

Case Report

Hyperferritinemia and Pyrexia of Unknown Origin.

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ABSTRACT

By the time a patient is formally categorized as having “Pyrexia of Unknown Origin”, a battery of tests have been performed and many physicians have run out of differential diagnoses. Adult Still’s Disease is considered a rheumatologic disorder and is, therefore, not considered if the patient does not have joint symptoms. We present the case of such a patient who presented with high spiking fever, and review how we gained confidence in establishing the diagnosis. (Rawal Med J 2005;30:41-42).

Key Words: Adult Still’s Disease, hyperferritinemia, fever

INTRODUCTION

Adult still’s Disease is an important differential in the diagnosis of Pyrexia of Unknown Origin. It can be missed if the typical clinical features are absent. Patients may present initially without arthritis,¹ and the characteristic rash occurs mostly in areas covered with clothing. The marked elevation of the leukocyte count and neutrophilia often lead the clinician astray into diagnosing

occult bacterial infection.² Also, the significance of elevated ferritin levels as a diagnostic as well as prognostic indicator in Adult Still's Disease should be understood by all clinicians.³

CASE REPORT

A seventeen year old girl presented with intermittent high grade fever for 1 month. The fever would spike up to 103° F and remain so for about 12-14 hours. It was followed by drenching sweats, spontaneous resolution and recurrence every 3-4 days. The fever was associated with a pruritic pale macular rash over the trunk, sore throat, dry cough, vague arthralgias and bone pains. The submandibular lymph nodes were palpable on admission, but regressed spontaneously. Her medication history over the past month included high-dose ceftriaxone for 8 days, and appropriate full courses of Chloroquine, Artemether, Mebandazole and cefixime. Despite all this, the fever pattern and associated symptoms persisted. Examination revealed a young female with tachycardia, fever of 38°C, pallor, minimal throat congestion and a faint, macular rash over chest and upper thighs. Submandibular lymph nodes were palpable for the first 3-4 days after admission.

An extensive list of investigations revealed mild microcytic hypochromic anemia and white blood cells >20,000 with neutrophilia (>70%) on repeated testing before and after treatment. ESR was in the 50-110 mm/hour range on repeated testing. Chest X-rays, abdominal ultrasounds, blood cultures, smears for malarial parasite, urine examination, echocardiography, liver and renal function tests, viral serology for hepatitis and Widal test failed to reveal any insight into the etiology of the fever. Bone marrow biopsy showed depleted iron stores and active granulopoiesis only. RA factor and ANA were negative. The serum ferritin level was 10,000 ng/ml. Applying this data to the most recently accepted criteria for the diagnosis of Adult Still's

disease revealed that all 4 major, and 3 of the 4 minor criteria were present, making a diagnosis of Adult Still's Disease at least 93% specific in our patient.

DISCUSSION

There is no specific test that can be used to diagnose Adult Still's Disease. This requires the presence of certain major or minor criteria, and the absence of certain exclusions (table 1). Adult Still's Disease has been associated with markedly elevated serum ferritin concentrations in as many as 70 percent of patients.³ The elevations correlate with disease activity, and has been suggested as a marker to monitor the response to treatment.^{4,5}

Table-1: Criteria Used For the Diagnosis of Adult Still's Disease

Major criteria	<ol style="list-style-type: none"> 1. Fever of at least 39°C lasting one week or longer 2. Arthralgias or arthritis lasting two weeks or longer 3. Characteristic rash 4. Leukocytosis (10,000/μL or greater) with >80% granulocytes
Minor criteria	<ol style="list-style-type: none"> 1. Sore throat 2. The recent development of significant lymph node swelling 3. Hepatomegaly or splenomegaly 4. Abnormal liver function studies 5. Negative tests for antinuclear antibody and rheumatoid factor
Exclusions	<ol style="list-style-type: none"> 1. Infection 2. Malignancy 3. Other rheumatic diseases
Diagnosis	<p>Japanese criteria require the presence of five features, with at least two being major diagnostic criteria.</p> <p>Japanese criteria have the greatest sensitivity in establishing the diagnosis of Adult Still's Disease.⁶</p>

Serum ferritin concentrations exceeding 3000 ng/mL (normal 40 to 200 ng/mL) have been observed in ASD, with some patients having values above 10,000 ng/mL.^{7,8} This degree of hyperferritinemia is not observed with other rheumatic diseases. In contrast to other

inflammatory diseases, the percentage of ferritin that is glycosylated is markedly lower (30 versus 3.7 percent).¹⁰ In one report, the combination of a five-fold or greater elevation of serum ferritin and a glycosylated fraction <20 percent had a modest sensitivity for Adult Still's Disease of 43 percent but a relatively high specificity of 93 percent.⁹

As an important differential diagnosis, both marked hyperferritinemia and a low fraction of glycosylated serum ferritin also occur in hemophagocytic syndromes, such as those due to lymphoma and severe drug reactions.^{10, 11} This is associated with a variety of disorders, including viral infections, neoplasms and immune-mediated diseases. Clinical features of the hemophagocytic syndrome include fever, rash, lymphadenopathy, hepatosplenomegaly, and pancytopenia. In contrast to Adult Still's Disease, arthritis is absent. Arthralgia, arthritis, and myalgias are universal features of Adult Still's Disease. Initially, however, the arthritis may be mild, transient, and oligoarticular, and thus easily overlooked. It may or may not evolve over a period of months into a more severe, destructive, polyarticular pattern.¹

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