Squamous Cell Carcinoma of the Lip Associated With Adalimumab Therapy for Ankylosing Spondylitis: A Case Report and Review of TNF-α Inhibitors and Cutaneous Carcinoma Risk

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Practice Points

- Approximately 3.5 million nonmelanoma skin cancers (NMSCs) are diagnosed annually in the United States; importantly, NMSC incidence in younger patients continues to rise.
- Tumor necrosis factor α (TNF-α) inhibitors are efficacious options for patients with inflammatory conditions. Specifically, adalimumab is approved for the treatment of ankylosing spondylitis; psoriatic arthritis; and moderate to severe cases of rheumatoid arthritis, plaque psoriasis, Crohn disease, ulcerative colitis, and polyarticular juvenile idiopathic arthritis.
- In recent years, increased NMSC risk emerged as a potential adverse outcome of anti–TNF-α therapy; however, a definitive correlation remains elusive.
- Increased skin cancer surveillance, including thorough evaluation of the skin and oral mucosa, is warranted for patients on TNF-α therapy for inflammatory skin disease.

Adalimumab is an anti–tumor necrosis factor α (TNF-α) agent approved for the treatment of ankylosing spondylitis (AS); psoriatic arthritis; and moderate to severe cases of rheumatoid arthritis (RA), plaque psoriasis, Crohn disease, ulcerative colitis, and polyarticular juvenile idiopathic arthritis. Evidence suggests that anti–TNF-α agents may increase a patient's risk for some types of cancers, including cutaneous squamous cell carcinoma (SCC). Cutaneous nonmelanoma skin cancers (NMSCs) have occurred during treatment with etanercept, infliximab, and adalimumab in the setting of RA and psoriasis, but data related to AS are less clear. We report the case of a 29-year-old woman with AS treated with adalimumab for 2 years who developed invasive SCC of the lower lip. We advocate increased NMSC surveillance in patients undergoing treatment with anti–TNF-α agents.

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The American Cancer Society estimates that 3.5 million basal cell carcinomas and squamous cell carcinomas (SCCs) are diagnosed annually in the United States.[1] Cutaneous SCC often is curable with early detection and definitive

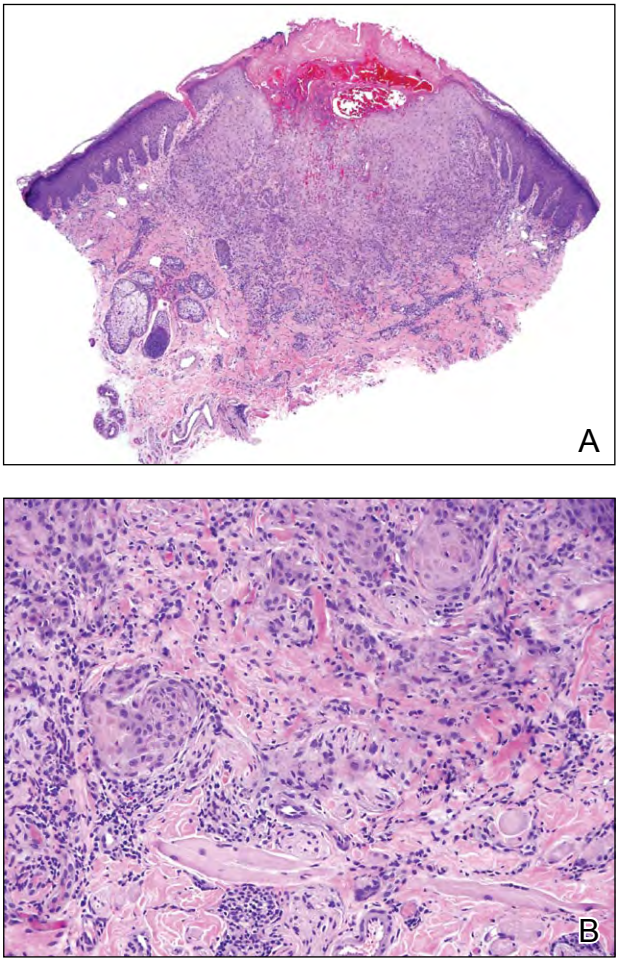
treatment; however, an approximately 2% to 3%[2] increased risk for metastasis occurs when the primary tumor develops on the central face, lip, ear, temple, or scalp, or within a scar.[3-8] Other risk factors for metastasis include advanced age and immunodeficiency.[1] Although SCC primarily occurs in older adults, its incidence in younger patients is rising.[9-12]

Adalimumab is a fully human IgG1 monoclonal antibody tumor necrosis factor α (TNF-α) antagonist approved by the US Food and Drug Administration for the treatment of ankylosing spondylitis (AS); psoriatic arthritis; and moderate to severe cases of rheumatoid arthritis (RA), plaque psoriasis, Crohn disease, ulcerative colitis, and polyarticular juvenile idiopathic arthritis.[13] In recent years, increased cutaneous malignancy risk emerged as a potential adverse outcome of anti–TNF-α therapy. Tumor necrosis factor α antagonists demonstrate efficacy in AS,[14-17] though data on nonmelanoma skin cancer (NMSC) risk are minimal.[17] We report a novel case of a 29-year-old woman with AS treated with adalimumab for 2 years who developed invasive SCC of the lower lip.

Case Report

A 29-year-old woman presented with a 4-mm white papule involving her lower mucosal lip of 3 weeks' duration. She had a 13-year history of AS and was currently undergoing treatment with adalimumab 40 mg every other week for the last 2 years. Her AS was well controlled. She denied other medications or medical history, including no personal history of NMSC or melanoma. Her family history was notable for a basal cell carcinoma in her father. The patient was a resident of California with substantial lifetime sun exposure and Fitzpatrick skin type III. She acknowledged using a tanning bed at least 10 times over the last year but covered her face with a towel. She denied tobacco use.

Histologic examination of the lesion revealed ulceration and scale/crust overlying a lobular proliferation of atypical keratinocytes with large hyperchromatic nuclei and irregular nuclear membranes emanating from an acanthotic epidermis into the underlying dermis (Figure). Round, somewhat jagged lobules were interspersed between the skeletal muscle fibers with an accompanying lymphocytic infiltrate. Many mitotic figures were present, including some that were atypical. A moderate amount of solar elastosis was noted. The patient was diagnosed with an ulcerated invasive SCC and referred for excision of the lesion via Mohs micrographic surgery.



Proliferation of atypical keratinocytes with overlying ulceration and dermal invasion (A)(H&E, original magnification ×40). Lobules of atypical keratinocytes interspersed near skeletal muscle fibers and accompanying lymphocytic inflammation also were seen (B)(H&E, original magnification ×200).

Comment

We report the case of a young adult without prior dermatologic history who developed invasive SCC on her lower lip while on TNF-α antagonist therapy. General risk factors for cutaneous SCC include advanced age, male gender, fair skin type, chronic sun exposure, failure to wear sun-protective clothing, ozone depletion, tanning bed or tobacco use, genetic susceptibility, and immunodeficiency, though each risk factor varies depending on the population studied.[9,18-21] Certain immunocompromised groups, such as solid organ transplant recipients[22] and human immunodeficiency virus–infected patients,[23] are at an increased risk for more aggressive and recurrent cutaneous SCC. In this case, it is unknown to what degree additional NMSC risk factors aside from relative immunosuppression with TNF-α inhibition, such as geography, skin type, chronic sun or UV exposure, or tanning bed use, contributed to greater susceptibility to SCC.

Although SCC is more common in advanced age, NMSC incidence continues to rise in younger patients.[9-12,24-26] Pearce et al[10] reported increased NMSC incidence in United Kingdom patients younger than 25 years from 1982 to 1995 compared with 1968 to 1981 (rate ratio, 1.7; 95% confidence interval [CI], 1.0-2.8). In another retrospective incidence case review, Christenson et al[12] reported that the incidence of cutaneous SCC in patients younger than 40 years increased from 0.9 per 100,000 people in 1976 to 1979 to 4.1 per 100,000 people in 2000 to 2003 ($P<.001$). The reason for increasing SCC incidence in younger patients is undetermined and likely multifactorial.

Tumor necrosis factor α is a central proinflammatory cytokine implicated in the pathogenesis of several inflammatory diseases. In the last few years, discussion ensues regarding potential for TNF-α inhibition to theoretically increase or decrease malignancy risk. On one side, TNF-α promotes apoptosis of tumor cells through natural killer cell stimulation and $CD8^+$ T-cell induction.[27,28] Therefore, TNF-α inhibition may potentiate tumor growth. Conversely, TNF-α alters tissue structures, which may facilitate tumor growth, and thus TNF-α inhibition may have antitumor effects.[28-30]

Fueling the discussion, although a trend toward increased NMSC risk with TNF-α inhibitors may exist, a definitive relationship remains elusive. Several observational studies in RA suggest increased NMSC risk with TNF-α inhibitors,[31-33] including a large national cohort of 20,648 veterans.[34] A meta-analysis of 74 randomized controlled trials of TNF-α inhibitors (adalimumab, etanercept, and infliximab) found 130 (0.84%) all-site cancers in 15,418 patients receiving TNF-α inhibitors.[35] Although the relative risk for all-site cancers was 0.99 (95% CI, 0.61-1.68), there was an overall statistically significant doubling risk for NMSC (relative risk, 2.02; 95% CI, 1.11-3.95), specifically in etanercept and adalimumab but not infliximab. Notably, the authors suggested that comprehensive analysis regarding elevated cancer risk across the TNF-α–inhibitor class was difficult due to inherent differences in original study design and reporting practices. Although a definitive conclusion remains vague, data suggest a consistent pattern for increased short-term risk for NMSC (as compared to all-site malignancy) during TNF-α–inhibitor therapy.[35] Newer agents, such as golimumab and certolizumab, fail to show increased NMSC risk to date.[36]

Notably, most data regarding increased malignancy risk with TNF-α inhibitors is from the rheumatologic literature. It is unclear how this information relates to dermatologic practice. For example, psoriasis patients are often treated with TNF-α–inhibitor monotherapy, whereas RA and inflammatory bowel disease patients often receive combination immunosuppressive agents.[37,38] Alternatively, in psoriasis patients specifically, NMSC risk may be confounded by prior treatment with phototherapy.[39] A comprehensive systematic review and meta-analysis of randomized controlled trials examined malignancy risk in plaque psoriasis and psoriatic arthritis patients treated with etanercept, infliximab, adalimumab, golimumab, or certolizumab pegol.[40] The authors analyzed 20 of 820 studies on 6810 patients, identifying a total of 28 treatment-group and 6 placebo-group malignancies. Of those, 70.6% were NMSCs with an odds ratio across all trials of 1.33 (95% CI, 0.58-3.04) and incidence rate ratio of 0.72 (95% CI, 0.42-1.24), though data were not statistically significant. In psoriasis patients, there is potential for detection bias, as dermatologists have enhanced training on skin cancer recognition compared to other specialty physicians. Additionally, unmasking bias may occur when psoriasis starts to clear with TNF-α agents, revealing skin cancers of undetermined duration.[40] Undoubtedly, individual patient NMSC risk is multifactorial.

Interestingly, increased SCC risk is observed with other immunomodulatory psoriasis treatments, regardless of the mechanism of immunosuppression. A gradient effect may exist in which cutaneous malignancies predominate in the setting of milder immunosuppression while solid organ tumors arise with more substantial suppression.[41] For example, Paul et al[42] conducted an international prospective, 5-year, cohort study of 1252 psoriasis patients taking cyclosporine. Data revealed malignancies in 3.8% of patients, 49% of which were limited to the skin. The authors additionally reported a 6-fold higher incidence of NMSC in the study cohort that was largely influenced by a 24.6-fold higher incidence of SCC.[42] The incidence of noncutaneous malignancy, however, was no higher than expected for the general population. Accordingly, evidence-based data for increased malignancy risk occurring with dermatologic use of cyclosporine seems to be limited to NMSC as opposed to solid organ tumors. Alternatively, at higher doses of cyclosporine (ie, as used for renal transplant patients), risk for solid organ tumors, especially lymphoma, is clearly elevated.[43-45] Therefore, NMSC occurring during treatment with TNF-α antagonists may reflect comparatively milder immunosuppression.[41] In our patient, anti–TNF-α therapy may have increased her risk for cutaneous SCC, though her significant history of UV exposure and tanning bed use most definitively contributed.

Conclusion

Anti–TNF-α agents are efficacious options for the treatment of otherwise potentially debilitating inflammatory conditions such as AS. However, our understanding of their long-term consequences continues to evolve. This case illustrates the utility of increased NMSC surveillance in young patients undergoing treatment with TNF-α antagonists. A thorough examination of the skin and oral mucosa is warranted, especially when other risk factors for skin cancer are present. Postmarketing experience and future clinical trials may more definitively reveal if younger patients undergoing anti–TNF-α therapy for chronic inflammatory diseases are at increased risk for developing NMSCs.

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