4. Buers I, Persico I, Schoning L, *et al*. Crisponi/cold induced sweating syndrome: Differential diagnosis, pathogenesis and treatment concepts. Clin Genet. 2020;97:209-21.
5. Crisponi G. Autosomal recessive disorder with muscle contractions resembling neonatal tetanus, characteristic face, camptodactyly, hyperthermia, and sudden death: A new syndrome? Am J Med Genet. 1996;62:365-71.
6. Alhashem AM, Majeed–Saidan MA, Ammari AN, *et al*. Crisponi/CISS1 syndrome: A case series. Am J Med Genet A. 2016;170A:1236-41.

X-linked Lymphoproliferative Disease (XLP1) Presenting as Non-Epstein Barr Virus (EBV) - Related Hemophagocytic Lymphohistiocytosis (HLH)

X-linked lymphoproliferative disease (XLP1) is a rare immunodeficiency disorder with immune dysregulation, caused by *SH2D1A/SAP* gene mutations. Clinical manifestations include fulminant infectious mononucleosis (FIM), hemophagocytic lymphohistiocytosis (HLH), lymphomas and dysgammaglobulinemia [1]. HLH in children can be primary/familial HLH or secondary/reactive HLH [2]. In 80% of familial HLH cases the genetic defect can be identified. To the best of our knowledge this is the first report of XLP1 in an infant with non-Epstein Barr virus (EBV) HLH in India.

An 11 months old male infant, born to third degree consanguineous parents presented with intermittent fever and loose stools for twenty days. There was no history of vomiting, blood in stools, bleeding manifestations, cough/cold, weight loss or past recurrent infections with an unremarkable family history. Child had normal nutritional status, some pallor and massive hepatosplenomegaly. Investigations revealed anemia with hemoglobin of 8.3 g/dL, neutrophilic leucocytosis, absolute neutrophil count of 1704/mm3, low normal platelet count and along with elevated liver enzymes (alanine transaminase: 210 U/dL; aspartate transaminase: 399 U/dL). He was started on antibiotics ceftriaxone and doxycycline. Further investigations including smear for malarial parasite, serology for scrub typhus, cytomegalovirus, EBV and retrovirus was negative. As his fever spikes persisted, ultrasound abdomen, echocardiogram and Immunoglobulin profile were done and found normal. .

Re-evaluation revealed decreasing neutrophil counts (ANC of 624/mm^3), thrombocytopenia (platelet count of 0.49×10^9/L) and coagulopathy (INR of 1.6). Antibiotics were escalated to meropenem and vancomycin because of worsening clinical condition and laboratory parameters though the blood cultures remained sterile. In view of pancytopenia, deranged liver functions, organomegaly and persisting fever spikes, hemophagocytic lymphohistiocytosis (HLH) was considered. Follow up investigations showed elevated serum ferritin (5498 ng/mL), serum triglycerides (278 mg/dL), soluble CD 25 levels, decreased serum fibrinogen (175 mg/dL), bone marrow hemophagocytosis, and cerebrospinal fluid lymphocytic pleocytosis, all consistent with the diagnosis of HLH [2]. He was treated with intravenous immunoglobulin, dexamethasone and etoposide. Workup for primary HLH showed normal perforin protein expression and CD 107a. With the background of consanguinity and male sex, XLP was considered. Next generation sequencing revealed mutation in *SH2D1* characteristic of XLP1. Unfortunately, the child had HLH progression and expired of fulminant hepatic dysfunction and coagulopathy. Parents were counseled regarding antenatal diagnosis of XLP in next pregnancy.

X-linked lymphoproliferative syndrome (XLP) is a rare inherited immunodeficiency affecting approximately one in 1,000,000 males. XLP patients have severe immune dysregulation often after viral infection (typically with Epstein-Barr virus [EBV]) [1]. However, a proportion of boys (approximately 10%) have immunological abnormalities before evidence of EBV infection [3] like in our case.

One of the manifestations of XLP1 is hemophagocytic lymphohistiocytosis (HLH) which is a multisystem inflammatory disorder characterized by cytokine overproduction by activated lymphocytes and macrophages.

XLP arises from 2 different genetic defects in *SH2D1A,* in Xq25 gene (XLP1, the most common) and *BIRC/XIAP* gene (XLP2). *SH2D1A* encodes the cytoplasmic protein *SAP* (*SLAM*-associated protein) which is a key regulator of normal immune function in T cells and naturalkiller cells [4]. Defects in SAP lead to the varied immune defects in XLP1 patients. Our child had a mutation in *SH2D1A* confirming XLP1.

Hematopoietic stem cell transplantation (HSCT) remains the most effective curative treatment for XLP though IVIG and rituximab have been used previously in prevention with questionable benefit [4,5].

Any male child with HLH or FIM should undergo genetic testing for therapeutic implications like bone marrow transplant. Early genetic confirmation of diagnosis also plays a major role in prenatal diagnosis and genetic counselling for the next pregnancy.

AJEITHA LOGANATHAN,[1]* DEENADAYALAN MUNIRATHNAM[1] AND BALASUBRAMANIAN SUNDARAM[2]
Department of [1]Pediatric Hematology and Oncology and [2]Pediatrics, Kanchi Kamakoti CHILDS Trust Hospital,

Chennai, Tamil Nadu, India.
drajeitha@gmail.com

REFERENCES

1. Purtilo DT, Cassel CK, Yang JP, *et al. X*-linked recessive progressive combined variable immunodeficiency (Duncan's disease). Lancet. 1975;1:935-40.
2. Henter JI, Horne A, Aricó M, *et al*. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124-31.
3. Seemayer TA, Gross TG, Egeler RM, *et al*. X-linked lymphoproliferative disease: twenty-five years after the discovery. Pediatr Res. 1995;38:471-8.
4. Booth C, Gilmour KC, Veys P, *et al. X*-linked lymphoproliferative disease due to *SAP/SH2D1A* deficiency: A multicenter study on the manifestations, management, and outcome of the disease. Blood. 2011;117:53-62.
5. Marsh RA, Bleesing JJ, Chandrakasan S, *et al.* Reduced intensity conditioning hematopoietic cell transplantation is an effective treatment for patients with SLAM-associated protein deficiency/X-linked lymphoproliferative disease type 1. Biol Blood Marrow Transplant. 2014;20:1641-5.

Perianal Abscess With Stellate Lacerations in a 3.5-year-old Previously Healthy Boy

Perianal abscesses are soft tissue infections of the perianal region and are common in infants [1-3]. Most of them are idiopathic, although there may be an association with congenital abnormalities of the crypts of Morgagni or an infection of the cryptoglobular glands [1-3]. They occur mainly in males, which may be due to androgen excess in cases of androgen-estrogen imbalance or to abnormal development of androgen-sensitive glands *in utero* [1]. In older children, the etiology shifts to underlying diseases, such as inflammatory bowel disease, immune deficiency syndromes, trauma, infected mass lesions and other immunodeficiencies [4]. The most common organisms isolated are mixed aerobic and anaerobic bacteria from gastrointestinal tract flora [5]. The appropriate management of perianal abscess is incision, drainage and antimicrobial treatment [3].

A 3.5-year-old boy presented with a three day history of pain, skin irritation and discharge of pus around the anus. Notably, fifteen days prior to admission, he developed an upper respiratory tract infection treated with oral second-generation cephalosprin. Five days later, while on antimicrobial treatment, he complained of pain during defecation and his mother noticed mild redness around the anus. The patient was afebrile. Laboratory investigations revealed severe neutropenia (absolute neutrophil count: 0.14×10^9/L). The patient was treated with topical corticosteroids, but showed no improvement. The child continued to complain of perianal pain and the inflammation worsened with purulent discharge. Three days prior to admission, he received oral metronidazole, without improvement.

Past medical history was unremarkable, and there was no history of constipation before or during the preceding viral illness. Physical examination demonstrated notable swelling, redness and tenderness in the rectum area with concomitant laceration of the anus leading to stool incontinence. His physical examination was otherwise unremarkable. A rectal examination revealed painful inflammation purulent discharge and stellate lacerations of the anal mucosa and skin (***Fig. 1a***).

Laboratory investigation upon admission revealed white blood cell count of 14.9×10^9/L (neutrophils: 35.4%, lymphocytes: 55.8%, monocytes: 8.3%) with normal hemoglobin and increased platelet count. Both C-reactive protein and ESR were mildly raised. Liver and renal function tests were normal. There was a family history of recurrent abscesses in mother and maternal aunt raising the suspicion of immunodeficiency disorder, but all immunological investigation came out to be normal including classes and subclasses of the immunoglobulins, immunophenotyping, dihydrorhodamine (DHR) test and cell adhesion molecules (CAMs). Physical examination findings also raised the possibility of sexual abuse, which was further ruled out after behavioral and psychological assessment of child and his parents. The family was daily reviewed by the pediatric team who found no evidence of child abuse or family conflicts. There was no evidence of any behavioral changes or psychological problems in the child during hospitalization and the follow-up consultation for the next 2 years showed no indication of psychological problems or any other changes in the behavior of the child.

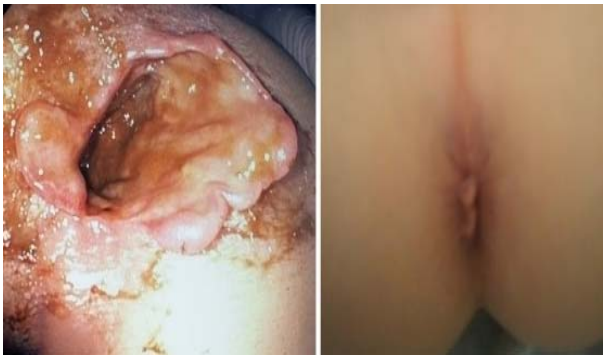

Fig. 1 *Perianal abscess of the 3.5-year-old child (a) on admission and (b) 10 days after treatment.*