Journal of Crohn's and Colitis (2012) 6, 792–795

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SHORT REPORT

Oral squamous cell carcinoma in a Crohn's disease patient taking azathioprine: Case report and review of the literature

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Received 2 February 2012; received in revised form 27 February 2012; accepted 5 March 2012

KEYWORDS
Crohn's disease;
Thiopurines;
Azathioprine;
Oral cancer

Abstract

Thiopurines are widely used for remission maintenance and post-operative recurrence prevention in Crohn's disease. The increased risk of cancer in transplant recipients on azathioprine is well recognized and there are concerns that this may also be true for inflammatory bowel disease patients.

We report a case of a 33-year-old Caucasian woman with Crohn's disease treated with azathioprine for 9 years who developed an ulcerated lesion at the right superior retromolar trigone. Biopsy specimen revealed a squamous cell carcinoma.

1. Introduction

An excess cancer risk in inflammatory bowel disease (IBD) patients is a controversial subject, as selection bias in studies and differences in treatment may have affected reported data.[1,2] A meta-analysis by von de Roon[3] including data from 34 studies (single center, multicenter and population-based studies) of 60,122 patients with Crohn's disease (CD), found an increased risk of colon, small bowel and extra-intestinal malignancies, but this work has the problem of including selected patient materials. A more recent meta-analysis of population-based cohort on extra-intestinal cancer in patients with IBD (Crohn's disease and ulcerative colitis) revealed that the overall risk among these patients was not significantly increased but for CD patients *per se*, the risk was increased for upper gastrointestinal tract, lung, urinary bladder and squamous skin cancer.[2] However, in a Danish population-based study on the risk of cancer in patients with CD, Jess T. et al.[1] found that extra-intestinal cancer did not occur more frequently than expected.

Thiopurines are nowadays widely used in the treatment of IBD. At present, azathioprine (AZA) is increasingly used for remission maintenance and for post-operative recurrence prevention in CD, offering an inexpensive treatment option in comparison with biological therapies.[4]

Increased risk of malignancy in transplant recipients and rheumatoid arthritis patients on AZA is well established.[5,6] There have been concerns that this may also be true for IBD[6] and several case reports have been published involving immunosuppression and its association with malignancy.[7–9]

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[1] First and second authors had equal contribute to the paper design and writing.

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doi:10.1016/j.crohns.2012.03.004

Recently the higher risk of lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease was observed in a prospective observational cohort study (CESAME study group).[10]

Herein we report a case of oral squamous cell carcinoma in a CD patient treated with AZA since 2002.

2. Case report

A 33-year-old Caucasian woman with a 13-year history of inflammatory ileal CD (A2L1B1p), complained with a non-painful ulcer in her mouth for the last 2 months. A 1-cm whitish ulcerated lesion was identified at the right superior retromolar trigone and the patient was immediately referred for an Oral and Maxillofacial Surgery consultation. The lesion biopsy revealed a keratinizing squamous cell carcinoma. She has never smoked and only sporadically consumed alcoholic beverages.

From her dental health history we know that she was regularly (once or twice a year) seen by her dentist since childhood and had periodontal therapy done with dental filling and exodontia because of a non-restorable tooth. She has no dental implant and never used orthodontic braces or worn a denture.

Besides CD, her personal history was unremarkable. She had been submitted to perianal surgery for abscess drainage by the time of CD diagnosis.

She has no family history of malignancy.

She was being treated with 5-aminosalicylates 3 g per day since CD diagnosis and AZA 2 mg/kg/day continuously for the last 9 years with good tolerance. The patient was submitted to lesion exeresis and closure using a Bichat ball complemented by levels I to V cervical lymph node dissection. The pathological examination revealed a well differentiated keratinizing squamous cell carcinoma without muscular invasion (Fig. 1). Multiplex PCR (Polymerase Chain Reaction) followed by *in situ* hybridization of DNA extracted from two formaldehyde fixed, paraffin embedded samples (with and without tumor) was negative for human papillomavirus (HPV).

None of the 18 removed lymph nodes showed signs of metastasis (pT1N0M0 R0). AZA was discontinued and the patient remains attending follow-up at the Gastroenterology and Oral Surgery outpatient clinics.

She is asymptomatic and colonoscopy reveals erythema of the ileum without ulceration. Seven months have passed since the diagnosis of oral cancer and the patient remains free of malignancy.

3. Discussion

Oral cancer holds the eighth position in the cancer incidence ranking worldwide. At least 90% are squamous cell carcinomas.[11] This cancer is rare in patients younger than 45 years of age, occurring preferentially in males in their 6th and 7th decades, however a rise in the incidence among younger adults has been recently reported in Europe and USA.[12] Prolonged treatment with immunosuppressive agents has been shown to determine an increased risk of a broad range of cancers in solid organ transplant recipients compared with the general population specially non-Hodgkin lymphoma and cancers of the lung, liver and kidney but also gastric cancer and melanoma.[13]

These patients are usually on two or three drug "cocktails", frequently including a thiopurine. In fact it is disputable if we can infer the increased risk of cancer other than lymphoproliferative disease in transplant recipients to a non-transplant group using a single immunosuppressive agent.[9] Furthermore, oral cancer in IBD is a rare event and meta-analysis may not be well enough powered to study its risk in these patients.

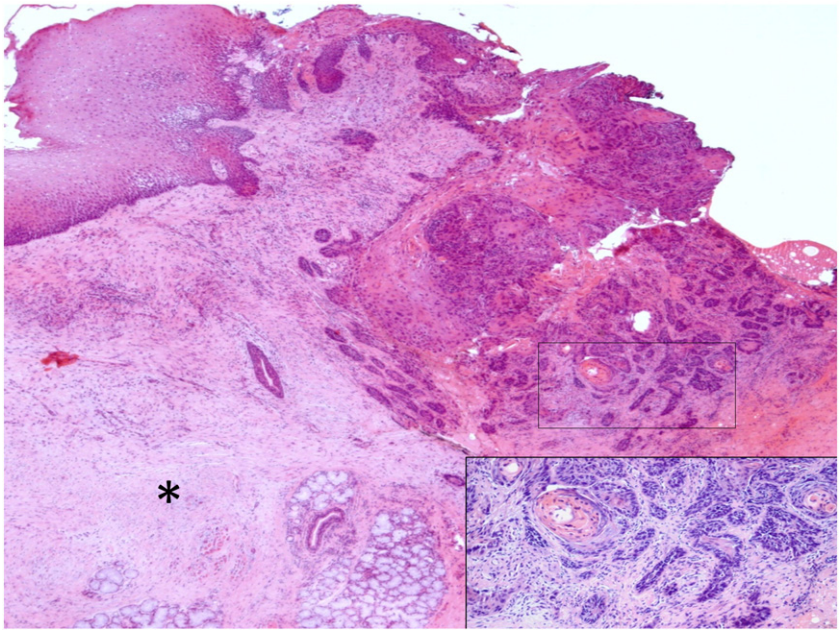

Figure 1 Epidermoid carcinoma of the oral mucosa. Low power (H&E, 20×); inset — high power of the invasive component (H&E, 200×). * — fibrous scar from previous biopsy.