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XIAP Deficiency Masquerading as Crohn's Disease in an Adolescent Male

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1. Introduction

X-linked lymphoproliferative (XLP) syndromes are a group of inherited autosomal recessive primary immunodeficiencies almost exclusively affecting males. XLP is divided into two types: XLP-1, caused by mutations in the signaling lymphocytic activation molecule-associated protein (SAP), and XLP-2, resulting from mutations in the X chromosome-linked inhibitor of apoptosis (XIAP) gene, formerly known as BIRC4 [1]. These conditions are often associated with a macrophage activation-like syndrome or hemophagocytic lymphohistiocytosis (HLH) with splenomegaly, hypogammaglobulinemia, cytopenia, periodic fevers, or prolonged mononucleosis. Additionally, XIAP deficiency can manifest with gastrointestinal symptoms resembling inflammatory bowel disease (IBD) and Crohn's disease early in life [1, 2].

Here, we present a case of a pediatric male patient who was initially diagnosed with Crohn's disease at nine-years-old after presenting with recurrent perianal abscess and fistula. His course was complicated by refractory disease, extraintestinal symptoms, and frequent infections, leading to additional evaluation that revealed a mutation in the XIAP gene at a later age

2. Case Discussion

Our patient presented with a history early infection with Escherichia coli meningitis at age two months with subsequent recurrent ear, sinus, and respiratory tract infections. Of note, he additionally had a history of multicystic dysplastic kidney. Around age nine years, he developed a perianal abscess with fistula that required drainage and seton placement, for which he was referred to gastroenterology. On initial endoscopy, macroscopic findings were normal while the stomach showed moderate chronic active gastritis with reactive changes on microscopic examination. A few months later, he started to develop gastrointestinal symptoms, including abdominal pain, diarrhea, nocturnal stools, and hematochezia. He underwent repeat endoscopy which showed mild gastritis, a large duodenal ulcer with associated duodenitis, and aphthous ulcers in the rectosigmoid and descending colon. Microscopic examination revealed chronic active gastritis and duodenitis, ileitis with granulomas, and mild active colitis in the descending/rectosigmoid colon (Figure 1). Between the clinical presentation and the pathologic features, the diagnosis was consistent with Crohn's Disease.

He underwent additional evaluation with imaging confirming perianal disease, including perianal abscess, associated trans-sphincteric fistula, and inter-sphincteric fistula. He was initially started on adalimumab with improvement of symptoms, but shortly after, he had a recurrence of his perianal disease with associated diarrhea. After five months, he was transitioned to infliximab at 10 mg/kg every eight weeks in combination with immunomodulator methotrexate. He developed transaminitis, so immunomodulatory therapy was transitioned from methotrexate to azathioprine. His symptoms continued, mainly perianal disease, followed by escalation of infliximab with an increase in frequency to every four weeks, then escalation of dose to 15mg/kg. Additionally, he was

on the Specific Carbohydrate Diet as adjunctive therapy.

His clinical course was notable for multiple skin manifestations with a psoriasiform rash and skin infections. He continued to suffer from recurrent sinus infections as well as pneumonia. At age 14, he was diagnosed with chronic recurrent multifocal osteomyelitis (CRMO) of the second and third anterior left ribs, bilateral acromion/scapula, and right lateral clavicle. He was followed by Rheumatology and managed with pamidronate. He was also treated for enthesitis and arthritis of his hands, knees, and elbows, which was initially managed with hydroxychloroquine. Given his ongoing gastrointestinal and musculoskeletal symptoms, he was transitioned from infliximab to ustekinumab after four years of anti-TNF therapy. His perianal abscess continued to recur, requiring drainage, seton placements, and multiple courses of antibiotics. At 16 years of age, he underwent repeat endoscopy three years after initiation of ustekinumab, which showed perianal skin tags, mild chronic gastritis, duodenitis, ileitis with granuloma, and mild active colitis (Figure 2).

Given the severity of presentation with refractory perianal disease and frequent associated infections, he underwent additional immunologic workup at 17 years of age.

Evidence of prior cytomegalovirus was found but testing for Epstein Barr Virus, hepatitis B, rubella, varicella, diphtheria, tetanus, and pneumococcus was negative. At this time, blood counts, inflammatory markers, complement C3, C4, anti-dsDNA, Anti-RNP, Anti-SSA, Anti-SSB, Anti-SM, Anti-SM/RNP, TSH, anti-thyroglobulin antibody, and anti-thyroid peroxidase were all within normal limits. ANA was elevated with at titer of 1:160, homogeneous pattern. Additional testing revealed low T-cell and B-cell subset counts, specifically decreased absolute CD3, CD4, and CD8 counts. However, NK cell numbers, IgG, IgA, IgM, and IgE levels were within normal limits. B-cell immunophenotyping showed decreased mature B cells and ELISA testing revealed elevated IL-18 level. Functional flow cytometry studies for FOXP3 and SAP performed simultaneously were normal. Flow cytometry showed abnormal peripheral B-cell immunophenotype notable for decreased memory and switched-memory B cells and uncovered low XIAP expression in all cell populations. Single gene sequencing for XIAP performed at the University of Washington, was positive for a hemizygous pathogenic variant in XIAP associated with X-linked lymphoproliferative disease type 2 (XLP2) (c.542del, p.P181Qfs*4), confirming the diagnosis. The single base pair deletion in Exon 2 is predicted to result in a loss of function due to a shift in the protein reading frame leading to a premature termination codon.

The abnormal flow analysis for XIAP was consistent with XLP2 (X-linked lymphoproliferative disease 2), which explained this patient's clinical phenotype, including both IBD and autoimmune manifestations. He was referred to Genetics once a diagnosis was made for further counseling. Treatment options, including potential bone marrow transplantation, were discussed with the patient and family but they have deferred for now.

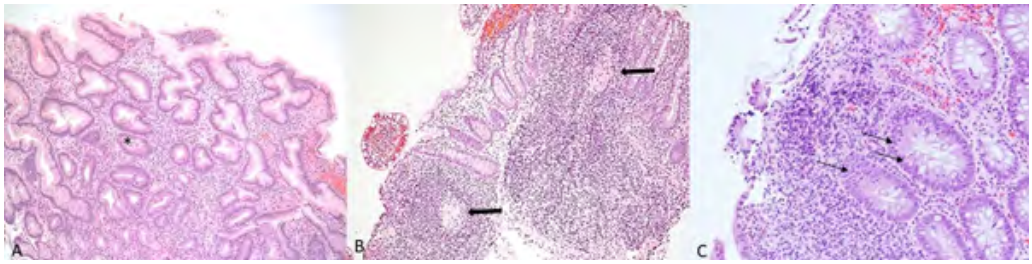

Figure 1: Initial diagnostic endoscopy with Crohn's Disease findings on biopsies at 9 years of age. A) Hematoxylin and eosin (H&E) 100x, chronic active gastritis, * neutrophils in gland. B) H&E 100x, ileitis with granulomas, bold arrows pointing to granulomas. C) H&E 200x, mild active colitis, thin arrows pointing to neutrophils in crypts.

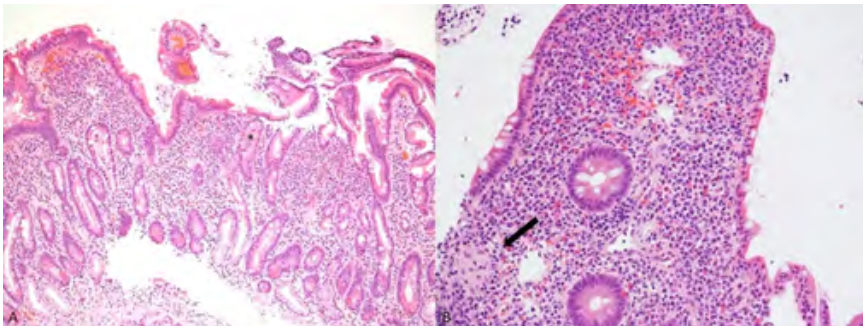

Figure 2: Follow up endoscopy with continued inflammation from Crohn's Disease on biopsies at 16 years of age. A) H&E 100x, duodenitis, * neutrophils in crypt. B) H&E 200x, ileitis with granuloma, bold arrow pointing to granuloma.

3. Discussion of XIAP and XIAP Deficiency

3.1. Presentation

Although XIAP deficiency is a rare diagnosis with an incidence of 1-2 cases per million live-born children, the true prevalence may be higher due to under-testing and, therefore, underdiagnosis [3]. XIAP deficiency is seen primarily in pediatric male patients, with symptoms presenting within the first few months to years of life. Increased severity of symptoms corresponds to younger age of presentation. The most common clinical manifestations of XIAP deficiency include hemophagocytic lymphohistiocytosis (HLH), recurrent splenomegaly in 57%, and IBD in 26% [4]. Common clinical manifestations of XIAP deficiency include hemophagocytic lymphohistiocytosis (HLH), recurrent splenomegaly, and inflammatory bowel disease (IBD) [1]. Epstein–Barr virus (EBV) is a common trigger for HLH, accounting for more than 60% of cases though other viruses such as cytomegalovirus (CMV) or human herpesvirus 6 (HHV-6) can also trigger HLH [4]. The evolution of HLH in XIAP patients can occur even in the absence of documented infectious agents [4].

The characterization of XIAP deficiency with inflammatory bowel disease (IBD) resembles Crohn's disease remarkably, making it challenging to differentiate diagnoses. In contrast with Crohn's disease, IBD in XIAP-deficient patients typically has a very early onset (<6 years of age), primarily in males. XIAP-deficient patients often follow a complicated course that may not respond to standard treatments, will often require surgical procedures, and will have an increase in the mortality rate [3]. Similar to Crohn's disease patients, individuals with XIAP mutations may present with inflammation along all segments of their gastrointestinal tract and may also develop skip lesions. They will commonly feature crypt abscesses, epithelioid granulomas, transmural inflammation, and perianal fistulas [1,5]. However, there are distinctions with CD; for instance, ileocecal involvement is less frequent in XLP-2 (approximately 33%) than in Crohn's disease (more than 80%) [1]. Additionally, extraintestinal manifestations of IBD are relatively common, and this may include arthralgia, uveitis, and erythema nodosum, which have also been reported in XLP-2 [1,5].

3.2. Mechanism of Action and Testing

XIAP deficiency, also known as X-linked lymphoproliferative syndrome type 2 (XLP-2), results from mutations in the XIAP (BIRC4) gene on chromosomal locus Xq25 [1]. Previously called BIRC4 gene, XIAP chromosome-linked inhibitor of apoptosis, is an important player in the prevention of apoptotic cell death by inhibiting caspases 3, 7, and 9 [3]. In addition, the XIAP gene is involved in various signaling pathways and cellular responses due to its ubiquitylation activity mediated by its RING domain, E3 ubiquitin ligase activity at protein's C-terminal region [1, 3]. Through this mechanism, XIAP is involved in with receptor-interacting protein 2 (RIP2) and inflammasome complexes. Downstream, this leads to the activation of the transcription factor NF-κB or the production of proinflammatory cytokines such as interleukin (IL)-1 and IL-18 [1]. XIAP participates in intracellular pattern-recognition receptor signaling, detecting peptidoglycan products like NOD1 and NOD2, leading to NFκB and mitogen-activated protein kinase (MAPK) cascade activation [3, 6, 7]. Interestingly, NOD2 was one of the first and strongest susceptibility genes associated with Crohn's disease (CD), and is often associated with XIAP deficiency [3, 8-10]. NOD2 receptors have previously been reported in the recognization of peptidoglycan products from bacterial cell walls in intestinal immune cells [1, 8]. The molecular significance of XIAP in the NOD2 pathway helps explain why patients with XIAP gene mutations clinically resemble Crohn's disease (Figure 3).

More than 50 different deleterious mutations in the XIAP gene have been identified. Advanced techniques like "next-generation" whole-exome DNA sequencing or targeted sequencing of specific candidate disease genes, including XIAP, can be employed to identify these gene mutations [1]. Next-generation DNA sequencing methods allow for multiplexed sequencing of additional candidate disease genes. This can be accomplished through existing gene panels, whether small or extensive, tailored for investigating inflammatory bowel disease (IBD), primary immunodeficiencies, or genetic disorders in general [1].

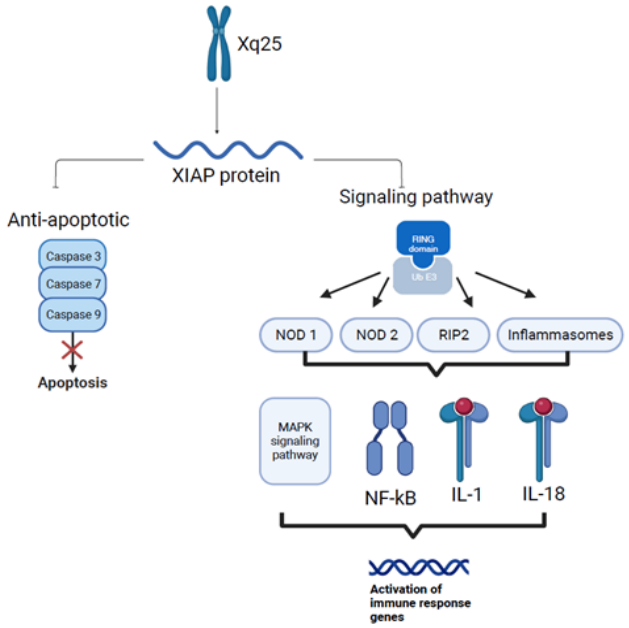

Figure 3: BIRC4/XIAP gene, found in chromosome Xq25, has two main roles: preventing apoptotic cell death by inhibiting caspases 3, 7, and 9 (left) and is involved in multiple signaling pathways and cellular responses (right). It has ubiquitylation activity that is mediated by its RING domain, E3 ubiquitin ligase activity that enables XIAP to influence receptor-interacting proteins like receptor-interacting protein 2 (RIP2) and inflammasome complexes, which can lead to either the activation of the transcription factor NF-κB or the production of proinflammatory cytokines such as interleukin (IL)-1 and IL-18. It participates in intracellular pattern-recognition receptor signaling, detecting peptidoglycan products like NOD1 and NOD2, leading to NFκB and mitogen-activated protein kinase (MAPK) cascade activation.

3.3. Treatment

In most XIAP-deficient patients, the inflammatory bowel disease (IBD) is severe and unresponsive to conventional medications like corticosteroids, azathioprine, or anti-TNF-alpha antibodies. As a result, colectomy can be recommended for some patients [8]. In other cases, complications from surgery and immunodeficiency can lead to fatal outcomes [8]. For a subset of patients with XIAP deficiency, allogeneic hematopoietic stem cell transplantation (HSCT) is a successful treatment option, leading to complete and sustained remission of IBD symptoms, as traditional therapies are sometimes ineffective [8]. A swift diagnosis can prevent unnecessary surgical and diagnostic procedures and therapies, facilitating the initiation of potentially life-saving allogeneic HSCT. Additionally, HSCT may help avoid the acute onset of HLH resulting from XIAP deficiency [1, 8]. It is important to note that while HSCT cures the defect in immune cells, it does not affect the defective intestinal epithelial cells, and thus, it may not necessarily improve intestinal disease [11]. In patients with monogenic IBD, it is crucial to thoroughly assess the potential advantages and drawbacks of HSCT. This procedure carries significant risks, such as sepsis, graft-versus-host disease, the development of secondary malignancies, and even mortality [11-13].

Our case report illustrates the need to consider immunodeficiencies, like XIAP deficiency, in medically refractory IBD patients in pediatrics even with a presentation later in childhood. Our patient is unique that his GI tract seems to involve all segments and he also developed CRMO, another autoimmune disease. Outside of our pediatric case, there is only one other case in the literature of a 17-year-old patient initially diagnosed with Crohn's disease (CD) [13]. The previous patient was started on standard treatment with an anti-TNFα but had relapses in IBD symptoms. At the age of 20, the patient was admitted for fever, splenomegaly, anemia, leukocytopenia, and other abnormalities, which were eventually linked to Epstein–Barr virus (EBV) as a possible trigger for hemophagocytic lymphohistiocytosis. Four years later, at age 24, the patient experienced an HLH relapse with the development of mediastinal lymphadenopathy, and genetic testing revealed a novel XIAP (BIRC4) gene mutation, c.266delA, leading to XIAP loss of function [14]. This mutation was identified as the primary cause of the patient's conditions, including CD and HLH [14].

4. Conclusion

As our understanding of monogenic causes of inflammatory bowel disease has expanded, it is crucial to consider the possibility of immune dysregulation in patients who display early-onset Crohn's disease or a severe clinical course that is unresponsive to conventional therapy regardless of the age of presentation. Accurate phenotyping with genetic diagnosis is critical to guide treatment options, improve outcomes, and provide appropriate genetic counseling when indicated. Our patient shows the complexities of diagnosing patients with XIAP deficiency and highlights the fact that not all patients present with severe disease in infancy.

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