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An Unusual Association of Adult-Onset Still's Disease, Aseptic Meningitis, and Concurrent Celiac Disease in a Young Patient

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Muneeb Rehman [1], Madeline A. Ungs [2], Imran Umer [1]

1. Rheumatology, OSF St. Francis Hospital & Medical Group, Peoria, USA 2. Med-Peds, OSF St. Francis Hospital & Medical Group, Peoria, USA

Corresponding author: Imran Umer, iumer45@yahoo.com

Abstract

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder that presents a diagnostic challenge for many clinicians because of its heterogeneous clinical manifestations and overlap with infectious and other inflammatory conditions. In contrast, celiac disease is a common immune-mediated disorder triggered by gluten ingestion, which damages the small intestine and prevents proper nutrient absorption. It affects only a small proportion of the global population. We present the case of a 24-year-old woman who was initially hospitalized with abdominal pain, high-grade fever, and sore throat, accompanied by leukocytosis and abnormal liver function tests, and later developed altered mental status. An extensive rheumatologic evaluation was negative; however, serologic testing for celiac disease was positive, and the diagnosis was subsequently confirmed by esophagogastroduodenoscopy with duodenal biopsy. The patient also met the Yamaguchi criteria for AOSD with concomitant aseptic meningitis presentation. AOSD-associated aseptic meningitis is uncommon, and its coexistence with newly diagnosed celiac disease has not been reported in the literature. This case highlights the importance of considering AOSD in patients presenting with aseptic meningitis and systemic inflammatory features, particularly when an infectious etiology is not identified. Early recognition and prompt initiation of appropriate therapy are essential for better clinical outcomes.

Categories: Rheumatology, Infectious Disease, Gastroenterology
Keywords: adult onset still's disease (aosd), aseptic meningitis, celiac disease, fever of unknown origin (fuo), salmoon rash, transaminitis

Introduction

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder characterized by high-spiking fever, an evanescent pink or salmon-colored rash, sore throat, myalgia, arthralgia or arthritis, and other manifestations of systemic inflammation [1]. Neurological involvement is uncommon, with a reported prevalence of approximately 7.5%; among neurological manifestations, aseptic meningitis accounts for approximately 64% of the cases [2]. AOSD is considered an orphan condition due to its low prevalence worldwide. The estimated incidence of AOSD varies geographically, ranging from 7 cases per million population in males and 15 cases per million in females in Japan to approximately 1.6 cases per million in western France [3,4].

The pathogenesis of AOSD is not completely understood but is thought to involve dysregulated activation of the innate immune system, resulting in excessive production of proinflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-18 (IL-18), in response to tissue injury, infections, or environmental triggers [5]. To the best of our knowledge, AOSD presenting with concurrent aseptic meningitis in the setting of celiac disease has not been reported in the literature. Here, we report a rare case of AOSD with aseptic meningitis associated with concurrent celiac disease.

Case Presentation

A 24-year-old woman, otherwise healthy, presented to the emergency room (ER) with a two-week history of abdominal pain, weakness, and chills, associated with sore throat, nausea, and vomiting. She denied sinus congestion, conjunctival injection, cough, shortness of breath, chest pain, diarrhea, melena, mucus in the stool, arthralgia, or myalgia. One week prior to her ER visit, she had presented to an urgent care clinic with a sore throat and chills. At that time, testing for influenza A and B and SARS-CoV-2 by polymerase chain reaction (PCR) was negative, and she was prescribed empiric oral cephalexin 500 mg every 6 hours for one week for a suspected upper respiratory tract infection; however, her symptoms had not improved.

Physical examination revealed a temperature of 39°C, a heart rate of 98 beats/minute, a respiratory rate of 18 breaths/minute, and a blood pressure of 116/78 mmHg. The remainder of the physical examination was unremarkable. Initial laboratory findings are shown in Table *1*. Urine drug screening, urinalysis, and urine pregnancy testing were negative. Serum amylase and lipase levels were within normal limits. An acute viral

hepatitis panel, including hepatitis A, B, C, and E, as well as fourth-generation HIV (p24 antigen and HIV 1 and 2 antibody) and syphilis screening, Epstein-Barr virus PCR, cytomegalovirus PCR, Toxoplasma serology, Leptospira IgM antibody, Q fever serology, and a respiratory viral panel, were all negative. The chest radiograph was normal. Abdominal ultrasound revealed mild hepatosplenomegaly. A computed tomography (CT) of the chest with contrast was normal. A CT of the abdomen and pelvis with contrast showed mild hepatosplenomegaly (Figures *1A*, *1B*) and gallbladder wall thickening without gallstones. There was no evidence of acute pancreatitis or biliary ductal obstruction.

Test	Result	Normal
White blood cell count	15.7 x 10^3/µL	4–11.0 x 10^3/µL
Neutrophils	81%	40–70%
Eosinophils	0.4%	0–5%
Hemoglobin	13.2 g/dL	12–15.5 g/dL
Platelet count	285 x 10^3/µL	150–450 x 10^3/µL
Sodium	131 mmol/L	135–145 mmol/L
Aspartate aminotransferase	75 units/L	0–34 units/L
Alanine aminotransferase	225 units/L	0–55 units/L
Alkaline phosphatase	314 units/L	40–150 units/L
Gamma glutamyl transferase	191 units/L	5–36 units/L
Total bilirubin	5.5 mg/dL	0.3–1.2 mg/dL
Direct bilirubin	4.7 mg/dL	0.0–0.3 mg/dL
Lactate dehydrogenase	229 units/L	120–220 units/L
Ferritin	481 ng/mL	11–336 ng/mL
C-reactive protein	23.8 mg/dL	0–0.8 mg/dL
Erythrocyte sediment rate	118 mm/hour	0–30 mm/hour
Procalcitonin	5.16 ng/mL	<0.25 ng/mL
Deamidated gliadin IgA	83.7 units/mL	<15 units/mL
Tissue transglutaminase IgA	250 units/mL	<15 units/mL
Total IgA	452 mg/dL	65–421 mg/dL

TABLE 1: Blood and other serum laboratory results.

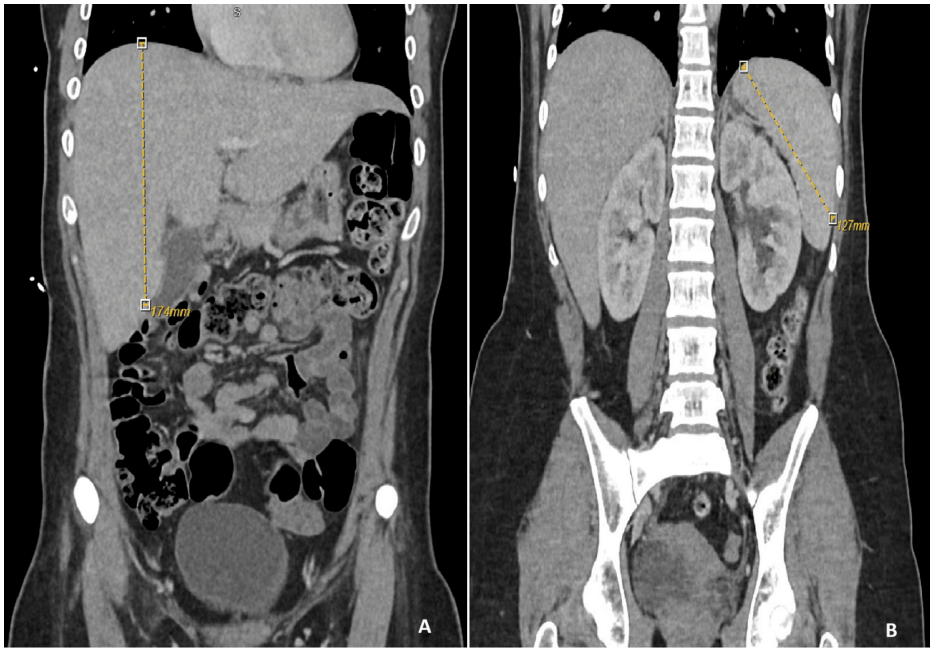


FIGURE 1: CT scan (coronal view) of the abdomen and pelvis with contrast showing mild hepatomegaly (174 mm) (A) and mild splenomegaly (127 mm) (B).

An Infectious Disease and Gastroenterology consultation was obtained. Empiric intravenous (IV) piperacillin-tazobactam 4.5 grams every 6 hours was initiated for suspected acute cholangitis. Further workup reported positive celiac disease serology (Table *1*). Abdominal pain resolved on hospital day 3. The patient subsequently underwent upper gastrointestinal endoscopy and endoscopic retrograde cholangiopancreatography (ERCP), both of which were unremarkable. Given the positive celiac disease serology, duodenal biopsies were obtained. Histopathologic examination demonstrated duodenal-type mucosa with patchy increased intraepithelial lymphocytes and moderate villous blunting, findings consistent with celiac disease (Figure *2*).

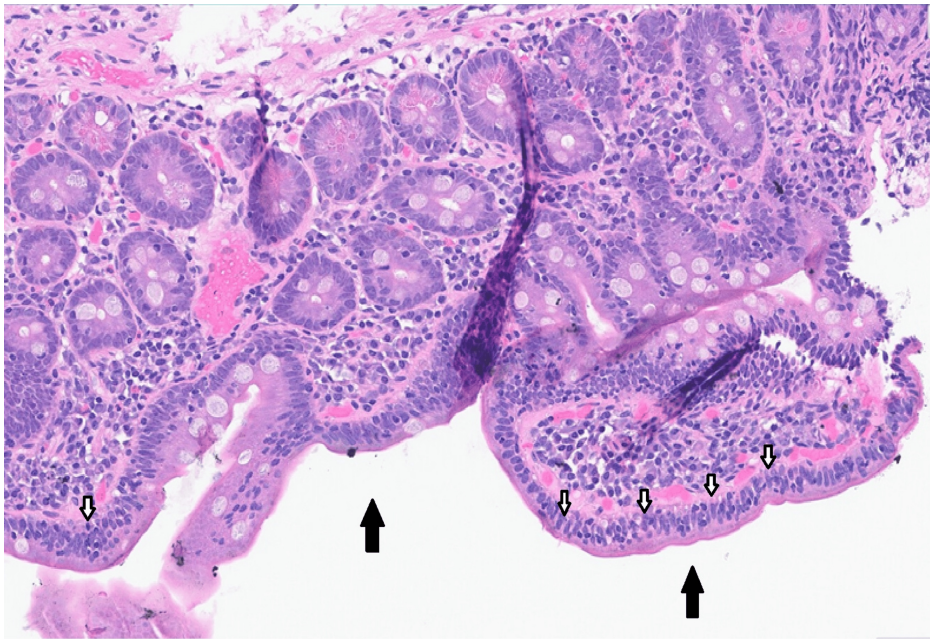


FIGURE 2: Duodenal histopathologic examination showing duodenal-type mucosa with patchy increased intraepithelial lymphocytes on hematoxylin and eosin stain x10 magnification (white arrows) and moderate villous blunting, consistent with Marsh-Oberhuber grade 3b (black arrows).

Blood and urine cultures showed no growth. On hospital day 5, the patient developed a nonpruritic, salmon-colored rash involving the trunk and all four extremities (Figure *3A*). The rash resolved as her fever subsided (Figure *3B*) and recurred with subsequent febrile episodes every 8-12 hours. She also developed altered mental status characterized by confusion and drowsiness, prompting Neurology consultation. A CT of the brain without contrast and magnetic resonance imaging (MRI) of the brain with and without gadolinium were unremarkable. A lumbar puncture was performed. Cerebrospinal fluid (CSF) analysis showed a white blood cell count of 100 cells/µL, with a predominance of lymphocytes (85 cells/µL). The CSF glucose level was 60 mg/dL, serum glucose level was 95 mg/dL, and CSF protein level was 27 mg/dL (normal 15-45 mg/dL); CSF opening pressure was 11 cmH_2O (normal 6-21 cmH_2O). The CSF meningitis PCR panel, CSF herpes simplex virus (HSV) 1 and 2 PCR, and Enterovirus PCR were negative, and CSF culture reported no growth. On hospital day 7, empiric piperacillin-tazobactam antibiotic was stopped after excluding infection etiology.



FIGURE 3: Photos of legs showing salmon-colored rashes on legs during the febrile stage (A) and resolving rash during the afebrile stage (B).

On hospital day 8, the Rheumatology team was consulted for the evaluation of suspected systemic autoimmune rheumatologic conditions for ongoing daily fever, abnormal labs, and new-onset change in mental status. An extensive rheumatologic workup was negative for antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCAs), lupus serologies, rheumatoid factor (RF), and cyclic citrullinated peptide antibodies (CCPs). The patient's clinical presentation fulfilled the Yamaguchi criteria for AOSD, including three major criteria of fever ⩾39°C for >1 week, leukocytosis >10,000 cells/μL with 81% neutrophils, and typical salmon-colored rash, and four minor criteria of sore throat, hepatosplenomegaly, abnormal liver function tests, and negative RF and ANA antibodies after exclusion of infection and malignancy. Her CSF study very likely reflected aseptic meningitis, with negative infectious workup and other causes of aseptic meningitis such as drug-induced meningitis. She was treated with high-dose IV methylprednisolone 1 mg/kg/day for three days, which resulted in complete resolution of fever, skin rash, and mental changes. IV methylprednisolone was then switched to oral prednisone 20 mg daily. Her liver enzymes subsequently improved in a few days. She received dietary counseling and started a gluten-free diet for celiac disease. She was subsequently discharged home on oral prednisone 20 mg twice daily, with a slow taper over an eight-week period for AOSD.

At the two-week follow-up visit, she remained asymptomatic while on oral prednisone 20 mg daily. Repeat laboratory testing demonstrated improvement in leukocytosis and liver function tests. Serum ferritin decreased to 261 ng/mL. She remained adherent to a gluten-free diet. Her AOSD has remained in remission during routine follow-up for the subsequent 24 months without the need for additional immunosuppressive therapy.

Discussion

AOSD is a rare systemic autoinflammatory disease characterized by an intense activation of innate immune cells (neutrophils and macrophages) and overproduction of proinflammatory cytokines IL-1, IL-6, and IL-18 in response to tissue damage from certain infections and environmental chemical factors [5,6]. George Frederic Still, a British physician, first described a form of childhood arthritis associated with fever in the medical literature in 1897, a disease today called systemic onset juvenile idiopathic arthritis or So-JIA [5,7]. AOSD was first described as a related inflammatory condition of young adults in the 1970s by Eric Bywaters [8]. The exact pathogenesis of AOSD is unclear, but there is observational evidence suggesting that this autoinflammatory syndrome may be triggered by environmental, infectious, and genetic components [9-11].

AOSD is characterized by four cardinal symptoms: fever, joint pain, rash, and elevated serum white blood cell count. Fever is quotidian (daily, spiking) or double quotidian, abrupt, ⩾39°C, and associated with chills. Almost 70% of patients have joint pain that affects the upper and lower extremities and is associated with fever [12]. Synovial fluid analysis confirms inflammation with a white blood cell count of more than 2,000 to 11,000. The typical AOSD rash is evanescent, also appearing with fever. It is macular or maculopapular, salmon or pink in color, and predominantly affects the trunk and extremities. A major increase in serum leukocyte counts (>10,000/mm^3) and neutrophil percentage (>80%) is also detected [12]. Other clinical manifestations include, but are not limited to, sore throat, myalgia, lymphadenopathy, splenomegaly,

abnormal liver function tests without fulminant hepatitis, and elevated inflammatory markers including ESR, C-reactive protein, and serum ferritin [5,12]. Diagnosis of AOSD also requires exclusion of other connective tissue diseases or inflammatory joint diseases with a negative immunological workup [13]. AOSD is diagnosed based on the Yamaguchi criteria (proposed in the year 1992), which include the following major criteria: fever ⩾39°C lasting for one week or more, arthralgia/arthritis lasting two weeks or more, typical nonpruritic salmon-pink rash, and leukocytosis ⩾10,000/mm^3 with >80% neutrophils. The minor criteria include the following: sore throat, lymphadenopathy and/or splenomegaly, abnormal liver function tests, and negative RF and ANAs, excluding infection, malignancy, or rheumatic disease that explain the clinical findings. For the diagnosis of AOSD, five or more criteria must be met, including two or more major criteria. In patients with any of the exclusion criteria, the diagnosis is not included [14].

In general, AOSD is initially treated with corticosteroids and/or NSAIDs, with conventional synthetic disease-modifying antirheumatic drugs (DMARDs) used as steroid-sparing or disease-modifying therapy. In less than 40% of patients who fail to respond to initial treatment or who experience recurrent flares despite initial treatment, advanced therapies such as biologic DMARDs may be considered. These targeted therapies can help achieve sustained disease control and prevent long-term flare-ups [15]. Evidence indicates that cytokine inhibitors targeting IL-1, IL-6, TNF, and potentially IL-18 could interfere with the inflammatory response in AOSD [16].

The association between AOSD and celiac disease has been reported in the medical literature. Kumar et al. reported a case of a young woman with AOSD associated with celiac disease, in whom the diagnosis of AOSD was delayed for approximately two years after the onset of symptoms [17]. Similarly, Frandah et al. reported a case of a young woman with AOSD and concomitant celiac disease who had experienced symptoms for approximately two years before diagnosis [18]. Neither of these patients had neurological involvement, in contrast to our patient, who presented with acute aseptic meningitis, was diagnosed with AOSD at an early stage, and was subsequently found to have asymptomatic celiac disease. More recently, Alhayali reported a case of refractory AOSD with concomitant celiac disease who was successfully treated with the Janus kinase inhibitor tofacitinib [19]. Aseptic meningitis as an initial manifestation of AOSD is uncommon, with only a limited number of cases reported in the literature [2,20].

In our patient, celiac disease was diagnosed incidentally in the absence of diarrhea or anemia. The diagnosis was supported by positive tissue transglutaminase IgA and deamidated gliadin IgA serology and subsequently confirmed by esophagogastroduodenoscopy with duodenal biopsy, demonstrating histopathologic findings consistent with celiac disease. Concurrently, the patient was diagnosed with aseptic meningitis based on CSF findings, excluding other common causes of aseptic meningitis such as viral causes and drug-induced meningitis. Our patient met the Yamaguchi criteria for AOSD; however, she was lacking musculoskeletal symptoms, which is common in 90% of cases [16]. Extensive infectious workup remained negative, and CT of the chest and abdomen was negative for malignancy. Serum procalcitonin was slightly high, which could be related to AOSD and inflammation. Unlike the previously reported refractory case, our patient did not require biologic or targeted synthetic disease-modifying therapy and demonstrated a favorable response to corticosteroid treatment.

To the best of our knowledge, based on the available published literature reviewed, this represents the fourth reported case of AOSD occurring in association with celiac disease and the first in our review to present with concurrent aseptic meningitis. This case highlights the importance of considering AOSD in the differential diagnosis of aseptic meningitis, particularly in patients with systemic inflammatory manifestations and negative infectious studies.

This report has some limitations, particularly the inability to determine whether the association between AOSD and celiac disease represents a true association or a coincidental finding, given the limited available data. Although AOSD commonly presents with transaminitis, our patient also demonstrated a cholestatic pattern in addition to hepatocellular injury. An extensive workup did not identify an alternative etiology for the cholestasis. We therefore hypothesize that the cholestatic pattern may have been due to intrahepatic cholestasis associated with hepatic inflammation. The underlying hepatocellular inflammation may also have contributed to the patient's abdominal pain at presentation. Serum sodium was mildly low at 131 mmol/L (normal range, 135-145 mmol/L), possibly related to syndrome of inappropriate antidiuretic hormone secretion (SIADH) secondary to aseptic meningitis associated with AOSD. However, in the absence of urine sodium and serum and urine osmolality measurements, SIADH could not be confirmed.

Conclusions

Aseptic meningitis associated with AOSD is uncommon, and its coexistence with newly diagnosed celiac disease has not been previously reported. This case is notable for an initial presentation suggestive of infection, followed by the development of neurological symptoms. Despite an extensive infectious evaluation that was unrevealing, the patient demonstrated a rapid and marked clinical response to corticosteroid therapy, supporting an underlying systemic inflammatory etiology. This case underscores the importance of considering AOSD in the differential diagnosis of patients presenting with systemic inflammatory features and aseptic meningitis, particularly when infectious workup and evaluation for other etiologies are unrevealing. Early recognition of this potentially treatable inflammatory condition and timely

initiation of appropriate therapy may facilitate rapid clinical recovery, as demonstrated in the present case. In addition, clinicians should remain vigilant for an association with celiac disease or its incidental detection, even in the absence of gastrointestinal symptoms.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Imran Umer, Muneeb Rehman, Madeline A. Ungs

Acquisition, analysis, or interpretation of data: Imran Umer, Muneeb Rehman, Madeline A. Ungs

Drafting of the manuscript: Imran Umer, Muneeb Rehman, Madeline A. Ungs

Critical review of the manuscript for important intellectual content: Imran Umer, Muneeb Rehman, Madeline A. Ungs

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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