Case Report

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Recovery fulminant hepatitis A in systemic juvenile idiopathic arthritis patient treated with tocilizumab: a case report

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Introduction: Systemic juvenile idiopathic arthritis (sJIA) is a rare systemic immune disorder that affects patients before 16 years of age. Several viruses have been reported to trigger this disease. Increased use of biologics, such as tocilizumab and anakinra, and decreased use of glucocorticoid may lead to improved outcomes in patients with sJIA. Serious liver injuries induced by tocilizumab include acute liver failure, hepatitis, and jaundice. Hepatitis A remains a highly prevalent disease in low-income countries.

Case presentation: A 14-year-old Syrian child was diagnosed with sJIA and treated with different DMARDs, including MTX. Tocilizumab was then added as monotherapy and stopped after 12 doses after full diseases remission and normal laboratory tests. He presented with a very high alanine transferase, aspartate transferase, a spiked fever, and fatigue. He was infected with hepatitis A.

Discussion: Liver abnormalities are uncommon in sJIA. Acute liver failure may develop a few months after the onset of sJIA. Although acute infections with the hepatitis A virus in children are self-limited, 0.1% of patients progress to fulminant hepatic failure, which spontaneously recovers in 40% of cases. No data are available concerning the coexistence of hepatitis A and sJIA. Our case was the first case presenting fulminant Hepatitis A in a sJIA patient treated with tocilizumab, which had recovered, and the authors initiated Anakinra as a treatment.

Conclusion: Further follow-up and cohort studies are needed to find the exact prevalence and coexistence of Fulminant Hepatitis A in the coarse of sJIA treated with tocilizumab.

Keywords: interleukin-6, juvenile idiopathic arthritis, tocilizumab

Introduction

Systemic juvenile idiopathic arthritis (sJIA), or Still's disease is a rare systemic immune disorder of unknown etiology, that affects equally both sexes before 16 years of age[1]. Activation of the innate immune system plays a pivotal role in this disease, by the activation of innate immune cells and the overproduction of proinflammatory cytokines including interleukin (IL 1, 6, and 18), and tumor necrosis factor-α (TNF-α). Human leukocyte antigen, macrophage inhibitory factor polymorphisms, IL-18, and IL-6 are associated with the occurrence of systemic juvenile idiopathic arthritis (JIA). Several viruses, such as rubella, measles, cytomegalovirus, hepatitis B and C, and many others, are reported to trigger the disease[2]. It is typically presented by a daily quotidian fever, a salmon-colored skin rash, and arthritis, association with leukocytosis and elevated acute phase reactants, while organ manifestations may include serositis and myocarditis, lymphadenopathy, and hepatosplenomegaly[3].

Corticosteroids are the first-line treatment for sJIA, but their long-term use side effects have increased the use of biologics[4]. Increased use of biologics such as tocilizumab and anakinra decreased the use of glucocorticoid (GC), which may lead to improved outcomes in sJIA[5,6]. It is known that tocilizumab may cause transient or intermittent mild to moderate elevations of hepatic transaminases. Serious liver injuries induced by tocilizumab, include acute liver failure, hepatitis, and

HIGHLIGHTS

- Systemic juvenile idiopathic arthritis is a rare systemic immune disorder, treated with corticosteroids, DMARDs, and biologics (interleukin 6 and 1 inhibitors).
- Hepatitis A remains a highly prevalent disease in low-income countries.
- Acute infections with the hepatitis A virus in children are self-limited, but 0.1% of patients progress to fulminant hepatic failure.
- Tocilizumab causes transient or intermittent mild to moderate elevations of hepatic transaminases. More serious liver injuries can occur, including acute liver failure, hepatitis, and jaundice.
- Our case was the first case presenting with fulminant Hepatitis A in an systemic juvenile idiopathic arthritis patient.

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jaundice[7]. This risk is increased when it is used in combination with potentially hepatotoxic drugs (e.g. methotrexate)[6].

Hepatitis A remains a highly prevalent disease in low-income countries. Although acute infections with the hepatitis A virus in children are self-limited, 0.1% of patients progress to fulminant hepatic failure that recovery[6]. No data are available concerning the coexistence of hepatitis A and sJIA.

We report the case of a patient with sJIA complicated with fulminant hepatitis A after cessation of Tocilizumab in 2 months, and it was dramatically improved.

Case presentation

A 14-year-old Syrian male with no significant family history or inherited disease or previous personal history.

He was diagnosed with JIA in June 2021 and was treated with different DMARDs to a 4 mg/kg intravenous (i.v.) monotherapy of tocilizumab in February 2022. Before the administration of tocilizumab, the blood counts and biochemical data were all normal, including liver and renal function tests. The clinical response was improved and the patient received tocilizumab, 400 mg i.v., once a month.

He weighed 120 kg, and his height is 170 cm.

He was diagnosed with JIA. According to the sJIA diagnostic criteria developed by the International League of Associations for Rheumatology (ILAR), a diagnosis of sJIA requires a high fever for at least 2 weeks and arthritis (joint pain and inflammation) in one or more joints for at least 6 weeks[3].

The laboratory tests included high white blood cell and platelet counts, anemia, high levels of ferritin, an elevated erythrocyte sedimentation rate, and C-reactive protein. The antinuclear antibodies or rheumatoid factor antibodies were negative.

He always had a fever (38.5°C), and arthralgia, with normal blood tests during steroid treatment and different DMARDs, including MTX.

After the third course of 4 mg/kg tocilizumab, the clinical manifestations improved but not disappeared, and after the sixth course the patient had no clinical manifestations. Tocilizumab was stopped, due to elevation of liver enzymes after the 12 infusions of tocilizumab in February 2023, as alanine transferase (ALT) was at 234 U/l (normal: 7–55 U/l), aspartate transferase (AST) was at 167 U/l (normal: 8–48 U/l). The rest of the liver function tests include ALP and albumin. Total protein, bilirubin, GGT, and PT were normal. At this point, there was no history of potentially hepatotoxic drug intake and no comedication with any DMARD. The patient was on 5 mg/day of predlone.

At follow-up, the liver enzymes keep increasing; even if the patient is under no treatment. ALT was at 543 U/l (normal: 7–55 U/l, and AST was at 432 U/l (normal: 8–48 U/l). The gastroenterology consultations revealed a diagnosis of fatty liver disease.

The patients presented after 3 months of tocilizumab cessation with fatigue, a spiky fever of 40°C, and arthritis in the proximal interphalangeal joints of both hands, wrists, knees, and ankles. The laboratory tests are shown in Table 1.

Two days later, a physical examination revealed: fatigue, a fever of 40°C, loss of appetite jaundice at the conjunctiva, yellow skin, and gums, mental confusion, and arthritis in the proximal interphalangeal joints of the hands, wrists, knees, and ankles, dark tea-colored urine, and light-colored stools. The laboratory tests are shown in Table 2.

Table 1

Laboratory tests table 1.

White blood cells	13.2 K/μl (normal: 4.0–11.0)
Neutrophils	88.5% (normal: 50–70%)
Lymphocytes	10% (normal: 25–40%)
Hemoglobin	8.1 g/dl (normal: 14–18)
Platelet count	300 000 K/μl (normal: 150 000–400 000)
Procalcitonin	< 0.5 ng/ml
Lactate dehydrogenase (LDH)	980 U/l (normal: 14–280 in adults)
Alanine transferase (ALT)	2061 U/l (normal: 7–55)
Erythrocyte sedimentation rate (ESR)	68 mm/h (normal: 0–20)
Aspartate transferase (AST)	1962 U/l (normal: 8–48)
C-reactive protein (CRP)	14 mg/l (normal: <6)
Serum iron level	36 μg/dl (normal: 65–176)
Total iron-binding capacity (TIBC)	178 μg/dl (normal: 261–462)
Serum ferritin	392 ng/ml (normal: 12–300)
Albumin	3.2 g/dl (normal: 3.5–5)
Urinalysis	Normal
Blood and urine cultures	Negatives
The immune profile	Negative

No specific treatment was applied to the patient, except providing nutritional support and using iced packs, and cold water showers to decrease his high temperature, and we used 500 mg i.v. of paracetamol occasionally.

On his 15th day of hospitalization, liver enzymes keep decreasing; meanwhile, direct bilirubin was elevated to 11.2 mg/dl. One week later, ALT was 123 U/l (normal: 7–55), AST was 96 U/l (normal: 8–48), and direct bilirubin decreased to 8.2 mg/dl, as the patient was under phototherapy.

After 4 weeks of hospitalization, our patient was feeling better and less tired and he began to eat. But his body temperature

Table 2

Laboratory tests table 2.

White blood cells	12.2 K/μl (normal: 4.0–11.0)
Neutrophils	88.5% (normal: 50–70%)
Lymphocytes	10% (normal: 25–40%).
Hemoglobin	8.2 g/dl (normal: 14–18)
Platelet count	450 000K/μL (normal: 150 000–400 000)
Procalcitonin	< 0.5 ng/ml
Serum iron level	33 μg/dl (normal: 65–176)
Total iron-binding capacity (TIBC)	174 μg/dl (normal: 261–462)
Serum ferritin	520 ng/ml (normal: 12–300)
Albumin	2.6 g/dl (normal: 3.5–5.5)
Alanine transferase (ALT)	8546 U/l (normal: 7–55)
Total bilirubin	4.9 mg/dl
Direct bilirubin	3.8 mg/dl
Indirect bilirubin	1.1 mg/dl
Ammonia at	130 μ/dl (normal: 15–45 μ/dl)
Aspartate transferase (AST)	7894 U/l (normal: 8–48)
Lactate dehydrogenase (LDH)	980 U/l (normal: 14–280 in adults)
Erythrocyte sedimentation rate (ESR)	70 mm/h (normal: 0–20)
C-reactive protein (CRP)	29 mg/l (normal: <6)
Triglyceride concentration	132 mg/dl (normal <150)
Hepatitis A, immunoglobulin M (IgM)	3.19 (< 0.80 nonreactive, 0.80–1.20 borderline reactive > 1.20 reactive)
Urinalysis	Normal
Blood and urine cultures	Negatives

remained high, ranging from 38.5°C to 39.2°C. ALT was 98 U/l (normal: 7–55), AST was 74 U/l (normal: 8–48), and direct bilirubin decreased to 6.8 mg/dl. Immunoglobulin M (IgM) antibody against Hepatitis A was positive but decreased to 2.89.

As he had a persistent fever and arthralgia, we prescribed Anakinra 100 mg/sub-cutaneous alternative therapy (every other day). Later, after 2 weeks of Anakinra administration, the patient became clinically better, with normal laboratory tests.

Our study is compatible with the Surgical Case Report (SCARE) Guideline[8].

This case is submitted on the research registry dashboard by number researchregistry9184[9].

Discussion

SJIA affects people less than 16 years of age. Females are consistently found to be at a higher risk than males, and the oligoarticular subtype was found to be predominant[10]. Our patient is a 14-year-old male with polyarticular type.

It is typically presented by a daily quotidian fever, a salmon-colored skin rash, and arthritis, with leukocytosis and elevated acute phase reactants, while organ manifestations may include serositis and myocarditis, lymphadenopathy, hepatosplenomegaly[3]. Our patient had fever and arthritis associated with leukocytosis and elevated acute phase reactants.

Liver abnormalities are uncommon in sJIA. Acute liver failure may develop a few months after the onset of sJIA, due to macrophage activation syndrome (MAS), drugs, in particular, nonsteroidal anti-inflammatory drugs. Well-activated intrahepatic macrophages/Kupffer cells are associated with acute liver failure ALF in sJIA[11].

MAS is characterized by an uncontrolled activation and proliferation of macrophage and T lymphocytes. It may present with continuous fevers, fatigue, headaches, mental confusion, hemorrhage, lymphadenopathy, and hepatosplenomegaly. Main laboratory findings include the following: cytopenias ($<4\times10^9$/l), decreased platelet count ($<262\times10^9$/l), hypofibrinogenemia (≤2.5 g/l), and elevated aspartate aminotransferase levels (>59 U/l). Although bone marrow aspirates are not the gold standard for the diagnosis of MAS, bone marrow aspirates did not show the finding of hemophagocytosis[12]. Our patient had clinical findings compatible with MAS, but at the same time, it may be due to sJIA. Our patient had no cytopenia or thrombocytopenia. We were unable to perform a liver biopsy due to the parent's refusal.

GCs are the first-line treatment for sJIA, but their long-term side effects have increased the use of biologics[4]. Our patient was on 5 mg/day of Predlone.

Increased use of biologics such as tocilizumab and anakinra, decreased the use of GCs and may lead to improved outcomes in sJIA patients[5,6], as we did.

The most common adverse events in patients on Tocilizumab are runny or stuffy nose, sore throat, sinus infection, headache, high blood pressure, and injection-site reactions. Rare, more serious side effects include infections and gastrointestinal perforations. Our patient had no adverse side effects during the 1-year treatment of tocilizumab. Serious liver injuries induced by tocilizumab, include acute liver failure, hepatitis, and jaundice[7]. This risk is increased when it is used in combination with potentially hepatotoxic drugs (e.g. methotrexate)[6]. Tocilizumab may stay in your body for about 3–13 weeks. Our patient had stopped methotrexate treatment when he started tocilizumab.

We did not find any data about the time of using these treatments together or their doses that trigger acute liver failure or hepatitis.

IL-6 blockade caused by tocilizumab may also limit other IL-6-dependent immune protective and organ regenerative processes, such as resistance against serious viral infection and activation of signaling for liver regeneration following hepatic insult, possibly leading to adverse events[13].

Anakinra is a recombinant human IL-1 receptor antagonist and it has an approved indication for sJIA[14]. Although there have been consolidated data on the efficacy of anakinra in treating GC-dependent patients with sJIA[14], and data on anakinra as first-line monotherapy in patients with new-onset sJIA[15].

Although acute infections with the hepatitis A virus in children are self-limited, 0.1% of patients progress to fulminant hepatic failure that spontaneously Z recovers in 40% of cases[6,16]. Defining the root cause of ALF is ambiguous. Hepatitis A and E account for an enormous percentage of cases worldwide of acute liver failure, with a mortality rate exceeding 50%, especially in developing countries[16].

A patient with fulminant hepatitis begins to deteriorate rapidly and may present with confusion (hepatic encephalopathy). This is seen in patients with chronic liver disease or people during pregnancy. There is even a risk of coma and liver and kidney failure[6,16]. Our patient had mental confusion.

Acute liver failure requires a multifaceted approach to management, which involves addressing the underlying cause, monitoring for progression, treating complications, managing hemodynamic stability, and providing nutritional support[17,18]. Our patient had recovered.

No data are available concerning the coexistence of hepatitis A and sJIA. We found two cases concerning ALF presented with other manifestations of sJIA in a 4-year-old female, and in 5-year-old male children[11].

Our case was the first case presenting with fulminant Hepatitis A in an sJIA patient treated with tocilizumab, which had recovered, and we initiated Anakinra as a treatment.

Conclusion

Further follow-up and cohort studies are needed to find the exact prevalence and coexistence of fulminant Hepatitis A in the course of sJIA treated with tocilizumab.

Ethical approval

It is waived at our institution (Faculty of Medicine of Damascus University) because it is a case report not a study.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

M.K.: described the case and collected the clinical data, reviewed, and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest disclosures

The authors declare that they have no conflicts of interest.

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None.

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