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CLINICAL QUIZ

An unusual cause of diarrhea in a child with nephrotic syndrome: Answers

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Answers

1) What are the possible causes of diarrhea in this patient?

Our patient was immunosuppressed at the time of diarrhea; peripheral $CD19^+$ and $CD20^+$ B cell count was still low due to the ongoing effect of rituximab (RTX). It is known that infectious gastroenteritis is the most likely cause of acute diarrhea in immunosuppressed patients; hence, the evaluation should be broad, including bacterial, mycobacterial, parasitic, and viral infections [1]. An extensive infectious workup was performed in our patient including cultures, serological tests, and assays which showed no obvious infectious cause.

Diarrhea can also be seen as a side effect of immunosuppressive drugs. Tacrolimus and mycophenolate mofetil (MMF) are immunosuppressives which are highly associated with diarrhea. Our patient was not receiving MMF treatment. Tacrolimus-induced diarrhea is usually self-limited [1]; therefore, we did not consider tacrolimus as a causative agent of the persistent and bloody diarrhea. Our patient's diarrhea persisted, acute phase reactants increased, bloody diarrhea and tenesmus developed, and a high fecal calprotectin level was detected. Therefore, inflammatory bowel disease was suspected, and eventually ileocolonoscopy and esophagogastroduodenoscopy were performed.

2) What is your diagnosis and what could be the underlying mechanism?

Histopathological findings of the colon biopsy were compatible with the diagnosis of ulcerative colitis (UC). Considering the patient's medical history, we thought RTX could be responsible for this condition.

The underlying mechanism of RTX-associated inflammatory bowel disease (IBD) is still uncertain. Mucosal immunity in the gastrointestinal (GI) tract is based on a balance of pro-and anti-inflammatory stimuli, involving innate, humoral, and cell-mediated immunity. B cells have important functions in the gastrointestinal system (GIS) like regulating inflammatory CD4 + T cells, clearing apoptotic cells and controlling self-antigens in the circulation. Depletion of B cells with RTX is non-selective and results in disruption of the inflammatory and anti-inflammatory balance in the GIS. In accordance, a number of studies and case reports have shown that RTX-induced IBD is associated with the complete depletion of B cells and infiltration of T cells in the intestinal mucosa [2–6]. In our patient, immunohistochemical analyses showed complete depletion of CD19 or CD20 + lymphocytes in the intestinal mucosa (Fig. 1).

3) How would you manage this patient?

For UC, prednisolone treatment was initiated, and the patient's symptoms and diarrhea rapidly resolved. Azathioprine was added on as a steroid-sparing agent. Tacrolimus

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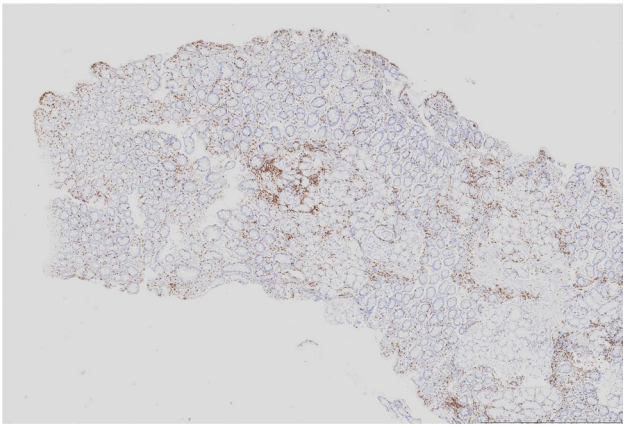

Fig. 1 Immunohistochemical staining of colonic specimen showed that all lymphocytes were CD3 positive; no CD19 or CD20 positive cell was observed

was tapered and discontinued in 2 months and prednisolone was tapered down slowly and discontinued after 1 year. A repeat colonoscopy after 6 months showed complete resolution of the ulcers and inflammation. However, in immunohistochemical analysis, staining with CD20 was detected only in a small number of lymphocytes and in one lymphoid follicle in the lamina propria, and CD19 was positive in a small number of lymphocytes and lymphoid follicles. No relapse of IBD or NS was experienced during the 2-year follow-up at the end of which azathioprine treatment was ceased. He is still in remission without treatment for the last 5 months.

Discussion

Steroids are the main treatment for idiopathic NS and remission is achieved in 80–90% of the patients. Up to 50% of patients develop multiple relapses and are defined as frequently relapsing nephrotic syndrome (FRNS) if they experience two or more relapses within a 6-month period. Fifty to sixty percent of children with FRNS also meet the criteria of steroid dependence. These patients get exposed to high doses of steroids and experience related side effects. To overcome this, cyclophosphamide, calcineurin inhibitors (tacrolimus, cyclosporine), and MMF can be used as steroid-sparing agents and still frequent relapses or steroid dependences are encountered in 10–20% of these patients [7, 8]. In such cases, RTX is an important alternative treatment whose effect has been demonstrated in both steroid-dependent and steroid-resistant NS [9–11]. However, there is insufficient data on the dosing schedule and long-term safety of RTX use in NS.

The underlying pathogenetic mechanism of idiopathic NS is still not fully understood and recent studies support the possible role of B cells. RTX is a chimeric anti-CD20 monoclonal antibody, resulting in depletion of B cells, reducing cytokine levels which are increased in NS and may also have non-immunological beneficial effects on podocytes [12]. In idiopathic NS, the remission period can be prolonged with RTX treatment, and consequently, other immunosuppressive treatments weaned [9, 10].

Rituximab is generally well-tolerated in most patients. Common side effects are infections and infusion-related reactions, most of which are mild and self-limited [9, 10, 13]. Occasionally, important reactions like anaphylaxis, lung injury, acute demyelinating neuropathy, and multifocal leukoencephalopathy can be seen [13–17]. De novo IBD or exacerbation of IBD is a rarely reported and severe adverse effect of RTX. Eckman et al. examined 460 adult patients with a history of diarrhea after RTX treatment and showed colitis histologically in 21 patients (12 IBD, 9 microscopic colitis). The median (interquartile range, IQR) time between the first RTX dose and the onset of diarrhea was 8 (4.5–29.0) months, and the median number of doses received before symptom onset was 6 (5.0–12.0). When compared to patients with microscopic colitis, patients with IBD received a higher number of RTX courses with longer treatment durations [18]. Knowledge on RTX-related IBD in the pediatric age group is scarce. Ardelean et al. reported the first pediatric case of RTX-associated IBD. They presented a 4-year-old male who was diagnosed with UC while he was being investigated for abdominal pain and bloody diarrhea 6 weeks after RTX treatment for steroid-dependent NS [5]. Morita et al. reported a 15-year-old boy with NS who developed Crohn's disease, which was thought to be related to RTX [19]. Recently, Machida et al. presented a 14-year-old girl, diagnosed with RTX-induced Crohn's disease 10 months after the first RTX dose [20]. Pediatric cases of RTX-induced IBD are summarized in Table 1.

Although the exact mechanism of RTX-associated IBD is unknown, it is suggested that imbalance between B and T cells in the GIS and the overactivation of T cells due to loss of B cells are responsible. In their study, Mizoguchi et al. reported that B cell-depleted T cell receptor α μ double-knockout mice developed severe colitis, and they speculated B cells, by producing cytokines like IL-10, play a regulatory role in inflammatory reactions [3]. In a mouse model, Yanaba et al. showed intestinal injury to be more severe in CD19-deficient mice compared to wild-type [2]. Cavalcanti et al. presented a case of RTX treatment-induced Crohn's disease and showed a total depletion of CD20 positive B cells in the ileal mucosa and an increased number of CD3 + T lymphocytes in the tunica propria and intraepithelial mucosa [4]. Similarly, Tsuzuki et al. reported a case who received RTX for mucosa-associated lymphoid tissue lymphoma and developed ileocolitis. They showed increased CD3-positive lymphocytes and complete depletion of CD20-positive lymphocytes in the colonic mucosa on immunohistochemistry [6]. With their pediatric case report, Ardelean et al. documented RTX-induced severe enterocolitis with complete absence of

Table 1 Rituximab-induced inflammatory bowel disease in pediatric cases with nephrotic syndrome

Author, year	Age (years), sex	Primary diagnosis	Presentation of IBD	Type of IBD	Rituximab regimen	Time to IBD symptoms following first dose of rituximab	Management	Follow-up time after IBD	Outcome for IBD	Outcome for NS
Ardelean et al. [5], 2010	4 y, male	NS	Abdominal pain, bloody diarrhea, buccal mucosa ulcers, intermittent fevers	Ulcerative colitis	4-week course (375 mg/m^2/dose per week) Total: 4 doses	6 weeks	Steroid, azathioprine	3 years	Rapid resolution following prednisolone (2 mg/kg/d); relapse following steroid discontinuation and complete endoscopic resolution on 7th month with steroid and azathioprine	Relapse occurred after 9.5 months, azathioprine was switched to MMF 4 months after first relapse due to frequent relapses and no relapse occurred in the following 2 years after MMF treatment
Morita et al. [19], 2019	15 y, male	NS	Abdominal pain, watery stools, weight loss	Crohn's disease	Initial dose of 375 mg/m^2, four doses for a 2-year period Total: 4 doses	27 months	Infliximab	20 months	No recurrence of symptoms following infliximab therapy	No relapse
Machida et al. [20], 2022	14 y, female	NS	Prolonged low-grade fever, abdominal pain, frequent diarrhea	Crohn's disease	2 doses with 12 months interval Total: 2 doses	10 months	Ustekinumab	NA	Clinical remission within 1 month and endoscopic improvement after 3 months	NA
Present case	10 y, male	NS	Abdominal pain, diarrhea with mucus, foul smell, and blood	Ulcerative colitis	Initial 4-week course (375 mg/m^2/dose per week), two more doses within 1-year period Total: 6 doses	20 months	Steroid, azathioprine	24 months	Clinical remission within 2 weeks and endoscopic improvement after 6 months	No relapse during 24-month follow-up, prednisolone discontinued after 1 year and azathioprine discontinued after 2 years

IBD, inflammatory bowel disease; *MMF*, mycophenolate mofetil; *NA*, not available; *NS*, nephrotic syndrome

CD19 and CD20 B cells and strong activation of mature CD3, cytotoxic CD8, and FOXP3 (forkhead box P3 gene) positive regulatory T cells in the inflammatory infiltrate [5].

It is not clear why the disease presents as Crohn's disease in some patients and as UC in others. Machida et al. emphasized that UC usually occurs within the first 1 or 2 months after RTX, and Crohn's disease occurs between 10 months to 4.5 years. According to this observation, it can be thought that the development of Crohn's disease after RTX is later than that of UC, but in our patient, this was not the case since the symptoms started 20 months after the initiation of the drug.

Treatment of RTX-related IBD is a challenge. Cessation of the offending agent and treating IBD is the most commonly used approach. Eckman et al. showed that along with IBD-directed therapy, most patients experienced resolution of their symptoms after discontinuation of RTX [18]. We did not reintroduce RTX, treated our patient with prednisolone and azathioprine for IBD, and showed complete resolution at the sixth month of therapy. Neither colitis nor nephrotic syndrome recurrence was observed during the 18-month follow-up period.

In conclusion, RTX is a quite effective salvage treatment for refractory NS and is often well tolerated. Although rare, this agent might have serious side effects. In cases with abdominal symptoms and accompanying weight loss after RTX therapy, IBD should be ruled out with upper and lower gastrointestinal endoscopy. Although the pathogenesis of RTX-related IBD is not fully understood, it is thought to develop secondary to immune dysregulation and T cell activation resulting from B cell depletion. Treatment directed against IBD and avoidance of RTX is the main management strategy. More data and preferably large-scaled studies are needed to explore and avoid this complication.

Data availability All data have been presented in the manuscript.

Code availability Not applicable.

Declarations

Ethics approval Not applicable.

Consent for publication An informed consent was obtained from the parents.

Conflict of interest The authors declare no competing interests.

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