Three Synchronous Malignancy in a Patient with Psoriasis Treated with Antitumor Necrosis Factor-Alpha: A Case Report and Review of Literature

Kathan Mehta1, Sudeep Siddappa Malleshappa1, Keyur Patel1, David Schwartzman2, Alison Sehgal2, and Roy Smith3*

1University of Pittsburgh Medical Center, USA
2University of Pittsburgh Center Heart and Vascular Institute, USA
3University of Pittsburgh Cancer Institute, USA

Abstract

Anti-tumor necrosis factor-α (anti-TNF) agents are used to treat different autoimmune conditions. Etanercept and Adalimumab are examples of this class of medications used for the treatment of Psoriasis. The Food and Drug Administration (FDA) released a review in 2003 of clinical trials using anti-TNF agents and reported a relative risk (RR) for lymphoma ranging from 2.3 to 6.4. In 2005, a randomized placebo-controlled trial of Etanercept versus placebo in patients with Wegener’s Granulomatosis found a statistically significant increase in solid malignancies in the experimental arm. Observational studies, several randomized clinical trials, and the subsequent meta-analysis has emerged with conflicting results. However, the association between anti-TNF therapy and occurrence of concurrent multiple malignancies have not been previously described. We present a case of three synchronous malignancies (diffuse large B-Cell lymphoma involving heart, multiple myeloma, and invasive ductal carcinoma of breast) presenting during the use of anti-TNF agents (Etanercept and Adalimumab) for psoriasis and review current literature focused on the association of this therapeutic modality and malignancies. One must remain cautious about the risk of malignancy with anti-TNF compounds, ensuring age-appropriate cancer screening and considering avoidance in patients with proved or suspected genetic predisposition for cancer.

Keywords: Anti-TNF; Adalimumab; Etanercept; Malignancy; Psoriasis

Introduction

Anti-tumor necrosis factor-α (anti-TNF) agents like Etanercept, Infliximab and Adalimumab are used to treat autoimmune conditions including moderate to severe chronic plaque forming psoriasis that is not responsive to topical or systemic alternative therapies. Anti-TNF agents are potent down-regulators of tissue necrosis factor; a major natural activator of macrophage function. TNF inhibition has been associated with major life threatening consequences including infection and occurrence of secondary malignancy which have been an area of concern. The risk of cancer associated with anti-TNF therapy was initially seen in anecdotal reports [1]. More recently the available data has evolved to larger case series, randomized trials and finally large meta-analysis [2-9]. Lymphoma has been reported in children and adolescents treated with anti-TNF agents (Etanercept and Adalimumab) for psoriasis and review current literature focused on the association of this therapeutic modality and malignancies. One must remain cautious about the risk of malignancy with anti-TNF compounds, ensuring age-appropriate cancer screening and considering avoidance in patients with proved or suspected genetic predisposition for cancer.

Case Presentation

67-Year-old Caucasian female with a history of persistent atrial fibrillation, tobacco smoking (7 pack years), benign breast nodule and psoriasis presented with 4 weeks of dyspnea on exertion,
non-productive cough, worsening fatigue and night sweats. She had prolonged history of chronic, diffuse and mild to moderate plaque forming psoriasis which was treated with anti-TNF agents. She received Etanercept 50 mg subcutaneously twice per week for 2-3 months followed by 50 mg weekly for 1-3 months based on response. This regimen was repeated intermittently with an average of 2 per year for approximately 7-8 years until 3 years before the presentation when it was discontinued. Psoriasis was fairly controlled on topical agents until 18 months prior to presentation when she received Adalimumab 80 mg one time followed by 40 mg every other week for 8 months. She was on a similar course of Adalimumab for 6 months before presentation.

A transthoracic echocardiogram (TTE) with micro-bubble contrast revealed a 1.5 x 1 cm mobile mass attached to the interatrial septum and severely thickened posterior left ventricular wall. A cardiac magnetic resonance imaging (MRI) confirmed a large mass encasing the entire atrioventricular groove with an invasion of the basal portions of both ventricles and the right atrium causing obstruction of the inferior vena cava-atrial junction (Figure 1) which were negative in CT chest 15 months prior. Endomyocardial biopsy was consistent with diffuse large B-Cell lymphoma (Figure 2). Staging CT scan, brain MRI, and cerebrospinal fluid analysis showed no evidence of metastasis. Staging bone marrow biopsy showed no evidence of lymphoma. Instead, it revealed 38% CD138 positive, CD10 negative, lambda-restricted plasma cells (Figure 3). Epstein-Barr virus by in-situ hybridization were negative. Cytogenetic analysis revealed no abnormalities. A skeletal survey was negative for osteolytic and osteoblastic lesions. Serum protein electrophoresis and immunofixation revealed the presence of M protein, IgA lambda type along with free lambda light chains. The serum free light chain...
indications. The study population included 3,010 patients with psoriasis treated with Etanercept, infliximab, adalimumab, golimumab and certolizumab showed no statistically significant increase of malignancy with short-term use [8]. A recent meta-analysis included 71 trials of adalimumab used for different indications. The study population included 3,010 patients with psoriasis who were analyzed separately. Overall malignancy rates for adalimumab-treated patients were as expected for a general population, except non-melanoma skin cancer incidence raised in psoriasis [2]. A large meta-analysis of 74 randomized controlled trials evaluated the risk of malignancy with adalimumab, Etanercept, and infliximab. It included 22,904 patients of which 15,418 randomized to anti-TNF therapy with 4 weeks of minimum duration of therapy. The authors concluded that the long-term effect of anti-TNF effect on cancer risk could not be answered by this data [7].

A week prior to her acute presentation, screening mammogram was concerning for left-sided breast cancer but management was deferred due to acute cardiorespiratory symptoms. She subsequently underwent a breast biopsy, which demonstrated an estrogen receptor and progesterone receptor positive, human epidermal growth factor receptor 2 (HER2) negative invasive ductal carcinoma, staged T1aN0M0 (Figure 4). She had no known history of exposure to chemicals, drugs, previous radiation therapy or family history of malignancy.

Since this patient presented with three different concurrent tumor types (lymphoma, multiple myeloma, and breast cancer) and a history of chronic, recurrent immunosuppressive therapy, therapeutic options were confounded. Because the cardiac lymphoma was immediately life threatening and the risk of cardiac perforation from tumor progression or tumor resolution was imminent, the patient was treated with rituximab monotherapy. After 8 weekly cycles, a repeat cardiac MRI showed a complete response but she had recurrence 1 year after initial diagnosis in heart and posterior chest wall. Before recurrence of lymphoma, breast cancer was treated with lumpectomy and sentinel lymph node biopsy (negative). She received radiation but refused hormonal therapy. She was initially diagnosed with smoldering myeloma but plasma cell percentage increased to >90% on subsequent bone marrow biopsy without end organ damage. While planning chemotherapy for high-risk smoldering myeloma she developed recurrence of lymphoma. She was treated with 6 cycles of R-CHOEP and post chemotherapy bone marrow biopsy showed no lymphoma with < 5% of plasma cells. She subsequently underwent high-dose chemotherapy with carmustine, etoposide, cytarabine, and melphalan (BEAM) conditioned autologous stem cell transplant. She was followed by serial blood work and bone marrow biopsy, which was negative for lymphoma, rare plasma cells, no evidence of monoclonal protein and normal k/λ ratio.

Discussion

To our knowledge, this is the first case of 3 concurrent malignancy in a patient treated with chronic, intermittent anti-TNF therapy. Since the introduction of anti-TNF, their role in the development of malignancy is subject of interest. In 2005, a randomized, placebo-controlled trial of Etanercept versus placebo in patients with Wegener’s Granulomatosis found a statistically significant increase in solid malignancies in the experimental arm [12]. Although several randomized control trials designed to evaluate their benefit provided insight of their malignancy potential, most of these data address such risk only in the short-term given the relatively short follow-up of randomized controlled trials.

A meta-analysis of 20 randomized control trial involving patients with psoriasis treated with Etanercept, infliximab, adalimumab, golimumab and certolizumab showed no statistically significant increased risk of malignancy with short-term use [8]. A recent meta-analysis included 71 trials of adalimumab used for different indications. The study population included 3,010 patients with
the risk of malignancy with anti-TNF compounds, ensuring age-appropriate cancer screening and considering avoidance in patients with proved or suspected genetic predisposition for cancer.

References


11. FDA. “Arthritis Advisory Committee Briefing Information: Update on the TNF-a Blocking Agents 2003.”


