# Rare Presentation of Adult-Onset Still's Disease Complicated by Acute Severe Hepatitis Refractory to Medical Treatment: A Case Report

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**Rare Presentation of Adult-Onset Still's Disease Complicated by Acute Severe Hepatitis Refractory to Medical Treatment: A Case Report**

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**Key Clinical Message:**

Managing adult-onset Still's disease (AOSD) complicated by severe hepatitis requires vigilant monitoring and adaptable therapeutic strategies. Standard treatments like Tocilizumab and Rituximab can cause adverse reactions or lose efficacy. The interplay of systemic inflammation and liver involvement highlights the need for ongoing research to find effective, safe treatment alternatives.

**Keywords:**

Adult-Onset Still's Disease**,** Severe Hepatitis, IL-6 Receptor inhibition, Tocilizumab, Rituximab.

**Introduction:**

Still's Disease is characterized by systemic inflammation, recurrent fevers, and arthritis. It poses significant challenges in management, particularly when complications such as hepatitis arise. Initial treatment often involves IL-6 receptor inhibition with Tocilizumab, as supported by clinical trials [1] and the use of rituximab as an alternative [2]. We present a complex case where these therapies were employed sequentially with varying outcomes.

**Case History:**

A 43-year-old female with a known history of Still's Disease, since 2020, presented with her fourth flare-up characterized by high-grade fevers and acute severe hepatitis in June 2024.

Her initial diagnosis three years ago led to treatment with Tocilizumab (Actemra) and steroid therapy, which controlled her symptoms until she became steroid-dependent and unresponsive after six doses. Her first flare-up in July 2021 involved a high-grade fever and elevated liver enzymes, followed by a second flare-up six months later, presenting with a high-grade fever and a diffuse salmon-colored rash as shown in [figure 1].

**Methods:**

Despite a normal liver biopsy in November 2023 during her third flare-up, she experienced severe hepatitis and was started on Rituximab, which was discontinued six months later due to anaphylaxis after the second dose. Currently, patient is experiencing high-grade fevers, diffuse salmon-coloured rash, icteric sclera, brown urine, and grey stools, complicating Still's Disease, refractory to previous therapies.

Labs indicate elevated liver enzymes, indicative of acute severe hepatitis. Figure 2 depicts the patient's latest labs, upon her $4^{th}$ flare up.

**Conclusion and Results:**

The patient's history of anaphylaxis to Rituximab and steroid dependence post-Tocilizumab complicates the management of her condition, highlighting the need for alternative therapeutic strategies. It is to note that she has not experienced any articular pain, which is strikingly unusual in a known Still's disease patient. With our patient, we had no option but to resume steroid therapy, as there is no data on any other forms of treatment. The patient will also be given a new trial of rituximab since other treatment options are very limited.

**Discussion:**

This case report presents the management of a 43-year-old female with Still's Disease who developed severe hepatitis as a complication. Despite initial responsiveness to Tocilizumab and steroid therapy, subsequent treatment challenges arose, including steroid dependency and anaphylaxis to Rituximab. This case underscores the complexities in managing Still's Disease and highlights the need for alternative therapeutic strategies.

The diagnosis of AOSD relies heavily on clinical evaluation, patient history, identification of characteristic symptoms, and exclusion of other diseases. Patients typically present with high spiking fevers, maculopapular rashes, arthralgia or arthritis, pharyngitis, and elevated levels of acute-phase reactants like ESR, CRP, and serum ferritin. [3] AOSD is often diagnosed through exclusion during an investigation for fever of unknown origin (FUO). Studies show that 10-20% of patients evaluated for FUO are diagnosed with AOSD. [3] Bilgin et al. proposed an algorithm differentiating AOSD from other FUO causes, emphasizing arthralgia, hyperferritinemia, sore throat, and neutrophilia as strong indicators of AOSD. [4]

Commonly used classification criteria include the Yamaguchi and Fautrel criteria. The Yamaguchi criteria, with a sensitivity of 96.2%, require a combination of major and minor criteria, excluding other conditions. The Fautrel criteria involve major criteria like spiking fever, arthralgia, transient erythema, pharyngitis, and polymorphonuclear cells, along with minor criteria. Biomarkers like glycosylated ferritin and heme-oxygenase-1 (HO-1) have shown potential in diagnosing AOSD. Elevated serum cytokines such as IL-1, IL-6, IL-18, and IL-37 also play roles in diagnosis and management. Despite advancements, the diagnostic process for AOSD remains challenging due to its non-specific symptoms and lack of a specific diagnostic test. Diagnosis delays are common, often due to the overlap of AOSD symptoms with other diseases and the absence of specific biomarkers. Median diagnostic delays range from 1 to 4.1 months across studies. [3]

Tirotta et al. compiled a comprehensive literature review focusing on cases of AOSD with acute hepatitis reported in the past ten years [16]. Data were collected on patient demographics, comorbidities, clinical manifestations, liver tests, inflammatory indices, autoimmunity tests, infectious etiology tests, liver biopsy results, treatment, and prognosis. Out of 79 cases reviewed, only six met the criteria for inclusion due to the presence of liver biopsy data and acute hepatitis [4-11]. These cases were categorized into four main types

of acute hepatitis in AOSD: autoimmune hepatitis (AIH), drug-induced liver injury (DILI), hepatitis due to AOSD, and hepatitis associated with hemophagocytic lymphohistiocytosis (HLH).

AIH can occur concurrently with AOSD or emerge as a complication. Histological examination of liver biopsies in AOSD patients often shows periportal mononuclear infiltration, Kupffer cell hyperplasia, lobular inflammation, and sub-massive hepatic necrosis, features that overlap with AIH and DILI [5, 11]. Differentiating AIH from AOSD is critical for treatment decisions, particularly regarding corticosteroid use. AIH in AOSD patients can exacerbate despite immunosuppressive treatment, and drugs like tocilizumab may trigger AIH-like responses [5].

Steroids and tocilizumab are notable causes of DILI in AOSD patients. The exact mechanism of corticosteroid-induced liver injury is unclear, though it may involve cytochrome P450 3A4 metabolism aberrations [7]. Tocilizumab-related hepatitis is rare but severe, potentially disrupting IL-6-mediated liver regeneration [13]. Early identification and management, including possible steroid withdrawal and N-acetyl-cysteine therapy, are crucial.

Liver dysfunction in AOSD can coincide with disease onset or occur during steroid tapering, sometimes years after remission. Elevated IL-18 levels and macrophage activation within the liver may mediate hepatotoxic effects [14]. Markedly high serum ferritin levels often indicate active AOSD and potential liver involvement, emphasizing the need for regular monitoring of ferritin and liver enzymes in AOSD patients [15].

HLH, a severe hyper-inflammatory condition, can be a life-threatening complication of AOSD, presenting with acute liver failure. Diagnosis involves clinical criteria and histological evidence of hemophagocytosis in bone marrow or liver biopsies [11]. Treatment typically includes immunosuppressive therapies, and in severe cases, liver transplantation may be necessary.

Acute hepatitis in AOSD encompasses a spectrum of conditions, including AIH, DILI, direct liver involvement due to AOSD, and HLH-induced hepatitis. Accurate diagnosis, guided by clinical, biochemical, and histological data, is essential for appropriate treatment and improved patient outcomes.

In this case, initial treatment with Tocilizumab aligned with findings from Article 1, showing efficacy in controlling systemic inflammation and reducing flare frequency. However, steroid dependence and diminished response after multiple doses necessitated a switch to Rituximab, as suggested by Article 2. The abrupt discontinuation of Rituximab due to anaphylaxis underscores the importance of monitoring for adverse reactions despite its potential benefit in refractory cases. With our patient, we had no option but to resume steroid therapy, as there is no data on any other forms of treatment. The patient will also be given a new trial of rituximab since other treatment options are very limited.

In conclusion, severe hepatitis as a complication of Still's Disease presents significant therapeutic challenges. This case highlights the complexities in managing recurrent flare-ups and underscores the need for alternative therapies in patients refractory to initial treatments. Further research is warranted to explore novel therapeutic strategies and improve outcomes in such cases.

**Figure 1 Legend:** Images of the patient's diffuse salmon-colored rash upon presentation

**Figure 2 Legend:** Patients Labs upon latest Presentation, fourth flare up

**Authorship List:**

1. Dr. Majed Ali: Investigation, Methodology, Writing original draft
2. Dr. Karam Karam: Investigation, Methodology, Writing original draft
3. Dr. Emanuel-Youssef Dib: Data curation, investigation
4. Dr. Elias Fiani: *Corresponding author:* Supervision, writing review & editing

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**Conflict of interest statement**

None.

**Consent:**

The patient in this manuscript has given written informed consent to publication of their case details.

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