Crohn's Disease treated with azathioprine and basal cell carcinoma : three cases and literature review

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Abstract

Three cases of basal cell carcinoma in Crohn's disease patients treated with azathioprine are described. A review of the literature is conducted concerning this association between the occurrence of basal cell carcinoma and the use of azathioprine. Recently, practical advice on screening and follow-up of these situations have been proposed but there are no validated dermatological recommendations. (Acta gastroenterol. belg., **2015**, 78, **436-438**).

Key words : Crohn's Disease, immunosuppressive therapy, basal cell carcinoma.

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) that often requires an immunosuppressive (IS) therapy to obtain remission and to avoid long term use of corticosteroid treatment. However, IS therapy is prone to side effects, including an increased risk of malignancies.

In addition to their use in IBD, thiopurines are used to treat autoimmune diseases and organ- transplant patients, and have been identified as risk factors for epithelial skin cancer, Kaposi's sarcoma and lymphoma (1,2).

The experience in kidney transplant patients incriminated azathioprine (AZA) in the occurrence of non melanoma skin cancer (NMSC) like basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) (2-4).

We describe 3 CD patients treated with AZA who developed BCC and review the literature regarding this association.

Case 1

The first case is a 36 year old female, active smoker, with a history of ileal CD for 10 years.

She has a skin phototype II (increased risk of skin cancer) and a repeated history of sunburn. She is examined by a dermatologist for moles yearly.

She was treated with 5-aminosalicylic acid (5-ASA), AZA and infliximab for 10 years.

Screening for thiopurine methyltransferase (TPMT) gene mutations was negative. Eight years after initiation of IS therapy, at the age of 34, three truncal superficial BCC were found and resected. One year later AZA was stopped but infliximab was continued. She is currently under strict dermatological follow-up every 6 months, and remains free of newly developed BCC.

Case 2

The second case is a male patient with ileocolonic CD since the age of 16 and a history of ileocaecal resection. He has a skin phototype II but without a history of sunburn. In 2002, he had a flare and was started with AZA and infliximab. Screening for TPMT gene mutation s was negative and dermatological screening for moles was also negative.

In 2012, at the age of 41, he developed a superficial BCC on the forehead under combined IS therapy. Subsequently, AZA was stopped but infliximab is continued. He is closely monitored by a dermatologist.

Case 3

The third case is a 64 year old male with longstanding ileocolonic CD since the age of 28. He was not compliant and used corticosteroids on demand. He developed a rectal stenosis in 2001, due to active CD, for which combination therapy of 5-ASA and AZA was started. TPMT gene mutation screening was negative. Although he has a skin phototype II, he was not in follow up by a dermatologist.

Two years later, at the age of 58 years, he developed a superficial BCC on the back (Fig. 1) which was locally resected. AZA was stopped and infliximab was initiated. He is advised to consult a dermatologist on a regular base.

Discussion

We describe 3 CD patients who developed BCC while under IS therapy including AZA, and 2 of them at a

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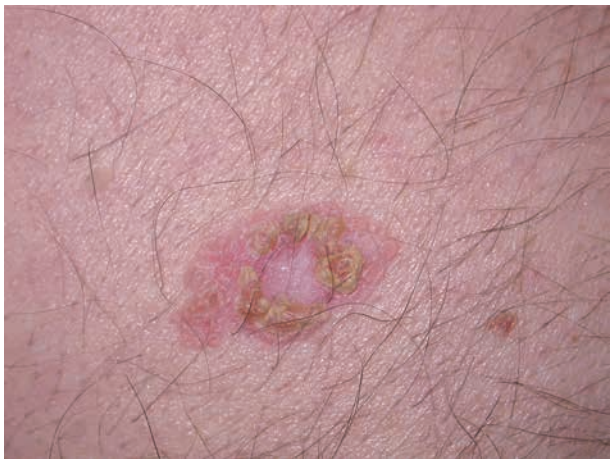

Fig. 1. — Superficial basal cell carcinoma on the back of a male patient (case description 3).

young age. NMSC including BCC and SCC, is the most common cancer among fair-skinned populations. The incidence of NMSC depends on patient profiles and varies according to skin phototype, underlying treatment and age. A history of painful sunburn, working in the open air and a family history of epithelial skin cancer increases the incidence of SCC and BCC (5). Local surgical resection is the standard of care therapy for BCC, with a low risk of recurrence if surgery is complete. However, the risk to develop new BCC in IBD

patients under continued AZA therapy is unknown (5). Therefore, it was decided to stop AZA therapy in all 3 patients.

Experience from renal transplant patients, classified the overall risk of cancer recurrence under IS therapy as low, intermediate and high risk depending on the type of cancer. Skin cancers are considered as "high risk", and therefore, IS therapy should be withheld until the patient has been free of cancer for at least 5 years. However, these guidelines on skin cancer do not differentiate between melanoma, SCC or BCC (4,6,7).

It seems a drastic decision for a superficial and non-invasive cancer like BCC. Therefore, prospective studies are needed to differentiate the real risk of each type of skin cancer.

In IBD patients little is known regarding the risk to develop NMSC (BCC and SCC). In the USA, the geographical distribution of NMSC in CD patients, shows that patients in the more sunny southern states are at greater risk than those living in the north (4). Skin phototypes I and II, blue eyes and blond or red hair are additional risk factors (4).

As it is the case in renal transplant patients, IS therapy, including AZA, is considered to be a risk factor to develop NMSC in IBD patients (2,3,4). The mechanism through which AZA predisposes to NMSC is double : it causes a decrease of the necessary immune response to inhibit precancerous conditions (3) and has a direct carcinogenic effect by incorporation thioguanines into the DNA of skin epithelial cells enhancing their photosensitivity to UV and damaging their DNA (3). AZA causes the accumulation of 6-thioguanine in DNA. Under the action of ultraviolet A (UVA), there is a production of reactive oxygen species, leading to DNA mutations and oxidative stress, linked to oncogenesis (5,7). Some studies (8,9) suggest that high thioguanines nucleotide (TGN) levels can be associated with an increased risk of malignancy (7). Expert opinion (7) suggests that avoiding repeatedly high TGN levels could reduce the occurrence of cancer in patients on AZA. None of our 3 patients had mutations of TMPT gene but TGN levels were not measured.

The Long study demonstrated that inflammatory bowel disease patients have an increased risk of NMSC, and the use of IS medications appears to be a key driver. Moreover, patients with long term use of thiopurines appeared to be at the highest risk of developing NMSC (4).

These findings were partly reinforced by French CESAME study which included 19,486 CD patients and found 32 NMSC (20 BCC and 12 SCC). This study concluded that ongoing and past exposure to thiopurines significantly increases the risk of NMSC in patients with IBD, even before the age of 50 years (6). Another study showed that the use of thiopurines in patients with inflammatory bowel diseases increased the risk of SCC (3).

On the other hand, a Dutch study (10) with a limited number of patients was not able to show any relationship between the use of thiopurines and the risk of NMSC. Moreover, many patients did not meet the Long criteria (4), defined as a recent thiopurine exposure (< 90 days before being diagnosed with NMSC) and a continuous treatment with thiopurines (> 365 days).

Based on these limited data, there appears to be an increased risk to develop NMSC in IBD patients, most likely related to the long term use of AZA. It is therefore recommended to limit AZA treatment over a maximal period of 3 to 5 years, especially if it is combined wit h a biological treatment and if the patient is in remission (7). Some even recommend stopping AZA treatment after 2 years with a risk of CD reactivation. The decision to stop thiopurines is difficult even after 4 years, as suggested by some (11), and unfounded, according to others, because sustained remission may require long term use of AZA (7,12). Moreover, according to the CESAME study (6), stopping thiopurines, may only prevent the development of lymphoma and not the development of NMSC.

Despite the relevance of some studies, the risk/benefit ratio of thiopurines in the treatment of IBD is in favour of pursuing this type of treatment with close monitoring on the risk of NMSC, especially if this treatment is used for a longer period in increasingly ageing patients.

Screening for a NMSC (BCC and SCC) in a high risk patient, such as a CD patient under IS therapy, is important (13) especially when the patient is young.

In conclusion, and based on the third ECCO workshop (5), practical advice can be given to help physicians

in the prescription of thiopurines to CD patients with the following checklist :

- Be sure that IS is necessary in the treatment
- Be careful with patients with a cancer history
- Take into account the patient's skin phototype, a history of sun burn as well as UV exposure
- Inform patients of the risk of NMSC (BCC and SCC) and explain UV protection, especially if they are fair-skinned.
- Advise the patient to undergo a yearly screening by a dermatologist
- Suggest to the patient to perform self-examination of the skin every three months, especially in sun-exposed areas, but also on the scalp and in interdigital areas, and to stop smoking
- If a NMSC is found in a patient under AZA therapy, it is advised to stop AZA. There are case reports of immune-reconstitution effectively eradicating malignancy in the absence of other therapy (7). Consider switching therapy to methotrexate or biological therapy.

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