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PEDIATRIC ONCALL
CHILD HEALTH CARE

TEACHING FILES (GRAND ROUNDS)

SIBLING DEATHS DUE TO INFECTIONS

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Clinical Problem:
A 6-month-old boy born of second-degree consanguineous marriage presented with diarrhea, papular reddish lesions over hands & feet and chronic bilateral ear discharge since 3 months of age. His eldest brother had died at 8 months of age due to respiratory infection. The 2nd sibling was an 8-year-old sister and was asymptomatic. The 3rd child was a girl who died at 2 years of age due to repeated skin infections and fever since 6 months of age. The 4th child was a boy who died at 18 months of age due to repeated skin infections and empyema. On examination, the present child had a maculopapular erythematous rash over the scalp, around the eyelids, hands, umbilical region, and perianal region with bilateral purulent otorrhea with hepatomegaly. Hemogram revealed eosinophilia [Hemoglobin = 11.8 gm/dl, WBC = 17,300 cells/cumm, 25% polymorphs, 61% lymphocytes, 11% eosinophils, 3% monocytes with absolute eosinophil count = 1903 cells/cumm, Platelets = 2,80,000/cumm and ESR = 5 mm at end of 1 hour]. HIV ELISA was negative. Serum immunoglobulins by nephelometry S. IgA = 46 mg/dl (Normal = 31-67 mg/dl), S. IgE = 148 µ/ml (Normal = 0-378 µ/ml), S. IgM = 139 mg/dl (Normal = 43-118 mg/dl), S. IgG = 300 mg/dl (Normal = 716-1103 mg/dl). His CD panel by flow cytometry was normal [CD3 = 4807/cumm (Normal = 1375-3769/cumm), CD4 = 1378/cumm (Normal = 174-1388/cumm), CD8 = 2199/cumm (Normal = 231-2394/cumm), CD19 = 1386/cumm (Normal = 739-2523/cumm)]. His ear swab grew *candida albicans* and *staphylococcus aureus* and stool culture grew *E. Coli* with stool routine showing 15-20 pus cells/hpf. Liver transaminases were elevated (SGPT = 172 IU/L) which reverted to normal after 15 days and USG abdomen revealed coarse echotexture of liver suggestive of liver parenchymal disease. He was treated with intravenous (IV) amikacin, TMP-SMX and fluconazole. He was started on TMP-SMX prophylaxis and advised regarding monthly intravenous immunoglobulin (IVIG) and bone marrow transplant.

What is the diagnosis?

Discussion:
Hyper IgM syndrome (HIGM) is a primary immunodeficiency caused by defect in the CD40 ligand which is normally expressed on activated CD4 + T lymphocytes. This defect in CD40 ligand interrupts B cell differentiation and switch of immunoglobulin M (IgM) to other immunoglobulin isotypes.[1] This CD40 ligand mutation can occur by gene defect on X chromosome leading to X-linked hyper IgM (XHIM) or by gene defect on chromosome 20 or chromosome 12 leading to autosomal recessive Hyper IgM (ARHIM).[2] HIGM leads to recurrent pyogenic infections by 1-2 years of life with increased incidence of cryptosporidium enteritis, liver disease and increased risk of malignancy.[3] HIGM is rarely reported in India with only case reported in a series of 27 children with primary immunodeficiency.[4] XHIM and ARHIM are characterized by severe pyogenic infections including recurrent otitis media, sinusitis, pneumonia, and diarrhea along with normal-to-high serum levels of IgM with low serum IgG, IgA and IgE. Both our patients presented with severe infections. Our patient had recurrent otitis media with chronic diarrhea by 6 months of age with elevated serum IgM levels with low IgA and IgG suggestive of HIGM syndrome. XHIM is seen only in males, whereas ARHIM may occur in both males and females. In patients with XHIM, the B cells are normal whereas the defect is in T cells and in patients with ARHIM, the B cells are intrinsically abnormal and cannot isotype switch whereas T cells are normal.[2] Though neutropenia is common in these patients and liver disease is common, our patient did not have neutropenia but had elevated serum transaminases suggestive of liver disease. In addition, that child also had eosinophilia which has never been reported earlier with Hyper IgM syndrome. However, liver disease may progress subclinically and hence liver function tests are recommended at 6 to 12 months interval.[3] Prognosis of patients with HIGM remains poor and in a retrospective study of 56 affected males from the Registry of the European Society for Immune Deficiency, it is found that only 20% survive above 25 years of age.[5] Mortality is mainly due to recurrent infections, progressive meningoencephalitis, and malignancies. However, with advent of intravenous immunoglobulin (IVIg) replacement, effective use of appropriate antibiotics and better recognition of infections, the morbidity associated with the disease has been reduced. Patients who receive optimal IVIg replacement have normal growth in infancy and childhood.[3] IVIg in the dose of 400-600 mg/kg/month is recommended. Curative treatment consists of HLA-identical bone marrow transplant at an early age.[2]

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Compliance with ethical standards

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