

# Development of Two Primary Malignant Melanomas after Treatment with Adalimumab: A Case Report and Review of the Possible Link between Biological Therapy with TNF- $\alpha$ Antagonists and Melanocytic Proliferation

A.C. Katoulis · A. Kanelleas · G. Zambacos · I. Panayiotides · N.G. Stavrianeas

2nd Department of Dermatology and Venereology, National and Kapodistrian University of Athens, School of Medicine, 'Attikon' General University Hospital, Athens, Greece

## Key Words

Biological therapy · TNF- $\alpha$  antagonist · Malignant melanoma · Eruptive melanocytic nevi · Immunosuppression · Adalimumab

## Abstract

Biologics, such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) antagonists, have revolutionized treatment of several significant inflammatory autoimmune diseases. Nevertheless, issues concerning long-term safety remain to be clarified. There is growing evidence linking biological treatments with the occurrence of malignancies or reactivation of latent ones, including malignant melanoma. We report the case of a 75-year-old male patient who developed 2 primary malignant melanomas (MM) after treatment with adalimumab for rheumatoid arthritis. He was under adalimumab treatment for approximately 12 months before the diagnosis of MM on his right lower leg. After surgical removal and staging, no evidence of metastases was found. A few months later, a second MM developed on the patient's scalp. The short duration of treatment with adalimumab and the unclear temporal relationship cannot adequately support a probable link

between this double MM occurrence and the adalimumab-induced immunosuppressive state. The result of a literature search regarding the possible association between anti-TNF drugs and melanocytic proliferation is provided.

Copyright © 2010 S. Karger AG, Basel

## Introduction

The use of biologics, such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) antagonists, in the treatment of psoriasis, rheumatoid arthritis (RA), or other significant inflammatory diseases has been a major therapeutic breakthrough. Nevertheless, issues concerning, mainly, long-term safety remain to be clarified. Furthermore, there is growing evidence linking biological treatment with the occurrence of malignancies or reactivation of latent ones, including malignant melanomas (MM) [1].

Adalimumab is a fully human recombinant IgG1 monoclonal antibody with specificity for human TNF- $\alpha$  [2]. TNF- $\alpha$  is a proinflammatory cytokine of the innate immune system with a key role in the surveillance of malignancies and response towards infections.

We report the case of a patient who developed 2 primary MM after treatment with adalimumab for RA.

## Case Report

A 75-year-old Greek male, skin phototype III, presented to the Dermatology Department of our Hospital in November 2007 with an asymptomatic pigmented skin lesion at the posterior aspect of his right lower leg. The lesion was round, 10 mm in diameter, with irregular border and color variegation. The patient recalled that he had had a 'mole' at the site, which changed during the last months. His medical history included arterial hypertension, diabetes mellitus type 2, and RA. For the latter, he was under treatment with adalimumab (40 mg s.c. every other week) for the last 12 months. There was no family or personal history of MM or dysplastic nevus syndrome. The lesion was excised and histology showed a superficial spreading malignant melanoma (Breslow thickness: 3.7 mm), arising on a preexisting melanocytic nevus. Adalimumab was promptly discontinued and instead methotrexate was introduced (10 mg weekly).

Subsequently, a wider excision of the lesion with 2 cm margin was performed, followed by removal of the ipsilateral inguinal sentinel lymph node. Both were free of melanoma. Laboratory investigations were within normal limits. Imaging investigations (including whole-body CT scan) were negative for metastases. Additionally, in March 2008, the patient underwent treatment with high doses of interferon  $\alpha$  for 20 days.

During the 3-month follow-up examination, a new pigmented lesion was identified on the partially balded (male-pattern alopecia) parietal area of the scalp. The patient could not provide information regarding the evolution of the lesion due to the anatomical site. The lesion was elevated, 19 mm in diameter, with irregular contour and color variegation. It was surgically removed and proved to be an MM (Breslow thickness: 4.1 mm, Clark's level III). Laboratory and imaging investigations showed again no sign of metastatic foci. Further investigations 6 months later were still negative.

In January 2009, 2 nodules were noticed on the right lower leg at the site of the previously excised melanoma. They were both surgically removed. Histology report showed that they had MM elements, and that they were incompletely excised. One month later, a further wider excision was performed, approximately 2 cm from the initial border of excision. A small satellite nodule was also identified and removed. Histology showed evidence of MM in both specimens. Two further wide excisions were performed in April and May, but completeness of excision could not be achieved. Again, laboratory and imaging investigations (including whole-body radioisotopic bone scanning) were negative. The patient remains under close monitoring.

## Discussion

Biologic agents represent a heterogeneous group of naturally occurring molecules, mainly proteins, engineered in the laboratory for pharmaceutical use [1]. TNF- $\alpha$  antagonists include infliximab, etanercept and adalimumab, and specifically bind both to soluble and transmembrane forms of TNF- $\alpha$ . Currently, their main indications are RA, psoriasis, psoriatic arthritis and Crohn's disease.

Most commonly, their adverse events are relatively mild and do not require dras-

tic treatment modifications [3–6]. Serious infections (such as tuberculosis), malignancies (mainly hematological) and neurological disorders may rarely complicate the use of biological therapy. Evidence for causality is still vague, although the immunosuppressive action of these agents provides material for plenty of logical hypotheses [7]. In a study of 618 psoriatic patients initially recruited in a placebo-controlled randomized trial of etanercept lasting 12 weeks, 464 were monitored open label up to 84 weeks. The study reported 23 malignancies, of which 14 were non-melanoma skin cancer. The standardized incidence ratio for any malignancies in etanercept-exposed patients compared with the general population was 1.89 (95% CI, 0.86–3.58). The investigator considered 3 of the malignancies – tonsil cancer, breast cancer, and Hodgkin disease – were possibly related to the investigational product [8]. In a systematic review and meta-analysis of 9 randomized controlled trials (3,493 people receiving active treatment and 1,512 people receiving placebo), adverse events with infliximab and adalimumab in patients with RA were assessed [6]. Pooled analysis suggested increased risks of malignancies and severe infections. The odds ratio for increased malignancies was 3.3 (95% CI, 1.2–9.1), with number needed to harm of 154 (95% CI, 91–500), meaning that 154 patients needed to be treated for 1 additional malignancy being diagnosed after a treatment period of 6–12 months. In particular, lymphoma development seems to be related with the use of TNF- $\alpha$  antagonists [9]. However, this association was not confirmed by other investigators [10]. A large-scale cohort study [11] in patients with RA concluded that there was an increased risk of non-melanoma skin cancer in those receiving TNF- $\alpha$  antagonists, when prescribed either alone (hazard ratio, 1.24) or in combination with methotrexate (hazard ratio, 1.97). There are a few recent case reports that underline the possible link between TNF- $\alpha$  antagonists and the induction or rapid reactivation of latent malignancies [12]. Furthermore, the reactivation of melanoma in immunosuppressed patients after solid organ transplantation is well established [13].

The possible link between biological therapy and the induction of melanocytic proliferation certainly needs further illumination. Melanocytic proliferation may be benign, as in eruptive melanocytic nevi,

or malignant, i.e. MM. Eruptive nevi appear abruptly as numerous similarly looking nevi or as large atypical lesions simulating MM. This rare phenomenon has been associated with dermatological diseases (e.g. erythema multiforme, epidermolysis bullosa, toxic epidermal necrolysis) and immunosuppression, either due to disease or following the administration of immunosuppressive medication, including biological treatment (infliximab, etanercept and alefacept) [14–18]. The etiology is largely unknown. A couple of hypotheses have been postulated based on the fact that this phenomenon is usually associated with an immunocompromised status. Immunosuppression might induce melanocyte-stimulating hormone or melanoma growth-stimulatory activity, which are endogenous growth factors for normal melanocytes. A higher expression of the melanoma growth-stimulatory activity protein could stimulate growth and development of melanocytes. Genetic factors could also be involved resulting in the formation of subclinical nests of nevus cells, which in turn may be triggered by immunosuppressive events into the formations of visible nevi [14, 19, 20].

There are scarce reports in the literature associating MM and biological therapy. Two cases of eruptive latent metastatic melanoma after initiation of TNF- $\alpha$  antagonist therapy have been reported [21]. The first patient, 6 years after she had been diagnosed with MM and a negative sentinel node biopsy, developed metastatic melanoma lesions on her thigh following 1-month treatment with etanercept for plaque psoriasis. Five out of 7 draining inguinal lymph nodes were found positive for melanoma. The second patient was being treated for RA with adalimumab monotherapy for 6 months before the development of a rapidly enlarging axillary nodule, which proved to be MM. Eight years before, the patient had been diagnosed with MM on his right arm. Recently, the occurrence of MM in a patient with recalcitrant moderate to severe psoriasis was reported [22]. He had been treated consecutively for a period of 30 months with infliximab, adalimumab and etanercept. Previously, he had received PUVA, cyclosporine A, methotrexate and fumarates. Another psoriatic patient, who had a history of PUVA exposure, developed MM 25 weeks after commencing adalimumab treatment [23]. Finally, there is a case of a primary melanoma in a patient with RA



**Table 1.** Melanocytic proliferation and biologics

| Biological drug                                   | Melanocytic proliferation           | Localization                                 | Reference              |
|---|-------------------------------------|--|------------------------|
| Infliximab  | eruptive benign melanocytic nevi    | trunk  | Katsanos et al. [18]   |
| Alefacept   | eruptive benign melanocytic nevi    | trunk, upper limbs, lower limbs              | Bovenschen et al. [17] |
| Etanercept  | eruptive benign melanocytic nevi    | trunk, upper limbs, lower limbs, palms, sole | Bovenschen et al. [17] |
| Etanercept  | eruptive latent metastatic melanoma | thigh  | Fulchiero et al. [21]  |
| Adalimumab  | malignant melanoma metastasis       | axilla                                       | Fulchiero et al. [21]  |
| Consecutive treatment with infliximab, adalimumab | malignant melanoma                  | n/a  | Kowalzik et al. [22]   |
| Adalimumab  | malignant melanoma                  | n/a  | Gordon et al. [23]     |
| Infliximab  | malignant melanoma                  | scalp  | Khan et al. [24]       |

treated with infliximab [24]. Reported cases of melanocytic proliferations following treatment with TNF- $\alpha$  antagonists are summarized in table 1.

In our patient, the occurrence of MM in sun-exposed sites, as well as the absence of careful dermatologic examinations prior to adalimumab introduction (to determine when the first lesion actually appeared) are not in support of an etiologic association with anti-TNF therapy. In addition, the relatively short duration of adalimumab therapy and the brief time interval between anti-TNF therapy and MM development suggest that this double oc-

currence was probably not related to treatment with TNF inhibitors. To the best of our knowledge, this is the first reported case of 2 primary MM occurring after treatment with a TNF- $\alpha$  antagonist. The importance of immunosurveillance in tumorigenesis is paramount. Although it cannot be documented in our case, a diminished immunosurveillance due to immunosuppressive therapy could lead to the appearance of malignant lesions *de novo*, or malignant transformation of benign ones.

In conclusion, there is growing evidence indicating a possible relation be-

tween biological therapy and melanocytic proliferation either benign or malignant. The exact role of biologics in tumorigenesis is difficult to be determined because patients often have a history of treatment with various immunosuppressives and there may also be other risk factors for carcinogenesis present. Further controlled studies, with large sample sizes and longer follow-up periods, are needed in order to evaluate the likelihood of this association. In the mean time, complete skin examinations and regular, close follow-ups, especially in high-risk patients under biological therapy, are strongly recommended.

## References

- Naldi L: Malignancy concerns with psoriasis treatments using phototherapy, methotrexate, cyclosporin, and biologics: fact and controversies. *Clin Dermatol* 2010;28:88–92.
- Mease PJ: Adalimumab: an anti-TNF agent for the treatment of psoriatic arthritis. *Expert Opin Biol Ther* 2005;5:1491–1504.
- Chaudhari U, Romano P, Mulcahy LD, et al: Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomized trial. *Lancet* 2001;357:1842–1847.
- Gordon KB, Blum RR, Papp KA, et al: Efficacy and safety of adalimumab treatment in patients with moderate-to-severe psoriasis: a double-blind, randomized clinical trial. *Psoriasis Forum* 2007;13:4–11.
- Gottlieb AB, Leonardi CL, Goffe BS, et al: Etanercept monotherapy in patients with psoriasis: a summary of safety, based on an integrated multistudy database. *J Am Acad Dermatol* 2006;54:S92–S100.
- Bongartz T, Sutton AJ, Sweeting MJ, et al: Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006;295:2275–2285.
- Descotes J, Gouraud A: Clinical immunotoxicity of therapeutic proteins. *Expert Opin Drug Metab Toxicol* 2008;4:1537–1549.
- Tyring S, Gordon KB, Poulin Y, et al: Long term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Arch Dermatol* 2007;143:719–726.
- Brown SL, Greene MH, Gershon SK, et al: Tumor necrosis factor antagonist therapy and lymphoma development. *Arthritis Rheum* 2002;46:3151–3158.
- Askling J, Forel SM, Baecklund E, et al: Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumor necrosis factor antagonists. *Ann Rheum Dis* 2005;64:1414–1420.
- Chakravarty EF, Michaud K, Wolfe F: Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. *J Rheumatol* 2005;32:2130–2135.
- Fryrear RS 2nd, Wiggins AK, Sanguenza O, Yosipovitch G: Rapid onset of cutaneous squamous cell carcinoma of the penis in a patient with psoriasis on etanercept therapy. *J Am Acad Dermatol* 2004;51:1026.
- Euvrad S, Kanitakis J, Claudy A: Skin cancers after organ transplantation. *N Engl J Med* 2003;348:1681–1691.
- Alaiabac M, Piassero S, Rossi CR, et al: Eruptive melanocytic naevi in patients with renal allografts: report of 10 cases with dermoscopic findings. *J Am Acad Dermatol* 2003;49:1020–1022.

- ▶15 Bauer JW, Schaeppi H, Kaserer C, et al: Large melanocytic nevi in hereditary epidermolysis bullosa. *J Am Acad Dermatol* 2001;44:577–584.
- ▶16 Shoji T, Cockerell CJ, Koff AB, et al: Eruptive melanocytic nevi after Stevens-Johnson syndrome. *J Am Acad Dermatol* 1997;37:337–339.
- ▶17 Bovenschen HJ, Tjioe M, Vermaat H, et al: Induction of eruptive benign melanocytic naevi by immune suppressive agents, including biological. *Br J Dermatol* 2006;154:880–884.
- ▶18 Katsanos KH, Christodoulou DK, Zioga A, et al: Cutaneous nevi pigmentosus during infliximab therapy in a patient with Crohn's disease: fallacy or coincidence? *Inflamm Bowel Dis* 2003;9:279.
- ▶19 Woodhouse J, Maytin EV: Eruptive nevi of the palms and soles. *J Am Acad Dermatol* 2005;52:S96–S100.
- ▶20 Richert S, Bloom EJ, Flynn K, et al: Widespread eruptive dermal and atypical melanocytic nevi in association with chronic myelocytic leukemia: case report and review of the literature. *J Am Acad Dermatol* 1996;35:326–329.
- ▶21 Fulchiero GJ Jr, Salvaggio H, Drabick JJ, et al: Eruptive latent metastatic melanomas after initiation of antitumor necrosis factor therapies. *J Am Acad Dermatol* 2007;56:S65–S67.
- ▶22 Kowalzik L, Eickenscheidt L, Komar M, Schaarschmidt E: Long term treatment of psoriasis with TNF-alpha antagonists: occurrence of malignant melanoma. *Hautarzt* 2009;60:655–657.
- ▶23 Gordon KB, Langley RG, Leonardi C, et al: Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol* 2006;55:598–606.
- ▶24 Khan I, Rahman L, McKenna DB: Primary cutaneous melanoma: a complication of infliximab treatment? *Clin Exp Dermatol* 2009;34:524–526.