4. A CASE OF AOSD WITH ACUTE HEPATITIS DURING PREGNANCY

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Introduction: Adult onset Still’s disease (AOSD) is a systemic inflammatory disorder, characterized by quotidian fevers, arthralgia/arthritis, classical salmon pink evanescent rash and leukocytosis (>10,000 WBC/mm3). Other common features include myalgia, sore throat/pharyngitis, lymphadenopathy, splenomegaly and abdominal pain. The aetiology of AOSD is not known and a combination of genetic and environmental factors, such as infectious triggers, have been proposed to play a role in the pathogenesis. There are no diagnostic tests for AOSD. Hyperferritinaemia, of at least five times the upper limit of normal (i.e. >1000 µg/L), although non-specific, is suggestive of the diagnosis. AOSD was first described by an English physician, Sir George Frederic Still, in children, in 1896, with what is now known as systemic juvenile idiopathic arthritis (sJIA). The adult-onset version was later described by Bywaters in 1971 in a series of adult patients with similar features to the children with sJIA who did not fulfil the criteria for classic rheumatoid arthritis (RA). The annual incidence is estimated to be 0.16 cases per 100,000 based on a retrospective study carried out by Magadur-Joly et al in 1995. The differential diagnosis of AOSD is broad and requires exclusion of infection, malignancy and other systemic autoimmune and inflammatory rheumatic diseases that may present in a similar manner. Several diagnostic criteria have been proposed with the Yamaguchi’s criteria being the most widely used. (6) Presence of 5 or more criteria of which at least 2 are major, has a 96% sensitivity and 92% specificity in making the diagnosis. Hepatic dysfunction is one of the minor criteria and in this report, we aim to describe the case of a pregnant patient who presented to us with some of these typical features and acute hepatitis.

Case description: A 26-year-old female who was 30 weeks pregnant, presented with a 4-5 weeks history of high fevers, sore throat, arthralgia and salmon-coloured maculopapular rash on her trunk and proximal limbs (see images below). She was normally fit and well with a past medical history of polycystic ovarian syndrome. She was a non-smoker and a non-drinker. On examination, as well as the rash, she had evidence of synovitis in both wrists, the right knee and left ankle. She was admitted under the medical team. Her initial laboratory investigations showed anaemia with a Hb of 66 g/L and leukocytosis with a WCC of 10.7 x 10^9/L. She had evidence of hepatic dysfunction with elevated transaminases. Her ALT was 306 U/l and alkaline phosphatase was also raised at 264 U/l. Her lactate dehydrogenase was 703 U/l. There was an acute phase response with a CRP of 119 mg/L. Urine MSU showed no growth. An ultrasound scan of her liver showed patent portal and hepatic veins with no significant organomegaly. Autoimmune screen including ANA, ANCA, RF, Anti-CCP, anti-smooth muscle and anti-mitochondrial antibodies was negative. Immunoglobulins and complements were normal. Blood cultures were all negative, as were HIV and hepatitis serology and anti-streptococcal antibody titres. She had evidence of previous infection with Parvovirus and EBV. The extended viral screen revealed CMV IgG and IgM to be positive and on recommendation of the gastroenterology team, she was commenced on Valganciclovir. The obstetrics team were in agreement with the initial plan and recommended consideration of corticosteroids if a preterm delivery was to be considered. Her Liver function tests continued to deteriorate with her ALT peaking at 837. Her CMV PCR was subsequently negative placing doubt on the diagnosis of acute CMV hepatitis.

In view of the persistent acute phase response, a rheumatology opinion was sought. Ferritin levels were elevated at 996 ng/mL and a working diagnosis of adult onset Still’s disease (AOSD) was made. High dose oral prednisolone was commenced, following which her symptoms of fever, arthralgia and rash improved significantly. Despite her symptomatic improvement, her bile acid levels were still rising and therefore she underwent an emergency C-section to ensure the safety of her unborn baby. Delivery was uncomplicated and she gave birth to a healthy baby girl. Her
liver function tests started to improve on prednisolone, nonetheless a liver biopsy was organised prior to discharge. Histology initially suggested microvascular steatosis and the stains for CMV were negative with no definite features of AOSD. A second opinion on the liver biopsy, revealed mild hepatitis of undetermined cause. Over the following 6 months she was successfully weaned off the corticosteroids and has continued to do well with no symptoms of fever, rash or sore throat. An ultrasound scan of her hands and wrists after cessation of steroids has shown no active synovitis and therefore further immunosuppression with methotrexate has been deferred at present.

**Discussion:** This case report highlights pertinent issues for clinicians who manage these complex and potentially life-threatening cases of AOSD. The non-specific nature of clinical features and the absence of characteristic serological biomarkers, often makes the diagnosis a slow and elaborate process. Furthermore, clinical decision-making becomes challenging when the diagnosis is unclear at the outset and investigations are slow to be available. As described in our patient, the liver is a frequently involved organ in AOSD and indeed hepatic dysfunction is part of the Yamaguchi diagnostic criteria. The incidence of hepatic dysfunction is reported to range between 35-85%. It commonly manifests in the form of asymptomatic elevation of transaminases but more life-threatening acute live failure (ALF) can ensue in a minority of cases. The value of a liver biopsy in the diagnosis of AOSD is undetermined. Andres et al performed liver biopsies in five patients with retrospectively established diagnosis of AOSD and in none of the patients, the diagnosis was suggested or supported by histology. They concluded that a liver biopsy in the context of AOSD is of limited value. It may be useful in ruling out previously undiagnosed infections, such as Hepatitis B/C, which may be aggravated by treatments for AOSD such as corticosteroids or Methotrexate. A diagnostic dilemma arose in our patient when the level of hyperferritinaemia was not as high as anticipated. In AOSD, ferritin levels of greater than 2000ng/mL are thought to result from cytokine secretion induced by the reticuloendothelial system. However such high levels are not specific to AOSD and can also be seen in infections, neoplastic conditions, or storage disorders such as Gaucher’s disease. Ichida et al in 2014 concluded that patients with high levels of ferritin or IL-18 presented with systemic inflammatory disorders (non-RA subtype) whereas those with low levels, developed erosive arthritis (RA subtype).

**Key learning points:** The diagnosis and management of AOSD, particularly in the context of pregnancy, requires multidisciplinary expertise. Collaborative clinical decision making ensures the delivery of optimal patient care for the mother and their unborn baby. Our patient was managed by a wide range of specialties including obstetrics, rheumatology, gastroenterology and dermatology. Close multidisciplinary monitoring is essential not only during pregnancy but also in the post partum period when these patients can have flares or recurrences. It is vitally important to always use all available clinical data in the diagnostic process. The described patient in our case report was initially seen by the gastroenterologist with regard to her worsening hepatic dysfunction and a persistent acute phase response. She was also found to have a positive CMV IgM serology and therefore an initial diagnosis of viral hepatitis and arthritis was made and anti-virals were commenced. However her Liver function tests continued to deteriorate despite treatment leading to a rheumatology opinion. It was then decided that the pattern of rash and the arthritis would fit better with a diagnosis of AOSD although the hyperferritinaemia was not high as expected. Nevertheless a decision was made to treat the patient with oral prednisolone once the viral DNA PCR was found to be negative and a liver biopsy was organised to ensure that no other causes were overlooked. This case report beautifully illustrates the fact that it is paramount to always keep an open mind when managing patients with multisystem involvement as the list of differential diagnoses is often broad. Corticosteroids are generally considered to be safe in pregnancy and effective first-line treatments in AOSD. In the Gerfaud-Valentin et al study, in all cases of women with AOSD during or after pregnancy, partial or complete responses were achieved with corticosteroids and/or IVIG treatment.