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# Electroconvulsive Therapy as a Potential Trigger of Adult Onset Still's Disease

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## Abstract

**Introduction:** Adult onset Still's disease (AOSD) is an inflammatory disorder of unknown etiology. Macrophage activation syndrome (MAS) is a complication of AOSD and may present with multiorgan failure including cerebral involvement.

**Clinical presentation:** We describe a 43-year-old female patient with major depression treated with electroconvulsive therapy (ECT). She presented with febrile pharyngitis, arthralgia, rashes, lymphadenopathy, hepatosplenomegaly, liver failure and aseptic meningitis. Elevated serum ferritin and negative blood cultures were consistent with the diagnosis of AOSD complicated by MAS. The patient was treated with corticosteroids and anakinra and recovered rapidly.

**Conclusion:** The case highlights aseptic meningitis, depression and multiorgan failure as a feature of AOSD/MAS possibly triggered by ECT. Anakinra is an effective treatment in severe MAS.

**Keywords:** Adult's onset still disease; AOSD; Aseptic meningitis; Electroconvulsive therapy; Multiorgan failure; Septicemia

## Introduction

Adult's still disease (AOSD) is an autoinflammatory disease presenting mostly in young adults. Yamaguchi's criteria has been proposed as a diagnostic criteria. Major criteria are fever, arthralgia, skin rash and elevated neutrophils, minor criteria are sore throat, lymphadenopathy, hepato/-splenomegaly, abnormal liver function and negative tests for antinuclear antibodies (ANA) and rheumatoid factor (RF). Several other features such as pleuritis, pericarditis, abdominal pain and liver failure have also been described [1]. Bacterial sepsis is an important differential diagnosis in patients with a suspected AOSD and organ failure. Serum ferritin has been proposed as a marker to differentiate between septicemia and AOSD [2].

Macrophage activation syndrome (MAS) can be a complication in patients with AOSD which is a potentially life threatening condition. MAS is characterized with hyperactivated mononuclear cells and hyper-phagocytosis of blood cells which leads to severe pancytopenia. Hyperphagocytosis and MAS can be confirmed with a bone marrow aspiration biopsy. However, since phagocytosis cannot be confirmed in every bone marrow biopsy, MAS remains a clinical diagnosis in the majority of patients [3].

Cerebral involvement is a rare complication of AOSD/MAS with unknown etiology [4]. Electroconvulsive therapy (ECT) may be a trigger for cerebral involvement in AOSD/MAS.

## Case Report

A 43-year-old female patient presented at the emergency department of a tertiary care center. She had suffered from severe episodes of major depressive disorder (MDD) for nearly two decades. Until six weeks before presentation, she had been treated with 12 cycles of electroconvulsive therapy (ECT) for MDD and concomitant venlafaxin, lamotrigine and valproate.

ECT led to significant improvement in symptoms of depression. Two weeks after her last ECT, she developed gradually worsening new onset arthralgia of her knees. Her general practitioner (GP) prescribed insoles without improvement of the arthralgia.

Seven days prior to admission, she developed a sore throat and spiking temperatures up to 40°C. Her knee arthralgia had worsened significantly, for which her GP prescribed doxycycline which neither relieved the fever nor the pharyngitis. She subsequently developed a maculo-papular rash on her body trunk (Figure 2) which had been considered as an allergic reaction secondary to doxycycline and prednisolone, 1 mg/kg, had been administered. However, the clinical course deteriorated rapidly in the following days, with worsening of her rashes, dysphagia and dyspnea and she was admitted to hospital.

Physical examination on admission revealed dyspnea with fine crackles in both lungs, tachycardia, a maculopapular rash on the body trunk, palpable cervical lymph nodes and an acute pharyngitis of the oropharynx. Her body temperature was 41.0°C.

Bacterial septicemia of pulmonary origin was suspected and the patient was started on meropenem and clarithromycin. A whole-body CT scan on the second day after admission revealed low volume ascites and bilateral pleural effusions. Echocardiography showed a moderate pericardial effusion.

Initial laboratory studies revealed an elevated white blood cell count (WBC) of 15,700/µl, lymphocyte count of 500/µl, hemoglobin level (Hb) of 13.4 g/dl and a platelet count (PLT) of 359,000/µl. Lactate dehydrogenase levels were 1788 U/l, total bilirubin 2.6 mg/l, international normalized ratio (INR) 1.51, C-reactive protein was 157.3 mg/l and procalcitonin was 1.27 mg/dl (Table 1). Extensive bacteriology cultures and virology all proved negative. Anti -nuclear antibodies (ANA) and anti-neutrophil-cytoplasmic antibodies (ANCA) were negative and complement C3 and C4 were low to normal. In the clinical course liver and kidney values deteriorated. Aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) peaked at 2749 U/l

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and 9191 U/l respectively 4 days after admission. Liver synthesis and excretion deteriorated subsequently.

Four days after admission, the patient developed confusion and respiratory distress and was endotracheally intubated for respiratory failure and hypercapnia. She had repeated generalized seizures which responded well to clonazepam. She was started on levetiracetam maintenance therapy.

We performed a cranial magnetic resonance tomography which showed T2 FLAIR hyper-intensive signals at the sulcus (Figure 1). For suspected encephalo-meningitis, acyclovir was added to therapy.

A lumbar puncture revealed an elevated cell count 106/µl (60% lymphocytes, 30% neutrophils) and elevated total protein (0.94 g/dl) in cerebrospinal fluid (CSF). CSF microbial and virological cultures were negative, and findings were consistent with aseptic meningitis. Acyclovir was discontinued.

| Variables | | Normal range |
|---|---|---|
| White blood cell count (WBC) | 15,700/µl | 4,000-10,000/µl |
| Lymphocyte count (LC) | 500/µl | |
| Hemoglobin level (Hb) | 13.4 g/dl | 12-15 g/dl |
| Platelet count (PLT) | 359,000/µl | 150,000-440,000/µl |
| Lactate dehydrogenase (LDH) | 1788 U/l | <308 U/l |
| Total bilirubin | 2.6 mg/dl | <1.0 mg/dl |
| International normalized ratio (INR) | 1.51 | <1.2 |
| C-reactive protein (CRP) | 157.3 mg/l | <5 mg/l |
| Procalcitonin (PCT) | 1.27 ng/ml | <0.05 ng/ml |
| Aspartate aminotransferase (ASAT) | 162 U/l | <50U/l |
| Alanine aminotransferase (ALAT) | 295 U/l | <50 U/l |
| Gamma-glutamyl transpeptidase (gGT) | 520 U/l | <35 U/l |

**Table 1:** Laboratory values on day of admission.

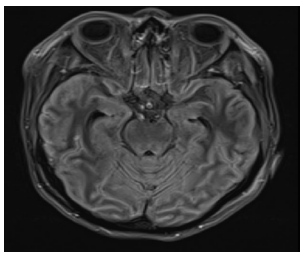

**Figure 1:** T2 FLAIR hyperintensity at the sulci indicating meningitis.

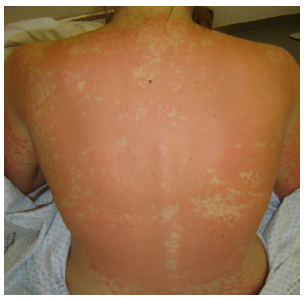

**Figure 2:** Maculopapular rash on patient's back.

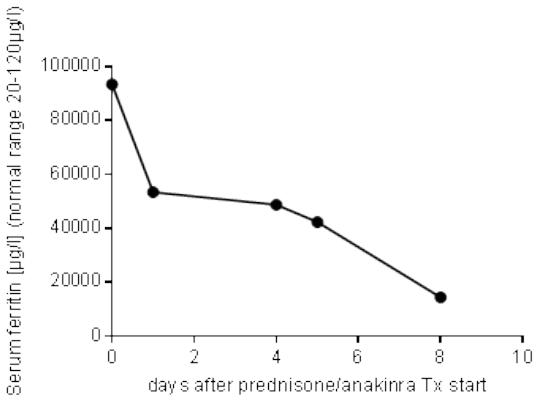


**Figure 3:** Serum ferritin level after treatment initiation.

Serum ferritin on day two after admission was severely elevated with 93,396 µg/l (<300 µg/l). At this point the patient fulfilled 8 out of 8 of Yamaguchi's criteria. The diagnosis of AOSD and MAS was confirmed and she treated with prednisone, 100 mg, and anakinra, 100 mg, per day.

After treatment initiation, the patient recovered rapidly. Kidney and liver function returned to her baseline values and seizures no longer occurred. Her ferritin serum level quickly returned to baseline (Figures 2 and 3). She was extubated after four days of mechanical ventilation.

She was discharged from hospital day 14 after treatment began. Anakinra was tapered on outpatient service to 100 mg subcutaneously every second day and prednisone was discontinued. She remains recurrence free 12 months after initial presentation.

## Discussion

AOSD is an autoinflammatory syndrome which can present with multiorgan failure and sterile meningitis. We describe a patient with MDD that was refractory to oral medication and ECT was initiated. Two months later the patient developed AOSD, MAS, multiorgan failure and sterile meningitis with seizures. At presentation, she fulfilled Yamaguchi's criteria for AOSD and recently proposed criteria for MAS in juvenile rheumatoid arthritis [5,6]. CNS involvement is a rare complication and has been estimated to occur in 7% of patients in an early case series on AOSD [7]. There are several case reports with AOSD patients presenting with concomitant aseptic meningitis [4,8]. The etiology of AOSD/MAS remains unclear. Viral infections are discussed as potential triggers in genetically predisposed patients [9,10]. In our patient, arthralgia began shortly after ECT. Single and repeat ECT has been shown to induce a transient immune response due to microglial activation leading to an increase of granulocytes, natural killer cells and monocytes in peripheral blood. 10 ECT also leads to an increase of interleukin-6 (IL-6), interleukin-1β (IL-1β) and tumor necrosis factor α (TNFα) in peripheral blood [11,12]. In comparison to proinflammatory cytokine blood levels in infectious or autoimmune disorders, the magnitude of elevation after ECT is small.

In contrast, in AOSD, these cytokines are largely elevated in peripheral blood. In particular, IL-1β has been implicated in AOSD etiology [13]. IL-1 antagonists (Anakinra) induced more beneficial responses than disease modifying anti-rheumatic drugs (DMARD) in patients with AOSD [14]. In case series of AOSD complicated by MAS, anakinra leads to complete recovery in most patients [15].

In this case report, we hypothesize that the proinflammatory response to ECT may have triggered AOSD with meningeal involvement

in our patient. We performed a comprehensive literature review. Until now, there is no published association between ECT and autoimmune disorders. ECT has been successfully used for the treatment of neuropsychiatric lupus erythematosus and autoimmune encephalitis but literature is limited to case reports and focuses on the psychiatric outcome [16,17]. The role of the immunomodulatory effects of ECT in these inflammatory disorders remains unclear. Ultimately, we cannot exclude a mere coincidence of ECT, meningitis and AOSD. It is possible that an unknown viral pathogen triggered AOSD and meningitis.

## Conclusion

This is the first case report to describe a potential link between AOSD and ECT. AOSD can mimic severe septic shock and multiorgan failure with cerebral involvement. Treatment with anakinra leads to a rapid and sustained recovery.

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