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Nalini Valluru
Virginia Commonwealth University, nvalluru@mcvh-vcu.edu

Venkata S. Tammana
Howard University Hospital

Michael Windham
Howard University Hospital

See next page for additional authors

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Case Report

Rare Manifestation of a Rare Disease, Acute Liver Failure in Adult Onset Still’s Disease: Dramatic Response to Methylprednisolone Pulse Therapy—A Case Report and Review

Nalini Valluru,1 Venkata S. Tammana,2 Michael Windham,2 Eyasu Mekonen,2 Rehana Begum,2 and Andrew Sanderson2

1 Department of Internal Medicine, Division of Gastroenterology and Hepatology, Virginia Commonwealth University, West Hospital, 14th Floor, 1200 East Broad Street, P.O. Box 980341, Richmond, VA 23298, USA
2 Department of Internal Medicine, Division of Gastroenterology and Hepatology, Howard University Hospital, 2041 Georgia Avenue NW, Washington, DC 20060, USA

Correspondence should be addressed to Nalini Valluru; nalinivalluru@gmail.com

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Adult onset Still’s disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology. It is characterized by daily fevers, arthralgias or arthritis, typical skin rash, and leukocytosis (≥10,000 WBC/mm³) with at least 80% neutrophils, fever, and arthralgias/arthritis [1]. Other common symptoms include sore throat, myalgias, lymphadenopathy, hepatomegaly, splenomegaly, and abdominal pain. Markedly elevated serum ferritin levels have been frequently seen. AOSD is a clinical diagnosis and several sets of classification criteria have been proposed to aid in the diagnosis. The most widely validated criteria cited in the literature are Yamaguchi’s criteria, with five or more criteria of which presence of two or more major criteria have a sensitivity and specificity of 96.2% and 92.1%, respectively [2].

Hepatic involvement is frequently observed in the course of AOSD. Mild elevation in transaminases is common. Acute liver failure (ALF) is a rare manifestation, occasionally requiring urgent liver transplantation [3–9]. We report a case of ALF in a patient with recently diagnosed AOSD who was successfully treated with IV pulse methylprednisolone therapy.

1. Introduction

Adult onset Still’s disease (AOSD) is a rare systemic inflammatory disorder with a typical evanescent salmon-pink non-pruritic maculopapular rash, leukocytosis (≥10,000 WBC/mm³) with at least 80% neutrophils, fever, and arthralgias/arthritis [1]. Other common symptoms include sore throat, myalgias, lymphadenopathy, hepatomegaly, splenomegaly, and abdominal pain. Markedly elevated serum ferritin levels have been frequently seen. AOSD is a clinical diagnosis and several sets of classification criteria have been proposed to aid in the diagnosis. The most widely validated criteria cited in the literature are Yamaguchi’s criteria, with five or more criteria of which presence of two or more major criteria have a sensitivity and specificity of 96.2% and 92.1%, respectively [2].

2. Case Report

A 22-year-old African American female with a past medical history significant for AOSD presented with fever, arthritis, and abdominal pain. Three months ago, she presented with fever, arthralgia, myalgias, generalized weakness, sore throat, maculopapular skin rash, and cervical and axillary
lymphadenopathy. Laboratory data showed mildly elevated transaminases and markedly elevated ferritin levels. After extensive work up including negative HIV and other acute viral illness and normal bone marrow biopsy, patient was diagnosed with AOSD based on Yamaguchi diagnostic criteria. She had met three major and four minor criteria. She was discharged on prednisone 20 mg/day. Currently, while on tapering dose of prednisone, she presented with fever, arthritis, and abdominal pain. On examination, she was slightly drowsy and was noted to have fever of 101.6°F, mild conjunctival pallor, and icteric sclera. Her abdominal examination showed epigastric and right upper quadrant tenderness. Laboratory findings included normal basic metabolic panel. Complete blood count showed leucocyte count of 4.2 x 10^9/L, hemoglobin 11.4 gm/dL, platelet count 144 x 10^9/L. Liver function tests showed total bilirubin of 5.4 mg/dL, aspartate aminotransferase (AST) of 4,974 U/L, alanine aminotransferase (ALT) of 2,522 U/L, alkaline phosphatase of 211 U/L, gamma glutamate transpeptidase (GGT) of 155 U/L, and albumin of 3 g/dL. Coagulation studies were prothrombin time (PT) of 18.1 seconds (151% of normal), international normalised ratio (INR) of 1.53, and activated partial thromboplastin time (APTT) of 29.1 seconds (116% of normal). Serum ferritin level was >15,000 ng/mL (normal: 40-200 ng/mL). Serum and urine toxicology screen was negative. Autoimmune workup including antinuclear antibody, rheumatoid factor, anti-mitochondrial antibody, anti-smooth muscle antibody, anti-liver/kidney microsomal antibody, immunoglobulins, ceruloplasmin, and alpha 1 antitrypsin were all negative. Serology for viral hepatitis A, hepatitis B, hepatitis C, hepatitis E, herpes simplex virus (HSV), Epstein-Barr virus, Cytomegalovirus, human immunodeficiency virus (HIV), West Nile virus, Leptospira, Borrelia, and Q fever were negative. Ultrasound of the abdomen showed normal liver morphology with normal echogenicity. She was diagnosed with ALF secondary to AOSD. She was promptly started on IV pulse methylprednisolone therapy 1 gram/day for 3 days. After 3 days of treatment with pulse methylprednisolone therapy, her liver enzymes began to trend down dramatically. IV steroids were then switched to peroral prednisone 40 mg/day. She was discharged in a stable condition with near normal liver function tests after 8 days of hospitalization. One year later, she remained in remission on low dose prednisone.

3. Discussion

Still's disease is named after George. F. Still, who originally described 22 cases of chronic polyarthritis usually referred to as juvenile rheumatoid arthritis in children in 1897. In 1971, Eric Bywaters described 14 cases resembling Still's disease that started in adult life, hence the name adult onset Still's disease [10]. In a retrospective study of 62 patients in West France, the estimated incidence of AOSD was 0.16 per 100,000 inhabitants. Mean age of the study population was 36 [11]. Based on an epidemiological survey conducted in Japan, estimated crude prevalence was calculated as 0.73 and 1.47 per 100,000 population for males and females, respectively, with a female to male ratio of 2:1 [12].

The etiology of AOSD remains unknown. AOSD is considered as multisystemic disorder in which several cytokines including interleukin (IL), mainly IL-1, IL-6, and IL-18, interferon (IFN) gamma, and tumor necrosis factor (TNF) alpha have been implicated in the pathogenesis [1]. IL-18 has been identified to play a key role in AOSD pathogenesis including high serum ferritin levels and liver injury in AOSD [8].

Clinical course of AOSD is usually benign. Rarely, serious complications such as ALF, macrophage activation syndrome/hemophagocytic syndrome, pericarditis, cardiac tamponade, disseminated intravascular coagulation, serous peritonitis, pleuritis, and respiratory failure are seen [1]. Our patient presented with ALF.

Hepatic involvement usually manifesting as asymptomatic elevation in transaminases with or without hepatoenlgeal is frequently seen in AOSD; indeed liver dysfunction is one of Yamaguchi's minor criteria. ALF is a rare complication of AOSD. ALF can occur at the time of AOSD diagnosis, during tapering of immunosuppressive therapy, or years after diagnosis when other symptoms of AOSD are well controlled. After extensive review of literature, seventeen cases of ALF in AOSD were reported [3–9, 13–21], of which seven (41.1%) required liver transplantation [3–9]. Characteristics of previously published cases of ALF in AOSD are highlighted in Table 1.

Of the seventeen cases reported, twelve patients (12/17 = 70.5%) are females, as our patient [3, 5, 7–9, 13–15, 17–19]. Seven patients had AOSD diagnosed at the time of ALF presentation (7/17 = 41.1%) [3, 9, 14, 15, 18–20]. Eight patients (8/17 = 47%) had AOSD diagnosed prior to the onset of ALF (timeline between AOSD diagnosis and onset of liver failure ranging from 10 days to 3 years) [5–8, 13, 16, 17]. One patient (1/17 = 5.88%) had AOSD diagnosed following liver transplantation for ALF when symptoms of the disease recurred with tapering of oral steroids and in one patient (1/17 = 5.88%) we were unable to obtain information regarding the timeline of AOSD diagnosis and onset of ALF [4, 21]. Eight patients (8/17 = 47%) were on steroids with or without combination with other immunosuppressant drugs for the treatment of AOSD prior to onset of ALF [5, 7, 8, 13, 14, 16, 17]. Of the eight patients with prior AOSD diagnosis, four received treatment with methylprednisolone pulse therapy for ALF [5–8]. All four patients subsequently received liver transplantation and recovered with uneventful follow-up. Two patients recovered with pulse dexamethasone therapy combined with cyclosporine and one patient recovered with prednisolone and anakinra without the need for liver transplantation [16, 17]. One patient was on prednisolone at the time of ALF and went into grade IV hepatic encephalopathy the next day and died [13]. Of the seven patients who were diagnosed with AOSD simultaneously at the time of presentation with ALF, two patients received therapy with pulse methylprednisolone; of them, one patient recovered and the other required liver transplant and died after transplantation from disseminated intravascular coagulation and intraventricular hemorrhage [9, 15]. Three patients were started on prednisolone
| Author [Reference] | Gender/Age (Years) | Interval between AOSD diagnosis and ALF | Hepatotoxics prior to the onset of ALF | Baseline AOSD treatment before ALF | Treatment of ALF associated with AOSD | Underwent liver transplantation | Outcome |
|------------------|-------------------|----------------------------------------|---------------------------------------|-----------------------------------|-------------------------------------|-------------------------------|---------|
| Lisie et al. [3]  | F/24              | Simultaneous                            | None                                  | None                              | Extracorporeal liver support        | Yes                           | Recovered|
| Terán et al. [4]  | M/23              | Simultaneous AOSD diagnosed after ALF when symptoms recurred | None                                  | None                              | Supportive care                     | Yes                           | Recovered|
| Taccone et al. [5] | F/28              | 1 month                                 | None                                  | Prednisolone 8 mg/day             | IV Methylprednisolone 500 mg and MARS, IV one pulse of Methylprednisolone 250 mg and then 20 mg IV BID | Yes                           | Recovered|
| Mc Farlane et al. [6] | M/21              | <1 month                                | Acetaminophen                         | Aspirin, Acetaminophen, Methylprednisolone 8 mg/day | IV Methylprednisolone pulse 500 mg/day for 3 days, 2 days of pulse IV Methyl prednisolone 1 gm per day and then plasma exchange | Yes                           | Recovered|
| Yamanaka et al. [7] | F/20              | 3 years                                 | None                                  | Cyclosporine, Prednisolone 15 mg/day | IV Methylprednisolone 1 gm/day for 2 days | Yes                           | Recovered|
| Ogata et al. [8]  | F/20              | 3 years                                 | None                                  | Prednisolone 15 mg/day            | IV Methylprednisolone 1 gm/day for 2 days | Yes                           | Recovered|
| Dino et al. [9]   | F/44              | Simultaneous                            | Aspirin 1.8 gram/day                  | None                              | IV MethylPrednisolone 1 gm/day for 2 days | Yes                           | Died    |
| Thabah et al. [13] | F/29              | 10 days                                 | Indomethacin                          | PO Prednisolone 40 mg/day and indomethacin, Prednisolone 16 mg/day for an undetermined rheumatic disease | Steroids                          | No                            | Died    |
| Ott et al. [14]   | F/25              | Simultaneous                            | None                                  | Acetaminophen, Ibuprofen          | NSAIDs                             | No                            | Recovered|
| Linde et al. [15] | F/39              | Simultaneous                            | Acetaminophen, Ibuprofen             | None                              | Oral betamethasone, methotrexate and Indomethacin | No                            | Recovered|
| Mylona et al. [16] | M/46              | 2 months                                | None                                  | Tapering dose of Prednisolone     | Oral dexamethasone, methotrexate and Indomethacin | No                            | Recovered|
| Nagashima et al. [17] | F/32              | 2 weeks                                 | None                                  | Prednisolone 50 mg/day and Cyclosporine 150 mg/day | Prednisolone 75 mg/day PO and Anakinra 100 mg/day PO IV Pulse dexamethasone 100 mg/day and Cyclosporine 120 mg/day, 3 days of IV dexamethasone pulse therapy 120 mg/day, dexamethasone 5 mg/day Cylosporine | No                            | Recovered|
Liver transplantation [3]. A patient was treated with ursodeoxycholic acid and recovered [19–21]. Ursodeoxycholic acid, NSAIDS-Nonsteroidal anti-inflammatory drugs, hrs-hours, NM-Not mentioned.

One case demonstrated that ALF can be a rare presentation of AOSD in the absence of other potential causes of liver failure. Prompt initiation of IV mega dose methylprednisolone pulse therapy may be indicated as a first-line treatment in AOSD associated ALF with favorable outcome.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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