

# Primary cutaneous anaplastic large cell lymphoma in a patient receiving adalimumab

Chad J. Hruska, MD,<sup>a</sup> Robert J. Bertoli, MD,<sup>a</sup> Yorke D. Young, MD,<sup>a</sup> Patrick H. Burkhart, MD,<sup>b</sup> and Paul B. Googe, MD<sup>a,c,d</sup>  
*Knoxville, Maryville, and Nashville, Tennessee*

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## INTRODUCTION

Anti-tumor necrosis factor (TNF) agents, such as etanercept, infliximab, and adalimumab, are increasingly used in the treatment of many chronic inflammatory diseases, including psoriasis, rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis, and inflammatory bowel disease.<sup>1</sup> Because of their profound immunoregulatory effect, anti-TNF- $\alpha$  agents have long been suspected to increase the risk of certain types of lymphomas, although this has never been definitively proven. To date, data from several studies and case reports have shown an increased incidence of lymphoma in patients treated with anti-TNF agents,<sup>1-4</sup> although other reports have failed to confirm or even refute these findings. The studies lacked statistical power to quantify the incidence of a rare disease after a rare exposure. Adalimumab is a monoclonal antibody against TNF- $\alpha$  (TNF- $\alpha$ ) and is approved for use in medical and dermatologic practice. We report a case of primary cutaneous anaplastic large cell lymphoma (PCALCL) in a patient with ankylosing spondylitis and rheumatoid arthritis treated with adalimumab.

## CASE REPORT

A 72-year-old woman presented to a dermatology clinic with a lesion located in the right medial lower forehead region. The lesion began as a small reddened area and after 1 week became a 2-cm raised, dark black, circular mass lesion (Fig 1). No lymphadenopathy was appreciated on physical examination. The patient had ankylosing spondylitis and rheumatoid arthritis treated with adalimumab

### Abbreviations used:

ALCL:	anaplastic large cell lymphoma
CTCL:	cutaneous T-cell lymphoma
LyP:	lymphomatoid papulosis
PCALCL:	primary cutaneous anaplastic large cell lymphoma
RA:	rheumatoid arthritis
TNF:	tumor necrosis factor

for 15 months. The medical history was otherwise noncontributory. A 5-mm punch biopsy specimen of skin was obtained and sent for pathology.

The skin biopsy specimen showed ulceration and loss of the epidermis, and the dermis was completely replaced by an infiltrate of large atypical mononuclear cells. These cells had ample cytoplasm, irregular nuclei, vesicular chromatin, and prominent nucleoli. Some nuclei appeared reniform. Mitotic figures were easily seen. The tumor cells were in sheets with interposed areas of necrosis and hemorrhage. The lesion contained neutrophils with scattered lymphocytes, eosinophils, and histiocytes. Lymphoid germinal centers, gland formation, and keratinization were not present (Figs 2 and 3).

The neoplastic cells were diffusely positive for CD3, CD4, CD30 (Fig 4), and vimentin. The neoplastic cells did not express CD1a, CD8, CD20, CD56, CD79a, anaplastic lymphoma kinase (ALK) 1, PAX5, S100, tyrosinase, and cytokeratin AE1/AE3.

The positron emission tomography/computed tomography scan showed a focal 1.1-cm soft tissue nodule in the skin of the right forehead

From the University of Tennessee Graduate School of Medicine, Knoxville, Tennessee<sup>a</sup>; Blount Dermatology, Maryville, Tennessee<sup>b</sup>; Knoxville Dermatopathology Laboratory, Knoxville, Tennessee<sup>c</sup>; and Vanderbilt University, Nashville, Tennessee.<sup>d</sup>

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Correspondence to: Paul B. Googe, MD, Knoxville Dermatopathology Laboratory, 315 Erin Drive, Knoxville, TN 37919. E-mail: pgooge@labpath.com.

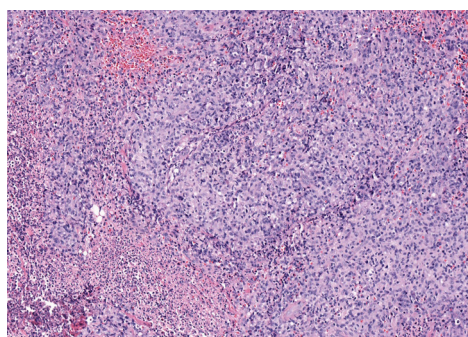
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**Fig 1.** Clinical photograph of lesion.

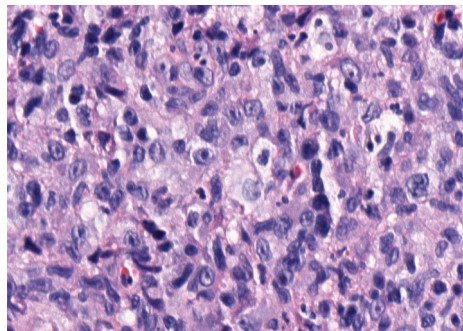


**Fig 2.** Low-power magnification of PCALCL. (Hematoxylin-eosin stain; original magnification:  $\times 100$ .) A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: [VM00490](#).

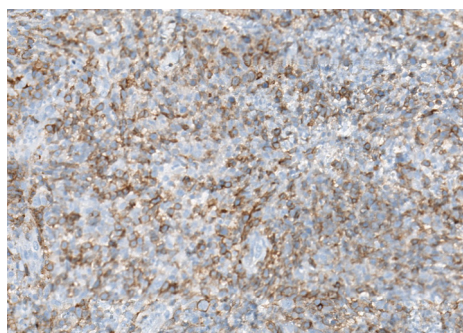
corresponding to the clinically evident skin lesion. The lesion had a maximum standardized uptake value of 20 (liver maximum standardized uptake value of 6.2). No destructive osseous lesion was noted adjacent to the skin nodule. No other abnormal subcutaneous  $^{18}\text{F}$  fluorodeoxyglucose uptake was identified, and there was no evidence for metastatic disease. Adalimumab was discontinued, and the lesion was treated with electron beam radiotherapy resulting in complete resolution. The patient had no evidence of disease 19 months after radiotherapy.

## DISCUSSION

Primary cutaneous CD30-positive lymphoproliferative disorders include PCALCL, lymphomatoid papulosis (LyP), and borderline cases. PCALCL is a neoplasm composed of large atypical lymphocytes of either pleomorphic, anaplastic, or immunoblastic cytomorphology and expression of the CD30 antigen by more than 75% of tumor cells.<sup>5</sup> It is the second most common form of cutaneous T-cell lymphoma (CTCL) with an incidence of 0.1 to 0.2 patients per 100,000.<sup>6</sup> CTCL mainly affects people in their sixth decade with a male to female ratio of 2 to 3:1.<sup>6</sup>



**Fig 3.** High-power magnification of PCALCL. (Hematoxylin-eosin stain; original magnification:  $\times 400$ .) A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: [VM00490](#).



**Fig 4.** CD30 positivity in PCALCL. (CD30 immunostain; original magnification:  $\times 200$ .) A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: [VM00489](#).

The most common sites of involvement are the extremities, head, and buttocks.<sup>5</sup>

Anaplastic large cell lymphoma (ALCL) usually presents as an asymptomatic, solitary firm nodule that rapidly grows and often ulcerates.<sup>5,6</sup> Approximately 20% of the patients have multifocal disease. The skin lesions may show partial or complete spontaneous regression. ALCL frequently relapses in the skin. Extracutaneous dissemination occurs in about 10% of the patients in which regional lymph node involvement is the most common manifestation.<sup>5,6</sup>

Histology shows diffuse, usually nonepidermotropic infiltrates with cohesive sheets of large CD30-positive tumor cells. Most commonly, the tumor cells show round, oval, or irregularly shaped nuclei, prominent eosinophilic nucleoli, and abundant cytoplasm.<sup>5</sup> Reactive lymphocytes are often present at the periphery of the lesion. The neoplastic cells show an activated CD4+ T-cell phenotype with variable loss of CD2, CD5, or CD3 and frequently express cytotoxic proteins.<sup>5,7</sup> CD30 is by definition expressed by most ( $>75\%$ ) of the neoplastic cells.<sup>5</sup> Most cases show clonal

rearrangement of the T-cell receptor genes.<sup>5</sup> Most PCALCL expresses cutaneous lymphocyte antigen but do not express epithelial membrane antigen (EMA) or ALK.<sup>8</sup> The prognosis is usually favorable with a 10-year disease-related survival rate of approximately 90%.<sup>6</sup>

The primary differential diagnosis for PCALCL includes LyP and secondary cutaneous involvement by systemic ALCL. LyP has overlapping histopathologic and phenotypic features with PCALCL<sup>5</sup>; therefore, the distinction must be made by clinical appearance and course. LyP generally is more indolent than PCALCL and is less likely to involve the face. A patient with PCALCL should not have clinical evidence or history of mycosis fungoides. In this setting, the diagnosis should be considered transformation of mycosis fungoides to tumor stage.<sup>5</sup> Systemic ALCL with cutaneous involvement is a separate disease with different cytogenetics, clinical features, and outcomes.<sup>9</sup> Systemic ALCL typically expresses EMA while PCALCL does not. ALK expression is a characteristic feature of systemic ALCL, whereas it is rarely if ever found in PCALCL.<sup>9</sup>

Lymphomas have been reported in patients treated with anti-TNF- $\alpha$  agents. TNF- $\alpha$  blockers used to treat inflammatory disorders are believed to reduce host immune responses to malignancy. Although it has been difficult to prove definitively an associated risk of malignancy, one report<sup>10</sup> suggested several possible mechanisms. First, the binding of TNF- $\alpha$  to the respective cell surface receptors is found to inhibit the programmed cell death (apoptosis) pathway as well as cell-mediated immunity. This blockade may also suppress the type 1 cytokine-mediated inhibition of type 2 CTCL or CD30+ lymphoma cells, thus, enabling more rapid growth.<sup>10</sup>

There are very few individually reported cases of several types of lymphoma in patients treated with adalimumab. These include Hodgkin's lymphoma,<sup>11</sup> adult T-cell leukemia/lymphoma,<sup>12</sup> hepatosplenic T-cell lymphoma,<sup>4</sup> and Epstein Barr virus-associated plasmablastic lymphoma.<sup>2</sup> One report of LyP in a patient treated with adalimumab was found.<sup>1</sup>

Meta-analysis by Wong et al<sup>3</sup> detected that 11 (11/5,179; 0.21%) patients receiving anti-TNF- $\alpha$  therapy developed lymphomas. The adjusted overall rates were 0.36 lymphomas per 1,000 person-years in patients who did not receive anti-TNF- $\alpha$  therapy versus 1.65 lymphomas per 1,000 person-years in patients who received anti-TNF- $\alpha$  therapy. There was a suggestion of increased lymphomas in the treated group, with the predominant subset being B-cell lymphomas. In their analysis, the occurrence

of lymphoma was rare and did not reach statistical significance.<sup>3</sup>

Systematic review of the literature regarding the safety of disease-modifying antirheumatic drugs by Ramiro et al<sup>13</sup> found that patients on TNF inhibitors compared with patients on conventional drugs had a higher risk of serious infections, a higher risk of tuberculosis, and possibly an increased risk of infection by herpes zoster. Patients on TNF inhibitors did not have an increased risk for malignancies in general, lymphoma, or nonmelanoma skin cancer, but the risk of melanoma may be slightly increased.

Burmester et al<sup>14</sup> reported that overall malignancy rates for adalimumab-treated patients were as expected for the general population; the incidence of lymphoma was increased in patients with RA, but within the range expected in RA without anti-TNF therapy; nonmelanoma skin cancer incidence was increased in RA, psoriasis, and Crohn's disease.

Meta-analysis of cancer risks of anti-TNF agents by Moulis et al<sup>15</sup> did not find any evidence for an excess cancer risk on TNF- $\alpha$  antagonists in adult rheumatoid arthritis patients, but an excess cancer risk after several years of exposure cannot be ruled out.

The risk of lymphoma is increased in patients with RA, and spontaneous reporting suggests that methotrexate and anti-TNF therapy might be associated independently with an increased risk of lymphoma. Although the risk is greatest for anti-TNF therapies, differences between therapies are slight, and confidence intervals for treatment groups overlap. The increased lymphoma rates observed with anti-TNF therapy may reflect channeling bias, whereby patients with the highest risk of lymphoma preferentially receive anti-TNF therapy. Current data are insufficient to establish a causal relationship between RA treatments and the development of lymphoma.<sup>16</sup>

Deepak et al<sup>4</sup> observed that the reported risk of T-cell non-Hodgkin's lymphomas was higher with TNF- $\alpha$  inhibitor use in combination with thiopurines.

We report an unusual case of a PCALCL in a patient receiving adalimumab. Like the reports from these previous cases, we suggest TNF- $\alpha$  blockers should be used carefully, and the adverse events should be reported in detail.

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