Introduction

Tumor Necrosis Factor (TNF) is part of a family of cytokines that cause tissue damage and play powerful roles in inflammation and immunity, as reviewed in (1). Small quantities of TNF are detectable in the microenvironment of many tumors, mediating various pro-tumor effects. These include the influx of inflammatory cells, angiogenesis, tumor growth, immune evasion, metastasis, pleural effusion, and resistance to chemotherapy. In chronic inflammatory conditions, TNF produced by damaged tissue induces macrophages and promotes genetic damage, partly explaining the increased propensity for malignancy.

TNF antagonists include Adalimumab, Certolizumab, Golimumab, and Infliximab. These are recombinant monoclonal antibodies that bind TNF alpha, while Etanercept is a soluble TNF receptor. These biological agents are indicated in the treatment of immune-mediated arthritides, psoriasis, and inflammatory bowel disease that are insufficiently responsive to conventional therapies or when treatment has been limited by toxicity or intolerance.

Adalimumab is administered as a fortnightly subcutaneous injection. Because local skin reactions are common, rotation of the injection sites is standard practice. TNF inhibitor use increases the risk of infection, particularly tuberculosis. Evaluation of the risk of malignancy in patients taking TNF inhibitors is complicated by the underlying dysregulation of the immune system in these patient groups, exposure to other immune-modulating drugs, the variable duration of drug exposure, and the small numbers of cancers reported.

Case Presentation

Figure 1 summarizes the clinical course of a woman of Greek ancestry over a 10-year period, starting in 2006, when she first developed psoriasis at the age of 65. Synovitis developed in the metacarpophalangeal joints in 2011. Over this decade, her treatment included methotrexate (Pfizer Australia Pty Ltd), Leflunomide (Sanofi-Aventis, Australia), and Etanercept (Pfizer Australia Pty Ltd) at various time points. In 2014, due to poor disease control with methotrexate, Adalimumab (Humira®, Abbvie Pty Ltd) was commenced.
at the standard dose of 40 mg/0.8/my, injected subcutaneously each fortnight, with good effect. According to standard practice, the injection site was rotated. Twenty months later, she noticed a new mass growing at the injection site in her left thigh. Rheumatologist and surgical review confirmed the presence of a 4x4x2 cm subcutaneous firm, fixed mass with intact overlying skin (Figure 2a). An ultrasound examination was non-specific. MRI showed an enhancing, discrete subcutaneous mass, 4.2x3.9x2.6 cm, close to, but not involving, the vastus medialis fascia, suggestive of a sarcoma. Following a core biopsy suggestive of a pleomorphic sarcoma, her Adalimumab therapy was ceased. Staging investigations were clear. As per multidisciplinary team recommendations, wide local excision was undertaken with

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**Figure 1.** Timeline of the patient’s disease course over 10 years, including treatment, exacerbations and development of a high grade epithelioid myxofibrosarcoma at the Adalimumab injection site, 34 months after this therapy was first commenced.

**Figure 2.** a-d. Ultrasound examination of the palpable lump of the left thigh, showing a heterogeneous, hypoechoic lesion within the subcutaneous tissues without extension into the underlying muscle. This showed marked internal vascularity. (a) Magnetic resonance imaging showing a discrete, enhancing mass at the anterolateral aspect of the left distal thigh, confined to the subcutaneous plane. Normal signal is maintained within the quadriceps musculature. (b) Clinical examination found a 4x4x2cm firm subcutaneous mass on the right thigh, fixed to the deep tissues. The overlying skin was warm but grossly normal. She had no palpable lymphadenopathy. (c) The resection specimen showed a glistening, lobulated, solid, pink to tan mass, 51x45x21 mm, covered by intact skin. This multinodular tumour traversed the dermis and subcutaneous fat to abut the fascia. The tumour was sharply delimited from the surrounding tissues. (d)
Lymphoid aggregates as well as large numbers of dispersed intratumoral inflammatory cells. (a) Immunohistochemistry showing large numbers of cells expressing CD163, a marker of histiocytes. Epithelial, naevomelanocytic, neural, myoid, endothelial and a range of inflammatory cells. (b) Immunohistochemistry showing large numbers of cells expressing CD163, a marker of histiocytes. Epithelial, naevomelanocytic, neural, myoid, endothelial and a range of inflammatory cells. An infiltrate of chronic inflammatory cells was conspicuous, both as dispersed cells and forming lymphoid aggregates. (b)

On transection, a multinodular, solid glistening mass, 51×45×21 mm, traversed the dermis and subcutaneous fat to the fascia (Figure 2b). On histology, coalescent tumor nests were subdivided by a rich vasculature. The cells had a predominantly epithelioid appearance, with enlarged, pleomorphic nuclei, a vesicular chromatin pattern, prominent nucleoli, and voluminous, eosinophilic cytoplasm. Chronic inflammatory cells were conspicuous, both as dispersed cells and forming lymphoid aggregates (Figure 3a, 4a). The mitotic rate was up to 37 per 10 high-power fields (Figure 3b). Focal myxoid change of the stroma was noted. The tumour cells had a predominantly epithelioid appearance, with enlarged nuclei, a vesicular chromatin pattern, prominent nucleoli and voluminous, eosinophilic cytoplasm. (a) Significant nuclear pleomorphism was noted, some cells being markedly enlarged with polylobated nuclei. Mitotic activity was readily apparent, including atypical division figures. An infiltrate of chronic inflammatory cells was conspicuous, both as dispersed cells and forming lymphoid aggregates. (b)

Immunohistochemical evaluation showed no reactivity for nevomelanocytic or neural markers (S100 protein, HMB 45, Melan A, SOX10, GFAP), epithelial antigens (AE1/3) or EMA, myoid markers (desmin, SMA, myogenin), or specific transcription factors (WT1, ALK, TFE3). INI1 expression was intact. CD31 was positive in the tumor cells, but ERG and CD34 were non-reactive. CD45 highlighted large numbers of inflammatory cells, including some that were CD5 positive and PAX5 positive, while CD30 and ERBER ISH were negative. CD68 and CD163 were diffusely expressed (Figure 4b). The MiB-1 labeling index exceeded 50% (Figure 4c). Flow cytometry for lymphocyte surface markers did not support lymphoma.

The morphology and immunophenotype provided no support for a reactive process, melanoma, lymphoma, carcinoma, epithelioid sarcoma, epithelioid malignant peripheral nerve sheath tumor, rhabdoid tumor, or alveolar soft part sarcoma. The morphologic features were those of an epithelioid myxofibrosarcoma (MFS) of high grade. The patient age, superficial location, and origin in the limbs were characteristic of this tumor. Excision margins were uninvolved.

At last contact, 12 months after the diagnosis, she remained well and was being followed with serial PET/CT scans.

**Discussion**

To our knowledge, this is the first instance of a sarcoma occurring at the injection site of a TNF inhibitor. While serendipity is possible, tumor development at the exact injection site makes coincidence unlikely. A predisposition to malignancy in patients with psoriasis, or a treatment-related phenomenon, may be considered.

**The association of psoriasis and malignancy**

Several series have confirmed modestly increased risks of non-melanoma skin cancer (NMSC), lymphoma, and several solid cancers, but not melanoma, in patients with psoriasis (2). Among patients treated with TNF inhibitors, the rate of NMSC was 5.5 times higher, and the onset of tumor faster, among patients with psoriasis compared to those with rheumatoid arthritis (RA), suggesting that treatment-related factors, such as prior phototherapy, might be contributing to the risk (3). To date, a link between psoriasis and soft-tissue sarcoma has not been established, and this patient had not had phototherapy to her thigh previously, although she had been using methotrexate intermittently for five years. She had no known predisposing problems, such as lymphedema, recurrent infections, vascular stasis, or intractable psoriasis of this specific site.

**Malignancy associated with TNF antagonists**

Meta-analysis of 74 randomized controlled trials of patients taking TNF inhibitors for at least 4 weeks showed that the relative risk of all malignancy was increased by 2.02 (95% CI 1.11-3.95), attributable chiefly to cutaneous malignancies (4). While NMSCs are far more common, these are rarely life-threatening malignancies, unlike melanomas or sarcomas.
RA patients treated with TNF inhibitors have a modestly increased risk of melanoma compared with RA patients not treated with these agents (HR 1.5, 95% CI 1.0-2.2). This risk amounts to 20 additional melanomas per 100,000 person years of treatment (5). In the treatment of Crohn’s disease, the co-administration of immunomodulator therapy and Adalimumab was associated with a five-fold rise in NMSC and a three-fold increased risk of other malignancies (6).

Several rarer skin malignancies have been reported in the setting of anti TNF therapy, including Merkel cell carcinoma and Kaposi’s sarcoma (7-9).

MFS is the most common soft tissue sarcoma of older adults, with a predilection for superficial locations in the limbs (10). Low-grade MFS might recur locally. Intermediate and high-grade MFS metastasize in at least 20-35% of cases. Epithelioid MFS is a recently described and more aggressive variant of MFS, characterized by an epithelioid appearance of the tumor cells, at least focally. Both conventional and epithelioid MFS display non-specific, complex chromosomal aberrations. Epithelioid MFS has a local recurrence rate of 70% and metastasizes in 50% of patients. In this specific case, given the association with anti TNF inhibitor therapy, the prominent inflammatory cell infiltrate is noteworthy.

TNF inhibitor therapy increases the risk of cutaneous malignancies, including a modestly increased risk of melanoma documented in RA patients. Case reports of Merkel cell carcinoma and Kaposi’s sarcoma of the skin have been reported in the setting of Adalimumab therapy. We now report the first instance of a sarcoma of the subcutaneous tissues at the injection site of Adalimumab in a woman with psoriatic synovitis.

More nuanced analysis of the subtypes of malignancies occurring among patients using TNF inhibitors is needed if the pathogenesis, natural history, and clinical outcomes of these iatrogenic diseases are to be elucidated.

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