# Recurrent oral ulcers due to XMEN syndrome

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**Case report**

A one and a half year old boy, born of a non-consanguineous marriage, a resident of Bangladesh, presented with a history of fever, respiratory tract infection and recurrent oral ulcers (almost monthly) since six months of age. Informant was the mother. Each febrile episode lasted 2 to 3 days and was accompanied by recurrent painful oral ulcers, due to which the child had difficulty in oral intake. Sometimes, these episodes were accompanied by cough and coryza. These episodes were mainly treated on an outpatient basis and there was a history of only one brief hospital admission at 9 months of age. The child had achieved normal milestones as per age and vaccination was complete according to the national immunization schedule. The child was the only offspring of the parents and there was no history of similar illness in the family.

On examination, the child was malnourished with a weight of 7kg (<3rd percentile) and a height of 85cm (3rd to 5th percentile)]. The general survey and systemic examination were essentially normal. Our working differential diagnoses were:

- Cyclic neutropenia
- Periodic Fever, Aphthous stomatitis, Pharyngitis and Adenitis (PFAPA) syndrome
- Infantile variety of Behcet's disease (A20 Haploinsufficiency)

Blood counts done thrice a week over 6 weeks showed total leucocyte counts in the range of 5000 to 6000/cu mm, with no evidence of neutropenia. Haemoglobin and platelet counts were normal. Inflammatory markers were not elevated. Infective serology (TORCH, HIV, cytomegalovirus, parvovirus) was also negative. However, Epstein Barr virus (EBV) polymerase chain reaction (PCR) was positive. The work up for primary immune deficiency showed normal immunoglobulin levels. The flow cytometry showed a reversal of CD4:CD8. (CD4-27.8% and CD8 20.8% of peripheral blood cells; CD4:CD8= 0.7) (Normal range 0.9 to 3.7). Genetic analysis by clinical exome sequencing revealed hemizygous deletion of MAG T1. Thus, the final diagnosis was a case of XMEN disease, occurring as a result of hemizygous deletion of MAGT1 receptor.

**Discussion**

XMEN disease is a type of primary immune deficiency, a combined variety, where there is a defect in the magnesium transport. Magnesium ion is the most abundant divalent cation in the eukaryotic cells and is involved in many physiological processes. Majority is in a bound form, present in the bones and in the intracellular compartment. Most of the intracellular magnesium is tightly bound to proteins, less than 5% being in the free ionized state and magnesium transporter 1 (MAGT1) plays a vital role in the transport of this ion[1]. MAGT1 controls the free basal magnesium concentration and is responsible for the rapid and transient influx of ionized magnesium after T cell receptor (TCR) stimulation[2]. This ionized magnesium helps in expression of NKG2D receptors in the Natural killer (NK) cells and CD8 + T cells and this helps to maintain their cytolytic functions[3].

In XMEN disease, loss of MAGT1 results in defective TCR signalling and this leads to chronic decrease in the basal levels of free intracellular ionized magnesium leading to reduced expression of activated receptor NKG2D on NK and CD8 + T cells. These two defects actually lead to failure to clear EBV and hence a chronic state of EBV viraemia. The major clinical feature thus occurs due to persistent elevation of EBV viral load and increased susceptibility to EBV associated lymphoproliferative diseases including lymphoma[2] which usually manifests in late childhood or adolescence. Other major manifestations include splenomegaly, lymphadenopathy and dysgammaglobulinaemia. These major manifestations are present in almost all XMEN patients. However, some of these patients may also

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have minor viral infections of skin like varicella and recurrent zoster, molluscum contagiosum[4] and upper respiratory tract infection resulting in sinusitis, pharyngitis, and otitis media. There may also be autoimmune cytopenia. Patients usually have normal development and growth without any evidence of mental retardation[5]. Our child had normal milestones but failure to thrive might have occurred due to recurrent respiratory infections, oral ulcers and poor intake.

This is an X-linked recessive condition and males are usually affected. In very rare cases like coexistence of associated X chromosome monosomy (Turner syndrome) or mutant X-chromosome, females may be affected.

In the largest study of 7 individuals with XMEN disease[6], ages ranged from 3 to 45 years. Of these 7 individuals, 4 were in the paediatric age group. Majority of them had a history of upper respiratory tract infection and one had viral pneumonia. As in our case, all had a CD4:CD8 <1. Our case is perhaps the youngest. He actually presented with only recurrent fever and oral ulcers. Though there was evidence of EBV by PCR, lympho-proliferation was not detected.

Since it is a case of chronic EBV viraemia, it needs to be differentiated from other similar states:

- *Interleukin-2 inducible Tyrosine Kinase (ITK) deficiency:* This is an autosomal recessive condition having a more severe and rapidly progressive clinical course[7].
- *XLP-linked lymphoproliferative disorder:* this condition, unlike XMEN, is characterized by fulminant infectious mononucleosis and EBV triggered haemophagocytic lymphohistiocytosis[8].
- CD27 deficiency: a form of combined immune deficiency characterized by hypogammaglobulinaemia but level of viral load is less compared to XMEN[9].

XMEN is a type of combined primary immune deficiency but unlike the commoner variety, severe combined immune deficiency (SCID), it is milder, has a later age of presentation and it usually does not have overwhelming infection. Treatment is usually symptomatic. Hypogammaglobulinaemia may benefit by replacement immunoglobulin therapy. For recurrent infections, antimicrobial and antiviral prophylaxis may be needed. A novel approach to this condition is oral magnesium L-threonate[3] which restores basal intracellular free magnesium leading to increased expression of NKG2D on NK and CD + T cells. However, it is not known whether this is sufficient to prevent EBV-driven lympho-proliferation. In the study by Li FY, *et al*[6], 2 patients received magnesium supplementation. Our patient has been put on L-threonate supplementation. He is on regular follow up and surprisingly, febrile episodes have decreased. Biologics like rituximab may control acute EBV infection and prevent fulminant infectious mononucleosis[10] but cannot completely deplete CD20+B cells. Haemopoietic stem cell transplant may be tried for those who have biopsy proven lympho-reticular malignancies. Of the 7 patients[6] studied so far, 2 underwent bone marrow transplant, but unfortunately succumbed to transplant related complications.

XMEN disease is a type of combined immune deficiency identified recently. Increased awareness of this disease may help to identify newer cases especially males with chronic EBV viraemia. XMEN disease also brings to light the novel role of magnesium in immune regulation. Diagnosis is important because in this type of immune deficiency, therapy with oral magnesium threonate may help. This case report emphasizes the importance of genetic analysis in all suspected cases of primary immune deficiency. In our case we had a differential diagnosis of cyclic neutropenia, PFAPA, A20 Haploinsufficiency but clinical exome sequencing revealed a novel mutation.

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