Rapid Growth of Merkel Cell Carcinoma During Etanercept Treatment of Psoriatic Arthritis: Cause or Coincidence?

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Merkel cell carcinoma (MCC) is an uncommon malignancy originating in epidermis. The anti-tumour necrosis factor (TNF)-α is used to treat psoriasis, rheumatoid arthritis and other inflammatory diseases. We report here a case of MCC in a relatively young patient that showed exceptionally rapid progression, which is uncommon for this type of tumour. The tumour appeared after 18 months of etanercept treatment. Cessation of its rapid growth was associated with interruption of anti-TNF-α treatment.

CASE REPORT

A 50-year-old white woman was referred to our clinic with an erythematous nodular lesion on her neck. Approximately 3 months previously she had first noticed a small (diameter approximately 1.5 cm) nodule that had rapidly increased in size and consistency and was soon associated with bleeding episodes following mild mechanical trauma. Physical examination revealed a shiny, firm, non-tender red polypoid nodule, approximately 2 × 2 cm in size with a wide erythematous base and no clinical lymphadenopathy (Fig. 1a). The lesion was scheduled for a diagnostic incisional biopsy. At the general physical examination the patient was in good health with no specific pathological signs or symptoms, apart from psoriatic arthritis without skin manifestations. This condition had been treated during the preceding 18 months with injections of etanercept (50 mg/week), with a good clinical response. The patient stated that she had never used any other immunosuppressive drugs or had phototherapy.

Two weeks after visiting our clinic, at the time scheduled for the incisional biopsy, the lesion appeared markedly enlarged (4 × 3 cm) and the patient reported pain at the site of the tumour and in adjacent neck tissue (Fig. 1b). At that time, etanercept therapy was discontinued and the patient was given 8 mg/day corticosteroid and 7.5 mg methotrexate every 10 days.

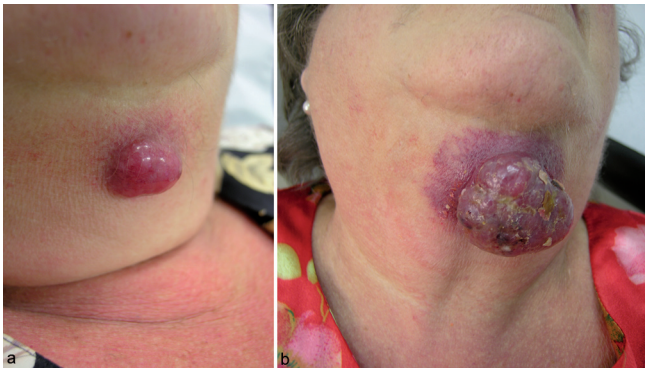

Fig. 1. (a) A 50-year-old-woman presented with a bright-red polypoid skin lesion, 2 cm in diameter, with a hard elastic consistency, on her neck which developed during etanercept therapy. The nodule had an erythematous base with fading margins. (b) The same lesion 2 weeks later. The polypoid lesion had doubled in size (to 4 cm diameter at its broadest) with a corresponding increase in its erythematous base, distinct and irregular margins and crust-like formations.

Fifteen days after the biopsy, when the stitches were removed, no further growth of the tumour was observed. The patient reported that the lesion had stopped growing 2 days after the withdrawal of etanercept therapy.

The histopathological diagnosis was MCC. The patient was referred to the plastic surgery department for removal of the lesion. On physical examination, no local or regional lymph nodes were detected and blood test results were normal. A computed tomography (CT) scan of the thorax and of abdomen detected no lesions. However, despite excision with wide margins, the patient developed laterocervical locoregional lymph nodal metastases 6 months later. She died 16 months after the diagnosis from systemic metastases due to MCC.

DISCUSSION

Previous reports have shown *in vitro* data on the ability of TNF-α and lymphotoxin to inhibit, by a synergistic action with interferon-γ (1), the proliferation of normal (2, 3) or tumoural (4) epithelial cells. Blocking of TNF-α by etanercept might therefore stimulate tumour growth. Although a mere casual association between the appearance of MCC and the administration of etanercept cannot be excluded, the present case provides several arguments for a cause and effect relationship between the etanercept therapy and MCC. Firstly, the MCC occurred during protracted therapy with etanercept in a 50-year-old patient, whereas this tumour is more frequent in older subjects, generally over 70 years of age. Secondly, the tumour showed a very rapid growth, almost doubling in size within 2 weeks (from the clinical examination to biopsy). Thirdly, the unusually rapid growth was arrested concomitantly with the withdrawal of anti-TNF-α treatment. These observations, and the recent proposal that MCC is of epithelial origin but with complete or partial neuroendocrine differentiation (5), support the hypothesis of a causal role of TNF-α TNF/lymphotoxin inhibition by etanercept in the unexpected onset and progression of the disease.

During the Wegener's Granulomatosis Etanercept Trial, a placebo-controlled trial of etanercept given in addition to standard therapy for the remission of the disease, a higher frequency of solid malignancies (including colon adenocarcinoma, metastatic cholangiocarcinoma, renal cell carcinoma, breast carcinoma, and

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recurrent liposarcoma) was observed in the etanercept group than in the group treated with standard therapy alone (6). However, a review in 2005 of the clinical studies and registries for different TNF-α antagonists showed no increase in the incidence of solid tumours in the rheumatoid arthritis population (7). Contrasting data have been reported on the possible increased risk of lymphoma in patients affected by rheumatoid arthritis who are treated with etanercept (8). While numerous case reports of lymphoma in patients treated with etanercept have been described, the relative risk of lymphoma remains constant for patients with rheumatoid arthritis regardless of therapy with TNF-α antagonists (8). However, two cases of cutaneous and systemic T-cell lymphoma that progressed rapidly after initiating TNF-α blockade (one with etanercept and one with infliximab) have been reported (9). To the best of our knowledge, no previous reports of MCC during etanercept therapy have appeared.

In conclusion, the present case underlines that the increasing use of biological drugs in chronic diseases, which is associated with a significant improvement in the quality of life of patients, must be accompanied by particular attention by physicians to the possible serious side-effects, including development of rare deadly skin tumours.

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