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STANFORD MULTIDISCIPLINARY SEMINARS

Stemming the Tide of Gastrointestinal Chronic Granulomatous Disease

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Case Presentation and Evolution

A 12-year-old male with chronic granulomatous disease (CGD) was evaluated at the pediatric gastroenterology clinic for diarrhea and bloody stools. He had been diagnosed with CGD in his infancy, when he was initially evaluated for a retroauricular suppurative granuloma. Growing up, he experienced several infections, including pulmonary histoplasmosis requiring prolonged course of antifungal therapy.

During his evaluation for bloody stools, he tested positive for *Clostridoides difficile* (*C. diff.*) infection and received treatment with metronidazole and then vancomycin. Despite such treatments, he experienced recurrence and though he underwent fecal microbiota transfer, his symptoms did not improve. Biopsies taken at colonoscopy showed a loose collection of histiocytes with possible granuloma formation in the descending colon (Fig. 1a). There was evidence of complex crypt branching as well as cryptitis, suggesting chronic and acute inflammatory findings (Fig. 1b, c). After multiple admissions to the hospital for intravenous steroids and oral steroid dependence, he was started on mesalamine and quadruple antibiotic therapy (vancomycin 250 mg 4 times a day, amoxicillin 50 mg/kg divided by three, metronidazole 5 mg/kg three times a day and doxycycline 2 mg/kg twice a day).

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He remained on mesalamine and the quadruple antibiotic regimen for about three months, after which he was evaluated acutely in the emergency room with symptoms of unsteady gait, dizziness and vomiting. Though physical examination revealed a wide-based gait, he was afebrile, and his vital signs were stable. He was admitted to the inpatient gastroenterology service where his laboratory evaluation included a complete blood count, C-reactive protein, procalcitonin, electrolytes, folic acid level, methylmalonic acid level, as well as a thiamine level, all of which were normal; Epstein–Barr virus antibody, COVID-19 PCR, respiratory pathogen panel, and blood culture were also negative. A brain MRI (Fig. 2) and axial FLAIR sequence of the brain showed bilateral symmetric hyperintense signal within the cerebellar dentate nuclei. Given that these findings were pathognomonic for metronidazole neurotoxicity, the medication was discontinued. Two days later, patient's symptoms had resolved, and he was discharged home with mesalamine, amoxicillin, doxycycline and vancomycin.

Due to recurrence of his gastrointestinal symptoms and his underlying immune deficiency, he was readmitted to the hematology/oncology service for conditioning and stem cell transplantation. His conditioning regimen consisted of rATG (rabbit anti-thymocyte globulin), clofarabine, melphalan, rituximab and fractionated total body irradiation (fTBI) of 200 cGy. His transplant was a 9/10 HLA-matched (human leukocyte antigens) from an unrelated donor that was alpha- and beta-depleted. Shortly thereafter, he rejected the graft and underwent second conditioning about one month later which included rATG, fludarabine, cyclophosphamide, fTBI and rituximab. His second transplant came from his mother, and the transplant was alpha-and beta-depleted as well (dose was 6.66×10^6 CD34 + cells/kg). He engrafted on day + 15. He was then discharged home on steroids, mesalamine and vancomycin. Steroids were weaned off over a course of six months, and patient had no further diarrhea or bloody stools. Fecal calprotectin steadily improved (from 496 to 15 µg/g). Repeat colonoscopy 8 months post-transplant showed normal histology (Fig. 1d); antibiotics were discontinued. He

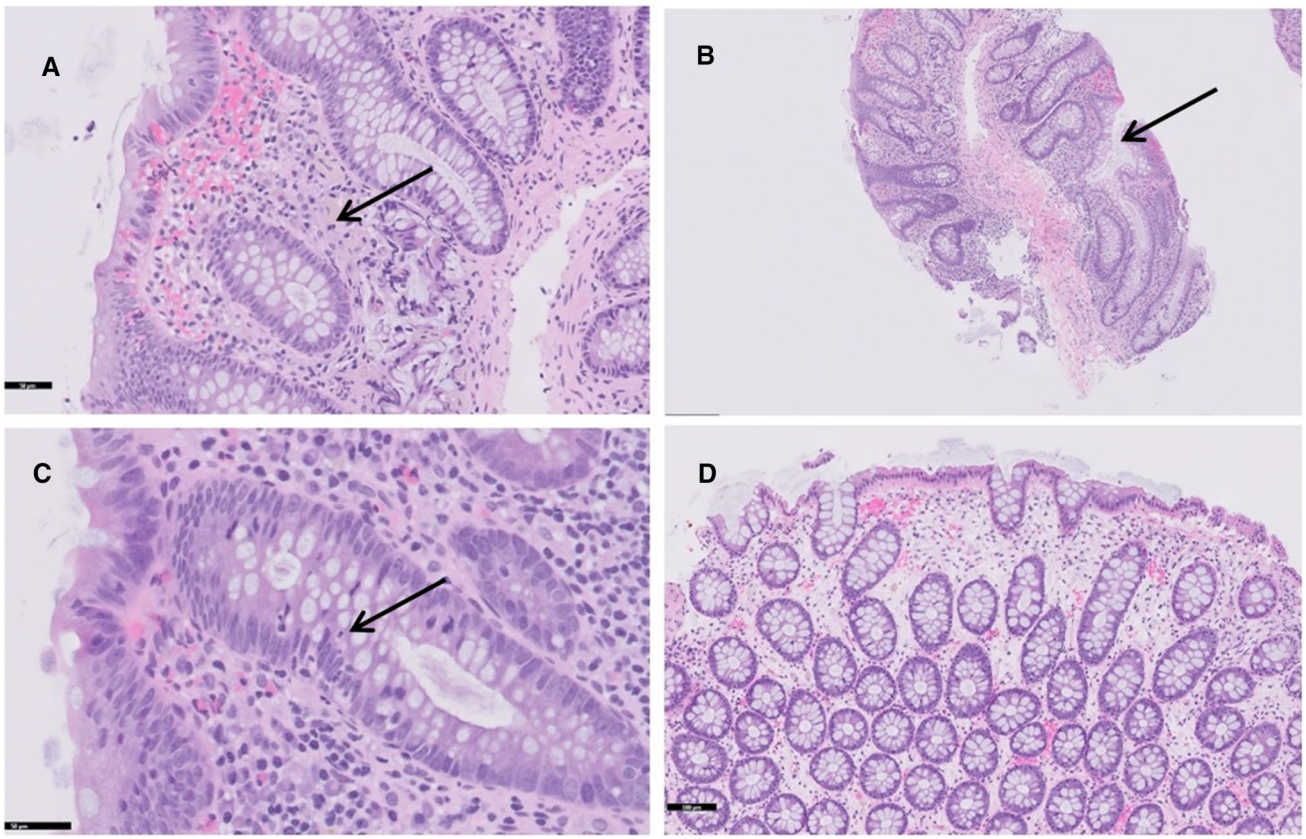

Fig. 1 H&E stain of descending colon biopsy pre-transplant (**a**, **b**, **c**) and post-transplant (**d**). Biopsy **a** shows loose collection of histiocytes indicating a possible granuloma (arrow). Biopsy **b** shows complex crypt branching (arrow) suggesting chronic inflammation. Biopsy **c** shows cryptitis (arrow) consistent with acute inflammation. Biopsy **d** shows normal mucosa post-transplant

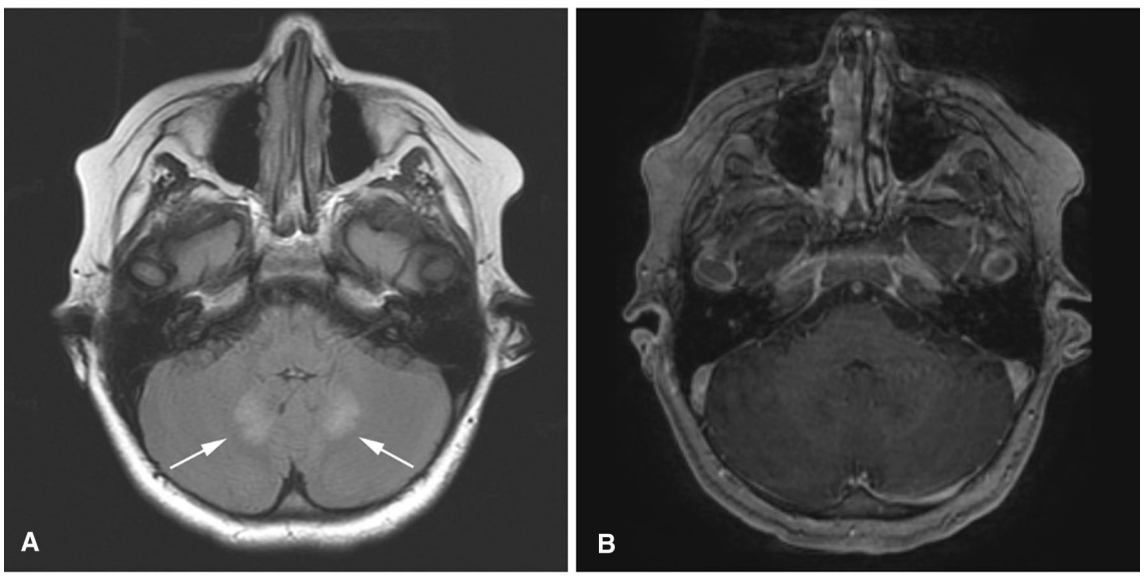

Fig. 2 Axial FLAIR sequence of the brain in **a** showing bilateral symmetric hyperintense signal within the cerebellar dentate nuclei (arrow). Non-constrast image of brain in **b** for comparison

had full immune reconstitution, and chimerism showed 100% donor subsets. On follow-up a year post-transplant, he remains clinically well with no further bloody stools or other gastrointestinal symptoms.

Discussion

CGD is a genetic disorder that results in severe potentially life-threatening infections. The disorder is caused by mutations in NADPH (nicotinamide adenine dinucleotide phosphate) oxidase pathway which impairs production of reactive oxygen metabolites [1]. Incidence of the disorder is 1:250,000. CGD patients come to medical attention due to the acquisition of infections particularly of the skin, lymph nodes, lung or liver [2]. As in this patient, CGD patients can have noncaseating granulomas composed of multinucleated giant cells, including the brain, lung, liver, spleen and the gastrointestinal tract [1, 2]. Digestive tract CGD granulomas can occur in any segment, ranging from the oral cavity to the anus and can obstruct the gastric outlet [2]. CGD patients frequently develop inflammatory conditions, thought to be due to elevated pro-inflammatory or decreased anti-inflammatory mediators [2]. CGD colitis can show cryptitis and crypt abscesses, crypt distortion and basal cell plasmacytosis, histopathologically resembling inflammatory bowel disease [3, 4].

Recent research has focused on the treatment of gastrointestinal CGD. A single center cohort study in France showed that since 78% of CGD patients who were treated with anti-TNF α (anti-tumor necrosis factor alpha) agents had infections, these agents were recommended as short-term therapy while awaiting stem cell transplant [5]. A National Institutes of Health (NIH) study reported 11 patients with CGD and IBD-like symptoms who were treated with the α4β7 integrin inhibitor vedolizumab. At 6 months, 57% had endoscopic improvement, though none improved after that time period [6]. In this study, no patients were able to discontinue steroids; vedolizumab therapy was discontinued in 36% of patients due to lack of meaningful response. About 36% of patients had adverse events, including pneumonia, abscess formation and infusion reactions.

In recent years, stem cell transplantation which was formerly considered an experimental or high-risk procedure has become a viable option for CGD, currently serving as the only known cure. In a study by the American Society for Transplantation and Cellular Therapy, 90% of 153 patients with CGD and colitis had resolution of the colitis 2 years post-transplantation [7]. Our patient has achieved clinical resolution of his gastrointestinal symptoms with improvement in his calprotectin and normal histopathology.

Metronidazole is very commonly used as part of the quadruple antibiotic regimen as a steroid-sparing medication for pediatric inflammatory bowel disease [8]. Though common adverse effects of the medication include nausea, vomiting and abdominal pain, rare neurological symptoms have been reported. Metronidazole may cross the blood–brain barrier with consequent axonal swelling or reversible localized ischemia [9, 10], diagnosable by brain MRI that can detect bilateral increased T2 and FLAIR signal in the dentate nuclei, pons and cerebellum without contrast enhancement [9]. Symptoms usually resolve shortly after discontinuing the medication but about 10% of patients have severe morbidity or mortality [10].

In conclusion, stem cell transplantation appears to be curative for CGD with gastrointestinal manifestations. Our patient was treatment-resistant despite undergoing a myriad of therapies, including fecal transplantation, long courses of steroids and quadruple antibiotic use. He also experienced the rare neurological side effect from metronidazole but was able to recover after discontinuation of antibiotic.

Key Messages

- CGD can have IBD-like manifestations that are often steroid-dependent and challenging to treat.
- Though treatments with steroids, mesalamine and other alternatives, including biologics have been tried, stem cell transplantation appears to be curative.
- Metronidazole use as part of the quadruple antibiotic therapy can cause neurotoxicity that should be considered in patients with neurological symptoms such as ataxia. Metronidazole toxicity resolves in most cases upon drug discontinuation.

Declarations

Conflict of interest We know of no conflicts of interest associated with this publication, and there has been no significant financial support for this work.

Consent for publication We declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

Informed consent Informed consent for publication of the case details was obtained from parent of patient discussed in the report.

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