

[CASE REPORT]

Crohn's Disease Accompanied with Small Intestinal Extramedullary Plasmacytoma

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Abstract:

We herein present the case of an immunocompetent 63-year-old man who had previously undergone resection of Crohn's disease (CD)-related small intestinal obstruction more than 30 years ago. He had not been receiving any medication for many years, but had recently started to suffer from ileus. A stenosed site of ileocecal anastomosis was identified and therefore was surgically resected, which was diagnosed as CD with small intestinal extramedullary plasmacytoma (EMP). The subsequent progression of CD was successfully controlled by anti-TNF α agents without any recurrence of EMP for over 3 years, implying the clinical benefit and safety of the biological therapy. This was the first known case of a patient who received anti-TNF α agents after a resection of small intestinal EMP accompanied with CD.

Key words: extramedullary plasmacytoma (EMP), plasmablastic neoplasm, plasmablastic lymphoma (PBL), Crohn's disease (CD), anti-TNF α agents

(Intern Med 58: 2019-2023, 2019)

(DOI: 10.2169/internalmedicine.1687-18)

Introduction

There are two types of plasmacytoma pathologically: namely, solitary plasmacytoma of bone and extraosseous (extramedullary) plasmacytoma (EMP). Solitary plasmacytomas are single localized tumors consisting of monoclonal plasma cells with no physical or radiographical evidence of additional plasma cell tumors and no clinical features of plasma cell myeloma (PCM), including M protein, anemia, hypercalcemia, or renal failure (1). Histologically, EMP is composed of monomorphic, well-differentiated plasma cells, or atypical neoplastic plasma cells that are indistinguishable from plasmablastic lymphoma (PBL) (2). Among EMP, the most commonly encountered site is the upper airway, while the gastrointestinal (GI) tract is only rarely involved (3). In

the GI tract, the stomach, liver and colon are the most frequent sites of EMP, whereas the small intestine (duodenum, jejunum and ileum) is a rare location (4).

Over the past few decades, there has been dramatic progress in the treatment of inflammatory bowel disease (IBD), including Crohn's disease (CD). Now we can effectively use various immunosuppressive agents such as azathiopurine (AZA) and anti-TNF α agents worldwide. But some clinical problems remain regarding what medical therapy for IBD should be administered for patients with a past history of neoplastic disease. Actually, the European Crohn's and Colitis Organisation (ECCO) guideline shows in the paragraph of management of IBD patients with past history of malignancy that "Physicians must be aware of the potential impact of immunosuppressants on cancers and on the risk of developing a second malignancy in cancer survivors" (5).

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Received: June 12, 2018; Accepted: January 20, 2019; Advance Publication by J-STAGE: March 28, 2019

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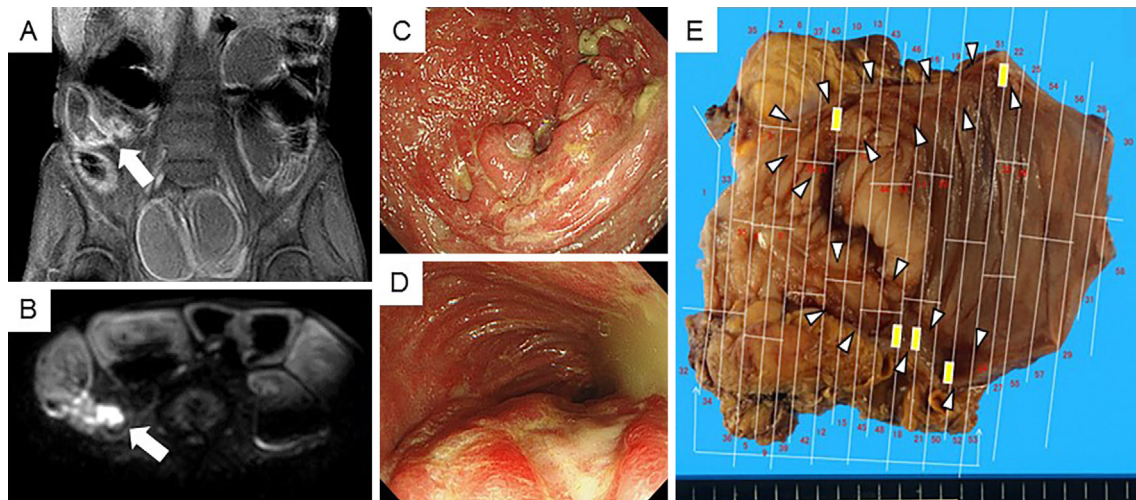


Figure 1. Image and macroscopic views of stenotic ileo-cecal anastomosis. (A and B) Magnetic resonance enterocolonography revealed ileo-cecal anastomotic obstruction. (C and D) Colonoscopic findings also showed the stenosis of ileo-cecal anastomosis with ulcer formation. (E) The macroscopic findings of the removed ileo-cecal anastomosis showed a stenosed lumen and longitudinal ulcers surrounded by white arrow heads (max 65 mm). Yellow bars indicate the histological accumulation of atypical lymphocytes observed in the area of longitudinal ulcers.

We herein present a rare case of CD accompanied with small intestinal EMP, who received anti-TNF α agents to control the progression of CD after a resection of EMP and thereafter remained recurrence free of EMP for more than 3 years after the surgery.

Case Report

A 63-year-old Japanese man re-visited our hospital in March 2015 suffering from a sense of abdominal distention and weight loss. He had a past history of undergoing two surgical operations in our hospital almost 30 years ago due to intestinal stenosis and a diagnosis of CD had been made histologically. He had been taking salazosulfapyridine for several years with no immunosuppressive agents, but he stopped visiting us after self-interruption of medication 7 years prior to this presentation and had taken no medication recently.

X-ray examinations and magnetic resonance enterocolonography (MREC) revealed an obstruction at the site of ileo-cecal anastomosis (Fig. 1A and B), which was thought to have been caused by CD. Colonoscopic findings also showed stenosis in the ileo-cecal anastomosis with ulcer formation (Fig. 1C and D). A stenotic lesion of small intestine had been removed surgically in April 2015. The macroscopic findings of the removed ileo-cecal anastomosis showed a stenotic lumen and longitudinal ulcers (Fig. 1E). A histological examination revealed severe ulcer with transmural infiltration of neutrophils, lymphocytes, plasmacytes and eosinophils accompanied with epithelioid granuloma, pyloric gland metaplasia, and severely atrophic villous, compatible with microscopic findings of CD. In addition, there was a dense accumulation of plasmablastoid cells with cen-

tral oval nuclei with prominent nucleoli around the surface of the ulcer (Fig. 2A and B), which were all immunohistologically positive for CD138, MUM1, IgG λ and epithelial membrane antigen, focally positive for CD56, and negative for CD3, CD5, CD10, CD15, CD20, CD21, CD23, CD30, CD43, bcl-2, bcl-6, cyclin D1, Epstein-Barr virus (EBV)-encoded RNA (EBER), anaplastic lymphoma kinase, latent membrane protein-1, cytomegalovirus, cytokeratin (AE1/AE3), S100, CD79a and PAX5 (representative pictures are shown in Fig. 2C-E). Ki-67 scoring was about 60% (Fig. 2F). These accumulating cells were observed in some areas in the longitudinal ulcers near the site of anastomosis (Yellow bars in Fig. 1E). The differential diagnosis included anaplastic EMP or PBL based on the morphological findings of plasmablastoid cells.

A bone marrow biopsy showed no abnormal findings. A fluorodeoxyglucose-positron emission tomography-computed tomography (FDG-PET/CT, May 2015) scan showed a slight uptake only around the site of ileo-cecal anastomosis. The laboratory data showed a normal range of serum globulin and interleukin-2, and his serum antibody to human immunodeficiency virus (HIV) was negative. Urine protein electrophoresis did not show the presence of Bence-Jones protein. In summary, there was no proof of any other organs being involved and the tumor appeared to have been completely resected surgically. The diagnosis was thus considered to be small intestinal EMP rather than PBL because of the negativity for EBER and the patient's normal immunological function (6, 7). Taken together, we decided to conduct a watchful waiting policy.

He initiated 5-aminosalicylic acid (5-ASA, 3,000 mg/day) and an elemental diet (ED) after the surgery. A few months later, the serum albumin level decreased and his abdominal

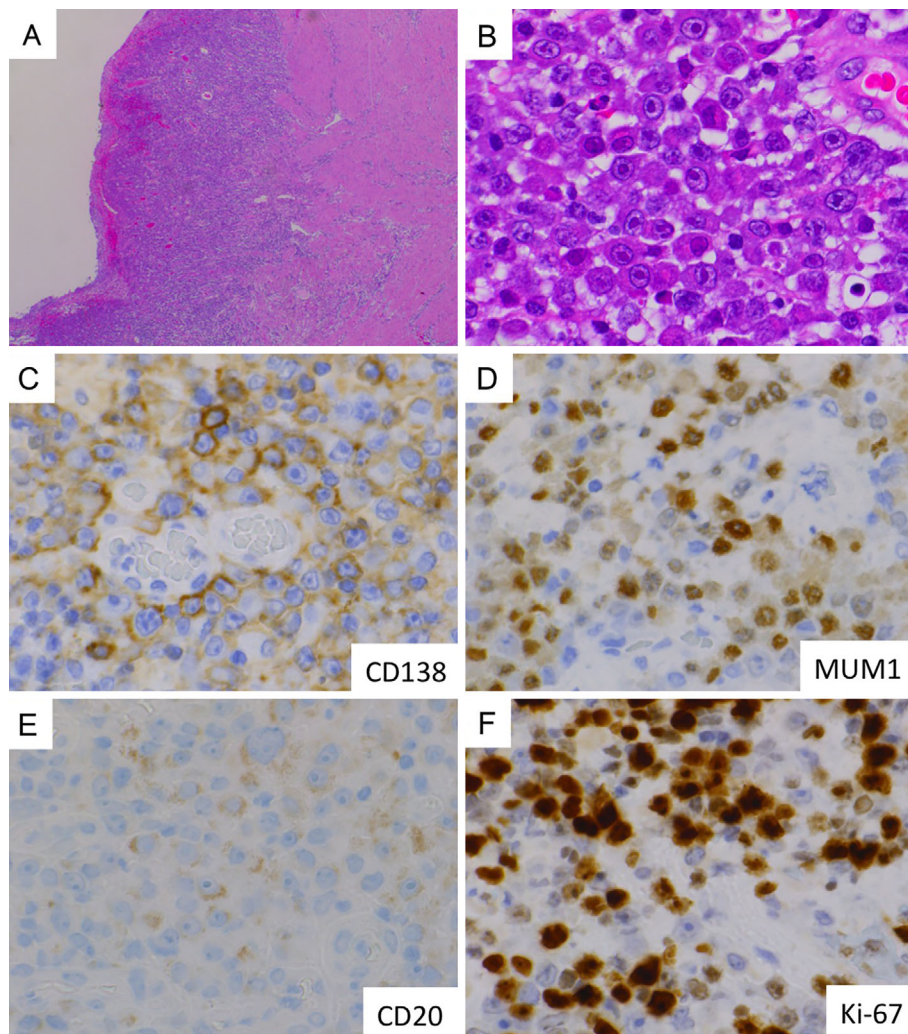


Figure 2. A histological examination of the resected stenotic ileo-cecal anastomosis. (A and B) The histological examination revealed that there was a dense accumulation of plasmablastoid cells with central oval nuclei with prominent nucleoli around the surface of the ulcer. (C-E) These atypical lymphocytes were immunohistologically positive for CD138 and MUM1, and negative for CD20. (F) Ki-67 scoring was about 60%. Each magnification; ×40 in A, ×400 in B-F.

symptoms gradually worsened. A second FDG-PET/CT scan (September 2015) showed an uptake around the ileo-cecal anastomosis again. In order to distinguish between the local recurrence of EMP and a progression of CD, we performed step biopsies of the total small intestine by balloon-assisted enteroscopy examinations inserted both from the mouth and anus, which could not pass through the ileo-cecal anastomosis (January 2016). Since the pathological findings showed no specific finding without any evidence of recurrence, the narrowing lumen was thus considered to be due to a progression of CD. Thereafter, hypoalbuminemia improved and prednisolone was administered around June 2016.

Although there was a transient decrease in the elevated CRP, inflammation again worsened along with intermittent abdominal pain and distention. The ECCO guideline showed the risk of immunosuppressants on the recurrence of malignancy (5), but it also showed no obvious excessive risk of developing new or recurrent cancer while being treated with anti-TNF α therapy although this was only based on prelimi-

nary data (5). In addition, since thiopurines were supposed to increase the risk of lymphoma (5), we preferred not to use thiopurines to control CD. Therefore, after carefully explaining to the patient and his family about the estimated risks of recurrence and other side effects, we decided to start administering one of anti-TNF α agents adalimumab (ADA) without any combination of thiopurines (October 2016), because ADA was supposed to cause secondary failure less frequently due to less immunogenicity even without combination of thiopurine than infliximab (IFX) (8). But just after two injection of ADA, he suffered from bacterial pneumonia and entered the hospital again. ADA was suspended for a while and it seemed to become less effective after re-administration. We switched ADA to IFX without any combination of thiopurine (February 2017), and his abdominal symptom thereafter improved with a gradual amelioration of hypoalbuminemia. Since a third FDG-PET/CT scan in December 2017 showed a slight uptake around the anastomosis of the small intestine, we performed anally inserted en-

teroscopy in January 2018 and were able to pass through the ileo-cecal anastomosis which could not be passed through 2 years previously, thus implying that the CD had been well controlled. Step biopsies simultaneously taken from the intestine showed no recurrence of the neoplasm, suggesting that the uptake around anastomosis observed in third FDG-PET/CT scan indicated inflammatory findings caused by CD. He has been doing well for over 3 years after the surgery with maintenance therapies of 5-ASA, ED, and IFX (May 2018).

Discussion

We herein describe a rare case of CD accompanied with small intestinal EMP, which is the first report including the clinical course of the treatments with anti-TNF α agents after the resection of the EMP.

In some cases of anaplastic plasmacytoma like ours, a definite distinction from PBL cannot be easily made (2), and a descriptive diagnosis, such as 'plasmablastic neoplasm, consistent with PBL or anaplastic plasmacytoma', may be acceptable according to the recently revised WHO classification in 2017 (1). But it is clinically important to distinguish anaplastic EMP and PBL because the optimal therapies and clinical courses are very different. Local radiotherapy is the preferred therapeutic modality for primary EMP owing to its radio-sensitivity (9). A surgical resection of the mass is also another good option. A retrospective study showed that there was no statistical difference in the overall survival between radiotherapy alone, radiotherapy plus surgery or surgery alone (10). EMP has a generally favorable prognosis with a 78% survival rate for 15 years and dissemination of EMP occurred in 15%, especially in the first three years (11). On the contrary, PBL has a poor prognosis with most patients dying within 2 years from initial presentation, and there are very few long-term survivors (12). PBL has been found in the oral cavity and other sites such as the GI tract, lymph nodes, and skin (13). The PBL is a high-grade malignant mature B-cell neoplasm characterized by a strong association with HIV and EBV infection (14, 15), and iatrogenic immunosuppression (16). The integration of EBV RNA into tumor cells is observed in about 60% of all PBL cases (7), but EMP is rarely associated with EBV and it also has a favorable prognosis (2, 11). A standard therapy has not yet been established for PBL and chemotherapies including R-CHOP are possible options (6). In our case, negativity for HIV and EBER, and non-compromised host with no usage of immunosuppressive agents before the surgery and subsequent good clinical course over 3 years even after the administration of immunosuppressive anti-TNF α agents for controlling CD suggested that the diagnosis of EMP in our case seemed to be clinically valid.

In recent clinical situations, the immunosuppressive agents are widely used and careful attention should be paid to what effects these agents have on the progression or recurrence of malignancy. The ECCO guideline showed the potential im-

pact of immunosuppressants on cancers and on the risk of developing a second malignancy in cancer survivors with IBD (5). But preliminary data demonstrate no obvious excessive risk of developing new or recurrent cancer while being treated with anti-TNF α therapy. In addition, thiopurines, calcineurin inhibitors, and anti-TNF α agents should be stopped at least until cancer therapy is completed. Therefore, we used anti-TNF α agents to control CD after confirming that the neoplasm had been successfully removed by surgery with no residual lesion in image examinations and explaining him the risk of recurrence. There has been no case report using anti-TNF α agents to control CD after the treatment of EMP or PBL except for ours. Since plasmablastic neoplasm cases will possibly increase in the future along with the current wide-spreading use of immunosuppressive agents, we hope that our case may therefore be informative for physicians who need to treat immune disease accompanied with EMP, and appropriate examinations to distinguish the criteria between PBL and anaplastic EMP should therefore be developed in the future.

EMP is a rare type of neoplasm that accounts for only 3-5% of all plasma cell tumors (17). The diagnosis of EMP requires the exclusion of associated PCM as shown by a negative finding of Bence-Jones protein in urine, normal serum electrophoresis and normal bone marrow biopsy (18, 19), and our present case met all the above criteria. Most EMP are found in the nasopharynx or upper respiratory tract (82.2%) and only 7.2% of cases involve the GI tracts (10). Among all segments of the GI tract, only 61 cases with EMP of the small intestine have so far been reported, which were reviewed by Rodrigo in 2012 (4). Among them, there was one case of EMP in the small intestine accompanied with an active lesion of CD in 1980's (20). There was also another EMP case involving the colon accompanied with an active lesion of CD in 1990's (21). Those two cases did not previously receive any immunosuppressive therapies. On the contrary, 4 cases among 5 CD cases with PBL received preceding immunosuppressive therapies (22-26), implying that PBL is strongly related with immunosuppressive therapies as already shown before (16). The causal relationship between CD and EMP seems to be very weak, but the co-localization of EMP with active CD lesions in 3 cases including ours suggests that the pathophysiology of CD might be related with the incidence of EMP (20, 21). As far as we could investigate, there have so far been no reports showing the relationship between intestinal surgery and the subsequent occurrence of EMP.

Conclusion

This is an informative case report on the indications of immunosuppressive agents to treat those with a past history of EMP to control the activity of immune diseases such as CD.

The authors state that they have no Conflict of Interest (COI).

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