Tocilizumab in Refractory Adult-Onset Still's Disease with Aseptic Meningitis—Efficacy of Interleukin-6 Blockade and Review of the Literature

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Adult-onset Still's disease is a multisystem inflammatory disorder of unknown etiology characterized by typical spiking fever, evanescent rash, arthralgia, and leucocytosis. Neurologic manifestations are infrequent, seen in 7 to 12% of cases. We present the case of a young male admitted with aseptic meningitis that satisfied the diagnostic criteria of Adult-onset Still's disease. Refractoriness to therapy with corticosteroids and cyclosporine A led to the use of humanized monoclonal anti-interleukin-6 receptor antibody "tocilizumab" with dramatic response. The case is reported for the rarity of presentation and the need to consider the diagnosis in related clinical scenarios. Also, current literature on the use of tocilizumab in intractable disease is reviewed.
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Adult-onset Still's disease (AOSD) is a multi-system inflammatory disorder characterized by high-grade fever, evanescent salmon-colored rash, arthralgias or arthritis, hepatosplenomegaly, lymphadenopathy, polyserositis, and sore throat. Markers of rheumatologic disorders, such as rheumatoid factor and antinuclear antibody, are negative (1). Other laboratory manifestations observed in AOSD include elevations in liver enzymes, abnormalities in hematologic function ranging from anemia to disseminated intravascular coagulation, and markedly elevated levels of ferritin in the active stage of disease. There is no specific test or combination of tests that can establish AOSD, making it essentially a diagnosis of exclusion. Almost every organ system involvement has been noted in patients with AOSD, although neurologic manifestations are uncommon. We describe the case of a young male presenting with meningitis who was diagnosed as AOSD and responded dramatically after the addition of tocilizumab to prednisolone and cyclosporine.

CASE REPORT

A 27-year-old male farmer presented to a tertiary center in western India with irritability, headache, and irrelevant talk for 2 days. He had a high-grade fever for the last 6 weeks and multiple symmetric peripheral (including small joint) arthralgias with morning stiffness. Frequent myalgias, sore throat with dry cough, and malaise were other prominent symptoms. He had been hospitalized for the fever twice in this period and had no respite with empirical cephalosporins, antimalarials, and analgesics.

On examination, his temperature was 39.8°C, blood pressure 80/60 mm Hg, pulse rate 116/min, and respiratory rate 26/min. An erythematous blanching maculopapular rash was evident over the forearms, thighs, abdomen, and back. There was diffuse muscle tenderness but no synovitis. Air entry was reduced in both lung bases with overlying dull note. He was disoriented to time, place, and person and had neck rigidity. There was no focal neurologic deficit. The remainder of the examination was unremarkable.

Abnormal blood investigations on admission are outlined in Table 1, prominent being microcytic anemia, neutrophilic leucocytosis, deranged liver enzymes, prerenal azotemia, and an extremely elevated serum ferritin level of 16,500 ng/mL (normal, 22-322 ng/mL).

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Table 1 Positive/Abnormal Blood Tests		
Variable	Value	Normal Range
Erythrocyte sedimentation rate (mm/h)	47	(0-20)
C-reactive protein (mg/L)	37	1-6
Hemoglobin (g/dL)	5.9	12-15
Hematocrit (%)	17	35-50
White blood cell count ($\times 10^3/mm^3$)	17	4-10
Platelet count ($\times 10^5/mm^3$)	1.01	1.5-4.5
BUN (mg/dL)	38	5-21
Creatinine (mg/dL)	1.7	0.7-1.2
Aspartate transaminase (U/L)	376	0-40
Alanine transaminase (U/L)	89	0-40
Total protein (g/di)	5.6	5.8-8
Albumin (g/dL)	2.6	3.5-5
Lactate dehydrogenase (U/L)	976	225-450
Ferritin (ng/mL)	16,500	22-322

Brain computed tomography was normal and cerebrospinal fluid revealed 19 cells/hpf with lymphocytic pleocytosis, protein 49 mg/dL, glucose 28 mg/dL, and normal adenosine deaminase level 9 U/L. Gram stain and culture were negative. Urine showed 2+ proteinuria, 3 to 4 pus cells, and 2 to 3 granular casts/hpf. Bilateral moderate pleural effusion with cardiomegaly was seen on the chest radiograph (Fig. 1), confirmed on computed tomography chest (Fig. 2) with additional findings of mild pericardial effusion. Pleurocentesis revealed 14 lymphocytes/hpf and protein 2.1 g/dL. Mild hepatosplenomegaly was seen on abdominal ultrasound scan. A battery of other tests performed in the workup for pyrexia of unknown origin (PUO) was normal as outlined in Table 2.

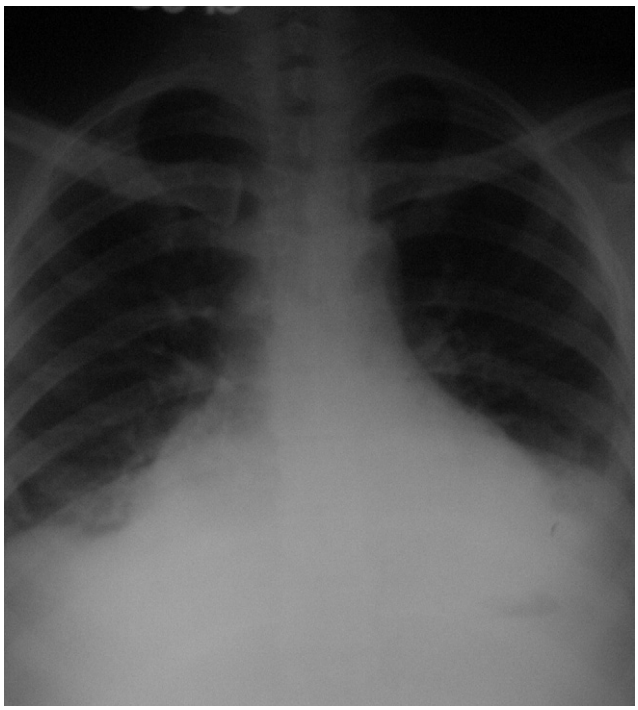

Figure 1 Chest radiograph—cardiomegaly with bilateral pleural effusion.

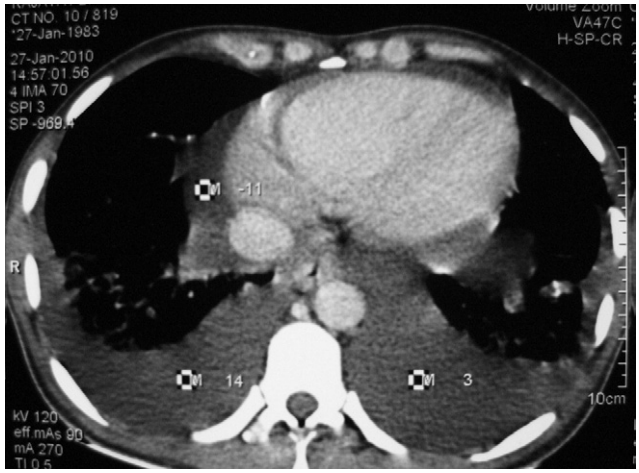

Figure 2 Computed tomography chest demonstrating polyserositis—bilateral pleural with pericardial effusion.

Thus, considering the compatible history, a negative investigation panel for most causes of PUO including infection, hematologic malignancies, and other connective tissue disorders and extremely high ferritin levels, a diagnosis of AOSD presenting as aseptic meningitis was made. After initial resuscitation with intravenous fluids and packed red cell transfusions, intravenous methylprednisolone was administered at 1 g/d for 3 days owing to the severity of disease flare. Rapid recrudescence of fever was achieved with this and the patient was started on oral prednisolone at 1 mg/kg/d along with cyclosporine A at 3 mg/kg/d in divided doses. However, on the fifth day, his symptoms (fever, rash, disorientation) recurred and the general condition deteriorated—pulse rate 120/min, respiratory rate 28/min, and pleural effusion increased in size. A therapeutic pleurocentesis was required. Therefore, it was decided to give tocilizumab, an interleukin-6 (IL-6) receptor monoclonal antibody whose efficacy has been proven in systemic onset juvenile idiopathic arthritis (soJIA) (2). An infusion of 8 mg/kg was given on day 6. Prompt and dramatic resolution of symptoms such as fever and serositis occurred with normalization of sensorium. There was improvement in all the biochemical parameters such as complete blood count,

Table 2 Negative/Normal Tests in Workup for PUO
Serology for dengue, leptospirosis, malaria, enteric fever, and brucellosis
Blood and urine cultures
Thyroid function tests
HIV-ELISA, HBsAg, anti-HCV
Bone marrow aspirate and biopsy
2D echocardiography for vegetations
Mantoux test
Serum ANA, ANCA, rheumatoid factor
Coagulation profile (PT, aPTT)