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Acute Hepatitis in Adult-Onset Still's Disease: Four Presentation Pattern Proposed

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1. Abstract

Acute severe hepatitis is an unusual manifestation of adult-onset Still's disease [AOSD], poorly described in literature. We performed sensible research of the medical literature on PubMed and Google scholar, investigating cases of AOSD patients with acute hepatitis. Six cases were collected including a new our case reported. We divided the spectrum of clinical manifestation of acute hepatitis into 4 main etiological/histological categories, because we think that the histological/etiological characterization of these unusual cases can influence the most appropriate therapy and therefore the prognosis of the disease.

2. Introduction

Adult-onset Still's disease [AOSD] is an unusual systemic auto-inflammatory disorder of the young adults. The typically onset of this disease is high spiking fever [generally above 39°C, lasting less than 4 hours, daily or twice-a-day , higher in the evening], specific salmon rash and arthralgias [1]. Tests usually show leucocytosis, neutrophilia, high ferritin, absent reumatoid factor and antinuclear antibodies. Diagnosis of AOSD is of exclusion. The most accepted criteria are Yamaguchi and colleagues' criteria, (Table 2) [2]. More recently, Fautrel et al have proposed serum ferritin and glycosylated ferritin, as more specific for AOSD [3]. The pathophysiology of liver involvement could be related to the activation of liver macrophages and production of pro-inflammatory cytokines, such as IL-18, but the mechanism and the potential trigger of severe hepatic necrosis is unknown. Liver dysfunction is frequent in AOSD [about 70% of AOSD] and it is often a marker of disease activity [4]. According to the Yamaguchi criteria, abnormal liver function test is a minor criterion of diagnosis.

Most cases of liver dysfunction in AOSD patients are drug-induced. Autoimmune hepatitis [AIH] is described, although not always histological examination of the liver was performed. Other described pattern of acute hepatitis includes acute hepatitis due to AODS and acute hepatitis associated to haemofagocitic lymphoistiocytosis syndrome. Liver involvement includes frequent asymptomatic increase of liver enzymes, but also rare life-threatening liver failure, requiring urgent liver transplantation, little described, because rares. The best treatment, especially of the life-threatening

Table 1: Yamaguchi Criteria for AOSD Diagnosis

Yamaguchi Criteria
Diagnosis: 5 Criteria, at least 2 Major
Exclusion Criteria: Infection, Malignancies and Rhematic Diseases
Major
Arthralgia> 2 weeks
Fever> 390, intermittent > 1 week
Typical Rash
WBC> 10.000(>80% ganulocytes)
Minor
Sore throat
Lymphadenopathy and/or
Splenomegaly
Liver Function Tests Abnormal

Table 2: Yamaguci Criteria for AOSD diagnosis

AIH	
1) Uchihara D, D, , Suzuki T, Koya Autoimmune hepatitis complicated by adult-onset Still's disease during treatment with tocilizumab: A case report from acute onset to recurrence. Y Clin Case Rep. 2023 2023 (4)	
Epidemiological data (gender, age)	Female, 31 year
Comorbidity	None
Clinical manifestations	Fever, arthralgia, typical rash, sore throat, lymphadenopathy, Hepatosplenomegaly presen
Liver tests	AST 2267/1884 U/L, ALT 1493/2072 U/L , ALP 513/371 U/, T Bil 8.46/6.86 mg/dL , D Bil 6.38/5.41 mg/dL , PT 104/62% , Alb 3.9/4.3 g/dL
Inflammatory indices	Leukocytosis (WBC 8000/5500 per µL , N 66%), hyperferritinemia (1650/2202 ng/mL), LDH 899/671 U/L
Autoimmunity test	Negative test for antinuclear antibody, and rheumatoid factor
Infective etiology tests	HBV, HCV, HIV serology negative, CMV dna negatives
Presence and grade of hepatic encephalopathy	None
Time to hepatitis onset	AIH after AOSD
Liver biopsy	In the present case, acute liver injury occurred twice, once in October 2017, and again in January 2021. During the first liver injury, histopathology revealed a collapse of hepatocytes around the central veins, an infiltration of eosinophils, and Kupffer cell hyperplasia. These findings evoked liver dysfunction of AOSD, acute-onset AIH, and DILI due to tocilizumab, but the findings were not specific. The second liver injury had typical pathological findings of AIH. Viewed retrospectively, the first liver injury might have been acute-onset AIH, and the second liver injury was AIH exacerbated by drug suspension for 4 months.
Treatment	The first-line treatment for AOSD and AIH is corticosteroids. Second line Cyclosporine and Tolicizumab
Prognosis	No relapse
DILI	
2) Lee CC, Peng YJ, Chi C et al. Corticosteroid-Induced Liver Injury in Adult-Onset Still's Disease. Medicina 2022 58 191	
Epidemiological data (gender, age)	Female, 29 years
Comorbidity	Familiarity for Sjogren
Clinical manifestations	Fever, arthralgia, sore throat and macular rashes, Enlargement of multiple lymph nodes
Liver tests	Elevated liver enzymes (alanine aminotransferase (ALT) 150 U/L, aspartate aminotransferase (AST) 119 U/L) on the 10th day and peak levels (ALT 1473 U/L, AST 722 U/L) on the 15th day. In the readmission new acute severe hepatitis (ALT 1652 U/L, AST 766 U/L)
Inflammatory indices	Leukocytosis (13,060/µL) with 85.5% of neutrophils and remarkable hyperferritinemia (12,585 ng/mL).
Autoimmunity test	Antinuclear antibodies and rheumatoid factor were negative
Infective etiology tests	HBV, HCV, HIV, CMV dna not specified
Presence and grade of hepatic encephalopathy	None

Time to hepatitis onset	Onset after AOSD(19 months after ocilizumab onset)
Liver biopsy	Infiltration of lymphocytes, neutrophils, and proliferative Kupffer cells as well as occasional apoptotic bodies in lobular and portal areas. Corticosteroid-induced liver injury was confirmed based on the clinical findings and the positive prednisolone re-challenge.
Treatment	Corticosteroid, then mycophenolic acid was substituted for prednisolone for treatment of AOSD on account of its lower risk of hepatotoxicity
Prognosis	No relapse observed
3) Drepper M, Rubbia-Brandt L, Spahr L. Tocilizumab-Induced Acute Liver Injury in Adult Onset Still's Disease. Case Reports in Hepatology Volume 2013, p 1-3	
Epidemiological data (gender, age)	Female, 18 year
Comorbidity	None
Clinical manifestations	Recurrent fever, polyarthritis, abdominal lymphadenopathy, liver and spleen enlargement , then nausea, abdominal discomfort, and pruritus
Liver tests	AST: 2622 U/L , ALT: 2628 U/L , ALP: 110 U/L, GGT: 272 U/L, and total bilirubin: 61 mol/L (335 moli/l). Prothrombin time 66% , International Normalized Ratio of 1.21
Inflammatory indices	WBC: 3500/L, platelets: 52000/L , Hyperferritinemia
Autoimmunity test	IgG, ANA, antiactin, anti LKM negative
Infective etiology tests	HBV, HCV, HIV, CMV dna, EBV, HSV serology negative
Presence and grade of hepatic encephalopathy	None
Time to hepatitis onset	After AOSD
Liver biopsy	Extensive centrilobular hepatocyte necrosis with collapse. Hepatocytes were ballooned with clear cytoplasm. Mild inflammatory periportal cell infiltrations as well as rare areas of micro- and macrovesicular steatosis were also observed
Treatment	Corticosteroid, then tocilizumab due to resistence to corticosteroid. Intravenous N-acetylcysteine
Prognosis	No relapse observed
Liver involvement due to AODS	
4) Bishara R, Moscovici BY, Gagan A et al. Severe hyperferritinemia a clue for severe hepatitis in a patient with adult onset Still's disease. Clin Rheum 2016 35:795-800 (7)	
Epidemiological data (gender, age)	Man, 19 year
Comorbidity	None
Clinical manifestations	High fever, malaise, sore throat, arthralgia, and widespread erythematous rash, Splenomegaly
Liver tests	Three weeks later blood tests revealed elevated aspartate transaminase 75 u/L and alanine transaminase 525 u/L. Levels of albumin and bilirubin were within normal limits. AST (u/L) 41>> 788 ALT (u/L) 91 >>3073 GGT (u/L) 96>> 305 ALP (u/L) 95 >>95 LDH (u/L) 240 >>441 Total bilirubin (mg/dl) 0.9 >>2.7 Direct bilirubin (mg/dl) 0.4 >> 1.4 Albumin (g/dl) 3.2 >> 2.9 9 INR – 1.4
Inflammatory indices	Leukocytosis, mild liver enzymes elevation, and high ferritin levels. Three weeks later Blood tests revealed a very high ferritin level (12,000 ng/ml), elevated CRP (21 ng/L), WBC (×103 /µL) 13.7>> 12.6 Hemoglobin (g/dl) 13.9>> 15 PLT (×103 /µl) 259>> 177 . Ferritin (ng/ml) 3481>> 12,000 ESR (mm/h) 80>> 10 CRP (ng/L) 225 >> 23.1
Autoimmunity test	ANA, FR, ACPA, ANCA, AMA, ASMA, IGg4 negative
Infective etiology tests	HBV, HCV, HIV, CMV dna, EBV, HSV serologynegatives
Presence and grade of hepatic encephalopathy	None
Time to hepatitis onset	After one month (corticosteroid tapering at 20 mg/die)
Liver biopsy	Unspecific reactive hepatitis with inflammatory cells infiltration, rich in neutrophils, occasional eosinophilic apoptotic bodies, and hepatocytes with ballooning of the cytoplasm. There were no signs of lymphoma, autoimmune hepatitis , or hemophagocytosis
Treatment	MTP pulse (500 mg/day for 3 days), then corticosteroid tapering and cyclosporine a
Prognosis	No relapsed observed
5) Our case (Morgagni-Pierantoni Hospital, Internal Unit)	

Epidemiological data (gender, age)	Man, 50 year old
Comorbidity	None
Clinical manifestations	Sore throat, diffuse arthralgia (knees, ankles, shoulders), palpable painful laterocervical lymphadenomegaly, intermittent high fever, mainly in the evening, weight loss in thinness, malaise.He first assumed amoxicillin for three days, then 3rd cephalosporin and azithromycin, without benefit. Also present: weight loss.Hepatomegaly.
Liver tests	Some weeks later blood tests revealed elevated aspartate transaminase 1096 u/L and alanine transaminase 1658 u/L, gamma GT 235. Levels of albumin within normal limits. INR 1.3
Inflammatory indices	Mild microcytic anemia (Hb 11.5, MCV 78), neutrophilic leukocytosis (WBC 19530, N 18680), biological inflammation syndrome (PCR 146 >>62). very high ferritin level (45066 U/l)
Autoimmunity test	ANA, FR, ACPA, ANCA, AMA, ASMA, IGg4 negative
Infective etiology tests	HBV, HCV, HEV, HHV6, HHV8, HIV, EBV, HSV serology negative, Bartonella Richetsia, Lheismania serology negative, CMV DNA 665 U
Presence and grade of hepatic encephalopathy	None
Time to hepatitis onset	After one week of AODS onset
Liver biopsy	Large foci of necrosis, mainly centrilobular, with neutrophilic granulocyte inflammation, apoptosis and presence of histiocytes. Immunohistochemical characterization for CMV negative. The picture suggests an acute damage with necrosis of the centrilobular area without alteration of the portal spaces.There were no signs of lymphoma, autoimmune hepatitis (AIH), or hemophagocytosis .
Treatment	MTP pulse (500 mg/day for 3 days), then corticosteroid tapering.Short course of therapy with ciclosporin A, then suspended due to increased transaminases and indometacine. Subsequent introduction of anakinra, with evolution of the picture towards acute hepatitis despite the clinical improvement with apyrexia and reduction in inflammation indices (stable CRP, slightly altered procalcitonin, but worsening transaminases and ferritin).Course of therapy with antiviral (Gangiclovir) and N acetyl-cisteine.Anakinra is not discontinued and after one week progressive improvement in liver tests resulted in remission
Prognosis	No relapsed observed (recurrence of fever for 2 days after two weeks of anakinra). Post-discharge follow-up of CMV viremia
HLS	
6) K Gananandana, , R Thomasb , N Burkea et al. Adult-onset Still's disease with secondary haemophagocytic lymphohistiocytosis induced acute liver failure: A case series. Journal of Liver Transplantation 5 (2022) p 1-5 Case 2 (9)	
Epidemiological data (gender, age)	Male, 21 year
Comorbidity	None
Clinical manifestations	Jaundice and a rash, a 3 week history of increasing lethargy, myalgia, and arthralgia, Splenomegaly
Liver tests	Total Bilirubin 315 umol/L, ALT 292 U/L, AST 208 U/L, ALP 121 U/L, Albumin 22 g/L, INR 3.9 (0.9−1.12)
Inflammatory indices	WBC 27 10^9/L (3.5−11), Neutrophils 21.79 10^9/L, Ferritin 16,904 ug/L , CRP 38 mg/L
Autoimmunity test	ANA (1:5120) with positive anti-centromere antibodies
Infective etiology tests	HBV, HCV, HEV, HAV, HIV, EBV, HSV serology, CMV DNA negatives
Presence and grade of hepatic encephalopathy	Yes (patient intubated and transferred in tertiary liver intensive treatment unit). Ammonia 62 umol/L
Time to hepatitis onset	Simultaneously with AOSD onset
Liver biopsy	First liver biopsy: Massive hepatic necrosis with some cholestasis but no morphological cause evident, Second liver biopsy: centrilobular cholestasis/ necrosis with no features of rejection.
Treatment	Transplantation, anakinra, methylprednisolone
Prognosis	Bone marrow aspirate and biopsy demonstrated evidence of extensive haemophagocytosis and a diagnosis of acquired HLH was made. The HScore was 214, Post liver transplantation, no relapse
7) K Gananandana, , R Thomasb , N Burkea et al. Adult-onset Still's disease with secondary haemophagocytic lymphohistiocytosis induced acute liver failure: A case series. Journal of Liver Transplantation 5 (2022) Case 2 (9)	
Epidemiological data (gender, age)	Woman, 31 year old
Comorbidity	None
Clinical manifestations	Arthralgia, fevers, classical rash, Hepatomegaly

Liver tests	Total Bilirubin 350 umol/L, ALT 492 U/L, AST 193 U/L, ALP 116 U/L, Albumin 39 g/L, INR 2.3, Post transplantation CMV viraemia
Inflammatory indices	WBC 8.93 10^9/L, Hb 97 g/l, Platelets 113 10^9/L, Neutrophils 5.55 10^9/L, CRP 9 mg/L , Ferritin 316 ug/L
Autoimmunity test	Negative
Infective etiology tests	HBV, HCV, HAV, HEV, HSV negatives, then CMV DNA 100-150 mcmol/l
Presence and grade of hepatic encephalopathy	No
Time to hepatitis onset	Three months later
Liver biopsy	Firtst liver biopsy: Massive hepatic necrosis with panacinar and multiacinar necrosis and a relative absence of active inflammation. (A bone marrow biopsy performed on day seven of admission showed increased histocytes). Second liver biopsy after liver transplantation: consistent with ischaemia secondary to reperfusion.
Treatment	Steroids intravenously, then oral, then vitamin k, n acetyl cysteine, metylprednisone e plasma exchange, then anakinra, hemofiltration, liver transplantation, tacrolimus and mycophenolate post transplantation
Prognosis	No relapse after transplantation

form, is also often uncertain.

3. Methods

A sensible literature review was performed on PubMed and Google Scholar. We used the Mesh "adult – onset Still's disease" and "hepatitis" and the key-words ''adult – onset Still's disease" and "acute hepatitis" to collect the data of the cases of AOSD with acute hepatic involvement. Limits: last ten years. Case series of AOSD containing at least one patient were selected. Collected data were: epidemiological data [gender, age], comorbidity, systemic clinical manifestations [fever, arthralgia/arthritis, rash, lymphadenopathy, sore throat/pharyngitis, hepatomegaly, splenomegaly], liver tests [AST, ALT, LDH, gGT, ALP, total bilirubin, INR, albumin], inflammatory indices [ferritin, C-reactive protein, and blood cell count]. We also collected presence of hepatic encephalopathy, time of hepatitis onset, infective etiology tests, results of liver biopsy, and, finally, treatment and prognosis.

4. Results

We obtained 79 cases, of which 73 were excluded due to lack of liver biopsy or because the absence of acute hepatitis, but only a transient elevation of liver enzymes [10-13, 16] (Figure 1 and 2) (Table 1). The pattern of acute hepatitis in AODS has been divided by etiological and histological category.

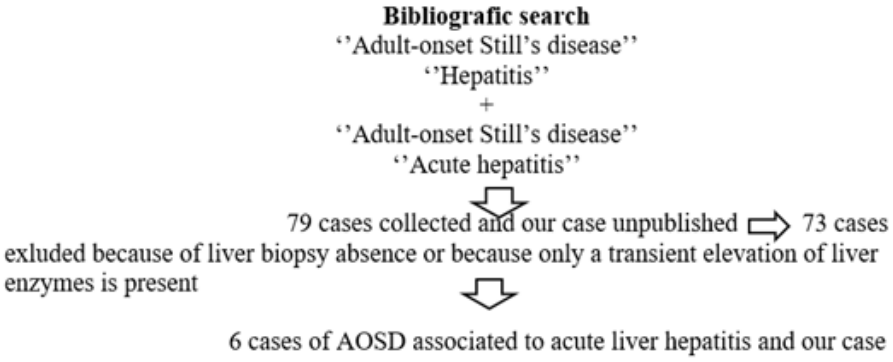


Figure 1: Our Research

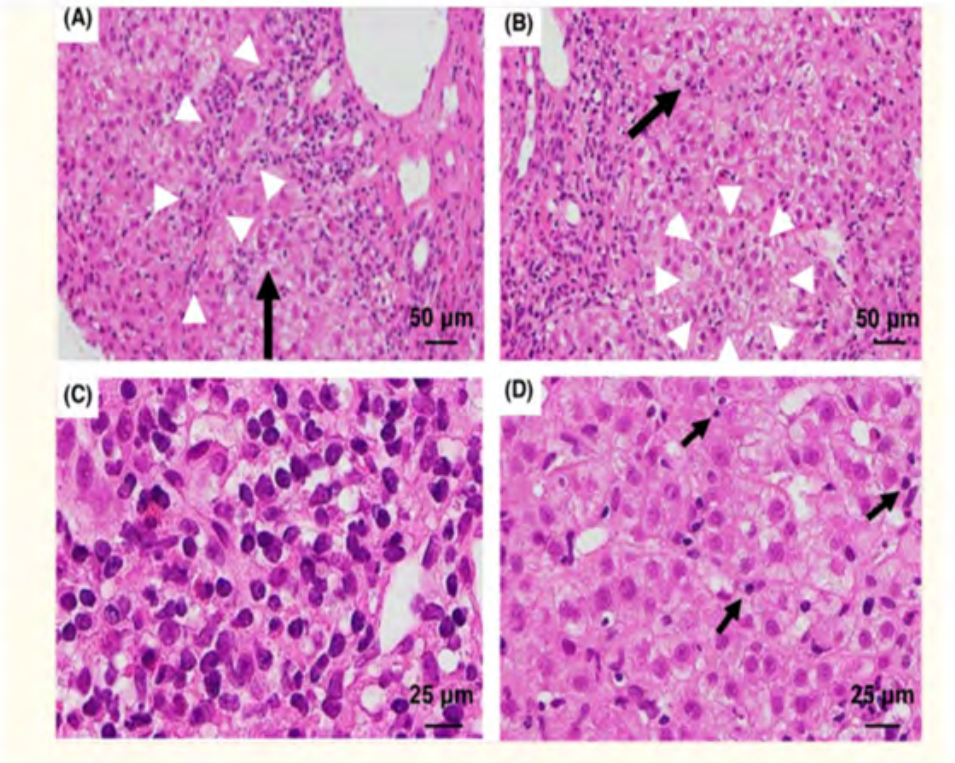


Figure 2: Autoimmune hepatitis (Case 1, References 4)

(A) Hematoxylin–eosin staining of a section: interface hepatitis and piecemeal necrosis. (B) Rosette and hepatocyte ballooning (C) Abundant infiltration of plasma cells , eccentrically placed nucleus and a perinuclear halo . (D) Emperipolesis, engulfment of lymphocytes.

4.1. Autoimmune Hepatitis and AODS

AIH can occur simultaneous with the onset of AOSD or the patient can first develop AOSD or, finally, an acute recurrence of AIH can complicate AOSD [3]. It is almost always difficult to distinguish AIH from AOSD. Histological features of liver biopsy of patients with AOSD include: periportal mononuclear infiltration, Kupffer cell hyperplasia, lobular inflammation, and massive or sub-massive hepatic necrosis, finally, ground glass-like cytoplasmic inclusions [3]. However, all these findings are a specific and described in both the AIH and the DILI. Histological features of liver biopsy of patients with AIH include: interface hepatitis, piecemeal necrosis, plasma cell-rich infiltrates, emperipolesis [engulfment of lymphocytes by hepatocytes due to an immune-mediated injury]. It is controversial whether acute-onset AIH often occurred despite the immunosuppressive treatment for AOSD. Antitumor necrosis factor alpha can cause AIH and Tocilizumab, a monoclonal antibody against the interleukin -6 receptor, may cause a similar immune response. The first-line treatment for AOSD and AIH is corticosteroids, but differentiating AIH from AOSD is important in deciding whether to continue or terminate corticosteroids treatment. Corticosteroids can be terminated in about 40–50% of AOSD, but if AIH is present, many exacerbations on discontinuing the treatment can occur.

4.2. Drug Induced Hepatitis [DILI] and AOSD

From our review, the drugs involved in Dili include steroids and tolicizumab. The mechanism of corticosteroid-induced liver injury is unknown. Corticosteroids are metabolized by cytochrome P450 3A4. Idiosyncrasy due to aberrant hepatic metabolism should be considered in corticosteroid-induced hepatotoxicity [5] (Figure 3). Acute and severe hepatitis may complicate tocilizumab treatment, but this is a rare event. Pathogenic mechanisms perhaps are due to interference of tocilizumab with IL-6-mediated liver regeneration. Careful monitoring of liver function tests should be applied to patients receiving tocilizumab. Timely recognition of the drug involved is important for therapeutic remodulation [e.g., steroid withdrawal, N-acetyl-cystein therapy, mycophenolic acid introduction]

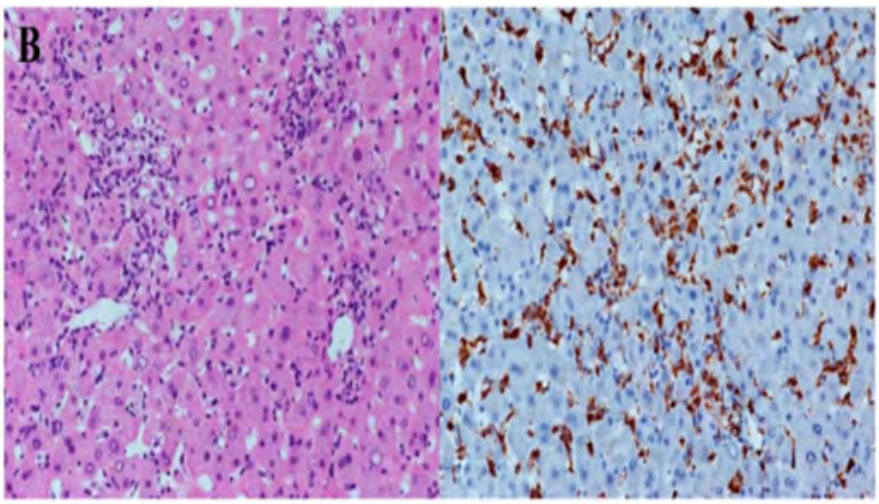


Figure 3°: (5). DILI due to corticosteroid. Acute hepatitis with neutrophils and lymphocytes infiltration in H&E stain and (right) Kupffer cell proliferation highlighted by CD68 immunohistochemical stain . H&E: hematoxylin and eosin.

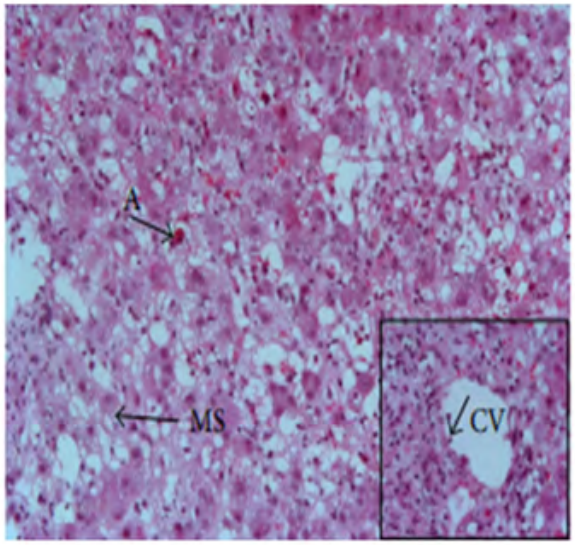


Figure 3B: (Reference 6). DILI to tolicizumab and AOSD Histological view (haematoxylin-eosin stain, original magnification ×200) demonstrating extensive areas of hepatocytes with necrosis, ballooning degeneration, macro- and microvesicular steatosis (MS), and acidophil bodies (A).

4.3. Acute Hepatitis due to AODS

Liver dysfunction may occur simultaneously with AOSD during the steroid tapering off, even many years after remission. The exact cause of liver dysfunction associated with AOSD is unclear: IL- 18 perhaps mediates the hepatotoxic manifestations of AOSD and IL18 is very increased in patients with fulminant hepatic failure compared to those with chronic liver disease. Activated macrophages and Kupffer cells within the liver parenchyma of AOSD patients with hepatic involvement overexpressed locally IL18. Markedly elevated serum ferritin could be the only manifestation of AOSD activity and a sign of a coming hepatic involvement. Therefore, monitoring of ferritin levels and liver enzymes is strongly recomended in AOSD patients, even if clinical improvement occurs. The role of liver biopsy in the diagnosis of AOSD-related liver disorder is limited, but it may be of high importance, because it can revealing other causes of liver failure and these causes can influence therapy and outcome of the patient [8] (Figure 4). In literature liver biopsy show periportal mononuclear infiltrates, Kupffer cell hyperplasia, lobular inflammation, focal hepatocellular degeneration, periportal fibrosis, massive or submassive hepatic necrosis, and ground-glass-like cytoplasmic inclusions. In this patient, liver biopsy revealed non-specific signs of hepatitis, but allowed exclusion of lymphoma, AIH, and hemophagocytosis.

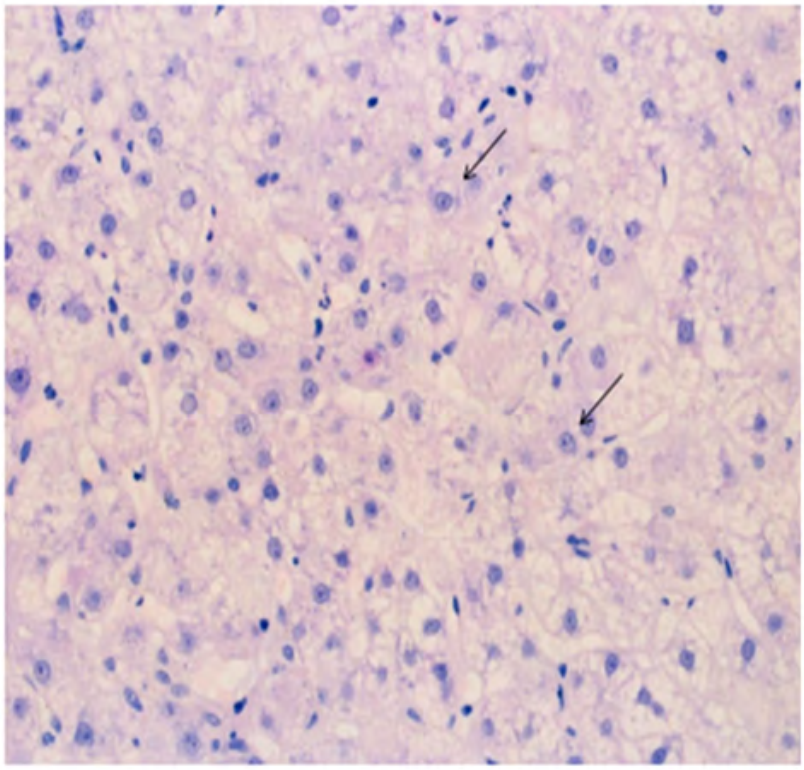
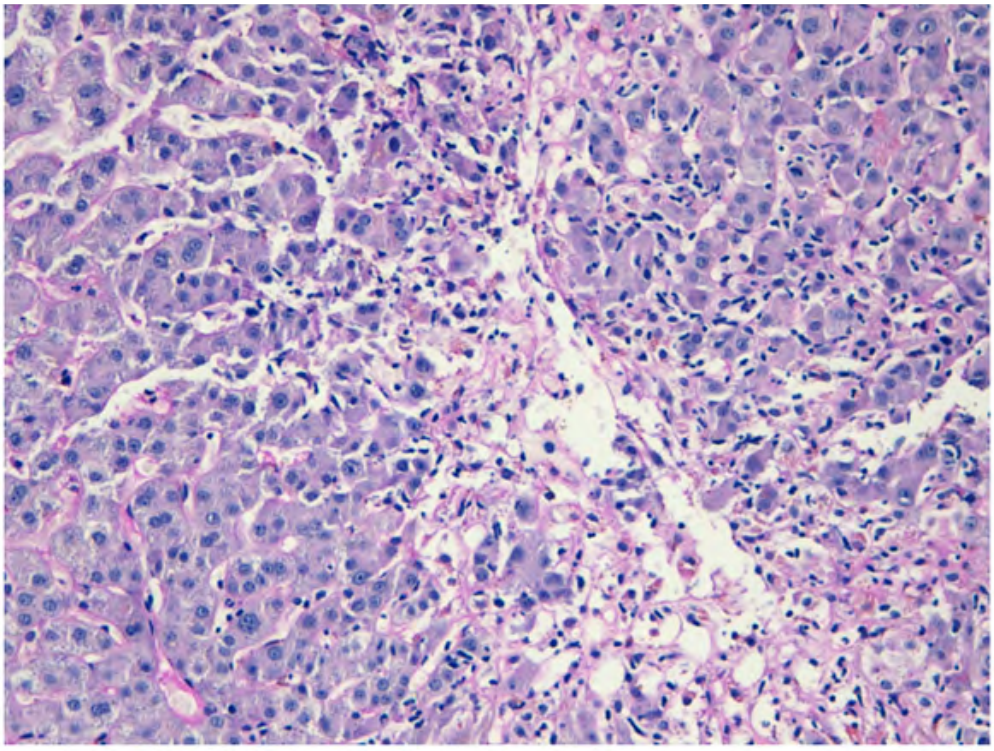


Figure 4: (Reference 8). Acute hepatitis due to AODS Ballooning of the hepatocytes with granulocytes



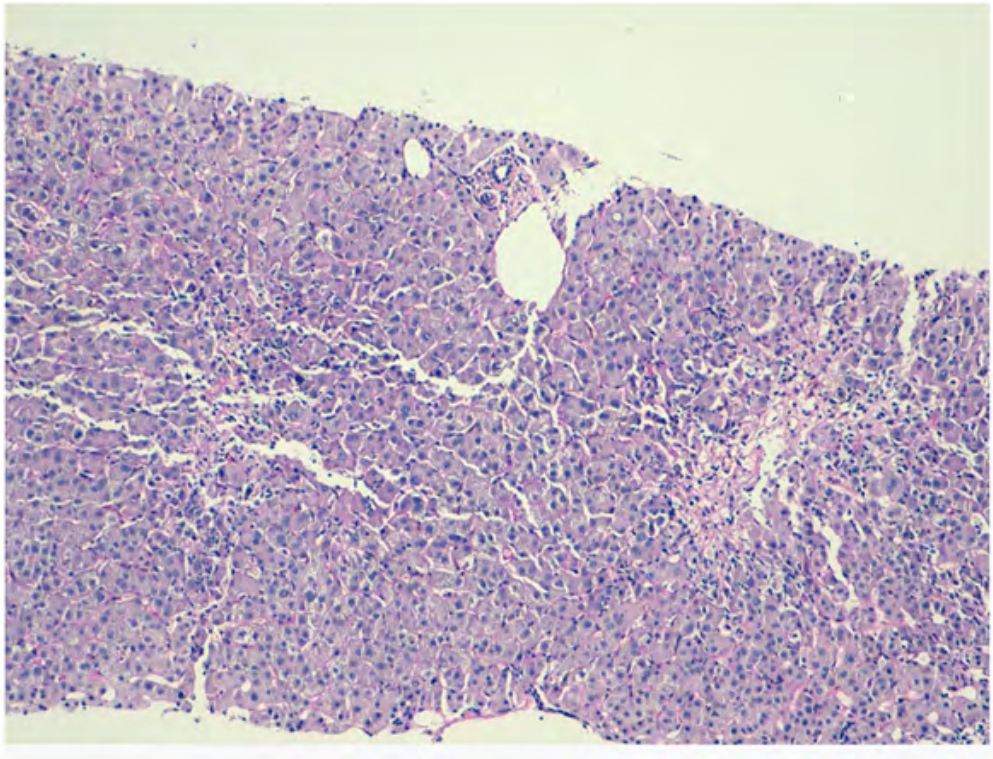


Figure 5: Liver biopsy of our patient . Morgagni-Pierantoni Hospital, Internal medicine Unit. Large foci of necrosis, mainly centrilobular, with neutrophilic granulocyte inflammation, apoptosis and presence of histiocytes. Immunohistochemical characterization for CMV negative,The picture suggests an acute damage with necrosis of the centrilobular area without alteration of the portal spaces.

4.4. Acute Hepatitis and AOSD Associated to Haemophagocitic Lymphohistiocytosis Syndrome

Haemophagocytic lymphohistiocytosis [HLH] is an ununusual and often life-threatening hyperinflammatory syndrome, characterised by high fevers, hepatosplenomegaly, cytopaenias and the presence of activated macrophages in haematopoietic organs. Serum ferritin is always elevated. The condition is more frequent in infants, but can develop in adults. Secondary HLH can also develop in patients with a genetic susceptibility to hyperinflammation due to a trigger [as autoimmune conditions, malignancy, particularly haematological, post organ transplantation or in the context of infection]. AOSD can become cause of secondary HLH, and also the overlap is described. It is important to recognize this cause, as this pattern is often severe and conduct to liver transplantation.

5. Discussion

Our review focuses on cases of acute hepatitis in AOSD over the past 10 years. From the etiological point of view, in the presence of acute hepatitis in AODS, the prevalent diagnostic hypotheses are: Liver involvement due to AODS. The alteration of the liver tests is generally present from the onset of the disease [it is however a diagnostic criterion]. DILI [evaluable especially if hepatitis arises after therapy]: hepatotoxicity from anakinra is generally transient and rare, toxicity from ciclosporin, however suspected in our case, is very rare. DILI is described associated to Corticosteroids and Tolicizumab. Infectious etiology in AODS: In our review cases of acute hepatitis in AODS due only to Cytomegalovirus [CMV] infection is not described as etiology of acute hepatitis. In old literature CMV is often a trigger or opportunist virus, even if the antiviral is used, because of the patient is immunodepressed, due to the disease and steroid therapy [1-14]. CMV infection is frequent in elderly onset patients, but decreased with early coricosteroid dose tapering and increased immunosuppressant [1, 14]. The levels of antibodies against CMV were significantly higher in AOSD and CMV DNA was found in plasma of AOSD patients with disease new-onset and relapse. Significant associations of the CMV DNA level with the levels of leukocytes, erythrocyte sedimentation rate, C-reactive protein and tumor necrosis factor is observed [1]. Involvement of the reticuloendothelial system in the context of a hemophagocytic syndrome [associated with Still]: usually pancytopenia, hypertriglycemia are described and the HS score is compatible Autoimmune etiology: rare, but onset under steroids has been described. Multiple organ failure in sepsisn and Reticuloendothelial activation in lymphoproliferative Syndrome: it is not the subject of this discussion. The histopathological characterization of acute hepatitis is very important for the therapeutic definition and prognosis of the disease. We have identified 4 etiopathological classes: autoimmune [AIH], DILI, hepatic involvement of AOSD, haemophagocytic lymphohistiocytosis Syndrome. In our case, the absence of CMV inclusions in the liver and the histology of non-specific hepatitis allowed us to conclude that the liver was involved in AOSD and therefore we did not interrupt,

but continued therapy with anakinra, with slow but progressive clinical and laboratory remission.

In the case of autoimmune hepatitis, which can arise during steroid therapy, the diagnosis of AIH allows therapy with steroids and azathioprine to be continued for a long time. Treatment otherwise is interrupted with relapse. In fact, in patients with AOSD, it is difficult to distinguish the cause of liver dysfunction as AOSD or AIH. We need to evaluate clinical symptoms, serological tests, and liver biopsy to determine the treatment. If AIH cannot be completely ruled out, treatment should be continued to avoid the possible relapse of AIH. From the clinical point of view often patients with severe acute hepatitis had less systemic symptoms [arthritis, macular rash, sore throat, lymphadenopathy, or splenomegaly] than patients without severe hepatitis. Also, cytopenia was more frequent in case of severe hepatitis. However, this did not happen in our case characterized by high fever persisting for several weeks, systemic symptoms and absence of pancytopenia. Although some cases worsened until transplantation, the clinical evolution is often favourable, despite the significant and persistent symptoms, but for a good prognosis an early and timely differential diagnosis is important. We think that the subdivision into 4 histopathological/histological patterns of acute hepatitis in AODS could be very helpful for correct patient management, therefore the number of livers histologies in these patients should be increased compared to what is described in the literature.

References

1. Bento DP ,Tavares R, Baptista Leite R. Adult-Onset Still's Disease and cytomegalovirus infection. Acta Reumatol Port. 2010; 35: 259-263.
2. Yamaguchi M, Ohta A, Tsunematsu T. Preliminary criteria for classification of adult Still's disease. J Rheumatol. 1992; 19: 424-430.
3. Fautrel B, Zing E, Golmard JL. Proposal for a new set of classification criteria for adult-onset still disease. Medicine (Baltimore). 2002; 81:194-200.
4. UchiharaD, Suzuki1 T, Koya Y. Autoimmune hepatitis complicated by adult-onset Still's disease during treatment with tocilizumab: A case report from acute onset to recurrence. Clin Case Rep. 2023; 11: e7530.
5. Lee CC, Peng YJ, Chi C. Corticosteroid-Induced Liver Injury in Adult-Onset Still's Disease. Medicina 2022; 58: 191.
6. Drepper M, Rubbia-Brandt L, Spahr L. Tocilizumab-Induced Acute Liver Injury in Adult Onset Still's Disease. Case Reports in Hepatology. 2013; 1-3.
7. Bishara R, Braun-Moscovici Y, Dagan A. Severe hyperferritinemia a clue for severe hepatitis in a patient with adult-onset Still's disease . Clin Rheumato. 2016; 35: 795-800.
8. . Lim KB, Schiano TD. Still disese and the liver—an underappreciated association. Gastroenterol Hepatol (NY). 2011; 7: 844–846.
9. Gananandana K, Thomasb R, Burkea N. Adult-onset Still's disease with secondary haemophagocytic lymphohistiocytosis induced acute liver failure: A case series. Journal of Liver Transplantation. 2022; 1-5.
10. Muller R , Briantais A , Faucher B. Acute severe hepatitis in adult-onset Still's disease: case report and comprehensive review of a life-threatening manifestation. Clin Rheumatol. 2021; 40(6): 2467-2476.
11. Aly L, Konert C, Quaas s. Subacute liver failure following anakinra tratment for adult-onset Still disease. J Rheumatol. 40(10): 1775-1777.
12. Mahfoudhi M, Rafik Shimi1 R. Still disease of the adult complicated by fulminant hepatitis. Pan Afr Med J. 2015; 20: 446.
13. Chi H, Wang Z, Meng J. A cohort study of liver involvement in patients with adult-onset Still's Disease: prevalence, characteristics and impact of prognosis. Frontiers in Medicine dec 2020; 7: 1-10.
14. KishidaD, Ichikawa T, Takamatsu R. Clinical characteristics and treatment of elderly onset adult-onset Still's disease. Scientific Reports 2022; 12(1): 6787.
15. Ahmed O, Brahmania M, Alsahaf M. Anakinra Hepatotoxicity in a Patient With Adult-Onset Still's Disease. ACG Case Reports Journal. 2(3): 2015; 173-174.
16. Roma M , Bonetto S , Giovo I. Liver involvement in adult-onset Still's disease: our experience in a third level liver unit and review of the literature. Minerva Gastroenterol. 2021.