New onset colitis in an adult patient with chronic granulomatous disease treated with hematopoietic stem cell transplantation: a diagnostic dilemma

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Abstract
Background: Chronic granulomatous disease (CGD) is a rare primary immunodeficiency characterized by recurrent life-threatening bacterial and fungal infections, granuloma formation and intestinal disease. This disease is caused by defects in NADPH oxidase, which result in the inability of phagocytes (neutrophils, monocytes and macrophages) to destroy certain microbes. The only established curative therapy for CGD is hematopoietic stem cell transplantation.

Case presentation: A 23-year-old Caucasian male with X-linked chronic granulomatous disease underwent a reduced-intensity conditioning, matched unrelated donor peripheral blood stem cell transplant, after which he was started on tacrolimus and mycophenolate for graft-versus-host disease prophylaxis. Seven months later, he was admitted to hospital for nutritional support secondary to odynophagia and anorexia. Upper endoscopy revealed ulcers in his esophagus, and he was initially treated with acyclovir due to the risk of CMV infection until biopsies came back negative for viral colitis. Following a sigmoidoscopy that showed nonspecific colitis, he was started on mesalazine. Although pathology showed a pattern of widespread inflammatory changes initially suggestive of CGD colitis, a peripheral blood chimerism study showed 100% donor alleles suggesting CGD remission. Since this patient’s colitis was refractory to other immunomodulators, and due to its severity, the patient underwent a partial colectomy 1 year after his HSCT and will likely require the removal of the remaining large bowel.

Conclusions: This case demonstrates a unique presentation of colitis in a post-transplant CGD patient. Since CGD colitis could be excluded due to the patient’s recent successful hematopoietic stem cell transplantation, a broad differential diagnosis is required for determining the etiology of this new-onset colitis in this patient with pre-existing chronic granulomatous disease. This case delineates the need for interdisciplinary care and describes a severe case of colitis after hematopoietic stem cell transplantation.

Keywords: Chronic granulomatous disease, Colitis, Hematopoietic stem cell transplantation

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seen in patients with CGD who demonstrate severe gastrointestinal symptoms such as abdominal pain, diarrhea, failure to thrive or microcytic anemia [7].

Treatment options for patients with CGD are often limited to infection prophylaxis with trimethoprim-sulfamethoxazole (Septara) for bacterial infection, itraconazole for fungal infections and immunomodulation with interferon gamma to alleviate the persistently pro-inflammatory state. Acute infections are often treated with empiric antibiotics given the immunocompromised state of patients with CGD and their significantly elevated likelihood of developing sepsis [8]. However, hematopoietic stem cell transplantation (HSCT) remains the only established curative therapy for CGD [9], and this has become the standard of care in the pediatric population.

After HSCT, immunocompetency is usually achieved with engraftment. However, the two main complications in a post-HSCT patient are graft-versus-host disease (GvHD) or graft failure [10]. GvHD may present acutely or chronically, with acute GvHD typically presenting in the first 100 days post-transplant [11]. The typical presentation of acute GvHD is characterized by a triad of cutaneous, hepatic and gastrointestinal manifestations. The cutaneous reaction manifests as a distinct erythematous maculopapular rash which can desquamate in late stages, while the hepatic manifestation usually presents hyperbilirubinemia before fulminating hepatic failure. The gastrointestinal manifestation of GvHD typically presents as diarrhea and anorexia which can become a complete ileus in late stages, mimicking the presentation of colitis [12]. Acute GvHD can occur in up to 30% of allogeneic matched post-HSCT patients despite a regimen of immunosuppressive therapies for GvHD prophylaxis. Chronic GvHD typically will manifest within the first 2 years post-HSCT outside of the acute GvHD window, and can present with a non-specific malar rash, sicca, arthritis, bronchiolitis obliterans, or bile duct degeneration and cholestasis. Chronic GvHD will develop in 20–50% of post-HSCT recipients, with unmatched donor or prior acute GvHD reaction as significant risk factors [13].

Late-onset acute GvHD has been described where a patient will develop the classic triad of signs characteristic to acute GvHD outside of the first 100 days post-HSCT [14], or even as an overlap with the manifestations of chronic GvHD [15]. As a result, a patient may develop cutaneous, hepatic or gastrointestinal disturbances on a background of non-specific systemic dysfunction well outside of the acute GvHD window [16]. However, graft failure in a post-transplant CGD patient would manifest as return of CGD with classic signs of CGD, such as recurrent abscesses, granulomas or colitis.

Here we describe the workup, clinical course and response to treatment of a patient with CGD who presents 7 months post-allogenic HSCT with a new onset colitis of unknown etiology, and the diagnostic dilemma to identify the etiology of this patient’s symptoms.

Case presentation

A 23-year-old Caucasian male with X-linked CGD (gp91phox mutation) underwent a reduced-intensity conditioning [17], matched unrelated donor peripheral blood stem cell transplant as curative therapy for his CGD. He was then started on tacrolimus and mycophenolate for GvHD prophylaxis post-HSCT. The transplant was well tolerated, with no documented evidence of acute GvHD, but 7 months later, he was admitted to hospital for nutritional support secondary to odynophagia and anorexia. Upper endoscopy revealed ulcers in his esophagus. He was initially empirically treated with IV acyclovir and biopsies were performed while the patient was on prophylactic doses of immunosuppressive therapy. However, these biopsies came back negative for HSV/CMV and IV acyclovir was discontinued. The pathology report showed a non-specific pattern of widespread inflammatory changes. There was no personal or family history of IBD or GI disease in either the donor or recipient prior to HSCT. Following a sigmoidoscopy showing nonspecific colitis, he was started on mesalamine. To rule out HSCT failure and recurrence of CGD, we performed NBT testing and peripheral blood chimerism studies. NBT testing demonstrated proper neutrophil functioning, and peripheral blood chimerism studies (VNTR) showed 100% donor alleles, showing no evidence of CGD or HSCT failure. It was then thought he might have chronic GvHD, and he was treated with IV steroids. Unfortunately, the patient was refractory to this treatment and subsequently had several episodes of lower GI bleeding.

A colonoscopy demonstrated patchy severe active colitis with ulceration and a solitary granuloma. CMV PCR, acid-fast bacilli and Epstein Barr virus testing was negative. The absolute lymphocyte count was \(20 \times 10^9\) cells/L and flow cytometry revealed CD4—19%, CD8—37%, CD56—69%, CD19—1%, CD45RA—10% and CD45RO—1% (Table 1). He was then started on IVIG at immunomodulatory dosing, his mycophenolate was discontinued, and prednisone and tacrolimus doses were reduced. Repeat colonoscopy 1 month later showed very severe disease with ulceration (Fig. 1) and mucosal bridging (Fig. 2) with no improvement or interval change.

Due to the severity of the colitis, the patient then underwent a partial colectomy. This demonstrated severe patchy chronic active colitis with deep mucosal ulcers and pseudo-inflammatory polyps, with pathology...
suggestive of Crohn's disease. The disease in the distal bowel remains active and the patient will likely require removal of the remaining colon.

Discussion

This patient with chronic granulomatous disease initially presented to us with a new-onset gastrointestinal inflammation and ulceration following HSCT. This was initially suggestive of a diagnosis of CGD colitis, a common gastrointestinal manifestation of X-linked CGD. However, CGD colitis is pathologically distinct from an inflammatory bowel disease colitis due to the presence of hyperpigmented macrophages, a predominantly eosinophilic inflammatory infiltrate, and a scarcity of neutrophils and within the colonic wall [18]. We were therefore able to exclude CGD colitis and HSCT failure with confidence in our patient. After allelic testing, GvHD was then suspected due to the widespread inflammation, and plethora of phagocytes and lymphocytes within the gastrointestinal lining. Although GvHD can manifest with nonspecific symptoms suggestive of upper and lower gastrointestinal tract involvement [19], GvHD serologically presents with marked proliferation of CD4+ and CD8+ T cells, and very few CD56+ NK cells [20], which was not seen on flow cytometry. We were therefore also able to exclude a typical presentation of GvHD from our differential, as the characteristic typical GvHD cutaneous and hepatic reactions were not seen in conjunction with this patient's gastrointestinal symptoms. However, there were three principle findings that prevent us from ruling out atypical GvHD in our patient. These include presence of apoptotic bodies, mucosal necrosis, ulceration, submucosal fibrosis, and crypt and gland destruction on pathology, as well as detection of alloreactive donor-derived cells against the patient's gut mucosa, and lastly, our observation of lymphocytic infiltration of the gut mucosa as important yet atypical elements seen in GvHD. As a result, we are not able to rule out an atypical presentation of GvHD for the etiology of this colitis.

In spite of our thinning differential, this post-HSCT patient has presented with esophageal and colonic involvement, and since allelic testing demonstrates entirely donor alleles, the possibility of Crohn's-like disease secondary to HSCT or atypical GvHD cannot be completely ruled out. The presence of mucosal bridges is a known phenomenon seen in Crohn's disease [21–24], but pathology only reported nonspecific granulomatous inflammation, not in keeping with the classic histologic findings of Crohn's disease. Although the risk of IBD is elevated in patients with CGD [25, 26], our gastroenterologist colleagues felt that the absence of autoimmune disease in both the patient's and donor's past medical history was not in keeping with an autoimmune inflammatory

Table 1 Lymphocytes by cytokine determinants

| Cytokine determinant | Relative abundance (%) |
|----------------------|------------------------|
| CD4                  | 20                     |
| CD8                  | 37                     |
| CD56                 | 63                     |
| CD19                 | 1                      |
| CD45RA               | 8                      |
| CD45RO               | 91                     |

Flow cytometry on serum lymphocytes shows the relative abundance of CD4+ and CD8+ T cells, CD56+ NK cells, CD19+ B lymphocytes, as well as CD45RA+ naive and CD45RO+ memory T cells.
bowel disease. Verification with the donor registry has confirmed that the donor has not experienced any gastrointestinal complications to date. Regardless, this case would be one of the first documented reports of colitis secondary to HSCT in a patient treated to cure CGD, but the pathology report notes that the possibility of an infectious etiology cannot be excluded, such as an unknown viral complication given this patient’s profound lymphopenia. As yet, we have been unable to determine if this colitis is secondary to IBD, atypical GvHD or an infectious etiology. The vast number of possible etiologies for this colitis presents a challenge in determining the underlying cause of this patient’s illness as well as providing treatment options.

Conclusion
A broad differential diagnosis is required for colitis presenting after HSCT in a patient with pre-existing CGD. We have been able to rule out common etiologies such as recurrent CGD, typical GvHD, and viral colitis, but we have yet to exclude another Crohn’s-like colitis, an atypical presentation of GvHD or other unknown viral etiology from our differential diagnosis, however the current plan for this patient’s colitis involves future elective total colectomy for disease control, with observation for disease recurrence. This case serves to delineate the importance for multidisciplinary care and describes a severe case of colitis after HSCT.

Abbreviations
CGD: chronic granulomatous disease; HSCT: hematopoietic stem cell transplant; GvHD: graft versus host disease; NBT: nitroblue tetrazolium.

Authors’ contributions
KR and LC interpreted the patient data regarding the case presentation, analyzed the results and prepared the manuscript. IA provided background information regarding the donor hematopoietic stem cells. TI performed independent histological examination of the gut biopsy. SC and DL provided guidance with their interpretation of the clinical data, and were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
All data is stored and available in the patient’s case files and may be requested to see a copy at any stage.

Consent for publication
Written and oral informed consent for publication has been obtained from the patients and stored in the case files and may be requested to see a copy at any stage.

Ethics approval and consent to participate
Written and oral informed consent to participate has been obtained from the patients and stored in the case files and may be requested to see a copy at any stage.

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References
1. Goldblatt D. Recent advances in chronic granulomatous disease. J Infect. 2014;69(Suppl 1):S32–5.
2. Finn A, Hadzić N, Morgan G, Strobel S, Levinsky RJ. Prognosis of chronic granulomatous disease. Arch Dis Child. 1990;65(9):942–5.
3. Winkelstein JA, Marino MC, Johnston RB Jr, Boyle J, Curnutte J, Gallin JL, Malech HL, Holland SM, Ochs H, Quie P, Buckley RH, Foster CB, Chanock SJ, Dickler H. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore). 2000;79(3):155–69.
4. Marciano BE, Spalding C, Fitzgerald A, Mann D, Brown T, Osgood S, Yockey L, Darnell DN, Barnhart L, Daub J, Boris L, Rump AP, Anderson VL, Haney C, Kuhns DB, Rosenberg SW, Kelly C, Zelazny A, Mason T, DeRavin SS, Kang E, Gallin JL, Malech HL, Olivier KN, Uzel G, Freeman AF, Heller T, Zerbe CS, Holland SM. Common severe infections in chronic granulomatous disease. Clin Infect Dis. 2015;60(8):1176–83.
5. Bortoletto P, Lyman K, Camacho A, Frichchione M, Khanolkar A, Katz BZ. Chronic granulomatous disease: a large, single-center US experience. Pediatr Infect Dis J. 2015;34(10):1110–4.
6. Rosenzweig SD. Inflammatory manifestations in chronic granulomatous disease (CGD). J Clin Immunol. 2008;28(Suppl 1):S67–72.
7. Marciano BE, Rosenberg SW, Kleiner DE, Anderson VL, Darnell DN, Anaya-O’Brien S, Hilligoss DM, Malech HL, Gallin JL, Holland SM. Gastrointestinal involvement in chronic granulomatous disease. Pediatrics. 2004;114(2):462–8.
8. Goldblatt D. Current treatment options for chronic granulomatous disease. Expert Opin Pharmacother. 2002;3(7):857–63.
9. Chirico A, Salfa I, Di Matteo G, Rossi P, Finocchi A. Chronic granulomatous disease: clinical, molecular, and therapeutic aspects. Pediatr Allergy Immunol. 2016;27(3):242–53.
10. Arnold DE, Heimall JR. A review of chronic granulomatous disease. Adv Ther. 2017;34(12):2543–57.
11. Zeiser R, Blazar BR. Acute graft-versus-host disease—biologic process, prevention, and therapy. N Engl J Med. 2017;377(22):2167–70.
12. Naymagon S, Naymagon L, Wong SY, Ko HM, Renteria A, Levine J, Colombel JF, Ferrara J. Acute graft-versus-host disease of the gut: considerations for the gastroenterologist. Nat Rev Gastroenterol Hepatol. 2017;14(2):711–26.
13. Attila E, Attila PA, Toprak SK, Demier T. A review of late complications of allogeneic hematopoietic stem cell transplantations. Clin Transplant. 2017. https://doi.org/10.1111/ctr.13062.
14. Dulley FL, Shulman HM, Massumoto CM, Loterio HA, Dorthiac-Llacer PE, Beiter B, Velloso RP, D’Amico EA, Garicochea B, Martinez GA, et al. Late onset of acute graft-versus-host disease. Clin Transpl. 1989;312.

15. Pidala J, Vogelsang G, Martin P, Chai X, Storer B, Pavletic S, Wersdorf DJ, Jagasia M, Cutler C, Palmer J, Jacobsohn D, Arai S, Lee SJ. Overlap subtype of chronic graft-versus-host disease is associated with an adverse prognosis, functional impairment, and inferior patient-reported outcomes: a chronic graft-versus-host disease consortium study. Haematologica. 2012;97(3):451–8.

16. Sung AD, Hassan S, Cardona DM, Wild D, Nichols KR, Mehdirikhani H, Balmadrid B, Detweiler CJ, Shealy M, Cinnincione C, Li Z, Poleski M, Dalton TE, Siamakpour-Reihan S, Chao NJ, Sullivan KM. Late gastrointestinal complications of allogeneic hematopoietic stem cell transplantation in adults. Biol Blood Marrow Transplant. 2017. pii: S1083-8791(17) 31676-2.

17. Güngör T, Teira P, Slatter M, Stussi G, Stepensky P, Moshou D, Vermont C, Ahmad I, Shaw PJ, Telles da Cunha JM, Schlegel PG, Hough R, Fasth A, Kentouche K, Gruhn B, Fernandes JF, Lachance S, Bredius R, Resnick IB, Belohradsky BH, Gennery A, Fischer A, Gaspar HB, Seger R, Rentsch K, Veys P, Hadad E, Albert MH, Hassan M. Inborn Errors Working Party of the European Society for Blood and Marrow Transplantation. Reduced-intensity conditioning and HLA-matched haemopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study. Lancet. 2014;383(9915):436–48.

18. Schäppi MG, Smith VV, Goldblatt D, Lindley KJ, Milla PJ. Colitis in chronic granulomatosus disease. Arch Dis Child. 2001;84(2):147–51.

19. Aslanian H, Chander B, Robert M, Cooper D, Proctor D, Seropian S, Jain D. Prospective evaluation of acute graft-versus-host disease. Dig Dis Sci. 2012;57(3):720–5.

20. Podgorny PJ, Liu Y, Dharmani-Khan P, Pratt LM, Jamani K, Luider J, Auer-Greisak I, Mansoor A, Williamson TS, Ugarte-Torres A, Hoehg-Petersen M, Stewart DA, Daly A, Khan FM, Russel JA, Storek J. Immune cell subset counts associated with graft-versus-host disease. Biol Blood Marrow Transplant. 2014;20(4):450–62.

21. Poller DN, Armitage NC. Mural bridging lesions in colonic Crohn’s disease. Arch Pathol Lab Med. 1993;117(5):550–2.

22. Goldberger LE, Neely HR, Stammer JL. Large mucosal bridges: an unusual roentgenographic manifestation of ulcerative colitis. Gastrointest Radiol. 1978;3(1):81–3.

23. Hammerman AM, Shatz BA, Susman N. Radiographic characteristics of colonic “mucosal bridges”: sequelae of inflammatory bowel disease. Radiology. 1978;127(3):611–4.

24. Samch MN, Train J. Demonstration of mucosal bridging in Crohn’s colitis. Am J Gastroenterol. 1980;74(1):50–4.

25. Gennery A. Recent advances in understanding and treating chronic granulomatous disease. F1000Res. 2017;6:1427.

26. Huang C, De Ravin SS, Paul AR, Heller T, Ho N, Wu Datta L, Zerbe CS, Marciano BE, Kuhns DB, Kader HA, Holland SM, Malech HL, Brant SR, NIDDK IBD Genetics Consortium. Genetic risk for inflammatory bowel disease is a determinant of Crohn’s disease development in chronic granulomatous disease. Inflamm Bowel Dis. 2016;22(12):2794–801.