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INTRAVENOUS ANAKINRA FOR TREATING MACROPHAGE ACTIVATION SYNDROME IN ADULT-ONSET STILL'S DISEASE

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ABSTRACT

Background: Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disease characterized by fever, rash, arthritis, and multi-organ involvement. Macrophage activation syndrome (MAS), a serious complication of AOSD, poses significant diagnostic and therapeutic challenges.

Case Presentation: A 32-year-old male was diagnosed with AOSD in 2020 after being hospitalized for a fever of unknown origin and elevated liver enzymes. The patient was initially treated with corticosteroids and methotrexate but subsequently discontinued both treatment and follow-up. In September 2023, he presented with fever, sore throat, and elevated inflammatory markers. After screening for infections, methylprednisolone (MP) treatment was initiated because of AOSD activation. The following day, the patient was admitted to the intensive care unit due to an altered state of consciousness. Brain magnetic resonance imaging revealed brainstem involvement. Empirical treatments were initiated, including intravenous MP, and immunoglobulin therapy. Due to suspected macrophage activation syndrome (MAS), anakinra (ANA) infusion was initiated. Significant improvement was observed after the ANA infusion.

Conclusion: This case highlights the complex management of severe AOSD complications, emphasizing the role of early recognition, aggressive therapy, and multidisciplinary care in improving outcomes.

KEYWORDS

Intravenous anakinra, adult-onset Still's disease, macrophage activation syndrome

LEARNING POINTS

- Macrophage activation syndrome (MAS) is a serious complication of adult-onset Still's disease characterized by systemic inflammation. Early recognition and prompt initiation of treatment are crucial due to the high mortality rate associated with MAS, especially when neurologic symptoms are present.
- Clinicians should not delay treatment pending confirmatory diagnostic tests when MAS is suspected, as early intervention can significantly impact patient outcomes.

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- Anakinra, an interleukin-1 inhibitor, is typically administered subcutaneously but has shown promise when administered intravenously, particularly in severe cases of MAS.

INTRODUCTION

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder characterized by fever, rash, arthritis, and multi-organ involvement. The management of AOSD primarily aims to control inflammation and prevent disease-related complications. Macrophage activation syndrome (MAS) is a type of hemophagocytic lymphohistiocytosis occurring in patients with AOSD, often triggered by viral infections and occasionally by autoimmune or autoinflammatory causes[1]. The diagnosis of MAS requires a comprehensive approach involving clinical evaluation, laboratory tests, and imaging studies.

Prompt recognition and aggressive management of MAS is required. The interleukin-1 (IL-1) cytokine plays a central role in the pathogenesis of MAS, triggering and perpetuating the hyperinflammatory state observed in affected individuals. Inhibition of IL-1 is acknowledged as the gold standard treatment for AOSD. Subcutaneous anakinra (ANA) is recognized as a valid therapy for AOSD, demonstrating a favourable safety profile. It is recommended to be administered subcutaneously or intravenously (IV) in high doses in patients with MAS[2]. Herein, we present a patient with severe AOSD developing MAS, who was treated with IV ANA and conduct a review of relevant literature.

CASE DESCRIPTION

A 32-year-old male was diagnosed with AOSD in 2020 after being hospitalized for a fever of unknown origin and elevated liver enzymes. Treatment with corticosteroids (CS) and methotrexate was initiated, followed by tapering the CS dose. However, the patient discontinued his medications and stopped attending follow-up appointments as he felt clinically stable. Upon retrospective examination, it was found that liver enzyme levels and C-reactive protein (CRP) remained elevated during the year without follow-up. The patient presented to rheumatology again on September 12, 2023, with a 1-week history of fever, sore throat, and elevated inflammatory markers. Abdominal ultrasonography showed hepatomegaly. Results of testing for viral and bacterial infection markers and coronavirus disease (COVID-19) were negative. Despite initiating methylprednisolone (MP) therapy at 1 mg/kg/day, the patient developed neurological symptoms and was urgently hospitalized on September 19th. During the neurological examination, it was observed that the patient exhibited inward deviation of the left eye, accompanied by limited outward gaze. Additionally, the patient reported diplopia and presented with horizontal nystagmus. The laboratory results for the patient were as follows: erythrocyte sedimentation rate (ESR) 77 mm/hour, CRP 199 mg/l, haemoglobin 7.6 g/dl, procalcitonin 0.2 µg/l, aspartate aminotransferase (AST) 154 U/l, alanine aminotransferase (ALT) 309 U/l, ferritin 4517 µg/l, triglycerides 417 mmol/l, fibrinogen 900 mg/dl. Serum electrolytes, creatinine and urine tests were normal. Brain magnetic resonance imaging (MRI) showed an expansive lesion affecting the brainstem *(Fig. 1)*. Due to the lesion's location, lumbar puncture was deemed inappropriate. The patient was admitted to the intensive care unit (ICU) due to an altered state of consciousness. Viral infection panels and COVID-19 tests were repeated. Blood cultures were taken. Although infection was not initially prioritized, empirical IV antibiotics and antiviral therapy were initiated. IV-MP

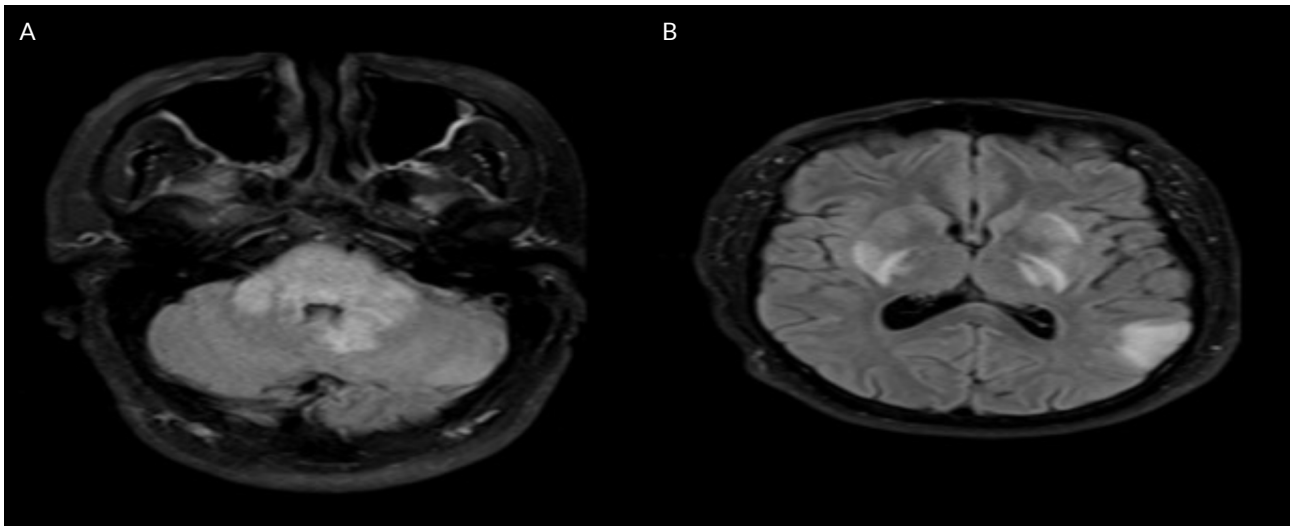

Figure 1. Brain magnetic resonance imaging. A) In the axial FLAIR-weighted sequence, hyperintense lesions with expansive features were observed in the pons bilaterally involving the cerebellar peduncles and extending into the left cerebellar hemisphere; B) Hyperintense lesions were observed in the bilateral basal ganglia at the level of the posterior limb of the internal capsule and in the cortex-subcortical white matter of the left parietal region.

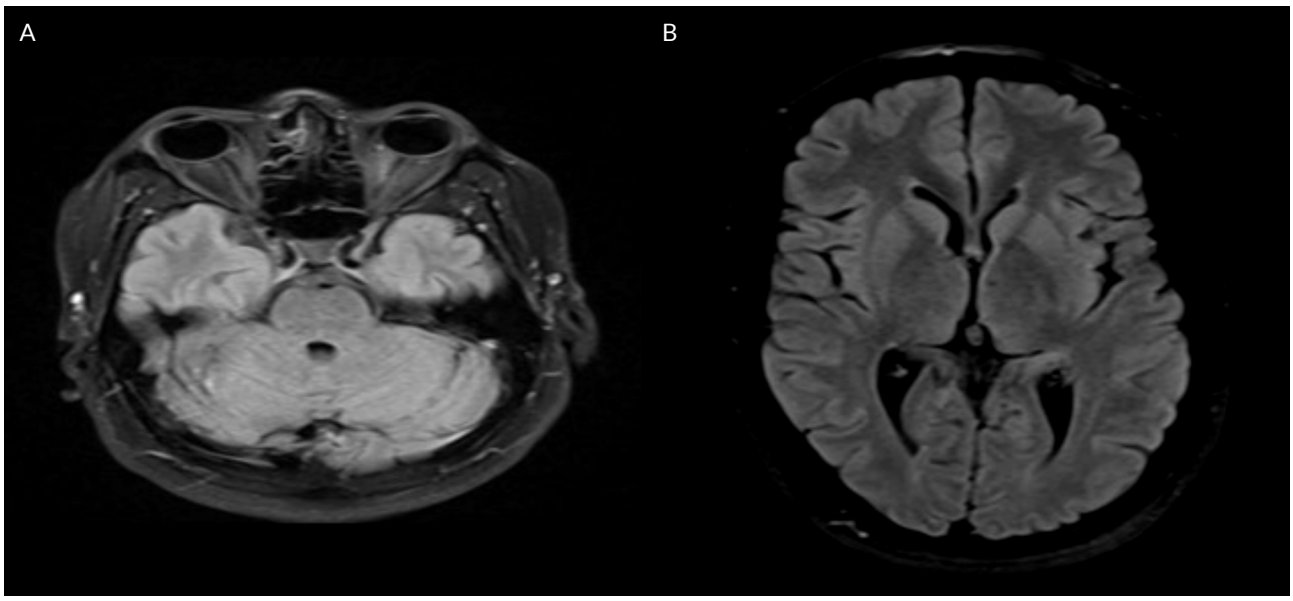

Figure 2. Brain magnetic resonance imaging at the 2-month follow-up after treatment. A) It was observed that the lesion detected at the level of the pons had disappeared; B) The disappearance of the lesions observed in the left internal capsule and left parietal region of the basal ganglia was observed.

and dexamethasone were initiated for brain oedema, along with IV immunoglobulin (IVIG). On the third day in the ICU, the patient developed bradycardia, revealing a complete atrioventricular (AV) block. Dobutamine infusion at 2 mcg/kg/min was started but the bradycardia did not resolve, leading to femoral pacemaker insertion. With a presumptive diagnosis of MAS, the patient was initiated on ANA infusion at a rate of 0.5 mg/kg/hour (total 700 mg/day). Clinically significant improvement in the patient's consciousness was observed at the 12th hour after infusion. The ANA infusion was continued for 3 days. Significant improvement was observed after the ANA infusion, and the patient was transferred from the ICU to the ward. ANA was continued as 4x100 mg sc for 1 week and 2x100 mg sc in the follow-up. Bone marrow biopsy could not be performed because the patient's vitals were not stable in the ICU. However, due to a progressive decline of the haemoglobin level, a bone marrow biopsy was eventually performed, revealing a cellular ratio of 40%, with preservation of the myeloid/erythroid series and no evidence of hemophagocytosis. After 10 days of IV-MP, the patient was discharged with oral MP and ANA. Brain MRI was normal in the second month *(Fig. 2)*. The patient is currently in stable condition.

DISCUSSION

This article presents the treatment process of a patient with AOSD who developed neurological involvement related to MAS. MAS is considered the most severe complication of AOSD, and it is estimated to occur in 10% of patients with AOSD[3]. In various studies, uncontrollable disease, splenomegaly, pericarditis, and elevated levels of liver function tests and ferritin have been identified as factors associated with the occurrence of MAS in AOSD[4]. Distinguishing MAS from other conditions like systemic infection and malignancy can be challenging due to its non-specific clinical features. Several criteria have been developed to help diagnose MAS[5,6]. However, treatment should be promptly initiated in cases with clinical suspicion regardless of whether the patient meets these criteria, as the mortality rate associated with MAS is close to 40%[7]. In the patient presented here, who had a history of AOSD, MAS was considered the primary differential diagnosis due to neurological deterioration, thrombocytopenia, elevated liver enzymes, ferritin, and triglyceride levels. A bone marrow biopsy was still performed due to the patient's severe anaemia to rule out underlying hematologic malignancies. Nevertheless, empirical anti-bacterial and anti-viral therapy were also initiated. In a patient being followed up for AOSD, if the neurological status worsens, MAS should be considered initially. For the evaluation of neurological involvement, either MRI or cerebrospinal fluid (CSF) sampling should be planned. However, these investigations should not delay empirical treatment. Since MAS is mostly seen as a complication of juvenile idiopathic arthritis, treatment recommendations for adult MAS are mostly based on paediatric literature. In the management of MAS, subcutaneous ANA therapy is a well-established approach. ANA is fast-acting and has a short half-life. Even when used at high doses in adults with bacterial sepsis (up to 48 mg/kg/day), it has been observed not to induce immunosuppression and to decrease mortality[8]. There is no study comparing subcutaneous and IV administration of ANA in MAS. However, IV administration may be preferred in time-critical situations where the rapid onset of action is needed. There may be handicaps of subcutaneous ANA administration in critically ill patients with MAS, concerns about absorption problems, or problems with multiple injections in a patient who may already have coagulopathy[1]. In a retrospective 5-patient series, 0.25-2 mg/kg/h continuous IV ANA infusion resulted in rapid serologic and subsequent clinical

improvement in adult patients with MAS[9]. In another case series, IV administration of 100 mg ANA every 6-8 hours was utilized to manage the cytokine storm associated with AOSD[10]. Tocilizumab, an IL-6 inhibitor, is recommended as a second-line treatment in the management of MAS[1]. Although IL-1 and IL-6 therapies have shown considerable efficacy in treating MAS, patients with AOSD may still develop MAS while undergoing these treatments.

CONCLUSION

IV anakinra infusion appears to be a promising therapeutic option for the management of MAS associated with AOSD. Further studies are warranted to establish its efficacy and safety profile in this context.

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