

# Adult Onset Still's Disease Associated with Necrotic Leukoencephalopathy: An Unusual Presentation

Talib S H<sup>1</sup>, Bhattu S R<sup>2</sup>, Hegde Rohan<sup>3</sup>, Punde Gaurav<sup>4</sup>, Vyawahare Suraj<sup>5</sup>

<sup>1</sup>Professor & Head of Medicine, Department of Medicine MGM Medical College, Aurangabad, 431003, India

<sup>2</sup>Associate Professor, Department of Medicine MGM Medical College, Aurangabad, 431003, India

<sup>3, 4, 5</sup>Post Graduate Residents in Medicine, Department of Medicine MGM Medical College, Aurangabad, 431003, India

**Abstract:** *A rare case of adult onset still's disease with necrotic Leukoencephalopathy is described and discussed. High clinical suspicion of entity with elevated ferritin levels and hepatic enzymes in a case of PUO should be strongly considered for AOSD. The presence of seizures and imaging studies are confirmatory for necrotic leukoencephalopathy.*

**Keywords:** AOSD, High ferritin, PUO, Seizure, Leukoencephalopathy

## 1. Introduction

Adult onset still's disease is a chronic multisystem disorder of unknown etiology. Often adult onset still's disease (AOSD) present as pyrexia of unknown origin. However AOSD is a rare cause of PUO and association of AOSD with Leukoencephalopathy is further rare. The incidence is described 0.01%. The disease etiopathogenesis is still unclear. Evidences support genetic and environmental factors responsible for the disease. The present case was hospitalized with high spiking fever, polyarthralgia, skin rash and seizures. In the present case acute phase reactants were marked with elevated ESR, C reactive protein levels, hyperferritinemia and white matter abnormalities on magnetic resonance imaging. The Patient's history, clinical examination and laboratory findings, fulfill the diagnostic Yamaguchi criteria of AOSD. The response to non-steroidal antiinflammatory drugs was poor.

## 2. Case Report

A 22 yr old normotensive and nondiabetic male had been ailing past 5 months. Prior to the present hospitalization he had high grade fever, multiple joint pains and nonpruritic skin rashes over whole body for which he visited private hospitals in series for the above said problem where he received NSAID, steroids & supportive therapy without fruitful outcome. He was investigated there for rheumatological disease with rheumatoid factor, ANA, Liver function test, Anti CCP which were negative. His hemoglobin was 8.2 gm%, TLC 45,500 cu/mm, PS was negative for malarial parasites and abnormal cells. Patient presented to this hospital with high grade fever, arthralgias and rash. On enquiry patient did not give history of sore throat in preceding months. There were no orogenital ulcers, urinary symptoms & ocular features. The examination revealed well-built, oriented young patient with macular rashes all over the body. His temperature was 103F with heart rate of 86 per min, blood pressure 100/68 mmhg. Hepatosplenomegaly was present on examination. There was no lymphadenopathy. Examination further revealed full range of movement of locomotor system. Other systemic examinations were not significant. Investigations done

revealed Hb 8.4 gm%, TLC 32500, with Neutrophil 78%, Lymphocyte 18%, eosinophil 2%, and monocyte 2%. Serum ferritin level was raised to 33000 ng/ml (Normal 15-120 ng/ml). Urine examination was normal. Test for tuberculin, Widal and peripheral blood smear for malarial parasite were all negative. X-ray chest PA and ultrasonography of whole abdomen revealed no abnormality. Bone marrow examination was suggestive of microcytic hypochromic anemia. Fundus examination was normal. There were no signs of meningeal irritation. Finally patient had five major and 2 minor Yamaguchi criteria. The patient's condition partly improved with short course of steroid and NSAID. However he continue to have febrile illness despite this therapy. Antimalarial and antituberculous therapy also proved unresponsive. Five days after hospitalization patient developed generalized tonic clonic seizures, persistent even after administration of antiepileptic medications. Magnetic resonance imaging was undertaken on emergency basis which revealed deep restriction and hyperintense signals in white matter and corona radiata on diffusion weighted images (Fig1). Subsequently he developed respiratory inadequacy after 2-3 hours and had to be put on assisted respiration. Patient succumbed to death on seventh day of the hospitalization. Post mortem permission was denied.

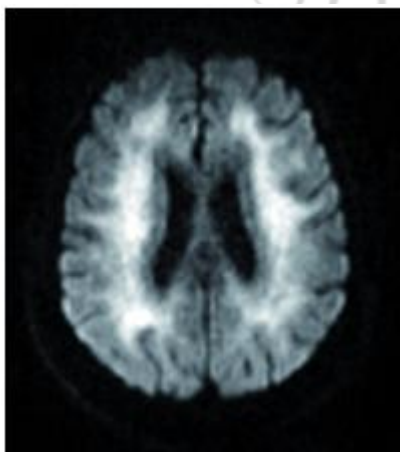
## 3. Discussion

AOSD is a rare inflammatory disorder of unknown etiology. Its major clinical manifestations include high spiking fever, evanescent rash, arthralgia/arthritis and multiorgan involvement. The disease is named after English doctor George still. George described this entity in children in 1897. The disease has bimodal age distribution with peaks at 15-25 and 36-46 yrs of age in both sexes (1). The diagnosis is of exclusion and striking constellation of clinical and laboratory abnormalities (2). The differential diagnosis includes autoimmune disorders, infections and neoplastic condition. The disease in fact has no cure as the etiology is obscured. Besides the present patient had repeated generalized seizures during hospitalization. The MRI done revealed deep restriction and hyperintense signals in white matter and corona radiata on diffusion weighted images. White matter involvement is conspicuously observed in

multiple sclerosis however seizures are rarely observed. The other causes of seizures in AOSD includes fulminant hepatic failure, meningoencephalitis and posterior reversible encephalopathy syndrome/thrombotic thrombocytopenic purpura. These conditions are ruled out in the case on clinical, serological and imaging studies. The features are consistent with diagnosis of Necrotic leukoencephalopathy with AOSD. The high ferritin levels with the clinical situation as in the case makes the diagnostic probability of AOSD stronger. The palliative treatment may offer symptom relief for the disease and may further reduce the complications. Still's disease is now considered same as juvenile rheumatoid arthritis. Yamaguchi has suggested clinical criteria on for adult onset still's disease (1) which is described in table no.1. The disease is considered as autoimmune with high levels of various proinflammatory cytokines which include IL6, IFN  $\gamma$ , IL 18, IL1 $\beta$  have been reported(3). The maturation of IL-1 $\beta$  and dysregulation of its function has been shown to have pathology of auto-inflammation, metabolic diseases. The strongest finding suggestive NLRP3 and IL1 $\beta$  involvement is the clinical improvement in condition with IL1 $\beta$  inhibitors. NLRP3 is considered as strong inflammasome and vital component of activation associated with this disease. The activation resolves upon disease remission. In all suspected cases of AOSD which is auto inflammatory 1, we need to asses NLRP3 – inflammasome activation and IL 1 $\beta$  production in such cases.

**Table 1:** Yamaguchi classification criteria (93.5% sensitivity)

Major criteria	Minor criteria	Exclusion criteria
Fever > 39 C intermittent for > 1 week	Sore throat	Infections
Arthralgia > 2 weeks	Lymphadenopathy and splenomegaly	Malignancies
Typical rash	Abnormal liver function	Inflammatory diseases
WBC > 10,000 (80% granulocytes)	RF, ANA : ( -ve )	



**Figure 1:** DWI, Diffusion weighted image showing bilateral and symmetric diffusion restriction in the deep white matter with extension to the corona radiata

Arthralgias are found in 98-100% cases whereas arthritis is often late onset and overshadowed by systemic features. The joints most commonly involved in decreasing frequency are

wrist, knee, ankle and elbows. Febrile episodes in the disease often are associated with other symptoms like rash, fatigue and arthralgia. The rash is often classical and is an evanescent salmon pink maculopapular eruption. Other clinical features include splenomegaly (45-55%), hepatomegaly (30-40%) and pleuritis (20-50%), pericarditis (24-35%). Such patient therefore may present with complications as the initial presentation of the disease such as hepatic failure, aseptic meningitis, disseminated intravascular coagulation. ESR is elevated in (90-100%) of cases. Neutrophilic leukocytosis in (70-95%). Anaemia (59-92%) cases, ANA (90-100%) of cases. The present case had high levels of ferritin (> 30000 ng/ml). High levels are also seen in liver diseases, infections, malignancies and hemophagocytic syndrome. The high levels are not related to iron metabolism and is believed to be a consequence of cytokine secretion. If the values of serum ferritin are increased fivefold, the diagnostic accuracy is enhanced with 41% specificity and 80% sensitivity (4). Serum ferritin levels correlate with disease activity and normalize after remission. Management of patient is based on use of NSAIDs, steroids and DMARDS. The response rates are variable. Methotrexates, Hydroxychloroquine has been used widely with controversial results. TNF $\alpha$  receptor blockers (Etanercept, Infliximab) are recent advance in therapy. The resistant cases should be treated with IV gammaglobulin, interferon gamma plus cyclophosphamide, Cyclosporine A, Mycophenolate mofetil (5). In one series 75% of patients had relapse in 6.9 yrs of follow up. Relapses are common when doses of corticosteroids tapered or insufficient steroid starting dose where used. The liver enzymes similarly depicts the progress and prognosis. Association of AOSD with leukoencephalopathy is extremely rare in world literature as described by Zwerling et al in 2006 (6)

The patient under discussion was provided aceclofen and prednisolone 1mg/kg body weight per day to which patient responded partly initially but had serious respiratory involvement. Despite assisted ventilation, steroid therapy had fatal outcome.

#### 4. Conclusion

A case of adult onset stills disease coexistent with leukoencephalopathy is described and the literature reviewed briefly. The possibility should be considered when the patient in the adult age group presents with high grade intermittent fever, polyarthralgia/arthritis, Skin rash for more than 2 weeks, and extensively has been evaluated to rule out other differentials of the condition. Hepatic enzyme levels, marginal or high with very high ferritin levels are considered strong markers for the disease, when other related conditions are duly ruled out. The present case with seizure, leukoencephalopathy and AOSD is described because of its rarity.

#### References

- [1] Chakr R, Dora JM, Nogueira FL, Seligman R: Adult-onset still's disease evolving with multiple organ failure: case report and literature review; CLINICS 2007;62(5):645-646.

- [2] Esdaile JM, Tannenbaum H, Hawkins D. Adult still's disease. *Am J Med* 1980;68:825-30
- [3] I. Kötter, A. Wacker, S. Koch et al., "Anakinra in patients with treatment-resistant adult-onset still's disease: four case reports with serial cytokine measurements and a review of the literature," *Seminars in Arthritis and Rheumatism*, vol. 37, no. 3, pp. 189–197, 2007
- [4] Fautrel B, Le Moel G, Saint-Marcoux B, Taupin P, Vignes S, Rozenberg S, Koeger AC, Meyer O, Guillevin L, Piette JC and Bourgeois P. Diagnostic value of ferritin and glycosylated ferritin in adult onset Still's disease. *J Rheumatol* 2001; 28: 322-329.
- [5] Musa AK, Nazimuddin K, Ahmed JU, Shaquib KA, Sarker RS. Adult onset Still's disease (AOSD): A case report. *Orion Med J* 2006;24:378.
- [6] Min L, Zwerling J, Ocava LC, Chen IH, Putterman C. Reversible posterior leukoencephalopathy in connective tissue diseases. *Semin Arthritis Rheum* 2006;35:388-95.

