Triple Trouble – Macrophage Activation Syndrome in a Case of Severe Leptospirosis and Scrub Typhus Co-infection

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Abstract

Macrophage activation syndrome is a potentially life threatening phenomenon characterised by aggressive proliferation of macrophages and T lymphocytes leading to haemophagocytosis of other blood cells and multi organ failure.

Here we present a very unusual combination of leptospirosis and scrub typhus infection leading to macrophage activation syndrome. Scrub typhus associated with macrophage activation syndrome has rarely been reported in India.

A 40 year old female presented with high grade fever, seizures, bodyache, arthralgia and severe breathlessness.

Investigations revealed persistent thrombocytopenia, impaired liver function tests, renal dysfunction, leptospiral IgM ELISA positive and a positive Weil Felix test. There was evidence of haemophagocytosis in bone marrow.

Macrophage activation syndrome if left untreated has been associated with rapidly fatal outcome and early treatment can help us save that one precious thing..called life..!

Introduction

Macrophage activation syndrome is a part of group of disorders collectively known as Haemophagocytic Lymphohistiocytosis. It was first described by Hadchouel et al in 1985. The term haemophagocytosis describes the pathologic finding of activated macrophages engulfing erythrocytes, leucocytes, platelets, and their precursor cells.¹

Our patient developed ARDS and multiorgan failure secondary to leptospirosis and scrub typhus infection and progressively showed features of fulminant Macrophage Activation Syndrome. Although varied causes like rheumatoid diseases, malignancies and inherited genetic disorders are implicated, infections (viral, bacterial, parasitic), continue to account for majority of cases of Macrophage Activation Syndrome, more so in our country.

Case Report

A 40 year old female presented to us with history of high grade fever and chills, severe headache, nausea, vomiting, arthralgia since 10 days. She had two episodes of generalised tonic clonic seizures prior to admission to our hospital. She had no significant prior medical history.

On examination patient was febrile, breathless with no focal neurological deficit. P-112/min, BP-100/60 mm Hg, RR-30/min SPO₂-89% on room air. Respiratory system examination showed bilateral basal crepitations. Arterial blood gas was suggestive of hypoxaemia. Treatment was started with IV Ceftriaxone 2 gm OD.

On investigations the blood examination revealed, Hb-7.7 Gm/dl, TLC-6100/cumm, platelets-15000/cumm, LFT-SGOT-404 IU/L, SGPT-300 IU/L, Serum Alkaline Phosphatase -218 IU/L,Total Bilirubin-2.8 mg/dl, Urea -131 mg/dl, S.creatinine-2.0 mg/dl. There was no evidence of fragmented RBC’s on PBS. Urine analysis showed...
mild proteinuria, mild haematuria. ECG was suggestive of sinus tachycardia. Chest radiograph revealed homogenous opacities in bilateral lung fields. Coagulation profile was grossly deranged with INR of 1.61, aPTT was 42.4 sec. Rapid Malarial Test, Peripheral smear for malarial parasite and dengue (IgG, IgM, Ns1) were negative. CSF examination was normal.

Ultrasonography of abdomen showed mild hepatomegaly with mild ascites. CT brain however turned out to be normal.

A semi-quantitative leptospira IgM ELISA was performed and was strongly positive (Observed value - 1.169). (Reference interval -- < 0.3 = negative, 0.3 - 0.5 = equivocal, > 0.5 = positive, kit used - Scimedx)

From third day onwards patient deteriorated, became severely breathless, tachypnoeic and was put on non invasive ventilation. Further investigations of the patient were ordered. HIV and HBsAg along with viral markers for Hepatitis (HAV IgM, HEV IgM) were negative. But serum LDH-2140 IU/L, S.Triglycerides – 733 mg/dl, Serum Ferritin-4662 ng/ml were high. 2D-Echo was normal. Weil Felix Test also turned out to be positive. Positive agglutination titres were seen upto OX-K 1:160 and OX-19 1:20. Doxycycline 100 mg BD was added. The repeat haemogram report of Hb-6.4 gm/dl, TLC (7100/cumm), Platelet Count (15000/cumm) showed bicitopenia and made us suspect macrophage activation.

High dose steroids were added in the form of methylprednisolone 1 gm for 5 days. The patient dramatically improved in next 4-5 days and was discharged after 14 days with all lab parameters almost touching baseline.

The diagnosis although was confirmed on bone marrow aspiration – haemophagocytosis (Figures 1, 2).

**Discussion**

Macrophage activation syndrome is a catastrophic phenomenon and has a rapidly fatal course. It is characterised by extensive proliferation of benign macrophages along with excessive production of several inflammatory mediators (Figure 3). It has been reported in several clinical situations and has been classified into primary and secondary types.

Primary or familial- is a constellation of rare genetic disorders mainly seen in younger age group.

Secondary or reactive- is seen in association with a multitude of conditions like severe infections (viral, bacterial, fungal, parasitic), malignancies as well as many rheumatological disorders.1,2 Common infectious diseases prevalent in our country like tuberculosis, HIV, malaria have been commonly associated with it. Leptospira continues to pose a public health challenge in developing countries like India. Leptospiral polysaccharide (LPS) has been studied and shown to be a potent activator of macrophages.3 Scrub typhus is a re-emerging infectious disease in our country however very rare documentations of scrub typhus leading to macrophage activation are available till date in India.4 Sporadic cases of scrub typhus in association with MAS have been mainly reported in East Asian countries like Japan, Korea.5

The hallmark of this syndrome is severe impairment of cytotoxic activity of natural killer (NK) cells and T lymphocytes which is mediated through release of cytolytic granules containing perforins.2

![Fig. 1: Showing erythrocytes engulfed by activated macrophage](image1)

![Fig. 2: Showing Haemophagocytosis on Bone Marrow Examination](image2)
Studies have shown that leptospiral outer membrane constituents activate macrophages through CD14 and the Toll-like receptor 2 (TLR2).

**Clinical Features**

Sometimes only neurological features may dominate the clinical picture. Pathognomonic feature is demonstration of haemophagocytosis on bone marrow examination (Figure 1). Evidence of haemophagocytosis may not be present in early stages however its absence does not rule out MAS.

Our patient met 5 of the required diagnostic criteria (fever, cytopenia, hypertriglyceridaemia, hyperferritinaemia and haemophagocytosis on bone marrow). Hyperferritinaemia is an important laboratory landmark that has received increased attention recently. Measurement of serum ferritin levels can be a useful indicator of diagnosis and severity of illness.2

Scrub typhus is caused by Oriental tsutsugamushia and is transmitted by the bite of chigger or trombiculid mite. Clinical picture may be complicated by renal failure, ARDS, septic shock, meningo-encephalitis. Necrotic eschar may be present at the inoculating site. Weil Felix test is the most easy and cost effective test for diagnosis of scrub typhus. Though Weil-Felix agglutination test is not a very sensitive test but when positive, it is rather specific test. The use of Weil Felix test is acceptable in conditions where definitive investigations are not possible and it is still not entirely obsolete but has to be interpreted in the clinical context.7

MAS should be tackled as a medical emergency. All patients should be treated in an ICU setup. High dose parenteral steroids form the crux of therapy.1,2 IV Methylprednisolone can be used to inhibit the secretions of various cytokines and suppress the activated macrophages along with lymphocytic overactivity. IVIG, etoposide, cyclophosphamide, anti TNF α agents have all been tried with conflicting results. Use of cyclosporine A has impressive clinical outcome in unresponsive cases and may play crucial role in induction of remission and survival.

**Conclusion**

This case report is presented to emphasise that MAS poses a diagnostic challenge for us clinicians and high degree of suspicion is warranted for recognition of symptoms in patients diagnosed with severe leptospirosis or rickettsial diseases or any patient in severe sepsis with cytopenia not responding to therapy.

Because macrophage activation if left untreated may masquerade a more sinister and fatal form and only early treatment can help us save that one precious thing.. called life..!
Solid Pseudopapillary Tumour of Pancreas: A Report of 5 Cases

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Abstract

A solid pseudopapillary tumour of the pancreas (SPT) is a rare neoplasm accounting for less than 2% of exocrine pancreatic neoplasms. SPT occurs in adolescent young females and is mostly benign. It is a low-grade malignant tumour that may evolve years before symptoms start and has a favourable prognosis. 1,3,5 In this report we present five cases (four females, one male, aged 16, 45, 23, 17 and 55 years, respectively) of SPT localised in the pancreas, and discuss the clinical, imaging and histologic findings with a review of the literature. We retrospectively reviewed these five patients with SPT who underwent surgical resection in our hospital with a definitive histologic diagnosis of SPT.

Introduction

SPT of the pancreas is an indolent exocrine pancreatic tumour which is well-known for its predilection for young women. 1,2,4 This rare entity was first described by the author Dr. Frantz in 1959, and was called “papillary tumour of the pancreas- benign or malignant?” 3 These neoplasms account for 1-2% of exocrine pancreatic neoplasms. 3,6 In 1996, the WHO renamed this tumour as SPT for the international histological classification of tumours of the exocrine pancreas. 1,3,6 We discuss diagnostic and differential diagnostic features of this unusual tumour and present five cases seen in our department.

Case Reports

We retrospectively reviewed the clinical data of five patients with histopathologically proved SPT at our hospital from August 2005 to August 2011. Among these, four were females- aged 16, 45, 23 and 17 years respectively and one was male- aged 55 years. Tumour specimens were confirmed on histopathology by at least two pathologists.

Clinical Features

The detailed clinical features of all these cases are as follows