Early-Onset Inflammatory Bowel Disease Caused by Mutations in the X-Linked Gene *IL2RG*

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Mutations in the X-linked gene *IL2RG* cause severe combined immunodeficiency (X-SCID), which is the most severe primary immunodeficiency (PID). In typical X-SCID, the disease is characterized by an almost complete absence of T and NK cells and nearly normal or high numbers of functionally deficient B cells [1]. Clinically, X-SCID presents in the first few months after birth as severe and persistent infection, usually of the lungs and gastrointestinal tract [2]. The disease is often fatal unless treated with allogeneic hematopoietic stem cell transplantation. Furthermore, patients with various PIDs exhibit clinical overlap with inflammatory bowel disease (IBD), which is one of their main symptoms at a very early age [3]. SCID patients often experience enteropathy and failure to thrive and rarely present with manifestations of IBD in the absence of severe infection [4]. To our knowledge, there have been no previous reports on the pathogenesis of X-SCID with manifestations of IBD.

A 6-month-old boy was referred to our hospital with a 2-month history of intractable diarrhea and recurrent perianal abscess with fever. He had no history of illness until the age of 4 months. He had not received live vaccines, such as BCG, polio, and rotavirus vaccine. Other than the perianal findings, his physical examination was unremarkable. At the time of referral, he had persistent chronic diarrhea with bloody stool and no sign of respiratory infection, although polymerase chain reaction assay yielded positive results for *Pneumocystis jiroveci* in gastric fluid. No other pathogenic microbes were detected in blood, respiratory tract secretions, gastric fluid, urine, or stool (Supplementary Material, Table 1). The immunological work-up revealed hypogammaglobulinemia (IgG, 10 mg/dL; IgA, 2 mg/dL; IgM, 9 mg/dL; and IgE <25 IU/mL) and severe lymphopenia (1363/μL), with a marked reduction in $CD3^+CD4^+$ T cells (5%), $CD3^+$ $CD8^+$ T cells (0%), and $CD3^-CD56^+$ NK cells (1%), but preservation of $CD19^+$ B cells (94%). Colonoscopy revealed multiple longitudinal ulcers from the transverse colon to the rectum (Figure), and biopsies demonstrated neutrophil infiltration, proliferative inflammatory granulation tissue, and small granulomata in the colon (Supplementary Figure). Immunohistochemistry revealed an abundance of CD3-positive cells in the inflammatory lesion. In contrast, there were no CD56-positive cells (Supplementary Figure).

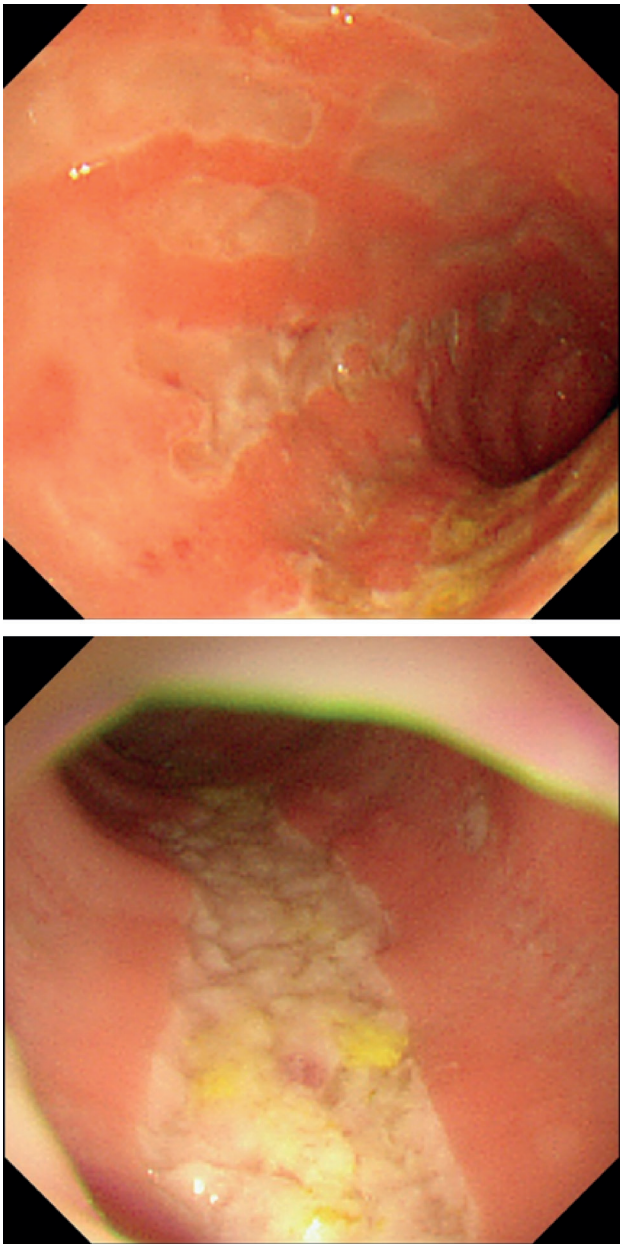

Figure. Endoscopic view of a typical ulcer in the sigmoid colon (upper part) and transverse colon (lower part).

P jiroveci infection was treated with sulfamethoxazole/trimethoprim, and the perianal abscess was treated with cefazolin and immunoglobulin replacement therapy. Fever, perianal abscess, and bloody diarrhea improved after these medical interventions, although watery diarrhea became persistent. Fifteen days after the intervention, sigmoidoscopy revealed that most of the ulcers in the rectum and sigmoid colon were healing. One month after referral, the patient received an HLA 8/8 matched cord blood transplant after a preparative regimen consisting of fludarabine (30 mg/m^2/d for 5 days) and melphalan (70 mg/m^2/d for 2 days). The watery diarrhea gradually ameliorated once the preparative regimen had started. Tacrolimus and short-term methotrexate (7 mg/m^2/d on day 1 and 5 mg/m^2/d on days 3 and 6) were used for prophylaxis of graft-versus-host disease (GVHD). The clinical course after cord blood transplantation was uneventful and diarrhea resolved completely 4 months after transplantation.

DNA sequencing showed a point mutation in the *IL2RG* gene (c.536_552delTGAACCACTGTTTGGAG; p.Leu179Argfs*26), representing the T(–)B(+)NK(–) phenotype of SCID. However, low numbers of CD3$^+$CD4$^+$ T cells had been observed in peripheral blood (81-141/μL). A subtle peak in the maternal allele was detected in peripheral blood using monitoring of chimerism by short tandem repeat analysis. DNA isolated from bead-selected CD3 T cells was detected in the maternal allele. All T cells expressed the T-lymphocyte activation marker HLA-DR$^+$, and a monoclonal peak pattern for T-cell receptor (TCR) γ was detected in peripheral blood. Similarly, maternal T cells and TCRγ clonality were confirmed in the biopsied gut tissue, which was infiltrated by a large number of T cells.

PIDs affecting intestinal immune and epithelial function can sometimes lead to IBD-like disease. PIDs caused by immune dysregulation, such as lipopolysaccharide-responsive beige-like anchor protein (LRBA) deficiency, also resemble symptoms of enteropathy presenting in immunocompetent individuals [5,6]. Azizi et al [6] showed the efficacy of sirolimus, which blocks the mammalian target of rapamycin for patients with LRBA deficiency refractory to conventional therapies. Therefore, it is considered that some of the PIDs associated with noninfectious enteropathy are caused by immune abnormalities. Little is known about the underlying mechanism of X-SCID.

Maternal T cells from fetal or perinatal transplacental passage can be engrafted and expanded in hosts with SCID, as they are unable to reject circulating maternal T cells due to severe cellular immune dysfunction, as occurs in 40% of patients with SCID [7]. Most SCID patients with maternal T-cell engraftment are asymptomatic, although some have mild symptoms and signs such as skin rash, elevated liver enzyme associated with an increased number of palpable lymph nodes, hepatosplenomegaly, and eosinophilia. In some rare cases, maternal T-cell engraftment causes GVHD manifesting as severe erythematous skin rash or chronic liver disease [7,8]; however, to date, the manifestations of GVHD due to maternal T cells have been limited to the skin and liver. In the present case, the patient showed no clinical signs other than gastrointestinal symptoms.

Various animal models for IBD have been developed, and the T-cell transfer model has been widely used. The IBD mice model showed that donor CD4$^+$ T cells induced colitis resembling IBD in SCID mice [9]. In general, CD4$^+$ T cells direct appropriate immune responses, maintain immune tolerance, and support differentiation of memory cells. However, CD4$^+$ T-cell subsets have also been shown to contribute to chronic intestinal inflammation, accumulating in the mucosa of IBD patients [10]. In the case we report, it was assumed that maternal CD3$^+$CD4$^+$ T cells expanded monoclonally in peripheral blood and caused colitis, similar to that in the IBD murine model. Following antimicrobial treatment, endoscopic findings improved. The colitis may have been associated with infection, although we were unable to detect any pathogenic microbes in the patient's stool.

Since the T-cell count was very low in the present case, we were unable to investigate detailed CD3$^+$CD4$^+$ T-cell subsets. Moreover, we were unable to rule out the coexistence of autologous T cells. Nonetheless, we showed the presence of maternal cells in the intestinal lesions, with significant T-cell infiltration despite there being only a few T cells in peripheral blood. Therefore, it is likely that these cells were strongly associated with pathogenesis of early-onset inflammatory bowel disease in the case we report.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

References

1. Fischer A. Severe combined immunodeficiencies (SCID). Clin Exp Immunol. 2000;122:143-9.
2. Notarangelo LD. Primary immunodeficiencies. J Allergy Clin Immunol. 2010;125:S182-94.
3. Uhlig HH, Schwerd T, Koletzko S, Shah N, Kammermeier J, Elkadri A, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology. 2014;147:990-1007 e3.
4. Bianco AM, Girardelli M, Tommasini A. Genetics of inflammatory bowel disease from multifactorial to monogenic forms. World J Gastroenterol. 2015;21:12296-310.
5. Azizi G, Abolhassani H, Habibi S, Rahamooz T, Mohammadi H, Jafarnezhad-Ansariha F, et al. Two Faces of LRBA Deficiency in Siblings: Hypogammaglobulinemia and Normal Immunoglobulin Levels. J Investig Allergol Clin Immunol. 2018;28(1):48-50.
6. Azizi G, Abolhassani H, Yazdani R, Mohammadikhajehdehi S, Parvaneh N, Negahdari B, et al. New therapeutic approach by sirolimus for enteropathy treatment in patients with LRBA deficiency. Eur Ann Allergy Clin Immunol. 2017;49(5):235-9.
7. Muller SM, Ege M, Pottharst A, Schulz AS, Schwarz K, Friedrich W. Transplacentally acquired maternal T lymphocytes in severe

combined immunodeficiency: a study of 121 patients. Blood. 2001;98:1847-51.
8. Kobayashi N, Agematsu K, Nagumo H, Yasui K, Katsuyama Y, Yoshizawa K, et al. Expansion of clonotype-restricted HLA-identical maternal CD4+ T cells in a patient with severe combined immunodeficiency and a homozygous mutation in the Artemis gene. Clin Immunol. 2003;108:159-66.
9. Maloy KJ. Induction and regulation of inflammatory bowel disease in immunodeficient mice by distinct CD4+ T-cell subsets. Methods Mol Biol. 2007;380:327-35.
10. Globig AM, Hennecke N, Martin B, Seidl M, Ruf G, Hasselblatt P, et al. Comprehensive intestinal T helper cell profiling reveals specific accumulation of IFN-gamma+IL-17+coproducing CD4+ T cells in active inflammatory bowel disease. Inflamm Bowel Dis. 2014;20:2321-9.

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