Clinical Immunology 198 (2019) 39–45

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Management of XLP-1 and ITK deficiency: The challenges posed by PID with an unpredictable spectrum of disease manifestations

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ARTICLE INFO

Keywords:
EBV
Lymphoma
XLP-1
ITK
Cancer
Hemophagocytic lymphohistiocytosis

ABSTRACT

The incorporation of next generation sequencing into routine immunological practice has enabled the identification of novel inborn errors of disease, helped define new categories of immune deficiency and extended the clinical spectrum associated with many long-recognised diseases. The family of EBV (Epstein Barr Virus)-sensitive primary immune deficiencies is one such group and in this paper we describe three families: two with X-linked lymphoproliferative disease type-1 (XLP-1) and one with deficiency of Interleukin-2 Inducible T-cell Kinase (ITK). Both diseases have a wide range of clinical manifestations and are united by an exquisite predisposition to EBV, dysgammaglobulinemia, hemophagocytic lymphohistiocytosis, and lymphoma. We detail our approach to diagnosis, treatment, and risk stratification in these diseases where both clinicians and patients must grapple with constant uncertainty.

1. Introduction

The warning signs of primary immune deficiency (PID) are generally considered to be recurrent, severe or unusual infections. However, the introduction of next generation sequencing (NGS), coupled with improved therapeutic options and survival rates, new categories of primary immune deficiency are being recognised [1]. Chief amongst these are diseases predisposing to infections with oncogenic viruses [2,3]. Another category of PID is the group of diseases predisposing to hemophagocytic lymphohistiocytosis (HLH). At the intersection of these two categories of PID sit disorders that lead to infections with Epstein Barr Virus (EBV), a virus that is both oncogenic and HLH-inducing.

In recent years, several novel EBV-associated PIDs have been described [4–9]. These diseases are united by a propensity for EBV viremia, lymphoma and immune dysregulation [4,6,7,9]. EBV is a DNA gamma herpes virus that was first suspected to be an oncogenic virus when it was detected in Burkitt lymphoma in 1964. Over 90% of the population are infected throughout their lifetime, with the vast majority suffering mild symptoms and a sizeable minority developing infectious mononucleosis [5,10,11]. Following initial infection of B lymphocytes, latent EBV infection persists in resting B cells [12–14] and occasionally in T- and NK-cells [5,15]. EBV expresses a range of proteins that are able to mimic activation and proliferation signals in B cells, thus preventing apoptosis and ensuring long-term survival of infected cells [15]. The Middle East is an area with higher rates of primary immune deficiency and combined immune deficiency is estimated to affect one in every 10,000 live births [16]. Due to a lack of registry data exact rates HLH are difficult to estimate, with the first case series of HLH from Saudi Arabia published in 2016 with only 12 patients [17]. Thus, we will focus on two diseases predisposing to EBV disease that we have cared for at our center: X-linked Lymphoproliferative Disease type-1 (XLP-1) and Interleukin-2 Inducible T-cell Kinase (ITK) [5,9–13,18,19].

XLP-1 is an X-linked disease caused by mutations in the *SH2D1A* gene, located at Xq25; mutations lead to a paucity of SAP (Signalling

Abbreviations: ATG, Anti-thymocyte globulin; ALL, Acute Lymphoblastic Leukemia; BFM, Berlin-Frankfurt-Munster; CT, Computed Tomography; EBV, Epstein Barr Virus; GVHD, Graft vs Host Disease; HG, Hypogammaglobulinemia; HLH, Hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; ITK, Interleukin-2 Inducible T-cell Kinase; IVIg, Intravenous immunoglobulin; MSD, Matched Sibling Donor; MFD, Matched Family Donor; NGS, Next Generation Sequencing; NKT, Natural Killer T; PID, Primary immune deficiency; SAP, SLAM-Associated Protein; SLAM, Signalling Lymphocyte Activation Molecule; XLP, X-linked Lymphoproliferative disease

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https://doi.org/10.1016/j.clim.2018.12.016
Received 7 September 2018; Received in revised form 9 December 2018; Accepted 15 December 2018
Available online 17 December 2018
1521-6616/

Lymphocyte Activation Molecule(SLAM)-associated protein) [13]. SLAM and SAP appear critical for EBV protection as males with XLP-1 are able to control infections with other viruses but are uniquely sensitive to EBV infection [5,12,20–22]. They also demonstrate dysgammaglobulinemia, immune dysregulation with a propensity to non-malignant lymphoproliferation, hemophagocytic lymphohistiocytosis (HLH),vasculitis, and lymphoma [13,23,24], particularly non-Hodgkin B cell lymphoma [7]; this is likely due to the impaired immunosurveillance and cytotoxic capacity of natural killer and CD8+ T cells [11,13,18,25]. Of note, lymphoma and HLH have also been described in EBV-naïve XLP-1 patients with 10% of patients demonstrating immune system abnormalities prior to detection of EBV [5,11–13,18].

ITK deficiency is an autosomal recessive disease, caused by biallelic mutations in the Interleukin-2-inducible T cell Kinase (*ITK*) gene, located on chromosome 5q31-34 [9,19]; ITK performs an important role in T-cell activation and proliferation, through its impact on calcium release and transcription [7,9,10]. Natural Killer T (NKT) cells are significantly reduced, with progressive CD4 lymphopenia as well as hypogammaglobulinemia [9,10]. Unlike patients with XLP-1, EBV viremia is universal and viral loads are much higher. The majority of reported ITK patients present with Hodgkin lymphoma or other B-cell lymphoma in the first decade of life, and five successful transplantations have been reported [9,26,27].

2. Materials and methods

We performed a retrospective review of all cases of XLP-1 and ITK at Hadassah University Medical Center and affected family members, compiling data on genetic mutation, presenting features, development of malignancy, EBV viral load, HLH disease markers, response to treatment (including HSCT), and survival data.

Written informed consent for publication of clinical details was obtained from patients above the age of consent, and from the parents of patients below the age of consent.

3. Results

Our population of 13 patients includes 10 with mutations in *SH2D1A* (leading to XLP-1) and three with mutations in the *ITK* gene. Baseline clinical data is presented in Table 1 and post-HSCT date in Table 2.

3.1. Patient clinical histories

3.1.1. XLP families

3.1.1.1. XLP-1: family A. The nine members of family A are part of a large Palestinian kindred with many cases of unexplained male death and early-onset lymphoma. [26] All affected members harbor the same c.158C > T, p.T53I mutation in exon 2 of the *SH2D1A* gene (Fig. 1).

Patients 1-5 are brothers; Patient 1 and Patient 2 died in Palestine many years ago and were never treated at our center, thus we have relied on history as provided by family members. Patient 1 initially presented with recurrent infections and hypogammaglobinemia. Despite intravenous immunoglobulin (IVIg) and antibiotics, at the age of three he died from pneumonia. Patient 2 presented similarly and died at age nine from lymphoma. Patient 3 was diagnosed with XLP-1 at two years of age on the basis of family history and recurrent infections, fever, hypogammaglobulinemia and failure to thrive. He commenced monthly IVIg and remained clinically well until age 32 when, after a six-month break in IVIg treatment, he again developed recurrent infections, fever and diarrhea, 10kg weight loss and night sweats. He was referred to our hospital, by which point he had developed hypoalbuminemia, deranged liver enzymes, pancytopenia, 3235copies/ml of EBV in his blood, and a ferritin of 21,126ng/ml. Computed tomography (CT) scans demonstrated bowel wall thickening and pulmonary cysts. Interstitial pneumonitis with chronic inflammation and secondary vasculitis were seen on lung biopsy. Bone marrow biopsy found focal hemophagocytosis and he was treated with the HLH-2004 protocol. Unfortunately, he did not respond to therapy and died of fulminant HLH.

Patient 4 presented to our hospital in 1991 at age six suffering from B cell acute lymphoblastic leukemia (ALL), having previously been treated with IVIg for hypogammaglobulinemia. He was treated according to the standard risk arm of the Berlin-Frankfurt-Munster (BFM) protocol and achieved remission. Bone marrow transplantation (BMT) was discussed but as no matched donor was found, this was not pursued and the patient continues on monthly IVIg replacement therapy to the present day. His brother (Patient 5) presented at age 14 with a history of hypogammaglobulinemia and new-onset ileocecal intussusception; he was diagnosed with a stage 3 abdominal Burkitt lymphoma. He was treated with an intermediate risk B cell lymphoma chemotherapy protocol and achieved remission; bone marrow biopsy showed evidence of macrophage erythrophagocytosis but he displayed no other features of HLH. As no matched donor was available, HSCT was not offered at the time. He is now 40 years old and he and his brother refuse plans for repeat donor search and HSCT.

Patients 6, 7, and 8 have been previously reported. [27] Patient 6 initially presented with hypogammaglobulinemia and developed rectal Burkitt lymphoma at four and seven years of age, was treated with high risk B-cell lymphoma chemotherapy protocol and achieved remission. He underwent HSCT from a matched cousin donor. He is currently 18 years' old with 100% chimerism and treatment-free. Patient 7 is the younger brother of patient 6 and he was diagnosed via Sanger sequencing at birth, given the family history. He did not develop lymphoma or HLH but demonstrated an EBV viral load of 9978 copies/ml prior to being transplant at 1.7 years of age; he currently a healthy nine-year-old boy. Patient 8 presented with recurrent ear infections at 1.5yo and was found to suffer hypogammaglobulinemia; infections ceased with the initiation of IVIg replacement. At 11yo he re-presented with abdominal pain, enlarged abdominal lymph nodes and liver lesions. Liver biopsy was done and Hodgkin lymphoma was diagnosed. Soon after successful chemotherapy treatment (Table 1) he underwent HSCT from a matched sibling donor (MSD). He is currently 14yo and treatment and symptom-free.

Patient 9 underwent Sanger sequencing at birth; his hypogammaglobulinemia was treated with IVIg. No matched bone marrow donors were found for HSCT and the family refused alternative donor transplantation. At the age of two years he developed abdominal Burkitt lymphoma and was treated according to high risk protocol and achieved remission. The family decided to attempt in-vitro fertilization (IVF) with pre-gestational genetic diagnosis and selection for an unaffected, HLA-matched fetus. Unfortunately, at three years of age and before the IVF attempts could be successful, the child developed fulminant HLH and died at a Palestinian hospital.

3.1.1.2. XLP-1 family B. Patient 10 is the fourth child to Palestinian parents who, at age two developed an EBV IgM positive febrile illness with hepatosplenomegaly and anemia. He initially had dysgammaglobulinemia (elevated IgA and IgM) and a normal bone marrow biopsy. He recovered from this illness but at three years of age developed pneumonia and pan-hypogammaglobulinemia. He was commenced on IVIg replacement and diagnosed with XLP-1 via WES, with a c.79G > A, p.G27S mutation found in the SH2D1A gene. He was referred to our center where he underwent HSCT from an MSD at 4.5 years of age (Table 2). He is currently five months' post-transplantation with 100% donor chimerism.

3.1.2. ITK family

Patients 11- 13 have previously been described in the literature [10,24] and all inherited the same homozygous c.1764C > G, p.Y588X mutation in the *ITK* gene. [10,24,27]

Table 1
Patient characteristics.

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
Gender (M = male, F = female)	M	M	M	M	M	M	M	M	M	M	F	M	M
Disease/ Mutation	XLP-1 c.158C > T p.T53I	XLP-1 c.158C > T p.T53I	XLP-1 c.158C > T p.T53I	XLP-1 c.158C > T p.T53I	XLP-1 c.158C > T p.T53I	XLP-1 c.158C > T p.T53I	XLP-1 c.158C > T p.T53I	XLP-1 c.158C > T p.T53I	XLP-1 c.158C > T p.T53I	XLP-1 c.79G > A, p.G27S	ITK c.1764C > G, p.Y588X	ITK c.1764C > G, p.Y588X	ITK c.1764C > G, p.Y588X
Presenting features	HG Recurrent infections Pneumonia	HG Recurrent infections Pneumonia	HG Recurrent infections, failure to thrive	HG	HG Ileocecal intussusception	HG	Family history for XLP-1	HG	HG Family history	HG Pneumonia	Recurrent infections	Recurrent infections	Psychomotor retardation Recurrent infections
Malignancy	No	Lymphoma	No	B cell acute lymphoblastic leukemia at 6yo	Burkitt lymphoma 14yo	Rectal Burkitt lymphoma at 4yo and 7yo	No	Hodgkin Lymphoma	Burkitt Lymphoma 2yo	No	Hodgkin Lymphoma 4yo	Hodgkin Lymphoma	Hodgkin Lymphoma
EBV Peak viral load (copies/ml)	N/A	N/A	3225	N/A	N/A EBV 'positive' at lymphoma recurrence	252	9978	667	0	450	171,300	664,657	28, 320
CMV Peak viral load (copies/ml)	N/A	N/A	Positive PCR (no viral load available)	N/A	Negative	3800	Negative	50	Negative	83	Negative	Negative	Negative
Fulfilled HLH criteria (Y/N)	No	No	Yes	No	No	No	No	No	Yes	No	Yes	No	Yes
HLH-defining criteria													
Fever: 38.5°C			Yes	N/A	No	No	No	No	Yes	No	Yes	No	Yes
Ferritin (peak) μg/L	N/A	N/A	21,126		N/A	3760	125	129	N/A	N/A	> 7500	428	2237
Triglycerides (peak) mmol/L (normal: 0–2.3)			N/A		N/A	0.8	1.0	N/A	N/A	N/A	3.4	3.3	4.0
Fibrinogen (nadir) MG% (normal: 140-400)			220		N/A	499	N/A	N/A	N/A	474	28.4	428	361
Hepatomegaly			Yes		No	No	No	No	No	Yes	Yes	No	Yes
Splenomegaly			Yes		No	No	No	No	No	Yes	Yes	No	Yes
Bone Marrow	N/A	N/A	Hemophagocytosis		High-grade malignant B cell lymphoma Necrosis Macrophages showed evidence of erythrophagocytosis	No disease	Not performed	No disease	Normal	Normal	Recurrence of Hodgkin lymphoma No HLH	Normal	Normal
Other disease features			Deranged liver enzymes Pulmonary nodules								Rash		
Hematology													

(*continued on next page*)

Table 1 (*continued*)

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
Gender (M = male, F = female)	M	M	M	M	M	M	M	M	M	M	F	M	M
WBC × 10^9/L (4-10)	N/A	N/A	0.3	N/A	6.8 (2012, in remission)	7.4	14.5	9.3	13.1	12.1	3.2	13.7	0.2
Hb g/dL (14–18)			10		14.1 (2012, in remission)	13.2	11.4	11.8	11.5	12.1	9.7	11.5	7.9
Platelets × 10^9/L (140-400)			19		185 (2012, in remission)	326	187	377	77	301	31	463	40
Lymphocytes × 10^9/L (1.5–4)			0.2		3.1 (2012, in remission)	1.9	10.4	2.1	9.2	4.2	0.7	2.8	0.0
Neutrophils × 10^9/L (2–7.5)			0.0		3.1 (2012, in remission)	4.8	2.1	6.4	2.8	6.9	2.2	9.6	0.1
Immunoglobulins (mg/dL)													
IgG	N/A	N/A	N/A	N/A	N/A	375 (↓)	463 (↓)	700 (↓)	607	50 (↓)	N/A	1038	N/A
IgA						N/A	< 42 (↓)	< 42 (↓)	72	< 5 (↓)		113	
IgM						N/A	< 32 (↓)	< 32 (↓)	61	15 (↓)		70	
Treatment													
Chemotherapy for lymphoma	No	Unknown	No	ALL BFM protocol	Intermediate risk B cell lymphoma protocol	High risk B cell lymphoma protocol		High risk HL protocol	Intermediate risk B cell lymphoma protocol		High risk HL protocol	High risk HL protocol	High risk HL protocol
HSCT	No	No	No	No	No	Yes (Table 2)	Yes (Table 2)	Yes (Table 2)		Yes (Table 2)	No	Yes (Table 2)	No
Other	IVIg antibiotics	IVIg antibiotics	HLH 2004 protocol		IVIg antibiotics				IVIg	IVIg	Rituximab High frequency ventilation CPR for cardiac arrest		Rituximab Pulse steroid IVIg
Current status													
Alive/deceased	Died at 3yo following severe pneumonia	Died 9yo secondary to lymphoma	Died at 32yo	Alive Monthly IVIg	Alive Monthly IVIg	Alive	Alive	Alive	Died at 3yo secondary to fulminant HLH	Alive	Died at 5yo secondary to Hodgkin recurrence and HLH	Alive	Died at age 14
Age (years)				35	40	18	9	14		4		14	

N/A = not available

Table 2
Post-transplantation data.

Pt	Dx	Age at transplant (years)	Donor HLA-Match	Conditioning	Chimerism	Ferritin ng/ml	WBC/Lymphocyte/Neutrophils/Hb/Platelets	EBV	IgG/A/M (mg/dL)	HSM	Triglycerides	Fibrinogen	Outcome age last follow-up (years)
6	XLP	7	MFD (cousin) 10/10	Fludarabine-Busulfan-Thiotepa-Rituximab-ATG	100% (March 2013)	150 (16/4/12)	6.8/1.4/4.7/12.4/288	Negative	N/A	No	N/A	N/A	Alive and well 18
7	XLP	1.71	MFD (cousin) 10/10	Fludarabine-Busulfan-Thiotepa-Rituximab-ATG	100% (July 2011)	124.9 (6/3/2012)	13.2/2.4/9.8/13.2/432 (17/2/2015)	Negative	N/A	No	N/A	N/A	Alive and well 9
8	XLP	11	MSD 10/10	Fludarabine-Busulfan-Thiotepa-Rituximab-ATG	100% (January 2011)	17.98 (6/8/12)	6.7/1.7/4.4/11.6/234 (2014)	Negative	N/A	No	N/A	N/A	Alive and well 19
10	XLP	4.61	MSD 10/10	Fludarabine-Busulfan-Thiotepa-Rituximab-ATG	100% (October 2018)	N/A	4.6/0.8/3.2/10.1/180	Negative	143/ < 5/10 (two months post-HSCT)	No	N/A	N/A	Stable three months post-transplant
12	ITK	3.9	MSD 10/10	Fludarabine-Melphalan-Rituximab-ATG	64% (2016) stable	N/A	9.2/1.8/7.0/14.8/244 (25/12/2017)	Negative	1038/113/70 (10 years post-HSCT)x′	No	N/A	N/A	Alive and well 14

Fig. 1. Family A pedigree (unaffected children not shown).

Patient 11 was successfully treated for Hodgkin lymphoma at age four but 18 months later represented with splenomegaly, fever, retroperitoneal lymphadenopathy, interstitial lung infiltration and high EBV viral load. Bone marrow biopsy demonstrated recurrent Hodgkin lymphoma (no hemophagocytosis), with 171,300copies/ml of EBV in blood. She failed to improve with forced diuresis, pulse steroids and rituximab. She met criteria for HLH (Table 1) and died of a cardiac arrest before the HLH2004 protocol could be enacted.

Patient 12 is the brother of patient 11 and was four years of age when he developed persistent fever and lymphadenopathy; lymph node biopsy demonstrated Hodgkin lymphoma and EBV. Bone marrow was normal and he was treated with an advanced stage high-risk Hodgkin lymphoma chemotherapy regimen, achieving complete remission and undergoing transplantation from a MSD. He is now 11 years post-HSCT with 64% donor chimerism, attends school and is living a normal, healthy life. His only treatment is thyroid hormone replacement for Hashimoto disease.

Patient 13, the cousin of patients 11 and 12, was initially diagnosed with moderate to severe psychomotor retardation, autistic features, and hearing impairment of unclear etiology. At five years of age he was successfully treated for high grade Hodgkin lymphoma and high EBV viral load. He received appropriate chemotherapy but six months later represented with EBV reactivation, recovering with Rituximab. In 2013 a full- HLA matched brother was born but the family refused HSCT. At 14 years of age he developed EBV reactivation with extensive lymphoproliferation, and lymph node biopsy demonstrated Hodgkin lymphoma. He fulfilled criteria for HLH but, given his medical history, the family decided against intensive chemotherapy. He received rituximab, IVIg and pulse steroids but died from multi-organ failure.

3.2. Survival

Overall survival was 54% (7/13), 60% for XLP-1 and 33% for ITK. Of the six surviving patients with XLP-1, four have undergone HSCT and two are treated with monthly IVIg. The only surviving ITK patient has undergone transplantation. All four patients who developed HLH died.

3.3. Malignancy

Six of 10 XLP-1 patients developed B cell malignancy (three Burkitt lymphoma, one B-cell ALL, one Hodgkin lymphoma, and one unspecified B cell lymphoma). All three patients with mutations in the *ITK* gene developed Hodgkin lymphoma. Nine of 13 patients in our cohort developed malignancy (69%).

3.4. EBV & Herpes Viruses

The average peak EBV viral load for the six XLP-1 patients for whom

results are available is 2429 copies/ml; average peak EBV viral load for the three patients with mutations in *ITK* is 288,092 copies/ml.

Patients 6, 8 and 10 had peak CMV viral loads available (Table 1). Patients did not develop PCR positivity for any other herpes viruses.

3.5. HLH Criteria

Average peak ferritin for patients who developed HLH was 10,288ng/ml. Of the patients who developed HLH, triglyceride levels were only available for patients 11 and 13, who both displayed elevated triglycerides of 3.4mmol/L and 4.0mmol/L, respectively. Fibrinogen levels were not available for patient 9, but the average fibrinogen level for patients 3, 11, and 13 was 203MG% (normal range). Three of the four patients displayed hepatosplenomegaly. Hemophagocytosis was only seen in the bone marrow of patient 3. Average Hb for patients with HLH was 9.8g/dL, platelets 42 $x10^9$/L, neutrophils $1.3x10^9$/L.

4. Discussion

It has long been recognised that the impaired immune surveillance inherent in PID enables cancer cells to escape destruction but the precise mechanisms by which malignancies arose in various PIDs remained unknown, with the exception of the DNA repair defects [27,28]. Our cohort of 13 Palestinian XLP-1 and ITK patients demonstrate an increasingly recognised category of PID-related cancer susceptibility and that of EBV predisposition [5,6].

EBV infection results in integration of viral DNA into the host cell genome, which can activate proto-oncogenes, inactivate tumor suppressor cells or stimulate growth factors with the development of B-cell polyclonal activation and proliferation, and eventually lymphoma [14,27]. Whilst exact rates of EBV seroprevalence amongst Palestinians are difficult to find, a Qatari study assessing EBV seroprevalence in the migrant worker population demonstrated 95.1% seropositivity in Jordanian/Palestinian workers. [29] A survey of Israel male army recruits demonstrated an 87% seroprevalence rate [30]. EBV is estimated to cause approximately 1.8% of worldwide cancer deaths, particularly in South East Asia where almost half of EBV-related cancer deaths occur [31]. An expanding list of PIDs demonstrate predisposition to EBV infection, including mutations in *BIRC4*, *CD27*, *CD70*, *MAGT1, PI3KD*, *DOCK8, STK4, LAT, NFKB1, RASGRP1* as well *SH2D1A* and *ITK*. [4–9,32,33] Each disease demonstrates a different mechanism leading to EBV infection [6]. Patients with XLP-1 have taught us that SLAM/SAP signalling is vital for EBV protection, as without SLAM/SAP EBV-infected B lymphocytes cannot activate CD8 cells to target infected cells. Mutations in *MAGT1* (X-MEN) have confirmed that impaired magnesium flux prevents downstream calcium flux and therefore T cell receptor-mediated activation, again prevent cytotoxic cells from destroying EBV-infected cells [5]. Different patterns of disease manifestations are also seen and, as demonstrated by our patient cohort, patients with mutations in the *ITK* gene suffer much higher EBV viral loads than patients with XLP-1.

Our cohort of 13 patients demonstrates the evolution, challenge and promise that exist in modern immunology. Patients 1-3 succumb to infection, malignancy and HLH before genetic diagnosis and effective treatment. Their family members developed malignancy, but because of earlier diagnosis, were treated before EBV viral load escalated or HLH developed. Patients 7 and 10 demonstrate how early the features of XLP-1 may appear: patient 7 was found to have asymptomatic EBV viremia and hypogammaglobulinemia, whereas patient 10 was hypogammaglobulinemic and suffered pneumonia. Early genetic diagnosis ensured both patients were transplanted before the development of lymphoma, HLH or organ damage.

Our cohort also demonstrates that HLH remains an overwhelmingly fatal diagnosis: all four patients with HLH died despite implementation of the HLH 2004 protocol. Patients 4 and 5, despite past malignancy, have remained well into adulthood receiving monthly immunoglobulin and are refusing HSCT. In the absence of any genotype-phenotype correlation, and with no predictive markers for disease progression, there is currently no way to predict which patients with XLP-1 or ITK will develop HLH and when they will do so [11,18]. In a 2011 multicenter study of 91 patients with XLP-1, Booth et al showed that overall survival had improved from 25% in Purtilo's original registry data [34], to 71.4% today. Post-HSCT survival was high, at 81.4%, and overall survival of untransplanted patients was only 62.5%. The most severe feature of XLP-1 was HLH: of XLP-1 patients who developed HLH, survival post-HSCT was 50%, and for untransplanted patients was only 18.8% [11,18]. In a recent review of 16 ITK patients by Ghosh et al, eight patients died (two from HLH), five are alive following HSCT and three patients were lost to follow up [9].

Thus, it appears clear that, just as lymphoma must be treated with chemotherapy, patients with either XLP-1 or ITK who have developed HLH should undergo HSCT. Allogeneic HSCT is curative for PID with good results in the setting of matched family or unrelated donor. In these patients, conditioning protocols based on a combination of fludarabine with alkylating agents, serotherapy, and appropriate supportive therapy can provide sustained engraftment and cure. No data is available regarding the results of transplants from alternative donors in the setting of XLP-1 or ITK. Haploidentical transplantation, which has traditionally required in-vitro T cell depletion, is not readily available in countries with limited health resources, impacting our Palestinian patients. However new approaches to haploidentical transplantation with the use of post-transplantation cyclophosphamide have demonstrated significantly improved results, extending the use of this procedure to countries with limited resources. This approach shows promise for patients without a matched donor but more data is required. [35,36]

Thus, although we are better able to diagnose inherited PIDs and treat their most serious manifestations, these diseases frequently remain unpredictable in their evolution, making prognostication daunting and a consensus approach to treatment difficult. Mutations in *SH2D1A* and *ITK* may result in a spectrum of manifestations ranging from an asymptomatic patient, isolated hypogammaglobulinemia, HLH, lymphoma, and death with differences being seen even amongst family members with the same genetic mutation [6,9–12,18,19,23]. Furthermore, patients may live lives unhindered by disease for many years before a sudden, rapid exacerbation that leads to rapid death. We must continue to research the molecular basis of these diseases, maintain accurate and long-term follow up data of patients in centralised databases to better understand natural disease progression, and learn to manage the increased promise and uncertainty. It may also be time to add new disease features such as high viral load, immune dysregulation and malignancy-predisposition to the modern warning signs of PID.

Funding information

Bella Shadur's position is supported by the Australian Government Research Training Program Scholarship.

This work was supported by the Deutsche Forschungsgemeinschaft (Discovery and Evaluation of new Combined Immunodeficiency Disease Entities; grant DFG WA 1597/4-2) and the ERA-Net ERARE Consortium EURO-CID.

Declarations of interest

None.

Acknowledgments

We would like to thank our patients and their families, as well as departmental nursing and administrative staff for their tireless commitment to patient care. In particular we would like to thank Mrs Maram Shweiki, without whose tireless work our ability to provide optimal care for our patients would be greatly diminished. We would

also like to thank Professor Zeev Rotstein, Director of The Hadassah Medical Center for his support of the department and our patients.

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