CASE REPORT

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Dengue and Haemophagocytic Lymphohistiocytosis – An Uncommon Sequelae of a Common Disease

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Abstract

Dengue is a viral illness endemic to many parts of India. A lot many complications can arise in dengue in addition to the usual clinical presentation. A 30-year-old male patient presented with prolonged fever, organomegaly and cytopenias. His dengue NS1 antigen was positive. Further evaluation revealed hyperferritinaemia, hypertriglyceridaemia and haemophagocytic lymphohistiocytes on bone marrow studies. A diagnosis of haemophagocytic lymphohistiocytosis (HLH) secondary to dengue fever was made and patient was treated with dexamethasone and etoposide leading to recovery. We intend to highlight the importance of keeping HLH in mind while dealing with patients of dengue fever presenting with prolonged or atypical clinical features.

Key words: Dengue, HLH, cytopenia, hyperferritinaemia.

Introduction

Dengue is an arboviral infection which is endemic in tropical and subtropical geographic locations. It is transmitted from person to person by the bite of mosquitoes belonging to the genus Aedes. Presentations in dengue can vary from asymptomatic infection to severe disease involving various organ systems[1].

Haemophagocytic lymphohistiocytosis (HLH) is a potentially life-threatening disease with a varied aetiology. It is characterised by a wide spectrum of clinical manifestations including fever, cytopenias, organomegaly and nervous system dysfunction. HLH can be either primary or secondary. Primary HLH has a familial or genetic basis while secondary HLH is related to a wide variety of causes including infections, malignancies, autoimmune and metabolic disorders[2].

Dengue fever, as an infectious trigger, has been associated with HLH[3]. This association presents a distinctive challenge to clinical practitioners due to its rarity, speed of progression and coinciding clinical features. Here we present a case of dengue complicated by the development of haemophagocytic lymphohistiocytosis.

Case report

A 30-year-old male patient without any known co-morbidities presented to the emergency with a history of fever since ten days associated with chills and generalised body aches. He had been taking treatment from a local practitioner and had tested positive for Dengue NS1 antigen. On presentation his pulse rate was 108 beats per minute, blood pressure was 100/60 mm of Hg, respiratory rate was 22 beats per minute, temperature was 101° F and oxygen saturation was 98% on room air. On systemic examination liver was palpable 3 cm below the right costal margin and spleen was palpable 4 cm below the left costal margin. Rest of the systemic examination was within normal limits. Investigations revealed a haemoglobin level of 12 g/dL, leucocyte count of 2,540 cells/cumm and a platelet count of 40,000/cumm. Total and direct bilirubin levels were 1.41 and 1.05 mg/dL, SGOT and SGPT were 91 and 38 U/L, ALP was 332 U/L and total protein and albumin levels were 7. 6 and 3.0 g/dL respectively. RFT was within normal limits. He was diagnosed as a case of dengue fever with thrombocytopenia and was started on IV fluids and other supportive treatment. Even after 14 days from the onset of illness, high-grade fever continued along with a progressive decline of haemoglobin levels from 12 g/dL on presentation to 7.4 g/dL along with persistent leucopenia, thrombocytopenia and progressive hepatosplenomegaly. Peripheral blood film examination did not reveal the presence of any atypical cells. There was no evidence of bleeding. This prolonged duration of illness associated with pancytopenia and hepatosplenomegaly warranted a relook into the diagnosis. Keeping a suspicion of HLH in mind patient's serum ferritin and triglyceride levels were measured and they turned out to be significantly elevated (serum ferritin of 2,000 ng/mL and triglycerides of 274 mg/

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dL). A bone marrow examination was performed which showed the presence of haemophagocytic lymphohistiocytes (Fig. 1 given below). A diagnosis of HLH secondary to Dengue fever was made as per the HLH-2004 criteria. The patient was started on Inj. Dexamethasone and Inj. Etoposide . After initiation of treatment, the patient's fever spikes started settling, hepatosplenomegaly started regressing and cell counts started improving. The patient was subsequently discharged in a stable condition. The dose of dexamethasone was tapered and stopped during subsequent visits to the hospital.

Discussion

Dengue is a febrile illness with widely varied clinical presentations. It is one of the major and rapidly expanding mosquito borne viral infections in the world currently. Worldwide incidence of dengue has exponentially increased in the recent decades and nearly half of the world's population is at risk of contracting dengue. It is endemic in tropical and subtropical countries, mostly in the urban and semi-urban settings. Around 100 to 400 million new cases of dengue occur worldwide every year according to conservative estimates[4].

As far as India is concerned, dengue is endemic in almost all states and is an important cause for hospital admissions[5]. As per the census published by the National Centre for Vector Borne Diseases Control, about 2 lakh dengue cases were reported during 2024 in India.

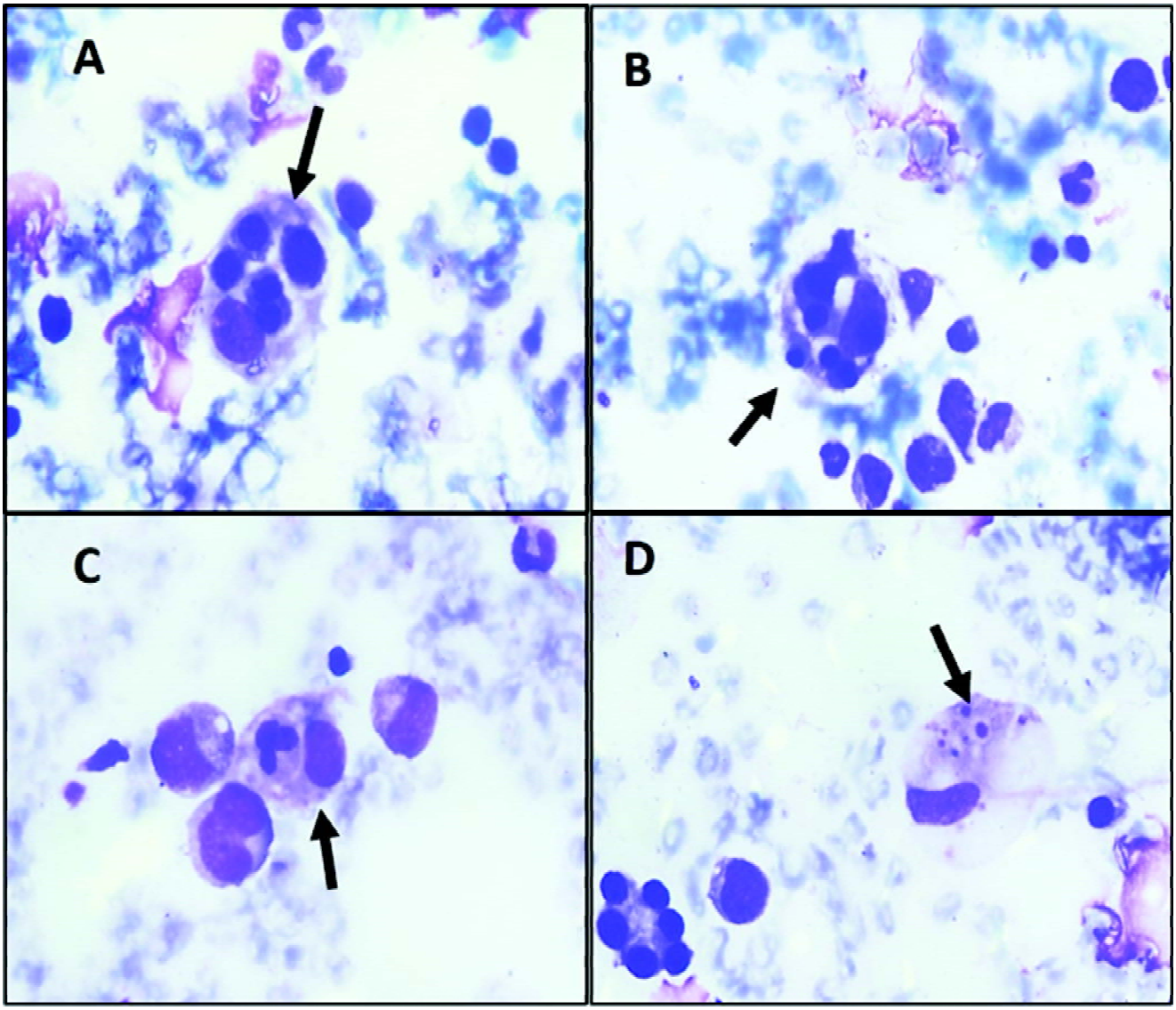

Fig. 1: *Haemophagocytic cells in bone marrow aspirate.* ***A and B:*** *Histocytes engulfing multiple erythroid precursors, MGG, x 1,000.* ***C:*** *Histiocyte with single engulfed Neutrophil, MGG, x 1,000.* ***D:*** *Histiocyte with engulfed Platelets, MGG, x 1,000.*

Dengue virus is transmitted in the community through the bite of infected mosquitoes. The primary vector is Aedes aegypti. Aedes albopictus is a secondary vector of dengue confined to only few regions in the world[1]. Major clinical features include fever, retro orbital pain and myalgias. A typical case of dengue infection passes through three phases, namely febrile, critical and recovery phase. Thrombocytopenia, the hallmark of dengue infection, starts during the febrile phase. The critical phase is characterised by systemic vascular leak and may lead to shock and multi organ dysfunction. The subset of the patients who develop organ failure are referred to as having expanded dengue syndrome. Complications which can arise are numerous and include encephalitis, Guillain-Barré syndrome, hepatitis, pancreatitis, nephritis, myocarditis, myositis and haemophagocytic lymphohistiocytosis[6-9]. The management of dengue is mainly supportive, including intravenous fluids, nutrition and support for specific organ-related complications[10].

Haemophagocytic lymphohistiocytosis is a grave, hyperinflammatory condition which can result in organ failure and death. HLH is classified into two. Primary HLH occurs as a result of inheried genetic mutations and usually presents early in childhood. Secondary HLH occurs due to an abnormal host response to various infections, malignancies or autoimmune disorders and presents in adults associated with an acute illness[11].

The prevalence of HLH in the general population is difficult to ascertain, even more so for secondary HLH. Estimates place it at 1 in 2,000 for adults admitted in critical care settings[12].

The clinical features of HLH are comprehensively covered under the HLH-2004 diagnostic criteria. Diagnosis is established by the presence of at least 5 out of the following 8 criteria – fever, cytopenias, splenomegaly, hypertriglyceridaemia with or without hypofibrinogenaemia, biopsy proven haemophagocytosis, ferritin levels greater than 500 ng/mL, low or absent natural killer (NK) cell activity and elevated soluble interleukin 2 receptor alpha levels greater than or equal to 2,400 U/mL[13]. Our patient had persistent fever, pancytopenia, splenomegaly, hypertriglyceridaemia, hyperferritinaemia and haemophagocytosis on bone marrow biopsy thereby fulfilling 6 out of the 8 criteria.

Pathophysiology of HLH primarily involves an innate immune system dysregulation, specifically involving the NK cells and CD 8+ cytotoxic T-cells. In an intact immune system these cells produce two apoptotic enzymes, namely perforin and granzyme. Perforin forms destabilising pores in the target cell membrane which paves the way for entry of the strongly proteolytic granzyme resulting in death and degradation of the target cell. In patients of HLH this process gets disrupted. In primary HLH, specific genetic mutations account for this disruption, while in secondary HLH it is proposed that a highly immunogenic stimuli such as a virus infected cell or a malignant cell brings about this disruption. This ineffective action of NK cells and CD 8+ cytotoxic T-cells on their targets promotes a vicious inflammatory cycle. A disproportionately large number of cytotoxic cells get recruited but are unable to neutralise the pathologic antigen further resulting in a massive increase in circulating cytokines. Hypercytokinaemia in turn causes widespread macrophage activation and resultant haemophagocytosis and organ damage[14].

The major cytokines implicated are interferon gamma (IFN-α, cytokines tumour necrosis factor alpha (TNF-α), interleukin 1 (IL-1) and interleukin 6 (IL-6). IFN-α and TNF-α act on haematopoetic cells leading to cytopenias. IL-1, IL-6 and TNF-α are implicated as the cause for prolonged fever. TNF-α further inhibits the enzyme lipoprotein lipase leading to hypertriglyceridaemia. The activated macrophages screte ferritin and plasminogen activator resulting in hyperferritinaemia and hypofibrinogenaemia respectively. The elevated number of NK and activated T-cells secrete increased amounts of interleukin 2 receptor alpha[2].

In HLH secondary to dengue, the viral infection triggers excessive cytokine secretion and rampant immune mediated organ destruction[15,16,17].

Treatment of HLH includes immunosuppression and cytotoxic therapy. HLH-2004 criteria recommends an initial 8 week therapy containing dexamethasone and etoposide. Based on individual case scenarios continuation treatment can be provided which includes dexamethasone and etoposide with or without cyclosporine A. Patients with progressive neurological symptoms can be given intrathecal methotrexate. Haematopoetic stem cell transplantation should be provided to patients with familial, relapsing or severe and persistent HLH[18]. This treatment should go hand in hand with treatment for the underlying trigger in cases of secondary HLH.

Patients with dengue associated HLH may not require cytotoxic therapy or stem cell transplantation. Corticosteroids alone can manage this condition many a times[19].

Conclusion

Non-specific clinical presentation and laboratory findings leave HLH underdiagnosed in dengue patients. Fever, pancytopenia and hyperferritinaemia can occur in both dengue and HLH. However, in contrast to patients just having severe dengue, patients with HLH complicated infections

commonly have atypical features such as prolonged fever of more than seven days, hypertriglyceridaemia, hypofibrinogenaemia and haemophagocytosis on bone marrow[19].

Clinicians should have a high index of suspicion for HLH in dengue patients with symptoms and signs out of proportion to the phase of dengue fever. Early identification and treatment initiation forms the cornerstone in the management of this life threatening entity.

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