Involved in this process are the cytokines IL-1β, IL-6, IL-18 and TNF-α with a lymphocyte response of Th1 and Th17 [1,5,7]. In healthy people 50-80% of ferritin is glycosylated. In Still's disease, on the other hand, despite the increase in total ferritin, glycosylated ferritin tends to be lower [8]. Levels below 20% are highly suggestive of the disease but few services have the examination available. In such cases, an increase 5 times above the upper limit of normality, in the presence of signs and symptoms and after excluding other causes, is highly suggestive of Still's disease, as seen in the cases described. Adjusted level of ferritin during the investigation might be a relevant measure to predict the disease progression and its prognosis offering improvement in patient's quality of life [9]. With regard to treatment, in both

cases corticosteroids were used as a first option of treatment until improvement or remission of symptoms [10]. They were replaced as soon as possible by methotrexate as a sparing treatment, due to high occurrence of adverse effects and even appearance of dependency in the therapy with corticosteroids [3].

Conclusion

Still's disease is an exclusion rheumatologic pathology underdiagnosed as it has a non-specific clinical manifestation which makes it a challenging diagnosis. Therefore, it must be always considered as a differential diagnosis in patients with fever of unknown origin and high ferritin, mainly when ferritin is 5 times above the upper limit of normality. High serum ferritin test along with high long-term fever of unknown origin, arthralgia, skin rash and leukocytosis with neutrophilia are the main signs of the disease. Treating the disease with high doses of corticosteroids, whether or not requiring to be associated with immunosuppressants, offers good disease control and quality of life.

References

1. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Sève P (2014) Adult-onset Still's disease. Autoimmun Rev 13: 708-722.
2. Yamashita S, Furukawa NE, Matsunaga T, Hirakawa Y, Tago M, et al. (2017) Extremely High Serum Ferritin: An Instrumental Marker of Masquerading Adult-Onset Still's Disease with Hemophagocytic Syndrome. Am J Case Rep 18: 1296-1301.
3. Zeng T, Zou YQ, Wu MF, Yang CD (2009) Clinical features and prognosis of adult-onset still's disease: 61 cases from China. J Rheumatol 36: 1026-1031.
4. Lee SW, Park YB, Song JS, Lee SK (2009) The mid-range of the adjusted level of ferritin can predict the chronic course in patients with adult onset Still's disease. J Rheumatol 36: 156-162.
5. Kim HA, Sung JM, Suh CH (2012) Therapeutic responses and prognosis in adult-onset Still's disease. Rheumatol Int 32: 1291-1298.
6. Gerfaud-Valentin M, Maucort-Boulch D, Hot A, Iwaz J, Ninet J, et al. (2014) Adult-onset Still disease: manifestations, treatments, outcome, and prognostic factors in 57 patients. Medicine (Baltimore) 93: 91-99.
7. Lin YT, Wang CT, Gershwin ME, Chiang BL (2011) The pathogenesis of oligoarticular/polyarticular vs systemic juvenile idiopathic arthritis. Autoimmun Rev 10: 482-490.
8. Chen PD, Yu SL, Chen S, Weng XH (2012) Retrospective study of 61 patients with adult-onset Still's disease admitted with fever of unknown origin in China. Clin Rheumatol 31: 175-181.
9. Zandman-Goddard G1, Shoenfeld Y (2007) Ferritin in autoimmune diseases. Autoimmun Rev 6: 457-463.
10. Fardet L, Coppo P, Kettaneh A, Dehoux M, Cabane J, et al. (2008) Low glycosylated ferritin, a good marker for the diagnosis of hemophagocytic syndrome. Arthritis Rheum 58: 1521-1527.