Acute liver transplantation in a 41-year-old male patient presenting symptoms of adult-onset Still's disease

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Abstract: Adult-onset Still's disease is a rare systemic non-infectious inflammatory disease of unknown aetiology. It is characterized by high spiking fever, sore throat, arthralgia, transient maculopapular rash, hepatosplenomegaly, liver cytolysis, weight loss, leukocytosis, neutrophilia, lymphadenopathy, myopathia and polyserositis. Mild or moderate liver involvement is common but fulminate liver failure is a rare manifestation. We report a 41-year-old male with undiagnosed adult Still's disease who underwent liver transplantation due to acute fulminate liver failure. He died 6 months after the liver transplantation in a septic condition. To date, six patients with adult Still's disease-related liver failure have been reported who required liver transplantation. We emphasize that adult Still's disease should be considered in the differential diagnosis of fulminate liver failure, especially in young adults with fever of unknown aetiology or typical features in the history.

Keywords: adult-onset, fever, fulminate liver failure, liver transplantation, Still's disease, unknown aetiology

Introduction

Adult-onset Still's disease (AOSD) is one of the aetiologic categories of fever of unknown origin (FUO). It is classified as a connective tissue disorder. According to the literature, 4% of patients that suffered from FUO had AOSD (54/1329 patients); however, the incidence of AOSD is underestimated [1]. The clinical presentation of AOSD is heterogeneous, but its clinical course is typical [2]. It consists of mild or moderate liver dysfunction [3, 4], acute liver failure (ALF) being a rare manifestation [5].

In this report, we present a patient with undiagnosed AOSD who underwent orthotopic liver transplantation (OLT) due to ALF and survived 6 months after OLT.

Case report

A 41-year-old man was admitted to our clinic on 25 January 2009, in an unconscious condition due to ALF of unknown aetiology. He had been healthy until October 2008, when sore throat, high spiking fever (with spikes in the afternoons), arthralgia (wrist, elbow, knee) and maculopapular rash occurred suddenly. The clinical course with relevant laboratory data and treatment are summarized in *Fig. 1*. At first, he was treated on outpatient settings with amoxicillin/clavulanate (875/125 mg/day) and diclofenac (2×50 mg) for 1 week. Based on the positive *Chlamydia pneumoniae* serology results (IgM 23 NTU, IgA 13 NTU, IgG 38.8 NTU), his drug course was changed first to doxycycline (2×200 mg daily) and then to clarythromycine (500 mg/day). Rash and arthralgia were permanently present during the fever spikes despite sustained antibiotic therapy. Serology tests including Epstein–Barr virus (EBV), cytomegalovirus (CMV), *Mycoplasma pneumoniae*, *Toxoplasma*, *Leptospira*, *Chlamydia psittaci*, HIV-1, -2, hepatitis B virus (HBV) and hepatitis C virus (HCV) were negative. Total immune panel including rheumatoid factor (RF) was negative. Anti-nuclear antibody (ANA) was 1:40 positive (aspecific level). All aetiologic factors of liver damage were definitely ruled out pre-operatively. Repeated throat culture and chest X-ray were normal. On the 11 January 2009, he was admitted to the Department of Infectology with high spiking fever and weight loss (15–20 kg in 3 months). The patient was treated with ceftriaxon (for 4 days), and then

	out - patient		in - patient					preOLT	postOLT	
date	10.14.	12.17	01.11.	01.14.	01.19.	01.22.	01.24.	01.25.	01.27.	02.12.
Leu[G/l]	9.36	8.54	14.9	8.9	21.8	13.4	24.1	17.7	16.9	5.7
Neu[%]	88.3	78.3	88.1	85.3	71.9	87	89.6	90.7	83.7	
CRP[mg/l]	54.26	117.5	254.5	205.8				13.6	32.9	21.8
INR			1.69	2.88	4.62	3.74	>4	5.84	3.65	1.36
GOT[U/l]	78	47	1415	3279	947	299	1465	269	1386	110
GPT[U/l]	115	43	1053	1639	880	257	631	244	1261	157
GGT[U/l]	124	76	319	183	83	47	38	31	41	302

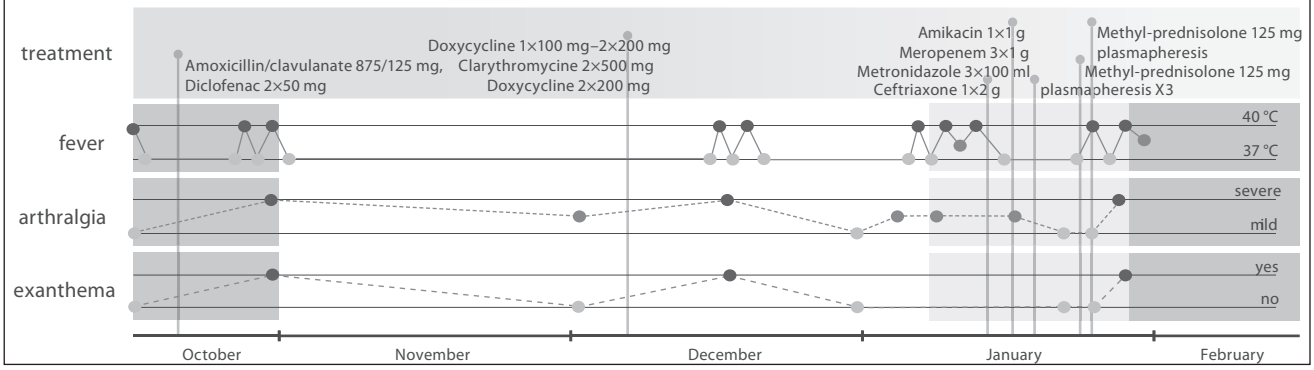

Fig. 1. Clinical course of the patient. Typical features, relevant laboratory data and treatment from the first visit to the early post-operative period

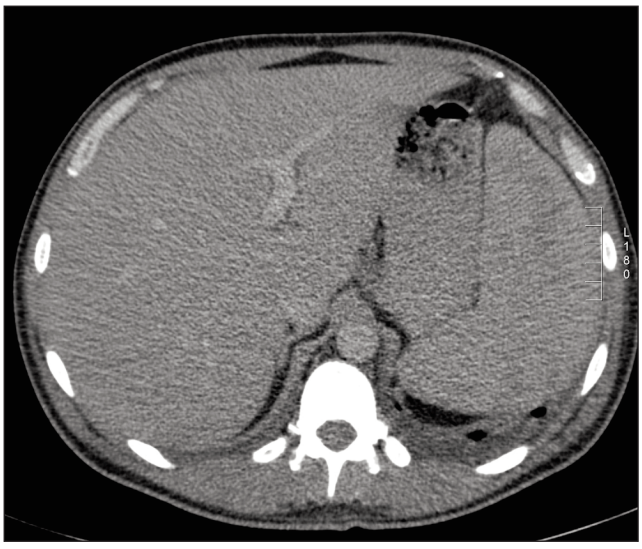

Fig. 2. CT image of the abdomen shows significant hepatosplenomegaly

with amikacin, meropenem (for 7 days) and metronidazole (for 3 days) *(Fig. 1)*. Ultrasonography and computed tomography (CT) found hepatosplenomegaly *(Fig. 2)* as well as pleural and pericardial fluid. The results of repeated blood, urine and throat cultures were negative. Aspecific, reactive leukocytosis was described on peripheral blood sample. It is worth mentioning that the patient had 32,200 μg/L serum ferritine level. From the 22 January, high fever and exanthema relapsed and jaundice developed which progressed daily. Toxic aetiology of ALF was suggested because the patient was a poor CYP3A4 metabolizer. On the 25 January, he was admitted to our clinic and underwent standard OLT (whole-sized donor liver from a 41-year-old deceased donor) without any intra-operative complication. The patient fulfilled King's College criteria for ALF having an increase in international normalized ratio (INR) of up to 6.87. Fulminant hepatic necrosis, but no specific aetiology, was described in the explanted liver *(Fig. 3)*. The patient was admitted to the intensive care unit (ICU) and was treated there for 6 months. In the early post-operative period, initial poor function developed. Liver biopsy made on the second post-operative day showed Banff grade 1/9 acute cellular rejection. Tacrolimus, mycophenolate-mofetil and prednisolone were given as immunosuppressive therapy. On imaging performed post-operatively, pleural fluid and ascites, but no abscess, were found (CT). Due to clinical signs of peritonitis, the patient underwent relaparatomy (drainage-lavage) for three times, and a feeding jejunostomy was implanted. Septic episode developed on the 4th week, without certain focus, despite the fact that *Enterobacter cloacae* was verified in the ascites. Relevant antibiotics were given. The patient was unconscious and in need of sustained respiratory therapy, and suffered of kidney failure. Despite an improvement in liver function and inflammatory markers, persistent polyserositis (ascites, pleural, pericardial), severe myopathy and catabolic state occurred. Critical-illness myopathy was described. The muscle biopsy revealed severe non-infectious myogen damage, as well as T- and B-lymphocyte infiltration *(Fig. 4)*. A repeated liver biopsy (in April) revealed non-specific alteration that could have been the sign of either rejection or other inflammatory processes. Due to this uncertain situation, no anti-rejection therapy was administered. He had taken exercises (passive–active) and took a few steps with help in June. On the 5 June, the feeding jejunostomy was changed to percutaneous endoscopic gastrostomy (PEG). During the disease, he had lost a total of 33 kg weight. In July, he was transferred to the rehabilitation department but he was turned back to our ICU due to

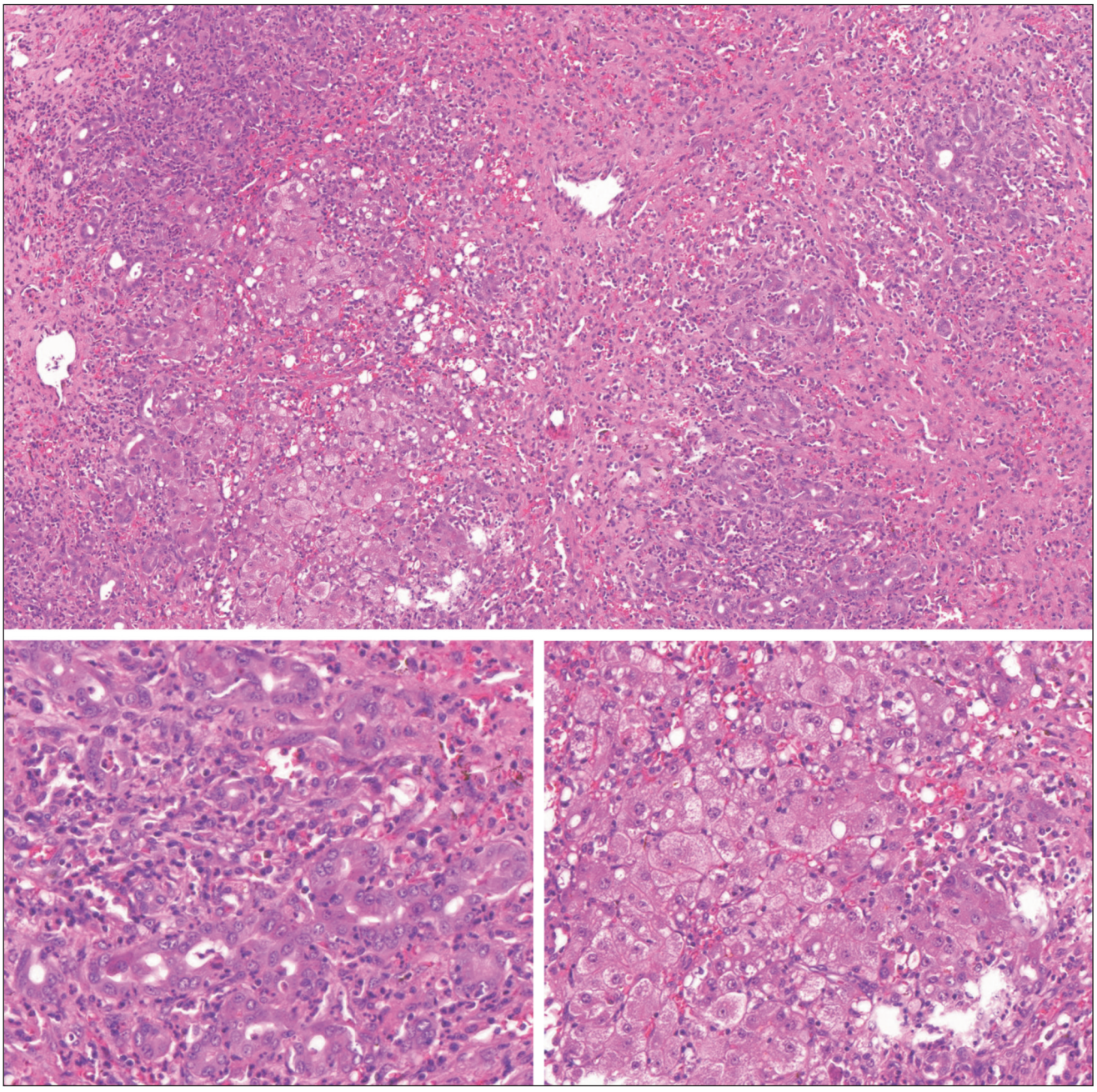

Fig. 3. Histology of the explanted liver. Up: fulminate necrosis can be seen on the histological slides from the explanted liver. The trabecular structure was destroyed (HE-stained slides, ×250 magnification). Left down: severe ductular proliferation could be recognized within a necrotic and inflammated tissue (HE-stained slides, ×400 magnification). Right down: only fewer than 10% hepatocytes were recognizable with vacuolated cytoplasm (HE-stained slides, ×400 magnification)

clinical relapse, fever, diarrhoea and vomiting. Multi-compartment abdominal fluid and severe pleural fluid was described, and the ascites puncture was suppurosus. He died on 29 July due to septic shock and multi-organ failure. At the autopsy, chronic abdominal abscesses were found.

Discussion

Still's disease is the systemic form of juvenile idiopathic arthritis. It was first described by George Still in 1897 [6]. In 1971, Bywaters [7] described a similar presentation of the disease in 14 adults and termed it "adult-onset Still's disease". This is a rare disease; about 25 cases have been reported in Hungary so far [8]. The mean age is 38.1 years in AOSD [8] and it affects slightly more women than men [9]. In the last 40 years, AOSD has become an important cause of FUO [10]. The pathogenesis is not completely understood, but immunopathomechanisms are responsible for the disease [11]. Rapid diagnosis is difficult because no relevant test for the disease exists. The diagnosis is based on a set of clinical and laboratory criteria [9]. The clinical course is typical as in our case *(Fig. 1)*. The most common

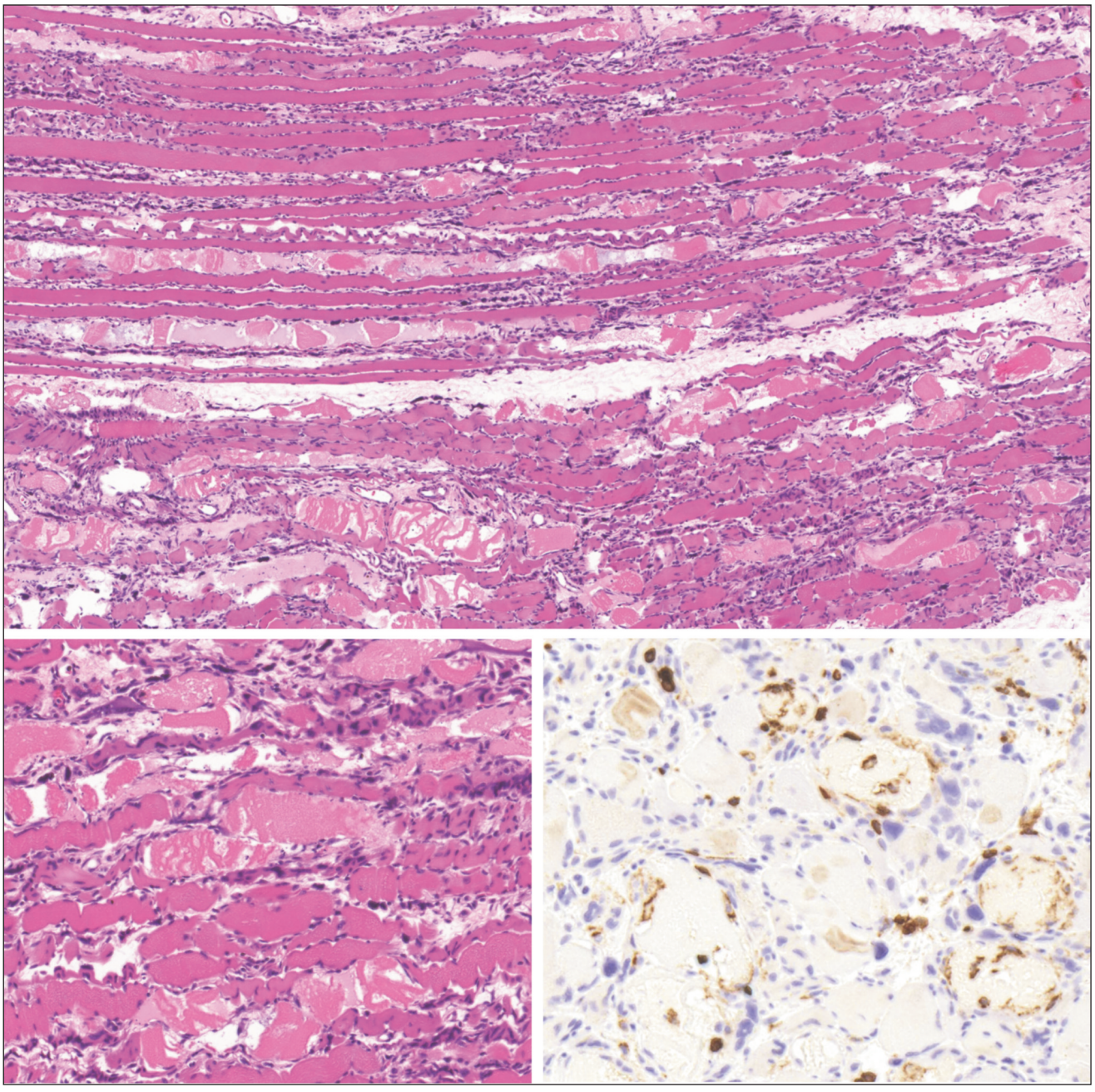

Fig. 4. Histology of the muscular biosy (m. quadriceps femoris). Up: severe impairment of the muscular structure can be seen (HE-stained slides, ×250 magnification). Left down: high variability of the diameter of the cells with more multinucleated giant cells and degenerated, necrotized muscle fibres can be seen (HE-stained slides, ×400 magnification). Right down: high amount of infiltrating leukocytes and fibrosis can be recognized (leukocyte common antigen immunohistochemically stained slides of ×400 magnification)

features (prevalences) are high spiking fever (95–100%), transient maculopapular rash (50–87%) correlated with fever spikes and arthralgia (92–100%), lymphadenopathy (15–74%), hepatosplenomegaly (25–56%), myalgia (60–84%), polyserositis (5–31%) and weight loss. Leukocytosis (90–92%), neutrophilia (88–90%), increased transaminases (65–70%), high serum ferritine and negative ANA (80–92%) and RF (93–100%) are the most common laboratory features [1, 9].

Several classification criteria have been published for AOSD [3, 4]. In our case, all the classification criteria were met. Infectious diseases, tumours and autoimmune disorders should be ruled out in the differential diagnosis. In our case, FUO protocol examinations were all negative. Tumours were ruled out (solid tumours, lymphoproliferative diseases, tumour markers), full autoimmune panel was negative and no pathogens were detectable in the pre-transplant setting. A high serum ferritine level (>3000 μg/L) has been reported to be a useful marker and is in good correlation with disease activity [10]. In our case, 30,000 μg/L was measured (repeated examination).

Liver involvement is frequently seen, and it is caused by AOSD itself [10, 12, 13]. Treatment for patients with liver involvement is aimed mainly at AOSD itself and most of the patients get complete remission with systemic corticosteroid therapy [12]. The therapy protocol for AOSD is non-steroidal anti-inflammatory drugs (NSAIDs), than corticosteroids combined with disease-modifying anti-rheumatic drugs (DMARDs) or cyclosporine; anti-IL1 or anti-TNF-α agents are also recommended [11]. In our case, the typical symptoms (arthralgy, spiking fever and rash) disappeared after OLT besides the immunosuppressive therapy. ALF in AOSD is rare [5, 14]. To date, six patients with adult Still's disease-related liver failure have been reported who required liver transplantation. One of them died within 48 h, and five were diagnosed in time and received proper treatment [15–17]. The aetiology of severe liver damage in AOSD is heterogeneous. Macrophage activation syndrome (MAS) is a severe, and potentially life-threatening complication of AOSD [18]. Extremely elevated serum ferritine levels (>10,000 μg/L) might reflect the presence of MAS [19]. In our case, MAS was also suggested (extremely high serum ferritine level) but the patient did not have the characteristic laboratory features and we did not find haemophagocytosis in the explanted liver. Bone marrow biopsy was not done. We cannot exclude the toxic aetiology of ALF since the patient was a poor metabolizer of CYP 3A4. However, he was not administered any drugs that would affect CYP 3A4 except for metronidazole, which was given only for 3 days (January) and clarithromycine for 1 week (November). NSAIDs might cause ALF in AOSD [10]. Our patient was treated with diclofenac in October but it was canceled because of stomach complaints. Rarely, the exacerbation of AOSD can cause severe liver damage itself [5].

In conclusion, we report a patient with AOSD. According to our data files, this is the first reported case in our centre since 1995 [20–22]. We emphasize that AOSD should be considered in the differential diagnosis of acute fulminate liver failure of unknown aetiology, especially in young adults and with FUO or typical features described in the history.

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