



Anal Carcinoma in Patients with Crohn's Disease: Three Cases Report and Literature Review

Yuan Zhao^{1,2}, Fan Lan^{1,2}, Lingya Yao^{1,2} and Qian Cao^{1,2,*}

¹Department of Gastroenterology, Sir Run Run Shaw Hospital, College of Medicine Zhejiang University, Hangzhou, Zhejiang province, China

²Inflammatory Bowel Disease Center of Sir Run Run Shaw Hospital, Hangzhou, Zhejiang province, China

* **Corresponding author:** Qian Cao, Inflammatory Bowel Disease Center of Sir Run Run Shaw Hospital, College of Medicine Zhejiang University, No. 3 East Qingchun Road, Hangzhou, Zhejiang province, China. Tel: +8613588706896; Email: caoq@zju.edu.cn

Received 2022 August 28; **Revised** 2022 October 6; **Accepted** 2023 January 24.

Abstract

Background: Anal cancer in patients with Crohn's disease (CD) is rare, and the relationship between infliximab and anal cancer is not clear yet. The present study aimed to report three patients with CD complicated with anal cancer who used infliximab with their basic features.

Case presentation: Three cases were reported, including two females and one male, aged 29-56 years old. All of them developed perianal lesions during the period of Crohn's disease. All three patients had used infliximab for Crohn's disease before the diagnosis of anal cancer, except one patient who stopped using infliximab three times due to allergy; the other two patients had used infliximab until the diagnosis of anal cancer. Two patients had a good prognosis with early therapeutic intervention.

Conclusion: Based on the results, Chinese and Western patients with Crohn's disease who developed anal carcinoma had similar features. Conventional perianal evaluation is important in patients with Crohn's disease. The association between infliximab therapy and anal cancer has not been fully established and needs to be fully evaluated before the use of infliximab in Crohn's disease.

Keywords: Anal cancer, Case report, Crohn's disease, Infliximab

1. Background

Crohn's disease (CD) is a chronic inflammatory granulomatous disease characterized by alternating periods of relapse and remission. Patients might present with abdominal pain, diarrhea, weight loss, and perianal involvement, such as fistula and abscess. Anal carcinoma is rare in the general population, accounting for 1%-2% of gastrointestinal tumors. Histologically, it is mainly squamous cell carcinoma (1). The risk of this cancer in patients with CD is 11 times higher than that in the general population (2). Nonetheless, anal carcinoma in patients with Crohn's disease is quite rare, and scant attention has been paid to patients with CD who developed anal carcinoma, especially those who had accepted infliximab.

In this study, we aimed to report three patients with CD complicated with anal cancer with their basic features listed in Table 1.

3. Case presentation

Case 1 was a 31-year-old female with a 7-year history of CD. Previous budesonide, mesalamine, and other medications did not improve the symptom effectively. She was treated with infliximab; nonetheless, it stopped due to an allergy. After the diagnosis of CD, the perianal symptoms kept repeating, especially the anal fistula, anal fistula

resection, incision, and suture hanging were performed. Lymph node biopsy pathology was performed due to the left swollen groin lymph node, and the pathologic result showed poorly differentiated mucinous adenocarcinoma. Enhanced computed tomography (CT) of the upper abdomen and pelvic cavity indicated CD with anal cancer, liver, bone, and lymph node metastasis (Figure 1). The patient received chemotherapy; moreover, radiofrequency therapy and capecitabine oral chemotherapy were performed after six cycles of chemotherapy. As a mass was found in the anal finger examination, targeted chemotherapy drugs were added for treatment. About 10 months after chemotherapy, anal cancer recurred and was accompanied by a large number of bloody ascites. Finally, cardiac arrest occurred due to hemorrhagic shock, and treatment was abandoned.

Case 2 was a 55-year-old female with a 13-year history of CD. Infliximab therapy was administered. Magnetic resonance imaging (MRI) showed the anal fistula (Figure 2). Anal fistula hanging operation had been performed twice before, and the perianal condition was stable after the operation. Postoperative pathological results demonstrated squamous cell carcinoma in situ. The patient received laparoscopic radical resection of anal cancer, ileocecal and terminal ileocecal resection, as well as sigmoid colostomy. The operation was successful and the postoperative recovery was good. Mesalamine

Table 1. Summary of clinical features of three patients with Crohn's disease complicated with anal carcinoma

	Case 1	Case 2	Case 3
Age	31 years old	56 years old	29 years old
Gender	F	F	M
Perianal lesions	Anal fistula	Complex anal fistula	Anal fistula
Pathological types of anal carcinoma	Mucous adenocarcinoma	Squamous cell carcinoma	Squamous cell carcinoma
The interval between Crohn's disease and anal carcinoma	7years	13years	8years
Anal carcinoma treatment	Chemotherapy + drug targeted therapy	surgery	Radiation therapy + chemotherapy
Outcome after treatment	Anal cancer recurred accompanied by massive bloody ascites. Dead of hemorrhagic shock occurred.	Follow up regularly and the condition was stable	Follow up regularly after treatment
Duration of infliximab use	47 months	11 months	30 months

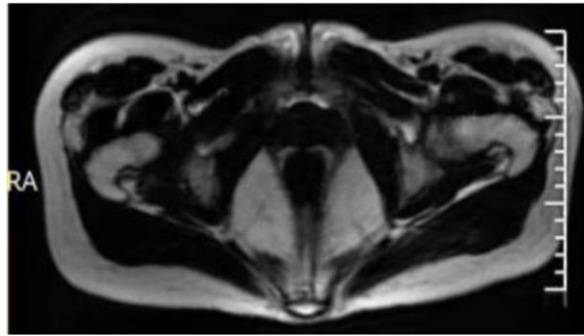
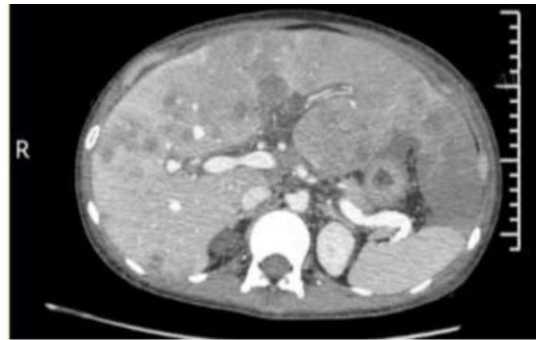


Figure 1. Enhanced computed tomography of upper abdomen and pelvic cavity of case 1 showed liver, bone and lymph node metastasis. The MRI of anal canal of case 1 showed anal cancer

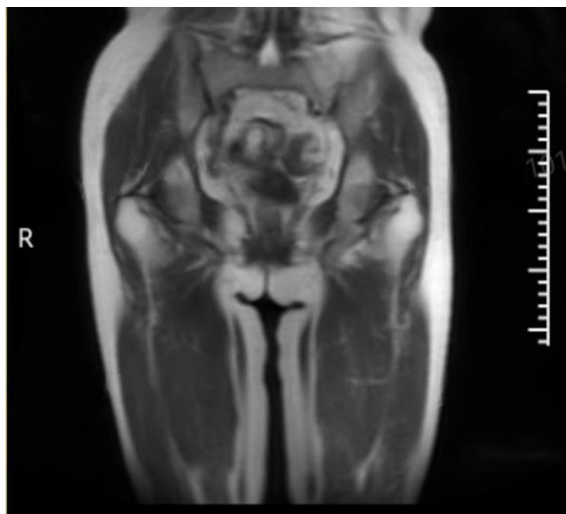


Figure 2. The magnetic resonance imaging of anal canal of case 2 showed anal fistula and anal abscess

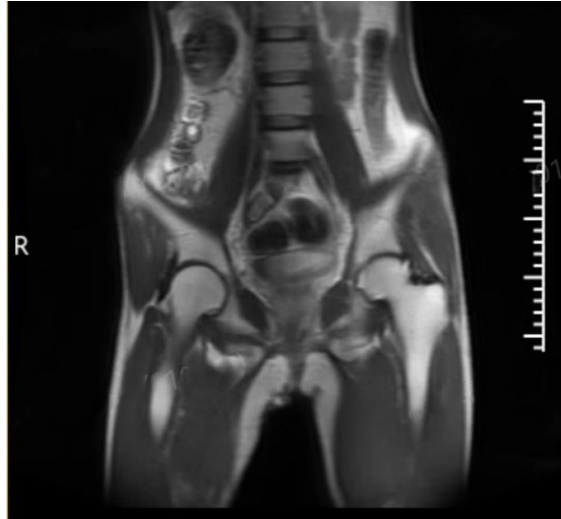


Figure 3. The magnetic resonance imaging of pelvic cavity of case 3 showed uneven thickening of the lower rectum and local thickening of the right perianal skin, anal fistula with small abscess formation

was treated with CD after surgery, and the condition was stable with regular follow-ups.

Case 3 was A 29-year-old male with an 8-year history of CD with anal fistula. Oral mesalamine treatment was discontinued due to unstable effects. Later, the treatment was changed to infliximab treatment, and the treatment interval was adjusted according to the condition of the combination of azathioprine and infliximab dose. The perianal condition was repeated, and MRI indicated the anal fistula, as well as an abscess (Figure 3). The perianal condition was improved after the anal fistula suture hanging operation was once performed. Postoperative pathological results showed (perianal) keratinized squamous cell carcinoma with high to medium differentiation. The patient received

radiotherapy: intensity-modulated field in pelvic tumor area (including anal mass and inguinal metastatic lymph nodes) 10MV-X SAD 100 DT 5400cGy/30F/ 41D. Chemotherapy with nedaplatin and capecitabine was performed regularly after the radiotherapy, and the condition is stable.

5. Discussion

From 2019-2020, three patients with CD combined with anal cancer were admitted and the incidence of CD combined with anal cancer in our hospital was 0.04% (3/8241), according to the number of CD patients in the hospital displayed in Figure 4. One patient died after multiple metastases due to a lack of timely diagnosis and treatment. The

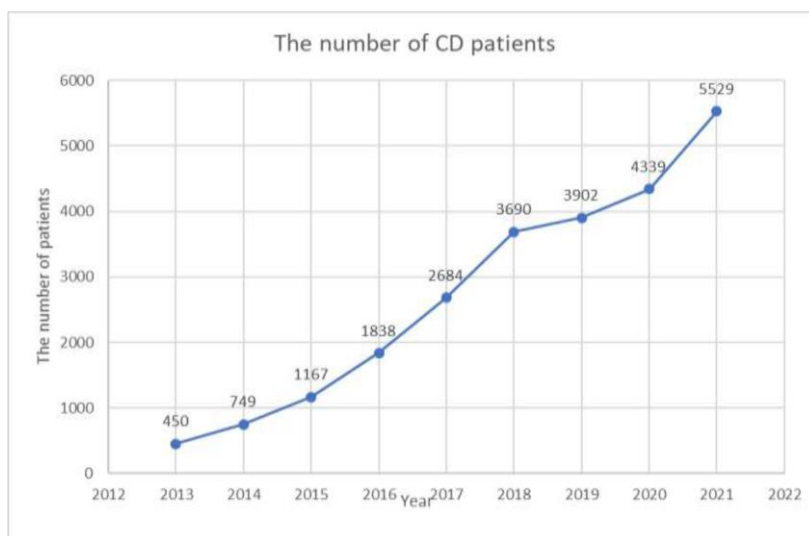


Figure 4. Number of patients with Crohn's disease in Sir Run Run Shaw Hospital, Zhejiang University, School of Medicine from 2013-2021

other two patients were detected early and treated with surgery, radiotherapy, and chemotherapy, respectively, and obtained stable conditions after therapy. According to the previous study, the CD patients who developed anal cancer were predominantly female at a relatively young age with perianal lesions. The main type of carcinoma is squamous cell carcinoma and adenocarcinoma, and the outcome was basically good (2-11). The clinical characteristics were similar to those of the three cases in the present study.

Clinicians should devote attention to the perianal symptom of patients with CD. Chronic complex anal symptoms, especially the anal fistula, in patients with CD seemed to be an increased risk of anal cancer, and changes in symptoms were important warning signs of anal cancer (12,13). The MRI can be an effective way to detect anal cancer (8). Nonetheless, no study has proposed the optimal frequency and method for monitoring long-term anal or perianal CD (14), as well as standardized screening methods (6). The lack of routine perianal management could lead to the untimely diagnosis and treatment of anal carcinoma(12).

The mechanism of CD with anal cancer has not been fully elucidated, and possible mechanisms include local and systemic chronic inflammation, HPV infection, decreased defensin function, and drug-induced immunosuppression (7, 9, 10, 12, 14). In addition, all three patients included in this study used infliximab to treat CD. Infliximab was considered to suppress tumor necrosis factor so as to promote the growth of the tumor, control inflammation, and alleviate anus symptoms to delay the diagnosis of anal cancer (2, 3). Although experiments on animal models have illustrated that infliximab has a certain promoting effect on the occurrence of cancer (15), no link has been found between infliximab therapy and the occurrence of anal cancer in existing studies and cases (16-18). Nevertheless, it is recommended that patients with CD with the perianal disease be fully evaluated before the use of the infliximab therapy, and biopsy is the best (19).

6. Conclusion

Crohn's disease with anal cancer is uncommon. Conventional perianal evaluation is important in patients with Crohn's disease. Treatment includes surgery and radiation therapy combined with chemotherapy. The association of infliximab therapy with anal cancer has not been fully established and needs to be fully evaluated before the use of infliximab in Crohn's disease.

Acknowledgments

This research was performed in the Inflammatory Bowel Disease Center of Sir Run Run Shaw Hospital,

College of Medicine Zhejiang University, China.

Footnotes

Conflicts of Interest: None to declare.

Authors' contributions: All authors contributed to this work and commented on the manuscript at all stages, and the last version was approved for publication.

Funding: None.

Ethical consideration: Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

References

1. Wisniewski A, Fléjou JF, Siproudhis L, Abramowitz L, Svrcek M, Beaugerie L. Anal neoplasia in inflammatory bowel disease: classification proposal, epidemiology, carcinogenesis, and risk management perspectives. *J Crohns Colitis*. 2017;**11**(8):1011-8. doi: [10.1093/ecco-jcc/jjx035](https://doi.org/10.1093/ecco-jcc/jjx035). [PubMed: [28379306](https://pubmed.ncbi.nlm.nih.gov/28379306/)].
2. Egea-Valenzuela J, Belchí-Segura E, Essouri N, Sánchez-Torres A, Carballo-Alvarez F. Adenocarcinoma of the rectum and anus in a patient with Crohn's disease treated with infliximab. *Rev Esp Enferm Dig*. 2010;**102**(8):501-4. doi: [10.4321/s1130-01082010000800009](https://doi.org/10.4321/s1130-01082010000800009). [PubMed: [20670073](https://pubmed.ncbi.nlm.nih.gov/20670073/)].
3. Maejima T, Kono T, Orii F, Maemoto A, Furukawa S, Liming W, et al. Anal Canal adenocarcinoma in a patient with longstanding Crohn's disease arising from rectal mucosa that migrated from a previously treated rectovaginal fistula. *Am J Case Rep*. 2016;**17**:448-53. doi: [10.12659/ajcr.897876](https://doi.org/10.12659/ajcr.897876). [PubMed: [27373845](https://pubmed.ncbi.nlm.nih.gov/27373845/)].
4. Melichar B, Bures J, Dedic K. Anorectal carcinoma after infliximab therapy in Crohn's disease: report of a case. *Dis Colon Rectum*. 2006;**49**(8):1228-33. doi: [10.1007/s10350-006-0647-6](https://doi.org/10.1007/s10350-006-0647-6). [PubMed: [16845561](https://pubmed.ncbi.nlm.nih.gov/16845561/)].
5. Freeman HJ, Perry T, Webber DL, Chang SD, Loh MY. Mucinous carcinoma in Crohn's disease originating in a fistulous tract. *World J Gastrointest Oncol*. 2010;**2**(7):307-10. doi: [10.4251/wjgo.v2.i7.307](https://doi.org/10.4251/wjgo.v2.i7.307). [PubMed: [21160662](https://pubmed.ncbi.nlm.nih.gov/21160662/)].
6. Lightner AL, Moncrief SB, Smyrk TC, Pemberton JH, Haddock MG, Larson DW, et al. Long-standing Crohn's disease and its implication on anal squamous cell cancer management. *Int J Colorectal Dis*. 2017;**32**(5):661-6. doi: [10.1007/s00384-017-2794-8](https://doi.org/10.1007/s00384-017-2794-8). [PubMed: [28293746](https://pubmed.ncbi.nlm.nih.gov/28293746/)].
7. Buchman AL, Ament ME, Doty J. Development of squamous cell carcinoma in chronic perineal sinus and wounds in Crohn's disease. *Am J Gastroenterol*. 1991;**86**(12):1829-32. [PubMed: [1962632](https://pubmed.ncbi.nlm.nih.gov/1962632/)].
8. Benjelloun EB, Abkari M, Ousadden A, Ait Taleb K. Squamous cell carcinoma associated anal fistulas in Crohn's disease unique case report with literature review. *J Crohns Colitis*. 2013;**7**(6):232-5. doi: [10.1016/j.crohns.2012.09.015](https://doi.org/10.1016/j.crohns.2012.09.015). [PubMed: [23069004](https://pubmed.ncbi.nlm.nih.gov/23069004/)].
9. Ball CS, Wujanto R, Haboubi NY, Schofield PF. Carcinoma in anal Crohn's disease: discussion paper. *J R Soc Med*. 1988;**81**(4):217-9. doi: [10.1177/014107688808100411](https://doi.org/10.1177/014107688808100411). [PubMed: [3373467](https://pubmed.ncbi.nlm.nih.gov/3373467/)].
10. Daly JJ, Madrazo A. Anal Crohn's disease with carcinoma in situ. *Dig Dis Sci*. 1980;**25**(6):464-6. doi: [10.1007/BF01395512](https://doi.org/10.1007/BF01395512). [PubMed: [7379680](https://pubmed.ncbi.nlm.nih.gov/7379680/)].
11. Barral M, Dohan A, Allez M, Boudiaf M, Camus M, Laurent V, et al. Gastrointestinal cancers in inflammatory bowel disease: An update with emphasis on imaging findings. *Crit Rev Oncol Hematol*. 2016;**97**:30-46. doi: [10.1016/j.critrevonc.2015.08.005](https://doi.org/10.1016/j.critrevonc.2015.08.005). [PubMed: [26315381](https://pubmed.ncbi.nlm.nih.gov/26315381/)].
12. Wisniewski A, Fléjou JF, Siproudhis L, Abramowitz L, Svrcek M, Beaugerie L. Anal neoplasia in inflammatory bowel disease: classification proposal, epidemiology, carcinogenesis, and risk management perspectives. *J Crohns Colitis*. 2017;**11**(8):1011-

1018. doi: [10.1093/ecco-jcc/jjx035](https://doi.org/10.1093/ecco-jcc/jjx035). [PMID: 28379306].
13. Devon KM, Brown CJ, Burnstein M, McLeod RS. Cancer of the anus complicating perianal Crohn's disease. *Dis Colon Rectum*. 2009;**52**(2):211-6. doi: [10.1007/DCR.0b013e318197d0ad](https://doi.org/10.1007/DCR.0b013e318197d0ad). [PubMed: [19279414](https://pubmed.ncbi.nlm.nih.gov/19279414/)].
 14. Beaugerie L, Carrat F, Nahon S, Zeitoun JD, Sabaté JM, Peyrin-Biroulet L, et al. High risk of anal and rectal cancer in patients with anal and/or perianal Crohn's Disease. *Clin Gastroenterol Hepatol*. 2018;**16**(6):892-9. doi: [10.1016/j.cgh.2017.11.041](https://doi.org/10.1016/j.cgh.2017.11.041). [PubMed: [29199142](https://pubmed.ncbi.nlm.nih.gov/29199142/)].
 15. Cohen RB, Dittrich KA. Anti-TNF therapy and malignancy - a critical review. *Can J Gastroenterol*. 2001;**15**(6):376-84. doi: [10.1155/2001/403102](https://doi.org/10.1155/2001/403102). [PubMed: [11429667](https://pubmed.ncbi.nlm.nih.gov/11429667/)].
 16. Malvi D, Vasuri F, Mattioli B, Gruppioni E, Fiorentino M, Gionchetti P, et al. Adenocarcinoma in Crohn's disease: the pathologist's experience in a tertiary referral centre of inflammatory bowel disease. *Pathology*. 2014;**46**(5):439-43. doi: [10.1097/PAT.000000000000123](https://doi.org/10.1097/PAT.000000000000123). [PubMed: [24977730](https://pubmed.ncbi.nlm.nih.gov/24977730/)].
 17. Biancone L, Orlando A, Kohn A, Colombo E, Sostegni R, Angelucci E, et al. Infliximab and newly diagnosed neoplasia in Crohn's disease: a multicentre matched pair study. *Gut*. 2006;**55**(2):228-33. doi: [10.1136/gut.2005.075937](https://doi.org/10.1136/gut.2005.075937). [PubMed: [16120759](https://pubmed.ncbi.nlm.nih.gov/16120759/)].
 18. Biancone L, Calabrese E, Petruzzello C, Pallone F. Treatment with biologic therapies and the risk of cancer in patients with IBD. *Nat Clin Pract Gastroenterol Hepatol*. 2007;**4**(2):78-91. doi: [10.1038/ncpgasthep0695](https://doi.org/10.1038/ncpgasthep0695). [PubMed: [17268543](https://pubmed.ncbi.nlm.nih.gov/17268543/)].
 19. Ogawa H, Haneda S, Shibata C, Miura K, Nagao M, Ohnuma S, et al. Adenocarcinoma associated with perianal fistulas in Crohn's disease. *Anticancer Res*. 2013;**33**(2):685-9. [PubMed: [23393368](https://pubmed.ncbi.nlm.nih.gov/23393368/)].