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

Talib S H1, Bhattu S R2, Hegde Rohan3, Punde Gaurav4, Vyawahare Suraj5

1Professor & Head of Medicine, Department of Medicine MGM Medical College, Aurangabad, 431003, India
2Associate Professor, Department of Medicine MGM Medical College, Aurangabad, 431003, India
3, 4, 5Post 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 non-diabetic 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 rheumatological disease with rheumatoid factor, ANA, Liver function test were negative. His 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.

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 disease is characterized by a triad of symptoms 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 obscure. 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 (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.
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 γ, IL 18, IL1ß have been reported(3). The maturation of IL-1ß and dysregulation of its function has been shown to have pathology of autoinflammation, metabolic diseases. The strongest finding suggesting NLRP3 and IL1ß involvement is the clinical improvement in condition with IL1ß inhibitors. NLRP3 is considered as strong inflamasome 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 assess NLRP3 – inflamasome activation and IL 1ß production in such cases.

Table 1: Yamaguchi classification criteria (93.5% sensitivity)

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt; 39°C intermittent</td>
<td>Sore throat</td>
<td>Infections</td>
</tr>
<tr>
<td>Arthralgia &gt; 2 weeks</td>
<td>Lymphadenopathy and splenomegaly</td>
<td>Malignancies</td>
</tr>
<tr>
<td>Typical rash</td>
<td>Abnormal liver function</td>
<td>Inflammatory diseases</td>
</tr>
<tr>
<td>WBC &gt; 10,000 (80% granulocytes)</td>
<td>RF, ANA: ( -ve )</td>
<td></td>
</tr>
</tbody>
</table>

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. TNFα 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 still’s 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, polyarthritis/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


