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Letter

Melanoma occurrence under long-term etanercept treatment for psoriasis: a case report

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Abstract

Melanoma occurrence during treatment with anti-tumor necrosis factor is considered an incidental event, although very recent studies suggest a risk. Etanercept is a fusion protein that binds the tumor necrosis factor receptor and is included among TNF inhibitors, approved for the treatment of several autoimmune diseases, such as psoriasis.

We described a 79-year-old man with psoriasis, being treated with etanercept, who presented with a new brown to black macule on his right shoulder; this was immediately surgically excised. Histology showed a superficial spreading melanoma, 1.2 mm Breslow thickness, one mitosis/hpf, with no vascular or neural invasion (stage T2b). Sentinel lymph node biopsy was negative. There were no apparent melanoma risk factors: normal total nevus count, photo type IV, no childhood sunburns, no family history of melanoma, and no previous immune suppressive drugs and/or phototherapies. Etanercept 50 mg/week had been administered continuously for 5 years before the melanoma occurrence. After etanercept withdrawal his psoriasis slowly, but progressively relapsed.

Conclusions

This is the first melanoma case reported in a psoriasis patient, among a cohort of 216 patients since 2008 treated with anti-TNF, living in Sardinia, an Italian region considered at low risk for melanoma. This case supports the role of drug-induced immune surveillance compromise, in the absence of other personal and environmental confounding factors for melanoma. The possible anti-tumor necrosis factor association with melanoma is a controversial issue. Questions remain about the validity of this association, recommendations about preventative measures, and timing of skin screening efforts. In addition, the best choice for psoriasis treatment after melanoma detection has not been thoroughly studied.

Key words: Melanoma, tumor necrosis factor inhibitors, anti-TNF alpha, etanercept, psoriasis treatment.

Introduction

Melanoma occurrence during long-term tumor necrosis factor inhibition is a controversial issue. Although an increased risk for non-melanoma skin cancer has been associated with all immunosuppressive treatments, melanoma cases are regarded as incidental [1]. Conversely, case reports suggest a risk for the entire class of anti-TNF drugs [2-8]. In psoriasis patients, a recent meta-analysis excludes an increased risk of melanoma related to the natural course of the disease [9], but also no increased risk for melanoma was observed during anti-TNF randomized controlled studies [10, 11].

Etanercept is a recombinant human fusion protein, which binds to the 75 kilo-Dalton portion of the tumor necrosis factor receptor (TNFR), functioning as a decoy receptor, decreasing the natural effects of TNF. Hence, it is included among TNF inhibitors, a well-documented class of disease-modifying therapy approved for several autoimmune diseases, such as rheumatoid arthritis, ankylosing spondylitis, and psoriasis [12]. The present report is unique, as it describes the first melanoma observed in Southern Sardinia, a major Mediterranean island, considered at low risk for melanoma [13], occurring in a 79-year-old man during etanercept therapy for psoriasis. The case supports the hypothesis that anti-TNF inhibitors might be a risk factor for melanoma development in psoriasis patients, especially during long-term treatment.

Case synopsis

Our patient presented to his tri-annual visit with a new brown to black macule on his right shoulder, 1 x 0.7 cm, with a finely raised, palpable surface (Figure 1).

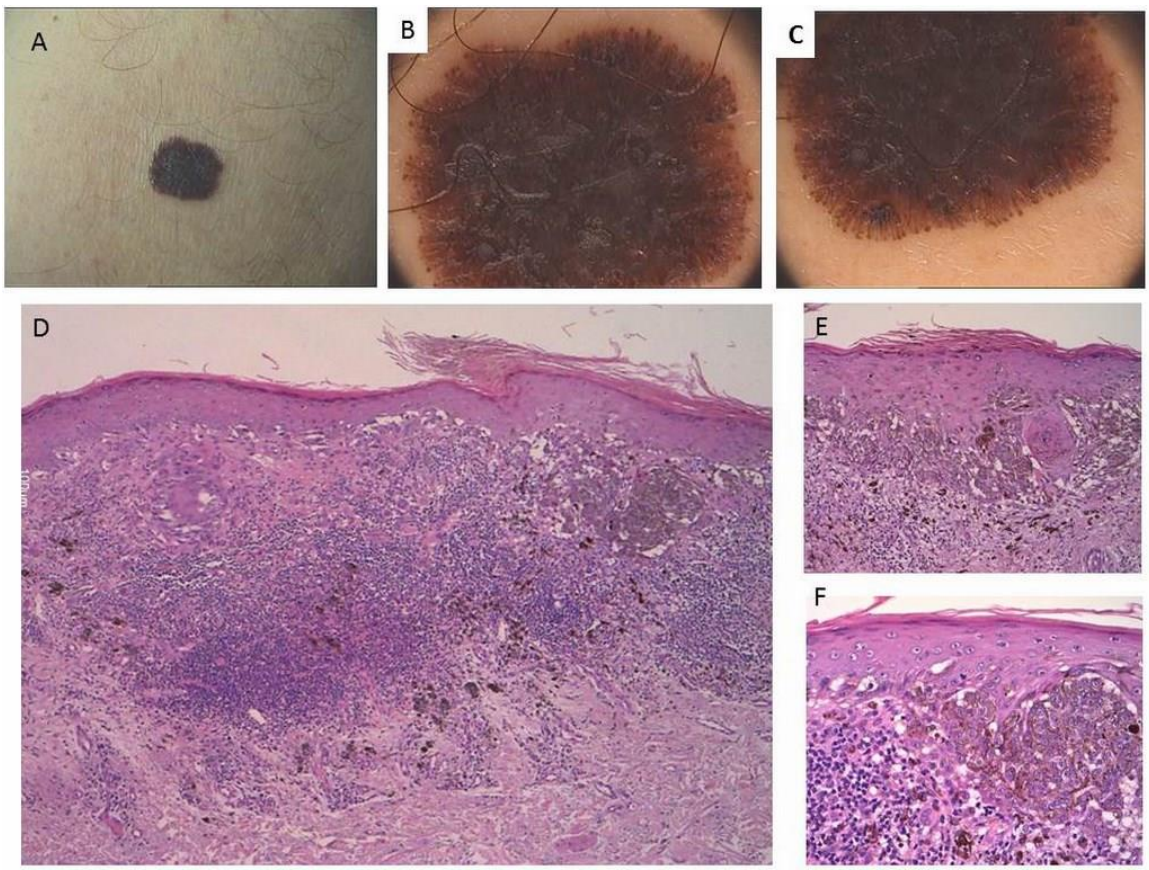

Figure 1. Brown to black macule on the right shoulder of a white Caucasian man, 1 x 0.7 cm, with a finely raised, palpable surface (inset A), Dermoscopy shows a compound pattern, with irregular network, de-structured central areas partially covered by grey-whitish veil, radial strikes, pseudopods; marginal brown globules (B, C). Histologic examination (D; H&E 4x) confirmed an irregular lentiginous proliferation of atypical epithelioid melanocytes, with extensive substitution of basal keratinocytes, dermo-epidermal clefts, and small nests of melanocytes with similar cytology predominantly in intra-epidermal location (D, H&E 4x; E, H&E 10x). A mild density pagetoid spread is detected at higher power (F; H&E 20x). An irregular dermal inflammatory infiltrate was also present.

Dermoscopy showed a compound pattern: an irregular network, de-structured central areas partially covered by grey-whitish veil, radial streaks, pseudopods, and marginal brown globules. Surgical excision produced a histologic diagnosis of superficial spreading melanoma (Figure 1): Breslow thickness 1.2 mm, one mitosis/hpf, no vascular or neural invasion (stage T2b). Sentinel lymph node biopsy was negative. Investigation for melanoma risk factors was unremarkable: normal total nevus count, photo type IV skin, no childhood sunburns, nor family history of melanoma. The medical chart reported mild hypertension, and atrial fibrillation treated with daily 5 mg enalapril, 8 mg doxazosin, and 250 mg ticlopidine. His psoriasis diagnosis dated back to 2000 and was controlled with topical therapy and cycles of oral retinoids. Periods of methotrexate use up to 15 mg/week were required at times. The use of etanercept had produced a sustained remission. Owing to melanoma, etanercept was dismissed and a slow, but progressive relapse of psoriasis and psoriatic arthritis occurred (Figure 2). Methotrexate treatment was reintroduced at 15 mg subcutaneously once weekly, with slow, but sustained improvement.

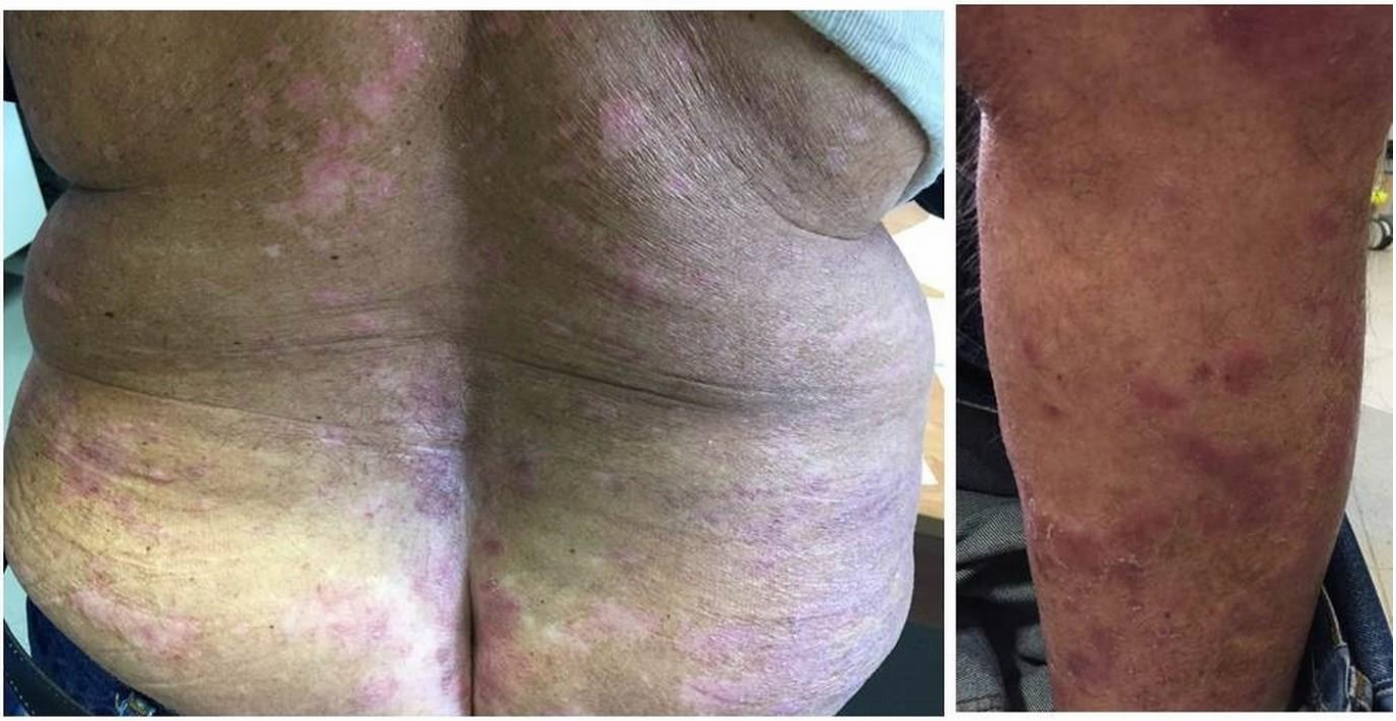

Figure 2. Psoriasis relapse after etanercept discontinuation, treated with methotrexate IM 15 mg/week with partial improvement

After 1 year, the patient's psoriasis is well controlled by the weekly 15 mg methotrexate subcutaneous injection and topical medication with emollients, short courses of calcipotriol ointment alone or with medium potency corticosteroid cream. There have been no melanoma recurrences and no new melanocytic lesions of concern.

Conclusions

This reported melanoma is the first observed among a cohort of 216 psoriasis patients, treated regularly with anti-TNF inhibitors at the Dermatology Clinic of Cagliari State University. With regard to the incidence of melanoma in the Italian population, data from the Italian Network of Cancer Registries (AIRTUM) confirm the well-known increasing melanoma trend, with an annual percentage change (APC) of 3.2 from 1999 to 2015, and a mean of 4000 new cases/year in males [13]. Considering the age of our patient, the expected rate in the 75-79 years rage is of 30 new skin melanoma diagnoses per 100,000 males. The Italian national statistical institute (ISTAT, census 2011) has registered 10,072 males in the same age range living in the Province of Cagliari, thus a frequency of 3 new melanoma cases/year is predictable. Our institute database on melanoma cases records 4 new diagnoses in males within the considered age between the years 2011 and 2015. However, the catchment area is somewhat wider than the province of Cagliari, being the reference public institution of Southern Sardinia (unpublished data).

The patient had no high-risk individual predisposing factors, nor had he undergone previous immune suppressive treatment. Of course, natural sun bathing was encouraged, as he was living on a Mediterranean island. In addition, one must also consider the recent suggestion of a paradoxical protective role of sun exposure [14, 15]. It has been postulated that chronic anti-TNF

treatment, affecting immune surveillance and collateral interferon inhibition could impair defenses against melanoma cell proliferation [2, 6].

Surprisingly, melanoma reports are few with respect to anti-TNF drugs worldwide [2-9]. A French study suggests that a critical point is observation timing; 47.6 months is the mean period from beginning treatment to melanoma occurrence in their experience [6]. Our patient was treated with etanercept for 5 years before his melanoma diagnosis. Local tumor behavior seems aggressive, as in the space of 3 months from the last visit it had reached 1.2 mm of thickness, with one mitosis. Single case reports support an aggressive behavior [2-5], as well as a Swedish population study, which found an increased risk (50%) of invasive, but not *in situ* melanoma associated with anti-TNF inhibitors, despite careful clinical vigilance [7]. With regard to diagnosis and therapy of the melanoma patients, our dermatology clinic follows the European guidelines [16], and the updated recommendation of the Italian Association of Medical Oncology (AIOM, www.aiom.it/). Therapeutic decisions are carried out by the oncologist, working in our interdisciplinary team.

Unanswered questions include characterization of the carcinogenesis risk, timing from drug exposure to melanoma occurrence, as well as consensus on recommended timing for skin screening. Our experience suggests that all patients eligible for anti-TNF agents should undergo a dermatologic examination before starting therapy and then every 3-6 months thereafter, to detect new pigmented lesions or changes in pre-existing nevi. Another crucial determination is how to treat psoriasis after removal of TNF inhibitors. Our patient was disappointed with the severity of the melanoma diagnosis, and its implications. He had not considered the possibility of melanoma when he initiated etanercept therapy, although a generic risk of skin cancer development had been discussed. The challenge of supporting and treating the patient prompted us to re-introduce methotrexate, encouraged by some anti-melanoma activity documented in experimental models [17, 18].

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