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CASE REPORT

Extremely high serum ferritin levels as diagnostic tool in adult-onset Still's disease

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ABSTRACT

The diagnosis of adult-onset Still's disease (ASD) is difficult to establish due to the nonspecific clinical and laboratory findings. A markedly raised serum ferritin level is a typical finding, although it is not well understood why ferritin levels are extremely high in ASD. We discuss several possible explanations leading to the extremely high levels of ferritin.

KEYWORDS

Adult-onset Still's disease, ferritin

INTRODUCTION

Still's disease is a rare clinical syndrome characterised by the classical triad of high-spiking fever, joint and muscle pain and an evanescent skin rash. The syndrome was first described by George Still in 1897 in children and it was not until 1971 that adult-onset Still's disease (ASD) was recognised as a distinct clinical entity by Bywaters.[1] The present case demonstrates that Still's disease is difficult to diagnose due to nonspecific clinical and laboratory findings except for a markedly increased serum ferritin level.

CASE REPORT

A 52-year old Caucasian man was admitted to the emergency department in March 2006. For four days he had suffered from fever of up to 40°C, generalised myalgia, sternal pain with dyspnoea and a sore throat. The patient's previous history revealed a period with fever, arthralgia, pericarditis and pleuritis in 1986. At that time adult-onset Still's disease was considered and patient recovered spontaneously.

Physical examination revealed a twice-daily spiking fever of up to 40.8°C and bilateral inspiratory crackles on auscultation of the bases of the lung. Further clinical examination was normal, including the absence of lymphadenopathy, skin rash or signs of arthritis.

Laboratory tests at presentation showed a C-reactive protein (CRP) of 175 mg/l, erythrocyte sedimentation rate (ESR) 16 mm/h (maximum 59 mm/h), haemoglobin 10.2 mmol/l, leucocytes 17.3 x 10^9 (93% neutrophils), platelets 129 G/l, normal renal function, lactate dehydrogenase (LDH) 1099 U/l, γ-glutamyltransferase (γGT) 67 U/l, serum aspartate transaminase (ASAT) 77 U/l, serum alanine transaminase (ALAT) 34 U/l, total bilirubin 30 μmol/l, ferritin 75,500 μg/l, iron (Fe) 6.5 μmol/l, iron saturation 26% and creatinine phosphokinase (CK) 33 U/l. Several serological results were negative (Rf, anti-CCP, ANA, ANCA). On the day of admission chest X-ray and electrocardiography were normal. Because an infectious disease was suspected, the patient received broad-spectrum antibiotics (cefuroxim and gentamicin) after blood, urine and sputum cultures had been taken. During his stay in hospital, the spiking fever persisted, while the patient developed signs of bilateral pleural effusion on chest X-ray. Bronchoscopy showed no signs of inflammation. Echography of the abdomen revealed only a slightly enlarged spleen. Electrocardiography showed atrial fibrillation with a normal ventricular response. Echocardiogram showed no abnormalities, especially no pericardial fluid. Blood, urine and sputum cultures were repeatedly negative.

A flare-up of adult-onset Still's disease was established, especially based on the clinical symptoms and the markedly increased levels of serum ferritin (75,500 μg/l). Antibiotic therapy was replaced by nonsteroidal anti-inflammatory agents. Because this provided little clinical effect, corticosteroids were added (prednisone 40 mg/

day). The patient's condition rapidly improved and he was discharged. Despite the clinical improvement and decrease in CRP and ferritin levels, the liver function tests rose to following levels: bilirubin 32 μmol/l, γGT 541 U/l, AF 329 U/l, ASAT 116 U/l and ALAT 526 U/l (*figure 1*). Corticosteroids were continued and after two weeks the liver tests has largely returned to normal.

Figure 1. *Laboratory findings*

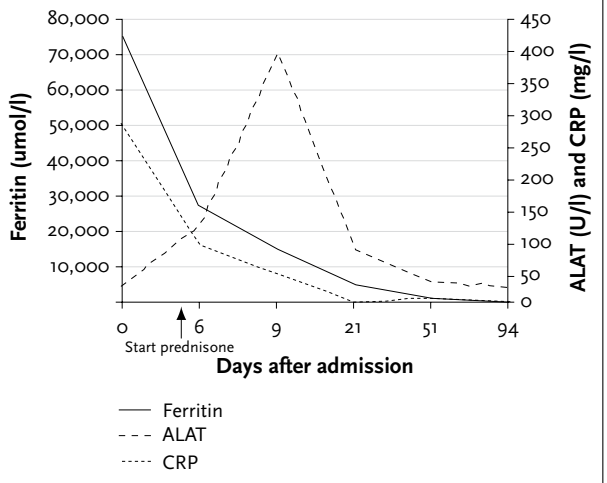

Table 1. *Diagnostic criteria for adult-onset Still's disease*[2]

Five or more of the diagnostic criteria listed below, of which two must be major criteria	
Major criteria	Fever ≥39°C (one week or longer)[+]
	Arthralgia and/or arthritis (two weeks or longer)[+]
	Nonpruritic, pink, macular or maculopapular rash, usually during febrile episodes
	Leucocytosis (>10,000 μmol/l, >80% neutrophils)[+]
Minor criteria	Pharyngitis[±]
	Lymphadenopathy and/or splenomegaly[±]
	Liver involvement (raised serum transaminases and/or lactate dehydrogenase)[+]
	Negative rheumatoid factors and antinuclear antibodies[+]
Exclusion criteria	Infectious diseases
	Malignant diseases
	Rheumatological conditions

[+]**Present in our patient;** [±]**partly present in our patient.**

DISCUSSION

In our patient ASD was diagnosed. This disease is frequently a diagnosis by exclusion, which may result in delayed intervention and unnecessary diagnostic procedures in many cases.

Several sets of classification criteria have been developed. The most frequently used criteria are those of Yamaguchi *et al.* (*table 1*).[2] Besides these criteria other manifestations may be present, including hepatomegaly and/or splenomegaly and/or cardiac and pulmonary features. Cardiac involvement includes pericarditis and less frequently myocarditis and pulmonary involvement is characterised by pleuritis and pulmonary infiltrates. Our patient in this case satisfied the criteria for ASD according to Yamaguchi (*table 1*) and suffered from pleuritis as well.

The aetiology of ASD is still unclear, although some studies have suggested a role for viral or bacterial triggers such as rubella, Epstein-Barr virus, cytomegalovirus and *Mycoplasma pneumoniae* in the pathogenesis of ASD.[3,4] The peak age of onset is usually between 15-25 and 36-46 years, and both sexes are equally affected.[5]

A raised ferritin level is often found during episodes of adult-onset Still's disease.[6] Serum ferritin levels are markedly increased during active disease and return to normal values during remission. Nevertheless, a serum ferritin level as found in this patient is exceptional and has been described in few other cases.[7,8] Other conditions in which ferritin levels may be elevated are infections, malignancies (leukaemia, lymphomas), liver diseases and haemochromatosis. However, in these conditions serum ferritin concentrations rarely exceed values of >3000 μg/l. Besides in adult Still's disease, serum ferritin levels of >10,000 μg/l have only been described in severe liver damage, after multiple blood transfusions or in the haemophagocytic syndrome. So the ferritin level may be an important diagnostic tool in the diagnosis of Still's disease and should be therefore included in the classification criteria.

The cause of the extremely high ferritin concentrations in adult-onset Still's disease remains unclear. Some studies suggest that ferritin is released into the plasma due to liver cell necrosis.[9] In this case, ferritin levels were already markedly increased before liver function tests started to rise, making this explanation not probable. Others have found increased production of ferritin mediated by several cytokines, mainly interleukin IL-1α, IL-1β, IL-6 and TNFα.[10] This so-called acute phase response seems to stimulate the synthesis of ferritin, although it does not explain why the ferritin levels in ASD are usually much higher than those found in patients with other inflammatory diseases and comparable levels of CRP. Fautrel *et al.* reported on a decrease in glycosylated ferritin, an isoform of ferritin, in ASD compared with other inflammatory conditions.[11] In healthy subjects, 50 to 80% of ferritin is glycosylated, in inflammatory diseases the glycosylated part drops to 20 to 50%, while in ASD the glycosylated part of ferritin is often <20%. Decreased clearance from the plasma of nonglycosylated ferritin by the histiocyt-macrophage system may partly explain the increased levels of ferritin.[12]

When combined with a fivefold serum rise in ferritin, glycosylated ferritin <20% reaches a sensitivity of 43% and a specificity of 93% to diagnose ASD.[13] Kirino *et al.* suggested ferritin synthesis to be stimulated by haeme-oxygenase-1, an inducible haeme-degrading enzyme.[14] Ferritin synthesis is stimulated by Fe^{2+}, which is a product of haeme degradation. Haeme oxygenase-1 is expressed on macrophages and endothelial cells in response to various forms of stress.

In conclusion, although the origin of the high ferritin concentration remains unclear, an extremely high serum ferritin level in addition to classification criteria makes it much easier to diagnose ASD.

REFERENCES

1. Bywaters EG. Still's disease in the adult. Ann Rheum Dis 1971;30:121-33.
2. Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol 1992;19:424-30.
3. Perez C, Artola V. Adult Still's disease associated with Mycoplasma pneumoniae infection. Clin Infect Dis 2001;32(6):E105-6.
4. Wouters JM, van d Veen J, van de Putte LB, de Rooij DJ. Adult onset Still's disease and viral infections. Ann Rheum Dis 1988;47:764-7.
5. Magadur-Joly G, Billaud E, Barrier JH, et al. Epidemiology of adult Still's disease: estimate of the incidence by a retrospective study in west France. Ann Rheum Dis 1995;54:587-90.
6. Gonzalez-Hernandez T, Martin-Mola E, Fernandez-Zamorano A, Balsa-Criado A, de Miguel-Mendieta E. Serum ferritin can be useful for diagnosis in adult onset Still's disease. J Rheumatol 1989;16:412-3.
7. Coffernils M, Soupart A, Pradier O, Feremans W, Neve P, Decaux G. Hyperferritinemia in adult onset Still's disease and the hemophagocytic syndrome. J Rheumatol 1992;19:1425-7.
8. Hamidou MA, Denis M, Barbarot S, Boutoille D, Belizna C, Le MG. Usefulness of glycosylated ferritin in atypical presentations of adult onset Still's disease. Ann Rheum Dis 2004;63:605.
9. Schwarz-Eywill M, Heilig B, Bauer H, Breitbart A, Pezzutto A. Evaluation of serum ferritin as a marker for adult Still's disease activity. Ann Rheum Dis 1992 ;51:683-5.
10. Rogers JT, Bridges KR, Durmowicz GP, Glass J, Auron PE, Munro HN. Translational control during the acute phase response. Ferritin synthesis in response to interleukin-1. J Biol Chem 1990;265:14572-8.
11. Fautrel B, Le MG, Saint-Marcoux B, et al. Diagnostic value of ferritin and glycosylated ferritin in adult onset Still's disease. J Rheumatol 2001;28:322-9.
12. Van RC, Le MG, Lasne Y, et al. Serum ferritin and isoferritins are tools for diagnosis of active adult Still's disease. J Rheumatol 1994;21:890-5.
13. Efthimiou P, Paik PK, Bielory L. Diagnosis and management of adult onset Still's disease. Ann Rheum Dis 2006;65:564-72.
14. Kirino Y, Takeno M, Iwasaki M, et al. Increased serum HO-1 in hemophagocytic syndrome and adult-onset Still's disease: use in the differential diagnosis of hyperferritinemia. Arthritis Res Ther 2005;7:R616-24.