



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

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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.

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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. These have been primarily hepatosplenic T-cell lymphoma, a rare form of lymphoma. Unfortunately patients who developed these types of lymphoma on anti-TNF medications had an aggressive and invariably fatal course. It remains uncertain whether anti-TNF agents alone or in combination with other drugs resulted in increased risk of developing secondary lymphomas or other malignancies as most of these patients were simultaneously treated with azathioprine or 6-mercaptopurine for regional enteritis or ulcerative colitis. Our understanding of the true risk has been limited by the shortcomings of each of these investigational modalities and the conflicting data that resulted [10]. We report a case of patient with psoriasis who developed 3 synchronous malignancies while receiving anti-TNF therapy and review literature relevant to risk focused on patients with psoriasis.

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,

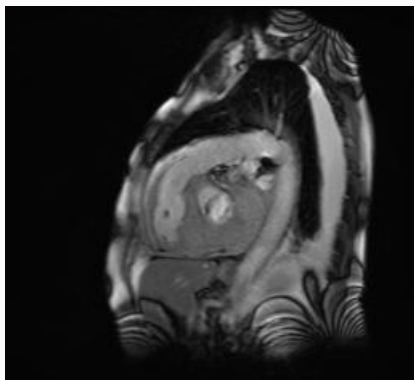


Figure 1: Cardiac MRI revealing a large mass encasing the entire atrioventricular groove with an invasion of the basal portions of both ventricles and the right atrium to result in the obstruction of the inferior vena cava-atrial junction.

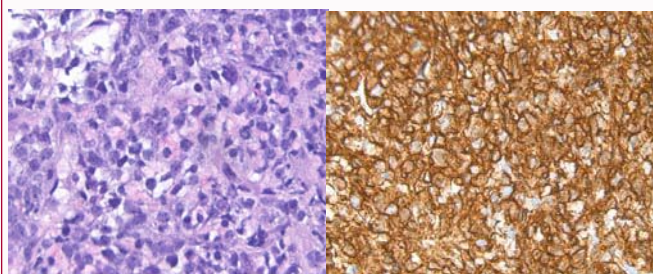


Figure 2: Right ventricle biopsy revealing diffuse large B-cell lymphoma. Microscopy reveals mitotic figures and sheets of large cells with nucleoli. Immunohistochemistry was positive for CD20.

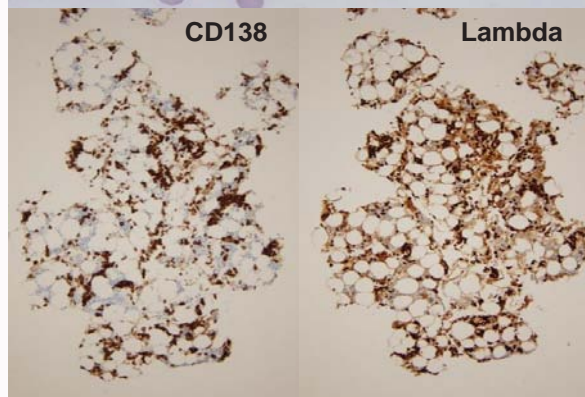
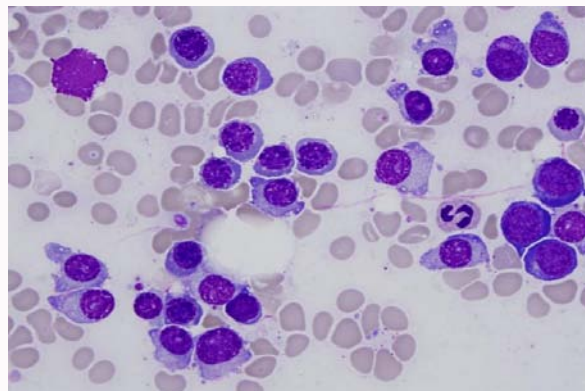


Figure 3: Bone marrow biopsy revealed a plasma cell dyscrasia with 38% lambda-restricted plasma cells which were CD138 positive, CD10 negative. This tumor is phenotypically different from the cardiac tumor.

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

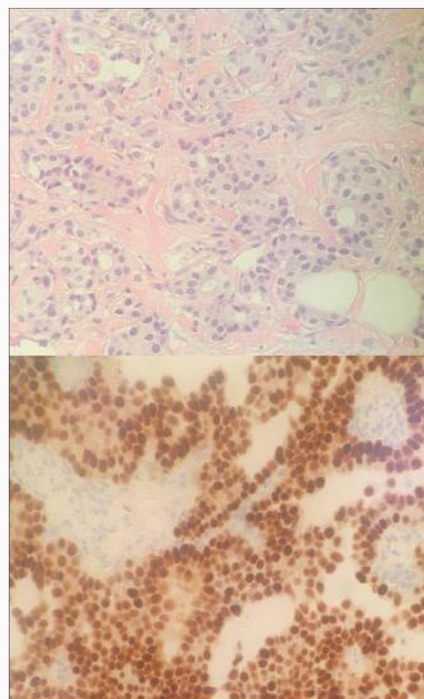


Figure 4: Breast core biopsy revealed a well differentiated ductal carcinoma. The majority of the tumor shows duct formation, small round uniform slightly enlarged nuclei and mild nuclear pleomorphism (above). There is strong nuclear estrogen receptor staining (below).

and immunofixation revealed the presence of M protein, IgA lambda type along with free lambda light chains. The serum free light chain

ratio analysis showed a serum free lambda light chain of 1494 mg/L and serum free kappa light chain of 9.5 mg/L with a free kappa/lambda ratio of 0.01. Immunoglobulin levels were reduced (IgA: 44 mg/dl, IgG: 326 mg/dl, IgM: 22 mg/dl). Serum beta-2-microglobulin concentration was normal (1.69 mg/dl). Urine protein electrophoresis and immunofixation noted elevated lambda chains of 43 mg/dl establishing the diagnosis of smoldering myeloma.

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 κ/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

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].

Wolfe et al. [9] did an observational study with longer follow-up designed to investigate the risk of cancer, related to anti-TNF agents in patients with RA. It compared the incidence of malignancy in this population by analyzing data from the US National Data Bank for Rheumatoid Diseases and compared the incidence of malignancy with that of the US National Cancer Institute Surveillance, Epidemiology and End-Results database. The study concluded that biologic therapy is associated with increased risk of skin cancers, but not for solid tumors or lymphoproliferative disorders which were consistent across different biologic therapies.

The time period from sentinel cellular event to symptomatic cancer or detection by current screening procedures may be years. Both clinical trials and observational studies have their own limitations to assess true risk. Most clinical trials have short term follow up and observational studies are limited by length-time bias, detection bias and selections bias in spite of longer follow-up [18].

The patient case presented here emphasizes the need for clinicians to be alert to the possibility of anti-TNF associated malignancies of various types. This patient showed complete remission of cardiac lymphoma initially by discontinuation of immunosuppressive agent and rituximab alone which in some respects parallels that seen in those with post-transplant lymphoproliferative disorder (PTLD) related malignancies. Since this patient received no other immunosuppressive agents for the treatment of her chronic psoriasis, it seems a reasonable to suspect this lymphoma occurring at an unusual location was associated with her anti-TNF treatment. The concurrent multiple myeloma also supports an immunosuppression-related PTLD like disorder in that both multiple myeloma and B-cell lymphomas are clonal disorders derived from the same category of lymphocyte. The fact the occurrence of both disorders simultaneously is exceedingly rare further points to some common underlying cause of both malignancies. Although less common, multiple myeloma is a well-described type of post-transplant disorder related to immunosuppression [19-21]. Furthermore, the regression of this patient's large B cell lymphoma in the face of progressive myeloma is also consistent with immunosuppression-related B-cell malignant disorders in that the post-transplant myeloma tends to be an aggressive disease poorly responsive to any intervention including withdrawal of the immunosuppressive agent. Additionally, the patient had a history of benign breast nodules and the development of breast cancer is concerning for a potential solid malignancy related to anti-TNF therapy. Although a meta-analysis [16] and 2 registry-based studies [15,17] showed no increased risk of solid malignancies including breast cancer, data regarding risk are mixed.

Conclusion

The case described here illustrates the rare presentation of 3 synchronous malignancies in a patient of psoriasis treated with Etanercept and Adalimumab. 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.

References

- Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum.* 2002; 46: 3151–3158.
- Burmester GB, Panaccione R, Gordon KB, McIlraith MJ, Lacerda APM. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis.* 2013; 72: 517–524.
- Kimball AB, Pariser D, Yamauchi PS, Menter A, Teller CF, Shi Y, et al. OBSERVE-5 interim analysis: An observational post-marketing safety registry of etanercept for the treatment of psoriasis. *J Am Dermatology.* 2013; 68: 756–764.
- Silva F, Cisternas M, Specks U. TNF- α blocker therapy and solid malignancy risk in ANCA-associated vasculitis. *Curr Rheumatol Rep.* 2012; 14: 501–508.
- Thyagarajan V, Norman H, Alexander K, Napalkov P, Enger C. Risk of mortality, fatal infection, and fatal malignancy related to use of anti-tumor necrosis factor- α biologics by rheumatoid arthritis patients. *Semin Arthritis Rheum.* 2012; 42: 223–233.
- Wong AK, Kerkoutian S, Said J, Rashidi H, Pullarkat ST. Risk of lymphoma in patients receiving antitumor necrosis factor therapy: a meta-analysis of published randomized controlled studies. *Clin Rheumatol.* 2012; 31: 631–636.
- Askling J, Fahrback K, Nordstrom B, Ross S, Schmid CH, Symmons D. Cancer risk with tumor necrosis factor alpha(TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. *Pharmacoepidemiol Drug Saf.* 2011; 20: 119–130.
- Dommasch ED, Abuabara K, Shin DB, Nguyen J, Troxel AB, Gelfand Jm. The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials. *J Am Acad Dermatol.* 2011; 64: 1035–1050.
- Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. *Arthritis Rheum.* 2007; 56: 2886–2895.
- Bagg A. "Therapy-associated lymphoid proliferations." *Adv Anat Pathol.* 2011; 18: 199–205.
- FDA. "Arthritis Advisory Committee Briefing Information: Update on the TNF- α Blocking Agents 2003."
- Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. "Etanercept plus Standard Therapy for Wegener's Granulomatosis." 2005; 352: 351–361.
- Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL. "Anti-TNF Antibody Therapy in Rheumatoid Arthritis and the Risk." 2006; 295: 2275–2285.
- Askling J, van Vollenhoven RF, Granath F, Raaschou P, Forede CM, Baecklund E, et al. "Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment?" *Arthritis Rheum.* 2009; 60: 3180–3189.
- Mercer LK, Lunt M, Low AL, Dixon WG, Watson KD, Symmons DP, et al. Risk of solid cancer in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Ann Rheum Dis.* 2015; 74: 1087–1093.
- Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. *Ann Rheum Dis.* 2009; 68: 1136–1145.
- Askling J, Forede CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N, et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. *Ann Rheum Dis.* 2005; 64: 1421–1426.
- Xavier Mariette, Marco Matucci-Cerinic, Karel Pavelka, Peter Taylor, Ronald van Vollenhoven, Rebecca Heatley, et al. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. *Ann Rheum Dis.* 2011; 70: 1895–1904.
- Caillard S, Agodoa LY, Bohem EM, Abbott KC. Myeloma, Hodgkin disease, and lymphoid leukemia after renal transplantation: characteristics, risk factors and prognosis. *Transplantation.* 2006; 81: 888–895.
- Wang TF, Klein JL, Woodard PK, Hassan A, Joseph SM, Ewald GA, et al. Plasmacytoma-like post-transplantation lymphoproliferative disease occurring in a cardiac allograft: a case report and review of the literature. *J Clin Oncol.* 2012; 30: e278–282.
- Perry AM, Aoun P, Coulter DW, Sanger WG, Grant WJ, Coccia PF. Early onset, EBV(-) PTLD in pediatric liver-small bowel transplantation recipients: a spectrum of plasma cell neoplasms with favorable prognosis. *Blood.* 2013; 121: 1377–1383.