# Nodular Fasciitis: A Possible Side Effect of Etanercept?

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**Practice Points**

- Although biologic agents have a well-established safety profile, it is important to monitor patients for new or unusual side effects.
- Nodular fasciitis was observed in a patient taking etanercept.

*Etanercept is a biologic agent prescribed by dermatologists for the treatment of moderate to severe plaque psoriasis and psoriatic arthritis. Although the safety profile of etanercept is well established, it is always important to be vigilant in noting the development of novel side effects associated with biologic agents. We report a case of biopsy-proven nodular fasciitis (NF) that developed in an otherwise healthy man with plaque psoriasis who was undergoing treatment with etanercept.*

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Etanercept is a biologic anti–tumor necrosis factor (TNF) α agent that has been approved by the US Food and Drug Administration (FDA) to treat moderate to severe plaque psoriasis in patients 18 years and older. Although the most commonly reported cutaneous side effects include injection-site reactions such as localized erythema and pain,[1] other more serious potential side effects of etanercept may exist. The package insert notes the occurrence of spontaneous subcutaneous nodules[1]; to date, the nature of these lesions have not been defined in the literature. We report a case of nodular fasciitis (NF) that developed in a patient who was taking etanercept for the treatment of plaque psoriasis. Given the unclear etiology of previously reported subcutaneous nodules, it is possible that NF should be considered in the differential diagnosis of lesions that develop during etanercept therapy.

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## Case Report

A 36-year-old man presented with worsening dry scaly skin on his back and bilateral arms and legs of several weeks' duration. The patient's medical history was remarkable for moderate to severe plaque psoriasis. He did not report any associated arthritis or joint pain. The patient's psoriasis initially had been well-controlled with acitretin; however, after experiencing adverse effects, acitretin was stopped and the patient was started on subcutaneous etanercept (50 mg twice weekly). Prior to the initiation of etanercept, the patient had a negative purified protein derivative (tuberculin) test result for tuberculosis. For 5 months the patient tolerated etanercept well and his plaque psoriasis improved. The etanercept dosage then was decreased to weekly injections (50 mg). Liver function tests were performed every 3 to 4 months. Values were within reference range until the patient developed elevated creatine kinase (CPK) values 7 months after initiation of etanercept, which were attributed to his recent self-reported increase in exercise. His CPK values were closely monitored thereafter. Over the ensuing months of treatment with etanercept, his CPK values trended back down to within reference range.

Nine months following the initiation of etanercept, the patient developed a tender 2-cm subcutaneous nodule on his right mid back (Figure 1). He was unaware of when the nodule first appeared and denied any precipitating events such as trauma or irritation to the area. He denied any history of similar nodules. At the time, the patient was in good physical health. His only current medication was etanercept, and his medical and surgical history was unremarkable with the exception of plaque psoriasis.

Prior to any treatment, both a dermatopathologist and a surgical pathologist reviewed a 0.5-cm punch biopsy of the lesion. Histopathology revealed fascicles of spindle-shaped cells, no uniform cellularity, foci of myxoid stroma with a microcystic pattern, a polymorphous infiltrate of lymphocytes, and a few giant cells (Figure 2). All stains (ie, S-100, factor XIIIa, HHF35, cytokeratin) revealed negative results. The final diagnosis reported by both the

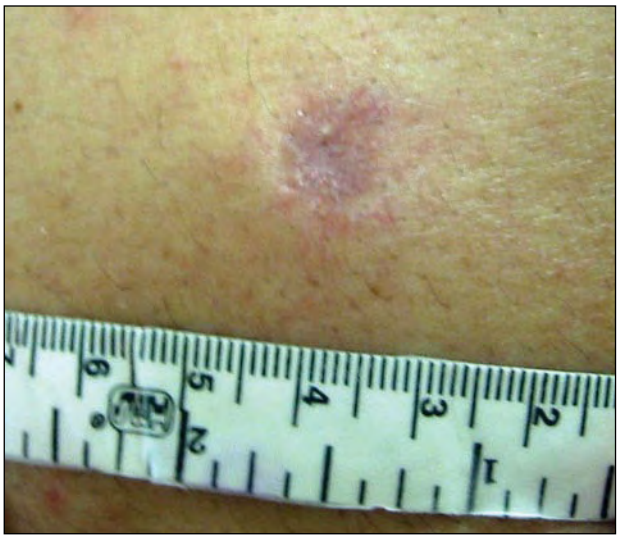

**Figure 1.** A tender 2-cm subcutaneous nodule on the right mid back.

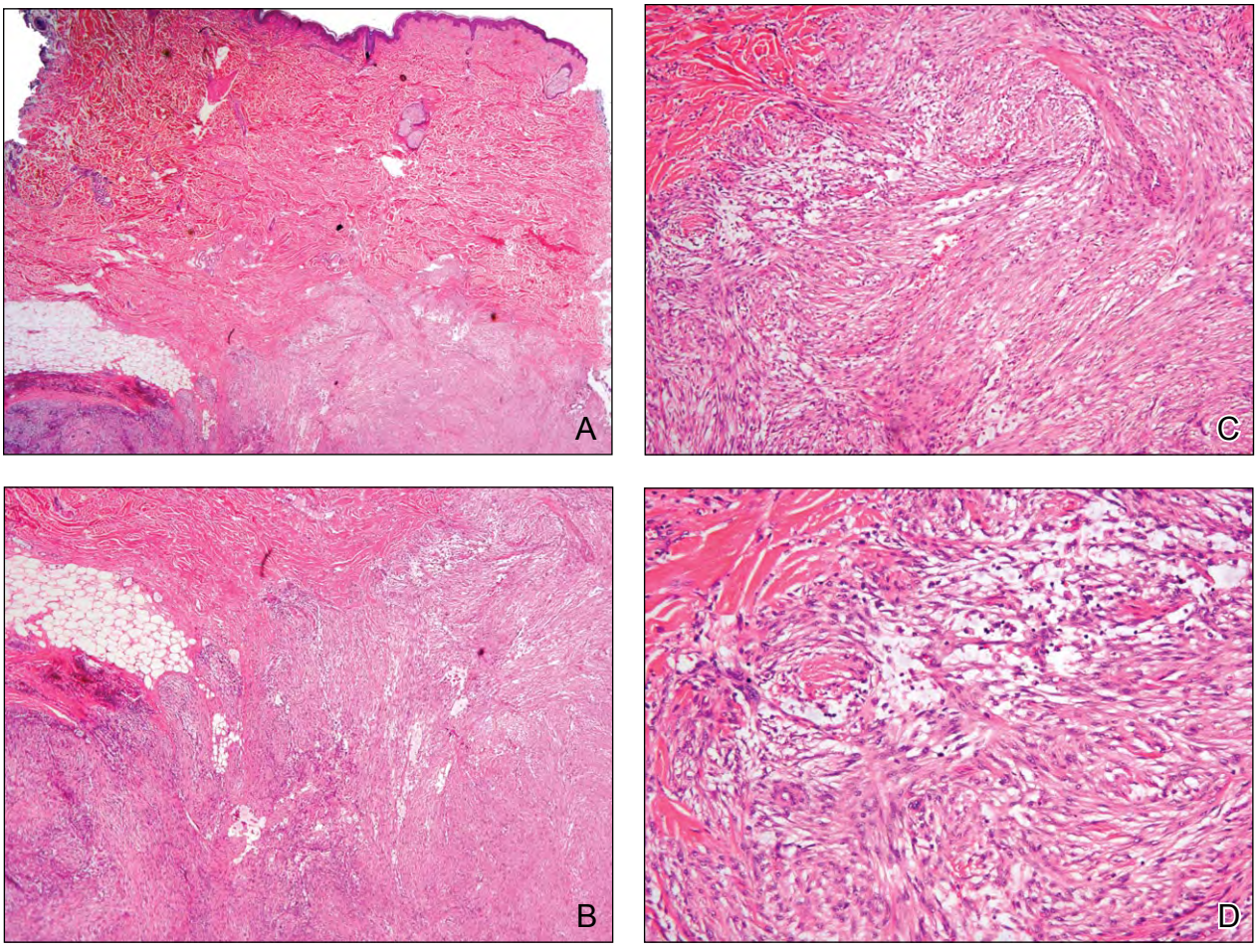


**Figure 2.** Histopathologic examination revealed cellular myofibroblastic proliferation with a prominent myxoid component consistent with nodular fasciitis (A–D)(H&E; original magnifications ×10, ×2, ×20, and ×40, respectively).

dermatopathologist and the surgical pathologist was NF. During the ensuing 5 months of therapy with etanercept, the solitary tender nodule on the back increased in size from 2.5×1.5 cm to 2.6×3.2 cm. At that time the nodule was surgically excised for both diagnostic confirmation and treatment purposes and was reexamined by a dermatopathologist and a surgical pathologist. Final histopathology revealed a diagnosis of NF with positive deep margins.

Two months following surgical excision, the patient returned for evaluation. A palpable subcutaneous nodule was still present at the site of the previously excised NF. The lesion was initially injected with intralesional triamcinolone acetonide 10 mg/cc at that visit and then again 3 months later when the lesion failed to resolve. At the latest visit, induration was noted over the excised area. Clinically, the lesion was unchanged in both size and appearance.

## Comment

Nodular fasciitis is a rare, benign, self-limiting reactive process of fibroblast proliferation within subcutaneous tissue and deep fascia.[2,3] Symptoms of NF include subcutaneous pseudosarcomatous fibromatosis or proliferative/infiltrative fasciitis.[2] Incidence rates are largely unknown; however, most patients with NF are aged 30 to 40 years and are otherwise healthy.[2,4] Roughly 10% of cases have been reported in children.[2] No gender or racial/ethnic predominance has been observed.

Clinically, patients often present with a small, solitary, rapidly growing nodule on the upper body. Head and neck lesions are common in infants, whereas adults are more likely to have lesions on their arms, legs, or trunk.[2] Ultimately, nodules can occur in any superficial soft tissue or extend deep into subcutaneous tissue and muscle.[4] In adults, the most common location of NF is the volar forearm.[2,5] Lesions generally measure less than 5 cm and occasionally are tender to palpation.[4]

Despite what is known about the physical characteristics and presentation of NF, the precise etiology is still unclear. It has been hypothesized that lesions may develop following local injury or trauma.[2,4,6] Because the main histologic constituent of NF is the myofibroblast,[4,7] it is possible that an inflammatory reaction in the body triggers an unusual proliferation of myofibroblasts, stimulating the development of a subcutaneous nodule.[2,4,8]

Depending on the depth of tissue involvement, there are 4 subtypes of NF: fascial, subcutaneous, intramuscular, and intradermal. The fascial subtype tends to be poorly circumscribed, whereas the subcutaneous and intramuscular subtypes tend to be well circumscribed.[3]

Histopathologically, NF consists of whorls of pleomorphic fibroblasts growing within a highly vascular stroma containing a mucoid substance, reticulum, and collagen.[4,9] Red blood cells and giant cells also can be found in addition to a peripheral border of chronic inflammatory cells.[4] Immunohistochemically, the spindle cells of NF stain positively for vimentin; variably positive for actin; and negatively for desmin, keratin, and S-100 protein.[4,10]

Along with microscopic evaluation, 2 types of radiographic imaging have been used to evaluate NF, including magnetic resonance imaging and ultrasonography. Magnetic resonance imaging typically reveals low-signal intensity on T1-weighted images and high-signal intensity on T2-weighted images, with varying homogeneity and enhancement patterns. Ultrasonography of NF varies from oval to lobulated, isoechoic to mixed isoechogenicity and hypoechogenicity.[5]

The diagnosis and treatment of NF often is achieved via wide local excision. Clear or negative margins should be obtained[7]; however, some reports have noted spontaneous regression of nodules following partial excision.[2,6] Intralesional corticosteroid injections also have been successful in treating NF, particularly when lesions cannot be completely excised (eg, intramuscular lesions).[8] Nodular fasciitis lesions usually are solitary and metastasis is rare. Roughly 1% to 2% of nodules can recur following local excision.[6] Nodular fasciitis is considered a benign, self-limiting reactive process; however, because both NF and sarcomas exhibit rapid growth patterns and high cellularity, the 2 diagnoses often can be confused histologically,[2,3] and patients with NF sometimes can mistakenly be diagnosed as having a sarcoma.

Etanercept is a recombinant human receptor fusion protein that competitively inhibits the interaction of TNF-α with cell-surface receptors, preventing TNF-α–mediated cellular responses and modulating the activity of other inflammatory cytokines.[11] Clinically, etanercept currently is prescribed for conditions associated with increased TNF levels, including rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, and moderate to severe plaque psoriasis. Some common side effects of etanercept include headache, dizziness, injection-site pain and erythema, infection, and upper respiratory tract infection–like symptoms. In July 2005, the FDA announced reports of spontaneous adverse drug reactions to etanercept including the development of subcutaneous nodules.[1] It is unknown if FDA reports of subcutaneous nodules in other etanercept patients also are due to NF or other causes.

## Conclusion

In our patient, etanercept may have contributed to the development of NF or NF may have coincidentally risen without any association to etanercept. The etiology of the patient's NF is unclear. Further analysis of future cases of subcutaneous nodules associated with etanercept will help to further define the nature of these lesions.

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