

Letters to the Editor

Malignant melanoma in a patient with Crohn's disease and treated with anti-TNF alpha

Key words: Crohn's disease. Malignant melanoma. Anti-TNF alpha drugs.

Dear Editor,

A possible association has been documented between the use of tumour necrosis factor alpha inhibitors (anti-TNF alpha) and the development of skin cancer, primarily described in patients diagnosed with rheumatoid arthritis and psoriasis.

The majority of cutaneous neoplasia associated with anti-TNF alpha therapy is non-melanoma skin cancer (NMSC), and while there are incidental cases of melanoma, none of them has been described in patients with inflammatory bowel disease (IBD).

We present a case of malignant melanoma (MM) in a patient with Crohn's disease (CD) and treated with anti-TNF alpha as well as a brief summary of literature to determine if further in-depth study is needed to detect these lesions in these types of patients.

Case report

We present a case of MM in a 29-year-old male with ileocolic CD for 18 years of evolution. Intervention included a subtotal colectomy followed by ileorectal anastomosis for severe intestinal bleeding associated with the disease. After surgical intervention (10 years ago) and due to the difficulty in preventing

recurrence, the patient was treated with azathioprine (which the patient had already been using for 10 years) and infliximab for 2 years. After the patient failed to respond to the medication, adalimumab was used, which the patient has received since 2008, but required dosage increase in the last year due to loss of efficacy. The patient had an appointment with the department of dermatology for a nevus on his back, which during the last 8 years has changed and bled from the rubbing of clothing against it. Given the suggestive malignancy, the lesion was removed and identified as ulcerated nodular melanoma at a depth of 7 mm (Breslow thickness 1.26 mm and Clark level III), no vascular and/or neural invasion, stadium pT2b of TNM classification (Fig. 1). Sentinel lymph node biopsy negative.

Discussion

Collectively, the biological drugs have been evaluated in thousands of patients demonstrating a clear benefit with safety and tolerability levels being more than acceptable. However, more and more frequently, anti-TNF alpha drugs are being associated with skin cancer progression (1). The most frequent is non-melanoma skin cancer (NMSC), both basal cell and squamous cell carcinoma.

The meta-analysis of Burmester et al. (2), based on the clinical trials of adalimumab in 23,458 patients treated for various disorders, it was demonstrated that patients with rheumatoid arthritis (RA), psoriasis and CD, have a higher risk of developing NMSC than the general population. In comparison to CD, patients with RA and psoriasis treated with adalimumab seem to have a higher risk of MM. In a large retrospective cohort study of patients with CD (n 26,403), Long et al. (3) found that patients treated with adalimumab or infliximab have a higher risk of NMSC (n 387) but not for MM.

Asking et al. (4) studied the short-term effects (with a mean exposure to anti-TNF alpha drugs of less than 6 months) of etanercept, infliximab and adalimumab, through a meta-analysis that included 15,418 patients. The study found an increased risk of NMSC development, but not for MM. The study shows that 95 % of patients with infliximab received concomitant immu-

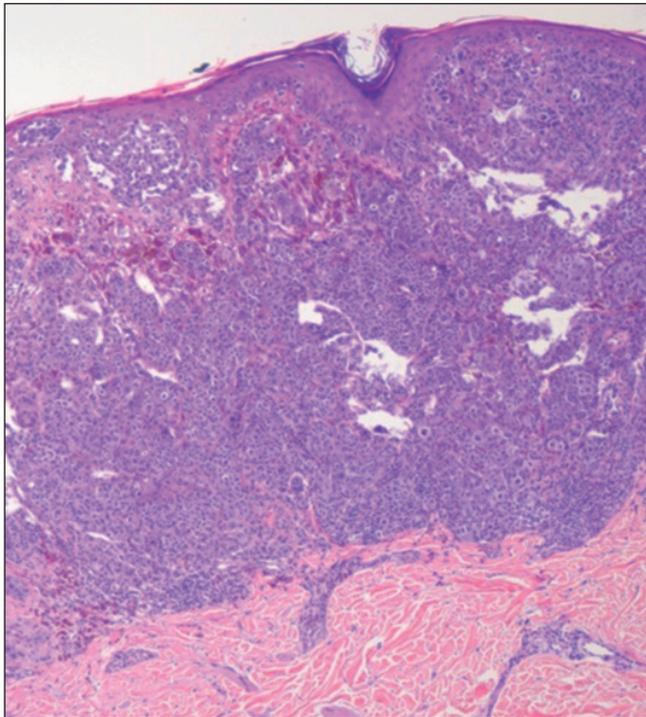


Fig. 1.

nosuppressive therapy, while this occurred in 71 % and 28 % of patients treated with adalimumab and etanercept, respectively.

In addition, this increased risk of MM in RA or psoriasis is usually also accompanied by the use of other treatments that are potentially carcinogenic (retinoids, cyclosporine, azathioprine) making it difficult to decide the role-played by these drugs in the carcinogenesis of the mentioned tumours.

Additionally, our patient concomitantly received azathioprine and its use was related to a greater risk of MNMC due to increased photosensitivity (3).

In fact, a recent prospective study carried out in France (5) on patients with IBD found that the use of azathioprine increases the risk of NMSC.

Besides the increase in photosensitivity, it seems that through the 6-thioguanine metabolite, thiopurines may provoke oxidative stress and, consequently, DNA damage, and it therefore shows potential for skin cancer development (6).

The biopathology of the initiation of melanocyte neoplasia is unknown. In experimental studies in mice, it has been observed that TNF alpha through the activation of specific molecules such as TNFR1, TNFR2 present protumoral activity (7). Different authors postulate that the participation of TNF alpha antagonists is probably linked to the progression of carcinogenesis (8) propelling tumour development. This would be especially

interesting in existing cases of a subclinical precursor lesion or carcinoma *in situ*.

The exact role of anti-TNF alpha drugs in carcinogenesis is uncertain. While they seem to intervene in tumoral progression, we cannot know if NMSC or MM development is a result or if it is due to a confluence of factors such as concomitant use of other immunosuppressants such as azathioprine, or the underlying immune dysfunction of CD.

In conclusion, we present a case of MM in CD treated with anti-TNF alpha associated with long-term azathioprine use. Given that there are multiple studies that have analysed the prevalence of cutaneous tumours without finding cases of MM in patients with CD, this case could be due to random circumstances. While we consider these patients under immunosuppressive treatment, and especially in the cases of combined therapy, prevention programmes should be carried out based on educational methods focusing on sun exposure and regular dermatological evaluations in selective patients in order to detect newly pigmented lesions or monitor possible changes in pre-existing nevus.

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