

High procalcitonin is a marker of activity in Adult onset of still's disease

Adult Onset Still's Disease (AOSD) is a rare inflammatory disorder characterized by the classical clinical triad of a daily high spiking fever, arthritis, and an evanescent rash. Diagnosis is clinical and requires exclusion of infectious, neoplastic, and other autoimmune diseases. High procalcitonin level in patient with Pyrexia of unknown origin is misleading of systemic infection and it is normalized after corticosteroid therapy.

A 22 years old Egyptian man presented by acute appendicitis associated with high spiking rash, an evanescent rash, and leukocytosis and underwent an appendectomy. One-week postoperative, He developed acute hepatitis and high procalcitonin level complicated by severe hyperferritinemia as well as haemophagocytosis. After exclusion of sepsis and other causes of liver disease (infection, metabolic, autoimmune hepatitis, malignancy, lymphoma), the diagnosis of AOSD complicated by severe hepatitis and haemophagocytosis is more likely. Corticosteroid-induced clinical remission with a resolution of fever, rash and arthritis and induced rapid normalization of liver function and reduction of ferritin level. Cyclosporine was added as maintenance therapy but the patient developed polyuria, hypocalcemia, and hypercalciuria, after stopping cyclosporine, urine output and calcium level became normal by one week after cessation of cyclosporine. Severe hepatitis and very high ferritin could be the only manifestation of disease activity of AOSD. Therefore, monitoring of liver function, blood picture, and ferritin level even after resolution of clinical symptoms of AOSD. Prompt initiation of corticosteroid can improve liver function and blood picture and prevents liver failure, bone marrow suppression, and death. High procalcitonin level was misleading of sepsis in AOSD. It is proven that the procalcitonin level is elevated in autoimmune diseases especially ASOD and related to hyperferritinemia.

Keywords: procalcitonin • adult onset still's disease • epstein-Barr virus • cytomegalovirus

Case report

After consent was taken from the patient A 20-year old male admitted in December 2017 by acute onset of high-grade fever, watery diarrhea associated with vomiting. On examination, a patient is lethargy and generalized abdominal tenderness more on right iliac fossa. Laboratory investigation revealed leukocytosis and high inflammatory markers. Ultrasonography of abdomen is normal, non-contrast CT revealed acute appendicitis, and appendectomy was done. Postoperative, first-day patient is well and fever subsides, the second-day patient is feverish (40 c), transient rash on back and upper chest. Third generation cephalosporin 2 gram /day, metronidazole 1500mg/day was started for suspected infectious cause without any improvement. Sepsis workup was done, blood, urine, wound cultures were sterile .chest x-ray and ultrasonography was normal. The patient denied smoking tobacco, use of alcohol, herbal supplements, or recreational

drugs. He had no recent travels or sick contacts. There was no family history of autoimmune diseases.

After one week of admission, a patient is still feverish (40 °^), fever is spiking more in evening and late night. He developed a sore throat, cervical lymphadenopathy, and arthritis in both temporomandibular joints and both ankle joints, jaundice. Laboratory tests revealed markedly increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), leukocytosis, severe liver enzymes elevation, direct hyperbilirubinemia, hypoalbuminemia, coagulopathy, very high ferritin levels (165000 ng/ml). Serology for viral hepatitis A, B, C, and E as well as markers for autoimmune and metabolic liver diseases was negative. FMF gene was heterozygous. Toxoplasma IgM, IgG were negative [1].

Tests for Epstein-Barr virus (EBV), cytomegalovirus (CMV), human

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immunodeficiency virus, Brucella, typhoid, and parvovirus were negative, as well as tests for antinuclear antibodies (ANA), rheumatoid factor (RF), anti-citrullinated peptide antibodies (ACPA), anti-double strand DNA and anti-neutrophil cytoplasmic antibodies (ANCA). Protein electrophoresis, immune-electrophoresis, complement levels, and urinalysis were normal. Clostridium difficile toxin was negative. Repeated thoracoabdominal CT scans and CT enterocolonography showed hepatosplenomegaly, mild free ascites, and mild bilateral pleural effusion.

A clinical diagnosis of AOSD was made based on spiking fever, skin rash, arthritis, and hyperferritinemia, in the absence of connective tissue diseases, infectious diseases, and malignancy. For this, the patient received methylprednisolone pulse therapy of 750 mg/day for 3 days with rapid resolution of fever, arthritis, and rash, and improvement in ESR, CRP, and liver enzymes. After 3 days from a corticosteroid, the patient developed thrombocytopenia. BM aspirate showed moderate hypercellularity, neutrophilic hyperplasia with toxic granulation, no leishmania or hemophagocytosis. Then the patient is on prednisolone 60 mg/day. Later, the patient is well clinically and liver enzymes are near to normal but patient develops pancytopenia (normocytic normochromic anemia with HB 8, WBC $0.8/\text{mm}^3$ with absolute neutropenia, platelets $50/\text{mm}^3$), hyponatremia, hypertriglycerides, normal ESR. Bone marrow biopsy was done and showed marked hypocellularity (25%) and characteristic hemophagocytosis. No abnormal lymphocytes in the bone marrow were found (Table 1).

Macrophage activation syndrome secondary to AOSD was diagnosed and according to HLH 2004 protocol, cyclosporine at 300 mg/day with high dose steroid (Dexamethasone 24 mg IV daily) were given together with improvement and normalization of CBC. Incidentally patient developed polyuria (9 liters per day) and new onset of hypocalcemia and hypercalciuria. Laboratory investigation of hypocalcemia showed normal PTH, normal phosphorous, normal alkaline phosphatase and Vit D. after stopping cyclosporine,

calcium level in blood and urine output were regained to a normal level. We down titrated corticosteroid through one month to 20 mg prednisolone and maintain on hydroxychloroquine 400mg/day and azathioprine 100 mg/ day.

On his follow-up examination, there was rapid normalization of liver enzymes and functions, blood picture as well as in ferritin levels, within the next 3 weeks. This effect was sustained during his more than 2 months follow-up despite the reduction in Prednisone dose (5 mg/day).

Discussion

Our patient fulfilled all major (high fever, leukocytosis, rash, arthritis) and most of the minor criteria (a sore throat, splenomegaly, elevated liver enzymes, and absence of ANA or RF) of AOSD based on the Yamaguchi criteria. The patient developed severe liver disease with incredible ferritin and transaminases elevation and severe hepatitis. The patient developed severe liver disease with incredible ferritin and transaminases elevation and severe hepatitis.

AOSD is a rare condition with unknown etiology. Advances in immunology explored the pivotal role of cytokines in AOSD pathogenesis. Th1/Th2 cytokine imbalance, in favor of Th1, is thought to play a key role in the pathogenesis of AOSD, followed by increased production of interleukin (IL)- 2, IL-18, interferon (IFN)- γ , and tumor necrosis factor (TNF)- α that, in turn, promote IgG production, activate macrophages and natural killer-cells. IL-18 induces other inflammatory cytokines production, enhances immune cells recruitment to the site of inflammation, and generates tissue damage. Very high circulating IL-18 levels (10 to 100 fold) were found in patients with AOSD compared with other systemic disorders, such as rheumatoid arthritis and systemic lupus erythematosus; IL-18 closely correlated with AOSD activity and severity, and ferritin levels [2].

Elevated serum ferritin levels are characteristic for AOSD, it is unclear whether high ferritin levels have a pathogenic significance or simply reflect acute and severe inflammation. High ferritin levels may be found in a variety of pathological conditions, such as infections, chronic liver and kidney diseases, storage diseases, malignancies, and iron overload. However, serum ferritin concentrations rarely exceed values of >3000 ng/ml in these conditions. Extremely high ferritin titers are highly suggestive of AOSD; levels $>10,000$ ng/ml have been described only after multiple blood transfusions,

Table 1. Laboratory investigation.

Hemoglobin	10.4 g/dl	Ferritin	110843 ng/dl
WBC	1.64 (10^3 UL)	Fecal calprotectin	40 ug/g
Platelets	80 (10^3 UL)	Direct Bilirubin	6.95 mg/dl
Urea	85 mg/dl	Albumin	2.31 g/dl
Creatinine	1.23 mg/dl	LDH	4045 U/L
ALT	950 U/L	INR	2.21
AST	350 U/L	ESR	5 mm/hr
Triglyceride	620		

in the hemophagocytic syndrome (HPS), and in AOSD patients with severe liver damage [3]. Liver involvement is well described in AOSD [4,5]. Elevated liver enzymes can range from mild elevation to fulminant [6] and even fatal liver failure requiring liver transplantation [7,8].

In some patients, liver disease is a part of AOSD itself; in other patients, it could be attributed to other causes. Severe liver disorder has been reported in AOSD with concomitant viral infections, such as EBV [9], CMV [10] and parvovirus [11].

One of the most urgent and difficult conditions in the course of AOSD is Hemophagocytosis (HPS). Hyperpyrexia, enlarged liver and spleen, cytopenia, and high ferritin levels characterize it. HPS is due to proliferation and activation of macrophages with hemophagocytosis throughout the reticuloendothelial system. HPS is reported in up to 12 % of AOSD patients. It is often resistant to treatment and could become a life-threatening complication. The absence of cytopenia and hemophagocytosis (on liver biopsy), exclusion of viral infections, drug toxicity, and lymphoma allowed us to address severe hyperferritinemia and liver dysfunction to AOSD [12].

Hitherto, 17 severe hepatitis cases in association with AOSD have been reported in the English literature [13-26]. The course of AOSD in our patient was complicated by severe hepatitis. Treatment with corticosteroids allowed achievement of clinical remission of AOSD. High and rapidly increased ferritin levels preceded the development of severe hepatitis. Hyperferritinemia serves as a marker of disease activity in AOSD. In this case, it was the only marker of disease activity and a prelude to liver impairment. Very high ferritin levels of >10,000 ng/ml in AOSD patients may serve a marker of uncontrolled disease and indicate possible development of hepatic failure or HSP [27].

In our case, increased concentrations of procalcitonin suggested a bacterial infection. In patients with systemic diseases, elevated concentrations of procalcitonin cannot serve as a marker of bacterial infection. In fever of unknown origin, procalcitonin does not allow a clear differentiation between bacteria and noninfectious etiology [28]. Nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids are the main therapies of AOSD. In refractory cases, treatment with DMARDs, such as methotrexate (MTX), AZA, CsA, leflunomide,

high doses of immunoglobulins, and cyclophosphamide may be used. In severe cases, not controlled with combined therapies, the use of biologic agents targeting pro inflammatory cytokines may be justified. Anti-TNF- α agents (infliximab, adalimumab, and etanercept) have been reported to induce clinical response and decrease inflammatory markers in AOSD refractory to standard regimens. Tocilizumab (IL-6 receptor monoclonal antibody), anakinra (recombinant IL-1 receptor antagonist), rilonacept (IL-1 trap molecule inhibitor) and canakinumab (anti-IL-1 β monoclonal antibody) have been shown to induce remission of AOSD in a several case series; biological agents in addition to AOSD control allowed the reduction of corticosteroid doses [29-32].

Cyclosporine (CsA) has been reported to be effective in some cases of AOSD with severe hepatitis and HPS; it was used in combination with corticosteroids and led to dramatic and stable improvement in ferritin levels and liver dysfunction within 3 weeks. CsA is a calcineurin inhibitor that targets T cells and prevents cytokine production. The optimal dose and duration of CsA treatment in AOSD should be estimated carefully. It is unclear whether the disease can remain in remission with no or minimal treatment. Marchesoni et al. reported that treatment with CsA could be discontinued in only 1/6 patients with AOSD, although it was possible to reduce the dose in another three patients [33,34]. CsA-induced renal tubular acidosis may enhance hypercalciuria, as pH is an important regulator of distal calcium reabsorption [35].

Conclusion

High procalcitonin in AOSD is a marker of activity rather than sepsis. Also, it related to the level of ferritin. Therefore, monitoring of ferritin levels and procalcitonin level is strongly recommended in AOSD patients, even in cases with clinical improvement. Treatment of severe liver impairment in the context of AOSD is challenging and is mainly aimed at treating AOSD. In the light of possible DMARD-induced liver toxicity, close monitoring of liver function. Corticosteroid is treatment of choice. It may rapidly control liver inflammation, improve liver function, prevent progression to liver failure, and allow corticosteroids dose reduction.

Disclosure of Interest

None declared

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