How genetic testing can lead to targeted management of XIAP deficiency–related inflammatory bowel disease

Ole Haagen Nielsen, DMSc¹ and Eric Charles LaCasse, PhD²

X-linked lymphoproliferative disease type 2 (XLP-2, OMIM 300635) is a primary immunodeficiency caused by the loss of X chromosome–linked inhibitor of apoptosis (XIAP), the X-linked inhibitor of apoptosis gene at Xq25. XLP-2 individuals are susceptible to several specific and potentially fatal infections, such as Epstein-Barr virus (EBV). Children with XIAP-related XLP-2 may present with either familial hemophagocytic lymphohistiocytosis, often triggered in response to EBV infection, or with a treatment-refractory severe pediatric form of inflammatory bowel disease (IBD) that might be diagnosed as Crohn disease. However, this monogenic cause of IBD is distinct from adult Crohn disease (a polygenic and multifactorial disease) in its etiology and responsiveness to therapy. XLP-2 and the associated IBD symptoms are managed by a reduced-intensity conditioning regimen with an allogeneic hematopoietic stem cell transplantation that causes reso-

lution of gastrointestinal symptoms. Exome sequencing has enabled identification of XIAP-deficient diseased individuals and has altered their morbidity by providing potentially lifesaving strategies in a timely and effective manner. Here, we summarize XLP-2 IBD treatment history and patient morbidity/mortality since its original identification in 2006. Since XLP-2 is rare, cases are probably underdiagnosed or misdiagnosed. Consideration of XLP-2 in children with severe symptoms of IBD can prevent serious morbidities and mortality, avoid unnecessary procedures, and expedite specific targeted therapy.

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X-linked lymphoproliferative (XLP) syndromes have only recently been recognized as recessive inherited primary immunodeficiencies, which are almost exclusively observed in males.¹ XLP is divided into two distinct groups: XLP-1 (OMIM 308240), which is caused by mutations/loss of the signaling lymphocytic activation molecule–associated protein (SAP) in the gene *SH2D1A* encoding for the SAP protein,² and XLP-2 (OMIM 300635), which is caused by X chromosome–linked inhibitor of apoptosis (XIAP) deficiency due to by mutations in the XIAP gene (previously referred to as the baculoviral IAP repeat containing 4 or *BIRC4* gene) at the chromosomal locus Xq25 (ref. 3) ([Table 1](#)). Both of these primary immunodeficiencies are frequently associated with a macrophage activation–like syndrome known as hemophagocytic lymphohistiocytosis (HLH), and intermittent splenomegaly associated with cytopenia and fever is preferentially observed in XLP-2 (ref. 1). Although female carriers of X-linked recessive disorders typically do not have symptoms, a few heterozygous female carriers of XIAP mutations have developed symptoms reminiscent of their male counterparts that demonstrate an abnormal skewed inactivation toward the mutated allele in women carrying one altered allele of the XIAP gene.^{4,5}

XLP-2 is usually, albeit not exclusively, considered in the setting of fulminant viral infection with Epstein-Barr virus (EBV).^{1,6} EBV is a ubiquitous virus reaching more than 90% of the adult population worldwide,⁷ which in healthy immunocompetent

individuals only causes infectious mononucleosis, at worst. Under usual circumstances, EBV, after the acute infection, remains dormant within the host and is primarily harbored in B cells.⁸ The virus is generally inactive (latent) and controlled by other lymphocytes (T cells) specifically targeting EBV-infected B cells.⁹ However, individuals with XLP-2 may respond to EBV infections by producing abnormally large numbers of T cells, B cells, and macrophages that can cause primary HLH, a life-threatening immunodeficiency disorder with associated hyperinflammation.¹⁰ This results in a violent immune response with accumulation of these cells in organs, as well as an uncontrolled infection producing huge amounts of proinflammatory cytokines initiating tissue damage and organ failure, which can ultimately be fatal.^{6,11}

XLP-1 syndrome does not present with inflammatory bowel disease (IBD)-like intestinal symptoms (although affected individuals may develop lymphomas that often arise in the ileocecal region of the intestine)¹² ([Table 1](#)). By contrast, symptoms involving the GI tract that mimic IBD and Crohn disease might in some cases be the exclusive disease manifestation of XIAP deficiency (i.e., XLP-2), and the diagnosis in those who have the mutation is reached solely with a confirmatory genetic test.^{5,13} Thus, the aim of this review is to emphasize to clinicians that XIAP deficiency should be considered in patients suspected to have Crohn disease with early onset or an aggravated clinical course resistant to conventional therapy, and that appropriate treatment strategies are available.

¹Department of Gastroenterology, Medical Section, Herlev Hospital, University of Copenhagen, Herlev, Denmark; ²Apoptosis Research Centre, Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada. Correspondence: Ole Haagen Nielsen (ohni@regionh.dk)

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Table 1 Clinical spectrum of presenting manifestations demonstrating phenotypic similarities and differences in patients with SAP deficiency (XLP-1) or XIAP deficiency (XLP-2)

	XLP-1	XLP-2	Ref.
Immunodeficiency and infection			
HLH ^a (due to EBV, CMV, and other infections)	++	++	3,29,36,69,70
Splenomegaly	+/-	++	3,36
Hypo- or dysgammaglobulinemia	++	++	12,70
Severe or fulminant infectious mononucleosis (due to EBV)	+	++	12,53
Intestinal Crohn-like inflammation	-	++	5,36,66,69
Aplastic anemia	+	-	71
Other infectious or inflammatory manifestations ^b	+	+	3
Biochemical or cellular defects			
Liver cytotoxicity/transaminitis and dysfunction (related to hepatitis)	+	+	3
Increased and sustained serum IL-18 (in association with HLH)	-	+	72
Increased or altered T-cell sensitivity to AICD/RICD ^c	+/-	+	73
Decreased NK/iNKT cell number or function	+	+/-	36,53
Defective fibroblast, monocyte, and PBMC responses to NOD1/2 ligands	-	+	4,27
Lymphoproliferative disorders			
Malignant lymphoma (often seen in the intestine ^d)	++	-	5,74

Note that considerable phenotypic variability can be present even within a family carrying the same gene mutation.

+, yes; ++, fairly typical; -, no; +/-, not typical or only partially affected or showing variable presentation at diagnosis.

AICD, activation-induced cell death; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis; IBD, inflammatory bowel disease; IL-18, interleukin-18; iNKT, invariant natural killer T cell; NK, natural killer cell; NOD1/2, nucleotide-binding oligomerization domain containing 1 or 2; PBMC, peripheral blood mononuclear cell; RICD, restimulation-induced cell death (i.e., another designation for AICD); XLP1, X-linked lymphoproliferative disease type 1 (OMIM 308240); XLP-2, X-linked lymphoproliferative disease type 2 (OMIM 300635).

^aHLH diagnosis is established either by fulfilling a molecular genetic confirmation for a familial syndrome HLH gene mutation or by having five out of eight of the following criteria: (i) fever; (ii) splenomegaly; (iii) cytopenia (affecting more than two cell lineages); (iv) hypertriglyceridemia and/or hypofibrinogenemia; (v) hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy; (vi) low or absent NK cell cytotoxicity; (vii) hyperferritinemia; and (viii) elevated soluble CD25/IL2R. ^bSuch as prolonged or periodic pyrexia, hepatitis, skin abscesses, uveitis, or vasculitis. ^cOpposite effects has been observed between SAP deficiency and XIAP deficiency. XLP1 T cells are more resistant than normal cells to AICD, whereas XLP-2 T cells are more sensitive to AICD than normal cells. ^dSeen primarily in the ileocecal region.

The table was compiled from the following references: 3-5,12,27,29,36,53,66,69-74.

SEARCH STRATEGY AND SELECTION CRITERIA

The search “BIRC4, hemophagocytic lymphohistiocytosis, SAP protein, XIAP, X-linked IAP, XIAP deficiency OR XLP-2” in combination with “inflammatory bowel disease, Crohn disease OR ulcerative colitis” was performed in the PubMed and Embase databases (cutoff date: 3 May 2016) to determine the extent of XLP-2 with inflammation of the gastrointestinal

tract. English-language reviews, practical guidelines, letters, editorials, and articles were evaluated. Subsequently, articles were selected according to their relevance as judged by the two authors, and additional papers were found in the articles’ reference lists. For some of the clinical data presented in Table 2, it was necessary to contact the corresponding authors to clarify information.

XIAP: IMMUNITY, NOD2 SIGNALING, AND IMMUNODEFICIENCY

The *BIRC4* gene encodes a caspase-inhibitory protein (XIAP) that protects cells from undergoing apoptosis in response to various death signals, including those coming from activated immune cells.¹⁴ In addition, XIAP mediates many aspects of innate immunity signaling and inflammation through XIAP’s E3 ubiquitin ligase activity located in the C-terminal portion of the protein¹⁵ (Figure 1). XIAP’s influence on receptor-interacting proteins, such as receptor-interacting protein 2 (RIP2), and inflammasome complexes allows either activation of the transcription factor NF-κB or generation of proinflammatory cytokines such as interleukin (IL)-1 and IL-18.¹⁶ XIAP deficiency may also preclude lymphomagenesis, which could normally depend on antiapoptotic effectors like XIAP for cancer cell survival and disease progression.^{15,17}

Importantly for IBD, XIAP is required for optimal signal transduction of the nucleotide-binding and oligomerization domain (NOD)-2 pathway, a pathway critical to intestinal immunity and susceptibility for Crohn disease.^{18,19} The binding of bacterial products, such as muramyl dipeptide (MDP), to NOD2 triggers self-association of the intracellular NOD2 receptor and the recruitment of a scaffolding protein, RIP2, and its polyubiquitination by XIAP and possibly E3 ubiquitin ligases, including Pellino3 or other IAPs such as cIAP1 and cIAP2 (refs. 19–23). The polyubiquitinated RIP2 acts as a signaling complex (or signalosome) by attracting another ubiquitin ligase, the linear ubiquitin assembly complex (LUBAC), and kinases, such as the IκB kinase kinase (IKK), leading to their proximity-induced phosphorylation and kinase activation. Both LUBAC-mediated Met1-linked ubiquitin chains and XIAP-mediated Lys63-linked ubiquitin chains are individually required for productive NOD2 signaling.²⁴ This is highly reminiscent of the RIP1 signalosome that forms on tumor necrosis factor-α (TNF-α) signaling through the TNF receptor that is dependent on RIP1 polyubiquitination by cIAP1 and cIAP2 (ref. 25). Activation of the kinases downstream of RIP2 (or RIP1) leads to the nuclear translocation of the transcription factor NF-κB and its gene modulatory effects on cytokine, chemokine, and defensin production to combat infections (Figure 2). XIAP gene mutations in XLP-2 individuals (Figure 3) are loss-of-function mutations that either lead to an absence of XIAP protein (decrease in the amount of full-length XIAP protein produced) or alter the function of critical regions (BIR2 and RING domains) in the expressed mutated protein that are required for XIAP-mediated NOD2 signaling in response to bacterial ligands (Figure 2). Hence, NOD2 signaling is severely compromised in XIAP-deficient individuals, leading

Figure 1 Influence of X chromosome–linked inhibitor of apoptosis (XIAP) in overlapping apoptosis inhibitory functions. Many domains of the XIAP protein support overlapping roles in immune signaling and in apoptosis inhibition, some of which are illustrated here for the BIR (baculovirus IAP repeat), UBA (ubiquitin associated), and RING (really interesting new gene) protein domains. The RING domain is an E3 ubiquitin ligase that acts along with an E2 and E1 complex to tag XIAP substrates with K48-branched, K63-branched, or possibly other branched ubiquitin chains. This overlap of functions may explain why mutations leading to XIAP loss of function or deficiency can have different effects on immunity and disease presentation. For example, mutations can result in loss of apoptosis suppression and therefore sensitize NK and T cells to activation-induced cell death and compromise immunity. Alternatively, mutations can impair NOD2 signaling and downstream inflammatory responses. NK- and T-cell responses may be more important to antiviral defenses (such as against EBV), whereas NOD2 signaling is more critical for antibacterial defenses in the gut and in the prevention of inflammatory bowel disease. The loss of XIAP protein function or expression is probably compensated for by other RIP2-binding E3 ubiquitin ligases, such as cIAP1, cIAP2, and Pellino3, but only partially compensated for because disease still manifests with XIAP deficiency.

Figure 2 Role of X chromosome–linked inhibitor of apoptosis (XIAP) in mediating NOD2 innate immune signaling. The recruitment of XIAP (and possibly other ubiquitin E3 ligases as well) to RIP2, upon NOD2 receptor stimulation by its ligand muramyl dipeptide (MDP), is shown. The XIAP-mediated Lys63 polyubiquitination of RIP2 (u-RIP2: ubiquitinated RIP2) creates a “signalosome,” which allows the recruitment of the ubiquitin ligase complex LUBAC, which in turn leads to additional Met1, or linear, ubiquitination of the attached chains. This dual ubiquitination of RIP2 leads to recruitment and activation of kinases and the subsequent activation of NF-κB and MAPK signaling. The translocation of nuclear factor-κB factors to the nucleus leads to the transcriptional induction of genes encoding cytokines, chemokines, and defensins. Then innate inflammatory response also recruits neutrophils and other immune cells to the site to help control the infection.

Figure 3 Overview of various deleterious mutations reported in the XIAP (*BIRC4*) gene in patients with XLP-2 (or in X chromosome–linked inhibitor of apoptosis (XIAP) deficiency presenting solely with inflammatory bowel disease (IBD)). Positions of the various XIAP mutations are shown against the diagram of the 497-amino-acid polypeptide–encoding human XIAP. Also shown are the various structural and functional homology domains in XIAP. These illustrated domains include the three BIR motifs, a zinc-finger domain that mediates many of the XIAP binding partner interactions, including binding and inhibition of caspases. The RING domain is a zinc-finger domain with E3 ubiquitin ligase activity, and the intervening UBA domain also participates in the recognition of ubiquitin and in the ubiquitination process. Missense mutations preferentially target the BIR2 region needed for binding to RIP2 and the RING domain needed for ubiquitination of RIP2 to mediate NOD2 signaling. The majority of the identified mutations may result in no XIAP protein being made or in a truncated polypeptide lacking the critical C-terminal RING domain. The 14 XIAP mutations identified in IBD patients in Table 2 are also shown here in red, as well as some additional reports of single case studies described in the text. *The missense mutation affecting the starting codon methionyl residue is included with the nonsense, frameshift, and deletion mutations because of the likely consequence of altering that critical initiating codon.

to a high degree of susceptibility to IBD developing with early onset and with a high degree of gene penetrance.^{26–28} Further, XIAP has recently been identified to play a role in fungal immunity through the dectin-1 pathway, because XIAP-deficient mice exhibit an XLP-2-like inflammatory syndrome on systemic *Candida* infection.²⁸ However, it remains to be clarified whether this pathway also contributes to human disease in the case of XIAP deficiency.

The mechanism by which the lack of a functional XIAP protein results in the constellation of signs and symptoms of XLP-2 is not completely clear. However, evidence points to several likely possibilities to account for these manifestations, for example, the increased susceptibility of immune natural killer (NK) and innate mucosal-associated invariant T (MAIT) cells to apoptosis (which may lead to EBV-associated HLH and splenomegaly), as well as defective monocyte/macrophage NOD2 signaling, which fails to control gut microbial homeostasis leading to manifestations of IBD. Nevertheless, in association

with a serum cytokine storm—with or without EBV—or with other viruses, such as cytomegalovirus (CMV) or human herpes virus 6 (HHV6) exposure,²⁹ macrophages might become inappropriately activated and may phagocytize bone marrow–derived immune or erythroid cells, observed histologically as HLH. The proliferation of immune cells can, however, in the context of XLP-2, be classified as an X-linked familial HLH syndrome, with similarities to other familial HLH syndromes with defects in NK cell functions affecting granzyme B and perforin degranulation and with the reduction of NK cytotoxicity toward infected target cells.^{29,30} This complication, which is characterized by an uncontrolled immune activation of macrophages with an overproduction of cytokines such as IL-6 and IFN- γ ,¹⁰ produces clinical symptoms in association with recurrent fever, splenomegaly, or even hepatitis.^{3,10} HLH is found in various forms of severity,⁶ for example, splenomegaly alone without any systemic signs (i.e., partial HLH),³¹ although in some cases it might take a fulminant course and be potentially lethal.⁶

EPIDEMIOLOGY

No epidemiological data regarding XLP syndromes are available, but XLP-2 cases constitute approximately 40% of well-established XLP syndrome patients,¹ without any racial or ethnic predilection.³² Nevertheless, XLP-2 may be overlooked or even misclassified¹³ because current assessments suggest that 4% of early-onset IBD cases considered Crohn disease are, in fact, XIAP deficiency.^{33,34}

Although clinical experience with patients known to have XLP-2 syndrome (first described in 2006 (ref. 35)) is limited, patients with XLP-2 syndrome have a slightly advantageous prognosis compared with XLP-1. Of the approximately 100 XIAP-deficient patients identified in a recent report, 22% have died prematurely.³⁶ Thus, individuals with HLH complications may experience a shortened life expectancy,³ although no increased rates of malignant lymphoma are observed in XLP-2 (ref. 5).

Table 2 summarizes the published clinical characteristics with comprehensive clinical data for 23 male individuals with Crohn disease–like symptoms. This cohort encompasses most of the XIAP-deficient IBD patients described in the literature (with a few exceptions). These patients have a 26% mortality rate, dying within a few years of onset of IBD symptoms or diagnosis. Of the six deaths, four were due to IBD, one to HLH, and one to medical treatment (i.e., complications due to hematopoietic stem cell transplantation (HSCT)). The severity of IBD in XIAP-deficient individuals is highlighted by the facts that nearly half (i.e., 45%) of the individuals have undergone abdominal surgery due to their bowel inflammation (**Table 2**) and that the median age of onset of IBD symptoms is 7 years (range, 0.1–41 years). By contrast, true IBD, or Crohn disease, as compared with symptoms related to XIAP-deficiency, is typically diagnosed later in life—after the age of 20.³⁷ Thus, Crohn disease has been shown to lead to abdominal surgery in 38 and 60% at 5 and 30 years after diagnosis, respectively, although most data are from the prebiologic treatment era;³⁸ however, because more efficient biologic therapies have been introduced in later years, this rate might decline in the future.

Furthermore, HLH seldom occurs in IBD,³⁹ whereas isolated splenomegaly is unrelated to Crohn disease. **Table 2** indicates that disease presentation is quite variable, even for members of the same family carrying the same XIAP mutation. A recent study in a Japanese cohort of 17 children with XLP-2 reported that six (35%) of the individuals suffered from colitis, and one patient died due to bowel disease at the age of 4.⁴⁰ Another patient with colitis underwent abdominal surgery (a colostomy) and one received HSCT. All XIAP mutations are included in **Figure 3**.

DIAGNOSIS OF XLP-2

The rarity of Crohn disease during the first years of life and/or resistance to conventional therapy should prompt a wider screening of such patients for possible other illnesses affecting immunologic or genetic defects. More than 50 distinct deleterious XIAP mutations have been found along all coding exons

(cf. **Figure 3**), including missense and nonsense mutations as well as deletions and insertions.²⁷ These comprise 29 mutations of the XIAP gene reported in a Japanese study as well.⁴¹

For identification of gene mutations, “next-generation” whole-exome DNA sequencing or sequencing of specific candidate disease genes might be used to sequence XIAP and other IBD candidate genes. These methodologies make it possible to capture all the possible XIAP mutations, including those not yet reported in the literature. Moreover, next-generation (DNA) sequencing techniques enable multiplexed sequencing of additional candidate disease genes at very little additional cost, such as can be done with existing small or large gene panels for IBD or for primary immunodeficiencies or genetic disorders in general. For example, a recent report describes the use of a 236-gene panel for primary immunodeficiencies (including several genes for monogenic IBD disorders) that identified a novel XIAP-deficiency mutation (Q111X) and that supports the benefits of using whole-exome sequencing to distinguish IBD secondary to a primary immunodeficiency.⁴² In another study, 21 patients presenting with macrophage activation syndrome (MAS) were screened for primary HLH, and 7 of them were sent for genetic testing of candidate genes; 1 was identified as having XIAP deficiency (S361X).⁴³

Genetic variants (polymorphisms and mutations) identified by sequencing can also be confirmed to be disease-causing by immunoblotting patients’ peripheral white blood cells for XIAP protein levels and protein size. Alternatively, flow cytometric screening of permeabilized peripheral blood mononuclear cells for intracellular XIAP immunoreactivity might be applied.⁴⁴ This method offers a quick XLP-2 screen with appropriate sensitivity and specificity.⁴⁵ Most loss-of-function mutations of the *birc4* gene appear to result in the loss or truncation of XIAP protein. However, the following caveat exists in that immunoblotting or flow cytometry should not be considered a conclusive diagnostic test for XLP-2 because point mutations, which might disrupt critical XIAP functions, may still lead to the appearance of full-length protein on a western blot or may preserve the epitope identified by flow cytometry, even though the XIAP protein is nonfunctional. Therefore, cellular functional assays of NOD2 signaling can be used to ascertain the function of XIAP variants in patient monocyte cell cultures treated with NOD2 agonists to facilitate the diagnostic process as well.⁴⁶ This assay is helpful not only for IBD cases but also for HLH, because it functionally demonstrates the loss of XIAP protein. Nevertheless, there is still the possibility that point mutations outside of the BIR2 and RING domains (important for NOD2 signaling) contribute to HLH via other immune pathways, but this remains to be clarified. Note that such assays are considered experimental.

XLP-2 SIMILARITIES TO CROHN IBD

IBD consists of various disorders, of which ulcerative colitis⁴⁷ and Crohn disease⁴⁸ are the two most prevalent entities. In recent years, genome-wide association studies have identified more than 160 IBD susceptibility loci involved in the regulation of intestinal barrier functions as well as innate and adaptive

Table 2 Clinical characteristics of XIAP-deficient male patients with IBD from 14 families in 2015 (n = 23)

Patient ID	XIAP mutation	Age of onset of IBD (y)	GI pathology and location	HLH (y)	Other manifestations	Surgery (y)	Medical treatment	HSCT (y)	Survival outcome and cause of death (y)	Ref.
P1.1	E99KfsX129	41	Colitis	18 mo	Splenomegaly, cholangitis	NS	NS	NS	Died (42, digestive bleeding)	5
P1.2	E99KfsX129	7	Ileitis, colitis, anoperineal lesions	7	Splenomegaly, cholangitis, skin abscesses	Colectomy (21)	Steroids, azathioprine, anti-TNF- α		Alive (26)	5
P2	I397NfsX405	3.5	Colitis	2			Steroids, cyclosporine		Alive (6)	5
P3.1	G466X	20	Colitis		Skin abscesses	NS	NS	NS	Died (27, IBD)	5
P3.2	G466X	33	Colitis, anoperineal lesions		Splenomegaly, arthritis		Anti-TNF- α , antibiotics		Alive (34)	5
P3.3	G466X	12	Gastritis, colitis, anoperineal lesions		Splenomegaly, skin abscesses		Steroids, mesalazine, azathioprine, cyclosporine		Alive (14)	5
P4	R381X	4	Colitis	NS	NS	NS	NS	NS	Died (4, IBD)	5
P5	Del. Exons 1-2	2	Colitis	0, 2, 3			Steroids, cyclosporine, anti-TNF- α		Alive (5)	5
P6.1	I494N	12	Colitis		Malignant tumor	Colectomy (NS)			Alive (43)	5
P6.2	I494N	7	Gastritis, colitis	12		Colectomy (13)	Anti-TNF- α , steroids, tacrolimus		Alive (14)	5
P7*	H220Y	7	Duodenitis, ileitis, colitis, anoperineal lesions	8	Splenomegaly	Colectomy (9)	Steroids, mesalazine, azathioprine, anti-TNF- α , thalidomide		Alive (14)	5
P8.1	Q332EfsX347	1	Gastritis, ileitis, colitis		Renal failure		Steroids, azathioprine, mycophenolate mofetil, anti-TNF- α		Alive (4)	5
P8.2	Q332EfsX347	11	Ileitis, colitis		Skin abscesses		Steroids, azathioprine, anti-TNF- α		Alive (27)	5
P9	Del. Exons 1-4	3 mo	Colitis			Ileostomy (NS)	Steroids, mesalazine, azathioprine, anti-TNF- α , thalidomide		Alive (8)	5
P10	C203Y	15 mo	Ileitis, colitis, anoperineal lesions		Seizures related to encephalitis	Colectomy (4)	Steroids, anti-TNF- α , G-CSF, tacrolimus, cyclophosphamide, azathioprine	5	Alive (11)	5

For patient identification, the first number refers to the family and the second number corresponds to the individual in that family. Time indicated in years (y) unless otherwise specified as months (mo). *These families also have affected heterozygous XIAP mutant females with IBD and/or erythema nodosum (female patients are not indicated in this table), including a “carrier” mother who underwent a colectomy with resection of distal ileum at the age of 32. The data are taken from previously published articles^{5,6,9} as well as from two recent single-case reports.^{59,75}

Del., deletion; GI, gastrointestinal; GVHD, graft-versus-host disease; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplant (allogeneic); IBD, inflammatory bowel disease; IVIG, intravenous immunoglobulin; LOF, loss of function; mo, month; NS, not specified; TNF- α , tumor necrosis factor- α ; TTD, time to death in years after onset of IBD; XIAP, X-linked inhibitor of apoptosis; y, year.

Table 2 Continued on next page

Table 2 Continued

Patient ID	XIAP mutation	Age of onset of IBD (y)	GI pathology and location	HLH (y)	Other manifestations	Surgery (y)	Medical treatment	HSCt (y)	Survival outcome and cause of death (y)	Ref.
P11.1	V279TfsX292	18	Colitis, anoperineal lesions		Splenomegaly, skin abscesses, arthralgia	Colectomy (21)	Steroids, azathioprine		Alive (34)	5
P11.2	V279TfsX292	8	Gastritis, colitis, anoperineal lesions	4	Splenomegaly		Azathioprine, anti-TNF- α , cyclosporine, steroids	11	Alive (13)	5
P12.1*	P225SfsX226	1 mo	IBD (NS)		Skin abscesses	Colectomy with ileostomy (17) additional surgery (24)	Azathioprine, anti-TNF- α		Alive (31)	62
P12.2	P225SfsX226	Early childhood (NS)	IBD (NS)		Skin abscesses		Steroids, immunosuppressives (NS)		Died (16, fulminant colitis)	62
P12.3	P225SfsX226	12	Ileitis, colitis		Skin abscesses, warts, chronic sinusitis and recurrent chest infections, epidermolysis bullosa dystrophica	Total colectomy (16)	Steroids, antibiotics (imiquimod cream for warts)		Alive (41)	62
P12.4	P225SfsX226	3	Ulcerative gastritis and pancolitis		Erythema nodosum, recurrent respiratory tract infection and otitis		Steroids, anti-TNF- α , cyclosporine, mycophenolate mofetil, JC virus-specific T-cell infusion	10	Died (12, after HSCT complications/infection/GVHD/renal failure/encephalopathy)	62
P13	A459GfsX472	3 mo	Anoperineal lesions, IBD (NS)	6 or 7	Splenomegaly, hepatomegaly		Steroids, azathioprine, anti-TNF- α , IVIG		Died (6 or 7, pulmonary edema)	75
P14	R238X	7	Colitis	1.7, 3	Splenomegaly (treatment-related hepatic chronic GVHD)		Steroids, cyclosporine, tacrolimus, mycophenolate mofetil, tocilizumab, methotrexate, etoposide	7	Alive (9)	59
Total: 23 pts	Total: 14 different LOF mutations	Median: 7 y (n = 22) (range: 0.1–41); rate of pediatric or early onset IBD: 87% (20/23)	Rate of ileitis: 32 % (6/19)	Before IBD: 3 pts; circa IBD: 2 pts; after IBD: 3 pts; before and after IBD: 2 pts; HLH rate 41 % (9/22)	Rate of splenomegaly: 48% (10/21)	Surgical rate: 45% (9/20)	Therapies involving anti-TNF- α : 68% (13/19)	Transplant rate: 30% (6/20) NB includes two cases of ongoing HSCts	Mortality rate: 27% (6/22) Average TTD: ~5 y (range: <1 to <16)	

For patient identification, the first number refers to the family and the second number corresponds to the individual in that family. Time indicated in years (y) unless otherwise specified as months (mo). *These families also have affected heterozygous XIAP mutant females with IBD and/or erythema nodosum (female patients are not indicated in this table), including a "carrier" mother who underwent a colectomy with resection of distal ileum at the age of 32. The data are taken from previously published articles^{5,62} as well as from two recent single-case reports.^{59,75}

Del., deletion; GI, gastrointestinal; GVHD, graft-versus-host disease; HLH, hemophagocytic lymphohistiocytosis; HSCt, hematopoietic stem cell transplant (allogeneic); IBD, inflammatory bowel disease; IVIG, intravenous immunoglobulin; LOF, loss of function; mo, month; NS, not specified; TNF- α , tumor necrosis factor- α ; TTD, time to death in years after onset of IBD; XIAP, X-linked inhibitor of apoptosis; y, year.

immunity, pointing to a close relationship between disturbance of the immune system and IBD.⁴⁹ IBD is a clinical trait associated with several primary immune deficiencies comprising chronic granulomatous disease. In this context, it is interesting that immunomodulatory therapy with thiopurines (used for controlling IBD)⁵⁰ may trigger the development of HLH,³⁹ and TNF inhibitor–induced skin lesions that might mimic manifestations observed in *XIAP*-deficient patients,³⁶ such as eczema, pustulosis, psoriasis, and xerosis cutis together with infections (e.g., bacterial folliculitis, impetigo, and herpes zoster), are well-recognized complications.⁵¹

Striking similarities in the pathological mechanisms between XLP-2 and IBD have been observed that affect the intestinal epithelial barrier function. Thus, patients with XLP-2 have clinical manifestations and gut histology resembling Crohn disease,^{5,13} probably due to compromised NOD2 signaling (NOD2 receptors recognize peptidoglycan products such as MDP derived from bacterial cell walls) in intestinal immune cells.^{18,27} However, other possibilities for disease pathology exist owing to the loss of antiapoptotic activity of XIAP in the MAIT cells, for example, but further studies are needed to address these possibilities. Nevertheless, *NOD2* is the strongest susceptibility gene associated with Crohn disease, and patients with *NOD2* mutations experience a more aggravated clinical course.⁵² XIAP is critically required for NOD2 receptor signaling through its interaction with RIP2, which is bound to NOD2. XIAP causes Lys63-linked polyubiquitination of RIP2 and enables recruitment of LUBAC, which is another ubiquitin ligase that adds Met1-linked ubiquitin chains to RIP2, and both of these ubiquitination reactions are required for NF- κ B signaling. This causes an increased production of cytokine, chemokine, and antimicrobial peptides required for gut immunity (Figure 2). Thus, the molecular importance of XIAP in the NOD2 pathway might explain why patients with *XIAP* gene mutations clinically resemble Crohn disease, especially because a substantial portion of patients with *XIAP* mutations report, or present with, inflammation from all segments of the GI tract,⁵ including skip lesions and inflammatory features together with crypt abscesses, epithelioid granulomas, transmural inflammation, and perianal fistulas.^{1,5,6,41,53} However, with the reservation for the low number of observations, it seems that ileocecal affection is more infrequent in XLP-2 (approximately 33%; Table 2) versus more than 80% in Crohn disease.^{54,55}

Moreover, extraintestinal manifestations of IBD are rather common;⁵⁶ among these, arthralgia, uveitis, and erythema nodosum have been reported in XLP-2 as well.^{6,46,53} Uveitis has also been reported in an *XIAP*-deficient child with HLH, and the authors noted that uveitis is linked to XLP-2 but not to other familial HLH syndromes.⁵⁷

TREATMENT

The clinical course in the subset of IBD patients diagnosed with XIAP deficiency is often severe, and there is no evidence that more aggressive treatment with conventional therapeutics (that is, glucocorticoids and immunomodulators such as thiopurines

and methotrexate)⁵⁰ and TNF inhibitors⁵⁸ is effective or beneficial to this group^{5,34,53} (Table 2). In this context, it should be emphasized that standardized medical treatment options for XLP-2 do not exist but need to be established through working groups and possibly in future randomized, controlled trials; however, a key issue is that it is difficult to accomplish this for a rare or even overlooked disorder.

A patient who is thought to have Crohn disease with an aggravated clinical course and resistance to conventional therapy should be tested for XLP-2. A prompt diagnosis can avoid unnecessary surgical and diagnostic procedures and therapies and might facilitate the initiation of lifesaving allogeneic HSCT that will cause resolution of Crohn disease–like symptoms. HSCT restores XIAP expression and function in immune cells derived from donor bone marrow precursors. This treatment option has been used with success in XLP-2 patients with intestinal symptoms⁵⁹ and may prevent the acute onset of HLH due to XIAP deficiency.^{34,53}

In addition, patients with XLP-2 as well as HLH should be monitored for EBV infection status and be screened routinely for hypogammaglobulinemia, which is transient in this condition and might require intravenous immunoglobulin (IVIG) treatment.¹² Allogeneic HSCT should be considered only in the setting of XLP-2-related IBD or HLH. Moreover, a recent clinical trial in adult patients with treatment-refractory Crohn disease (without a genetically identified primary immunodeficiency) demonstrated that autologous HSCT is not superior to conventional treatment.⁶⁰

There is no established consensus or guideline regarding the criteria for deciding when to proceed to allogeneic HSCT for XLP-2. Nevertheless, it is recommended that allogeneic HSCT be considered as early as possible for most patients with XLP-2.^{61–63} However, some additional issues need to be considered. Considerable initial morbidity and mortality may be associated with donor HSCT in patients with XIAP mutations (versus other primary immunodeficiencies), owing primarily to XIAP-deficient individuals experiencing increased toxicity to a busulfan-containing conditioning regimen.⁶⁴ However, the risks related to the HSCT are not as serious when using non-busulfan conditioning regimens,^{36,59,61,63,65} indicating that conditioning regimens with reduced toxicity are promising alternatives and that therapy—other than HLH—should be limited to selected individuals with symptoms of severe Crohn disease refractory to conventional treatment. Thus, there is an urgent need for transplantation protocols associated with reduced toxicity, and current data indicate that combining a minimal intensity immunoablative antibody-based conditioning regimen with a high stem cell and T-cell dose graft makes it possible to secure curative engraftment with low toxicity for XIAP deficiency.^{61,65} The fact that allogeneic HSCT from an XIAP-proficient individual is a lifesaving option for XIAP-deficient individuals with IBD clearly suggests that the disease-causing defect due to XIAP loss is within the immune effector cell population and not within enterocytes and other cell types (because the gut

cells are still XIAP-deficient in the XLP-2 individuals who have undergone transplantation).

SUMMARY

XIAP deficiency–related intestinal inflammation may be indistinguishable from Crohn disease, and the contribution of *XIAP* mutations to intestinal inflammation and its effects on responsiveness to therapy and any other associations with morbidity or mortality should be thoroughly assessed. This syndrome may be more prevalent than previously thought, especially for the subset of Crohn disease patients with an early age of onset (<18 years old) or a more aggravated clinical course refractory to conventional medical therapy, or both.

In addition, identification of individuals carrying *XIAP* mutations will enable notification of those families and their physicians (as well as genetic counselors) so that they may informed decisions. Asymptomatic individuals (family members identified as carrying the same disease-causing mutation) may develop a fatal disease (e.g., HLH) related to their underlying primary immunodeficiency, which could be mitigated in part via patient education, attentive screening (e.g., EBV testing), and prevention (e.g., IVIG administration), as well as aggressive therapy with antivirals and other supportive care and eventually with allogeneic HSCT. Carrier females with this X-linked disorder would be counseled about the mode and likelihood of transmission to their offspring who may be carriers as well or may be affected, depending on the child's sex.

Diagnosis and treatment of these patients will require collaboration among a multidisciplinary team of physicians that includes pediatricians, gastroenterologists, geneticists, rheumatologists, immunologists/infectious disease specialists, intensivists, emergentologists, and hematologists. Diagnosis and targeted therapy can dramatically change the outcome for individuals with XLP-2, as seen in several case reports. Such an outcome was described in the case of a 15-month-old infant with intractable IBD,⁶⁶ as well as for others (see [Table 2](#)). A recent report described a protracted diagnostic odyssey and treatment history for a child with very-early-onset IBD (presenting at 3 weeks of age) who underwent abdominal surgeries at the ages of 7 and 10. This patient was eventually diagnosed with XIAP deficiency (complete gene deletion, exons 1–6) at the age of 17 and referred for HSCT.⁶⁷ Another detailed case report of very-early-onset IBD in an infant with XIAP deficiency encompassed the presentation of symptoms at 1 month of age to numerous interventions over the course of more than a year to an ultimate diagnosis of XIAP deficiency and allogeneic HSCT at 15 months.⁶⁸ An earlier genetic diagnosis could have promoted timely HSCT and thus avoided a colectomy.

CONCLUSION

Recently reported results pertaining to XLP-2 (XIAP-deficient) individuals with IBD symptoms have provided us with a greater understanding of this primary immunodeficiency that leads secondarily to Crohn disease. The experiences gained in treating

these individuals with reduced-intensity HSCT might facilitate improved survival and quality of life. Physicians and surgeons alike should be cognizant of this X-linked primary immunodeficiency syndrome so as to properly diagnose and treat it. This is especially important for individuals with early onset and an aggravated clinical course demonstrating resistance to conventional therapy. Guidelines need to be established for when to use lifesaving allogeneic HSCT with reduced-intensity conditioning regimens for XIAP-deficient individuals who present with, for example, IBD, HLH, or MAS-like syndromes.

DISCLOSURE

The authors declare no conflict of interest.

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