

X-Linked Lymphoproliferative Disease: A disease with many presentations

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Capsule Summary:

XLP1 can present in many different ways with no genotype phenotype correlation making close monitoring extremely important, especially in those with a family history

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Abstract

Background: X-linked lymphoproliferative disease (XLP1) is caused by mutations in the SH2D1A gene, which affect SLAM-associated protein (SAP). Children with this condition may present with hemophagocytic lymphohistiocytosis (HLH), lymphoma, severe immune dysregulation and dysgammaglobulinemia. It is associated with increased susceptibility to EBV, however, a third of patients have no evidence of previous EBV infection and many patients are diagnosed based on family history alone.

Objective and Method: Here we report 3 siblings from a family with hemizygous deletions of exon 2 of the SH2D1A gene manifesting with different phenotypes at different ages.

Results: Patient 1 presented with chest infection and hypogammaglobulinaemia at 21 months of age. He commenced immunoglobulin replacement and later developed persistent EBV viremia and cytopenias. Patient 2 developed EBV-negative non-Hodgkin lymphoma at 3 years old and underwent hematopoietic stem cell transplant (HSCT). Patient 3 developed EBV-negative CNS-HLH at 11 months of age and also underwent HSCT but died of multi-organ failure.

Conclusion: It is strongly recommended that genetic screening be carried out in families with a history of XLP1. However, patients diagnosed at birth still carry a significant risk of mortality despite close monitoring as demonstrated here. Early curative treatment with HSCT may improve outcome especially if undertaken before developing significant morbidities as we know that active disease at the time of transplant and a mismatched donor reduce survival to almost 50%.

To the Editor,

X-linked lymphoproliferative disease (XLP1) was first described in the 1970s¹ and is a rare primary immunodeficiency (PID) caused by mutations in the SH2D1A gene. This gene encodes the SLAM-associated protein (SAP) which is a key regulator of immune function in T, NK, and NKT cells and defects in this protein may lead to the cellular and humoral immune defects characterized in patients². Clinical manifestations vary and include hemophagocytic lymphohistiocytosis (HLH), lymphoma and dysgammaglobulinemia²⁻⁴ but patients can experience a wide range of phenotypes associated with immune dysregulation, even independent of Epstein-Barr virus (EBV) infection⁴⁻⁵. Although historically associated with EBV infection, a recent study showed 35% of patients with XLP1 had no evidence of previous EBV infection and many patients are diagnosed based on positive family history alone⁵⁻⁷. No clear genotype phenotype correlation has been identified^{5, 8}. Here we report 3 siblings from a nonconsanguineous Yemeni family with hemizygous deletions of exon 2 of the SH2D1A gene who manifested different phenotypes at different ages (Table 1).

Patient 1 was well until 21 months of age when he developed bilateral bronchopneumonia and pleural effusion requiring hospital admission. Further investigation confirmed severe hypogammaglobulinemia, marked lymphocytosis and subsequently a hemizygous deletion of exon 2 of the SH2D1A gene. He commenced immunoglobulin replacement therapy and was monitored regularly. A donor search for hematopoietic stem cell transplant (HSCT) identified no suitable donor therefore HSCT was not undertaken at an early age. He developed EBV viremia first at 6 years old and received several courses of rituximab over the next few years. Upon depletion of B cells, EBV viremia persisted and further analysis confirmed the presence of EBV in T and NK cells. Recently he developed autoimmune hemolytic anemia (AIHA) requiring Rituximab and intravenous immunoglobulin (IVIG). He developed lower lobe lung collapse associated with *Hemophilus influenza* and chest CT confirmed bronchiectasis. He remains on immunoglobulin therapy and prophylactic antibiotics awaiting HSCT.

Patient 2 was diagnosed at birth based on the positive family history. He remained well until 3 years of age when he developed intermittent abdominal pain. This was not associated with fever, night sweats or diarrhea/constipation. Further investigation confirmed raised LDH, anemia and negative EBV PCR. Abdominal CT scan demonstrated marked thickening of the distal ileum with pathological mesenteric and right iliac fossa enlarged lymph nodes. A biopsy was consistent with non-Hodgkin lymphoma and he received 2 cycles of R-GRAB (Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone, Methotrexate, Folinic acid, Etoposide, Tioguanine, Cytarabine, Intrathecal Methotrexate and Rituximab) chemotherapy before proceeding to a mismatched (8/10) unrelated cord blood transplant (Table 2) and successfully engrafted with 100% donor engraftment at last follow up 2 years post-HSCT. He developed gut and skin graft versus host disease (GvHD) with complete resolution. He also developed AIHA post-HSCT requiring steroid, rituximab, high dose IVIG and cyclosporine (which was stopped following the development of posterior reversible encephalopathy syndrome (PRES)). Currently he is fit and well.

Patient 3 was again diagnosed in infancy based on family history. He thrived and developed normally until 11 months of age when he developed generalised seizures. Brain CT and MRI scans showed multiple areas of signal abnormality in the cerebral hemispheres, internal capsules and cerebellum but no hydrocephalus or hemorrhage (Figure 1). He required PICU admission and ventilation to control his seizures. A lumbar puncture showed a raised protein in CSF with no cells present. There was no evidence of hemophagocytosis on bone marrow aspirate and trephine. He never developed any systemic features of HLH; ferritin was modestly raised to a peak of around 2,000 µg/L, triglycerides of 3 mmol/L and soluble CD25 of 10,000 pg/ml. He was commenced on the HLH 94 protocol⁹; however, he received only 2 doses of etoposide due to developing mucositis. A repeat brain MRI showed more significant abnormalities and progressive lesions with herniation. An external ventricular device was inserted to relieve oedema and brain biopsy confirmed a lymphocytic infiltrate and features of immune dysregulation but no specific hemophagocytosis. He then was treated with Campath 1-H 0.3 mg/kg in total which led to modest improvement. He developed a right lower zone consolidation which impaired his ventilation. His nasopharyngeal secretion was positive for Respiratory syncytial

virus and treatment with zanamivir and ribavirin was initiated. A lung biopsy performed pre-transplant showed scarring with significant fibrosis and macrophage infiltrates with negative cultures and PCRs. He underwent a TCR alpha/beta CD19 depleted HSCT from a MMUD (8/10) (details in Table 2) with 100% donor engraftment on whole blood. However, he developed numerous complications post-transplant including thrombotic microangiopathy (TMA), Grade III skin GvHD, *Mycobacterium abscessus* and *Stenotrophomonas* lung infection and widespread skin breakdown. After several months abdominal distention and discomfort was noted with raised lactate and an abdominal CT scan demonstrated fatty infiltration of a grossly distended liver. He rapidly developed liver failure progressing to multi-organ failure and sadly died.

XLP1 is a disorder of severe immune dysregulation, with HLH, lymphoma and humoral abnormalities amongst its spectrum of manifestations⁵⁻⁶. It is associated with an increased susceptibility to severe EBV infection, however, 35% of patients are EBV negative at diagnosis and may already display a clinical phenotype. There appears to be no significant difference in mortality seen between EBV positive and EBV negative patients⁵. Considering the high morbidity and mortality rate, it is strongly recommended that genetic screening and counselling be carried out in families with a history of XLP1. However, patients diagnosed at birth due to positive family history still carry a significant risk of mortality despite monitoring as demonstrated here; highlighting the severity of this disorder. Considering the lack of genotype-phenotype correlation and unpredictable course of XLP-1^{5,8,10}, close monitoring remains critical to allow the prevention of infections, organ damage such as bronchiectasis, and to permit early treatment of EBV infection and other serious complications. Early curative treatment with HSCT may improve outcome especially if it is carried out before developing significant morbidities as we know that active disease at the time of transplant and use of a mismatched donor reduce survival to almost 50%⁵.

Author Contribution:

ZN and NR equally contributed in writing the manuscript .

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Table 1: Patients Characteristic

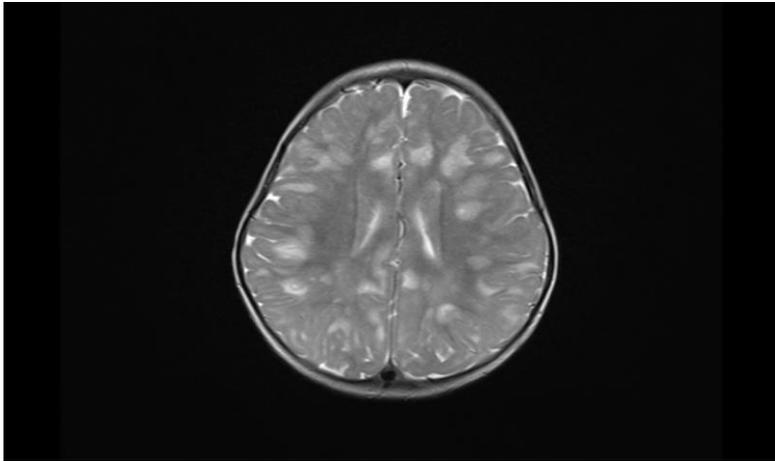
	Age @ DX	Age @ presentation	SAP expression	Presentation	Ig (g/L)	Vaccine responses	Lymphocyte subset (Cells x 10 ⁹ /L)	Pre-transplant prophylactic	Infections Pre-transplant
P1	2 years	21 months	Absent	Chest infection bronchiectasis panhypogammaglobulinemia	IgG 4.3 IgA <0.06 IgM 0.05	NA	CD3 6.13 CD19 2 CD56 0.35 CD4 3.4 CD8 2.6 Naïve T cells normal	IVIG	EBV
P2	birth	3 years	Absent	Non-Hodgkin lymphoma in ileum	IgG 4.5 IgA 0.52 IgM 0.66	Low then normal after booster vaccine	CD3 5.4 CD19 0.36 CD56 0.64 CD4 4.5 CD8 0.86 Naïve T cells normal	Nil before presentation Then IVIG	Nil
P3	8 months	11 months	Absent	Uncontrollable seizures CNS HLH Chest infection	IgG 2.76 IgA 0.36 IgM 0.58	Normal	CD3 6.7 CD19 1.25 CD56 1.54 CD4 5.66 CD8 0.96 Naïve T cells normal	Nil before presentation then IVIG/ABx	RSV Adenovirus HHV6

Dx: Diagnosis; P: Patient; CNS: Central nerve system; HLH: Hemophagocytic lymphohistiocytosis; EBV: Epstein Barr Virus; RSV: Respiratory Syncytial virus; HHV6: Human herpes virus type 6; Ig: Immunoglobulin; IVIG: Intravenous immunoglobulin; ABx: Antibiotic, NA: Not available.

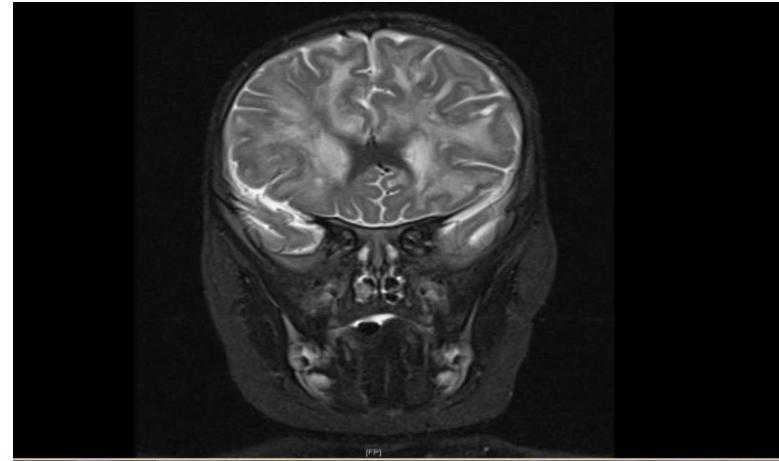
Table 2: Hematopoietic stem cell transplant characteristic

	Donor	Conditioning	GVHD Prophylaxis	CD34 dose	Donor Engraftment	Infection post-HSCT	Complication post-HSCT	outcome
P2	MMUD Cord 1 A mm 1 DQ mm	Treosulfan 14 g/m ² Fludarabin 150 mg/m ² Thiotipa 10 mg/kg	CSA MMF	4.6 x 10 ⁵ /kg	100%	CMV Adenovirus EBV	Engraftment syndrome	Alive & well
P3	MMUD PBSC 1 A mm 1 DQ mm TCR ab depleted	Treosulfan 14 g/m ² Fludarabin 160 mg/m ² Thiotipa 10 mg/kg ATG 15 mg/kg Rituximab 200 mg/m ²	CSA	10 x 10 ⁶ /kg	100%	Coronavirus Mycobacteria Stenotrophomonas	TMA Skin GVHD ATM lung infection MOF	Died

P: Patient; MMURD: Mismatched unrelated donor; mm: mismatched; TCR ab: T cell receptor alpha/beta; CSA: Cyclosporin A; MMF: Mycophenolate mofetil; CMV: Cytomegalovirus; EBV: Epstein Barr Virus; TMA: Thrombotic microangiopathy; GvHD: Graft versus host disease; ATM: Atypical mycobacteria; MOF: Multi organ failure; GVHD: Graft versus host diseases.



A



B

Figure 1: Brain Imagings

A: Brain MRI at the time of diagnosis of CNS HLH:

There are multifocal enhancing lesions involving white matter, area of cortical and deep grey matter. Leptomeningeal enhancement is also noted.

B: Brain MRI post-HLH 94 protocol therapy:

The multiple brain lesions appear more extensive in keeping with disease progression.