American Journal of Medical Case Reports, 2016, Vol. 4, No. 9, 298-300
Available online at http://pubs.sciepub.com/ajmcr/4/9/1

DOI:10.12691/ajmcr-4-9-1

Golimumab Induced CNS, Pulmonary, and Cardiac Sarcoidosis - A Case Report and Literature Review

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Abstract Tumor necrosis factor alpha (TNF-α) antagonist has been widely used in the treatment of inflammatory conditions such as rheumatoid arthritis (RA). Recently there have been case reports of the development of sarcoidosis in patients receiving TNF-α antagonists. Agents such as Infliximab, Adalimumab, and Etanercept have all been linked. However, incidents related to Golimumab, another member of the class, has not yet been described. We present the first case of Golimumab induced CNS, Pulmonary, and Cardiac sarcoidosis in a patient who presented with weakness and weight loss and was later found to have multi-organ (lung, brain, heart) sarcoid like involvement. Patient was diagnosed with seropositive (RF and CCP) RA maintained on Golimumab and Methotrexate for 2 years prior to diagnosis. Resolution of symptoms was achieved through the cessation of Golimumab and the use of systemic steroids.

Keywords: *sarcoidosis, Golimumab, Simponi, TNF-α antagonist, Cardiac Sarcoidosis, Pulmonary Sarcoidosis, CNS sarcoidosi*

Cite This Article: Zhen Wang MD, Eugenio Capitle MD, Michael Jaker MD, Smita Mahendrakar MD, and Riju Banerjee MD, "Golimumab Induced CNS, Pulmonary, and Cardiac Sarcoidosis - A Case Report and Literature Review." *American Journal of Medical Case Reports*, vol. 4, no. 9 (2016): 298-300. doi: 10.12691/ajmcr-4-9-1.

1. Introduction

Tumor necrosis factor alpha (TNF-α) antagonist has been effective in treatment of various inflammatory condition such as Rheumatoid Arthritis (RA), Psoriasis (PsA), and inflammatory bowel disease (IBD). It is postulated that CD4 T-helper1 cells and alveolar macrophages that secrete interferon gamma (IFN-γ) and TNF-α play a vital role in induction and maintenance of granulomas. [1] Paradoxically these agents are associated with cases of sarcoid-like granulomatosis in those patients receiving TNF-α antagonist. [1] Sarcoidosis is a chronic, inflammatory disease characterized by non-caseating granuloma formation in various organs. A number of cases have been published reporting development of sarcoidosis in patients receiving this drug class for the treatment of underlying inflammatory conditions. Three drugs Infliximab, Adalimumab and Etanercept have been reported suggesting a class effect. [1] However, such adverse side effect has not been described for Golimumab, which is also marketed under trade name Simponi. Golimumab is an IgG1κ monoclonal antibody specific for TNF-α approved for use to treat RA, ankylosing spondylitis (AS), PsA, and ulcerative colitis (UC). [6] We present the first case of Golimumab induced CNS, Pulmonary, and Cardiac sarcoidosis.

2. Case Report

45-year-old black female with a history of non-erosive seropositive (CPP and RF) RA presented for evaluation of progressive generalized weakness and a 15 lb unintentional weight loss in the last two months. She could not ambulate without using a walker and had to quit work due to this debilitating condition. Severe diffuse bilateral symmetrical RA was diagnosed 2 years prior and symptoms had been controlled with Methotrexate and Golimumab since diagnosis. Patient had no known history of pulmonary disease.

On presentation, patient was cachectic with BMI of 16.8 kg/m^2. Her head was normal cephalic and atraumatic. Sclera was anicteric. There was no nystagmus, conjugate gaze or ocular dysmetria. Patient was tachycardic. Rhythm was regular with normal S1 and S2. There were no murmurs, rubs, or gallops. Chest was clear to auscultation bilaterally with no wheezes, crackles or rhonchi. Abdominal exam was normal. There was full range of motion in all joints however diffuse muscle atrophy was noted. Skin exam revealed no rash or lesions. She was alert and oriented to person, place and time. Cranial Nerves II to XII were all intact. Motor strength was 4/5 in both upper and lower extremities, reflexes were 2+, Babinskis was negative bilaterally. No fasciculation was noted and tone was normal with no spasticity. Sensory was intact in upper and lower extremities. There was no tremor at rest. There was no dysmetria or spasticity.

Initial labs revealed hgb 10.7 g/dl, hct 34.6%, MCV 58.7 fL, RDW 24.9%, PLT 594 x 10^9/L. Serum chemistry showed Na 140 meq/L, K 3.9 meq/L, Cl 100 meq/L, Bicarb 24 meq/L, BUN 9 mg/dL, Cr 0.7 mg/dL, Glucose 92 mg/dL, Ca 10.7 mg/dL, Mg 1.9 mg/dL. CK was 36 units/L. ESR and CRP were elevated 62 mm/h and 53 mg/L respectively. Iron studies revealed low iron of 22

μg/dL. Ferritin, TIBC, Vitamin B12, Folate were normal. Liver function test was significant for AST of 43 units/L but otherwise unremarkable. Urinalysis revealed moderate blood but was otherwise unremarkable.

EKG showed sinus tachycardia. Chest x-ray showed mediastinal lymphadenopathy and subsequent CT of the chest revealed multiple enlarged mediastinal lymph nodes as well as para-tracheal nodes. (Figure 2) EMG result was unremarkable. Lumbar puncture revealed clear CSF, WBC 138 x 10^6/L, RBC 52 x 10^6/L, LDH 22 units/L, glucose 36 mg/dL and elevated protein of 175 mg/dL. Gram stain and culture of the CSF were negative. MRI of the brain was consistent with leptomeningeal enhancement involving the bilateral cerebellar folia, along the optic chiasm, bilateral trigeminal nerves, Meckel's cave, as well as bilateral internal auditory canals. (Figure 1) A transthoracic echocardiogram was performed for persistent tachycardia with intermittent shortness of breath revealed global hypokinesis and ejection fraction of 40% with grade I diastolic dysfunction.

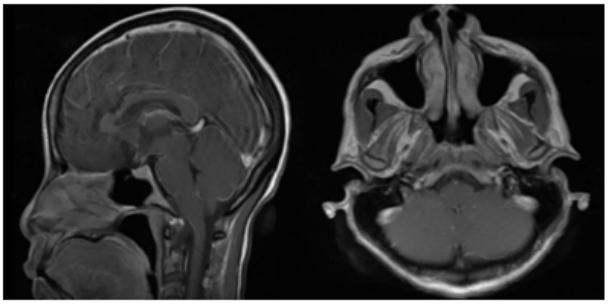

Figure 1. MRI of the brain with contrast in sagittal and axial view respectively. There is minimal mildly nodular leptomeningeal enhancement involving the bilateral cerebellar folia and enhancement along the optic chiasm, bilateral trigeminal nerves and Meckel's cave's as well as the bilateral internal auditory canals

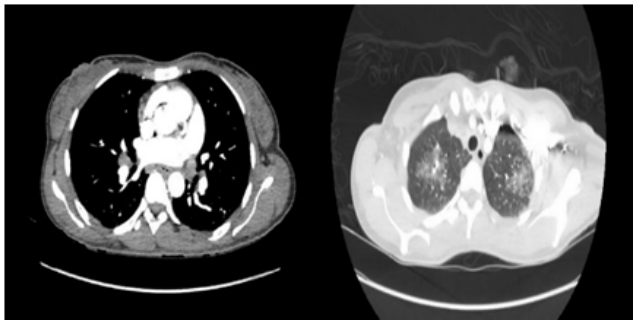

Figure 2. CT of the chest with IV contrast in axial lung view. Multiple enlarged mediastinal and para-tracheal lymph nodes. Patchy ground-glass consolidations in bilateral upper lobes

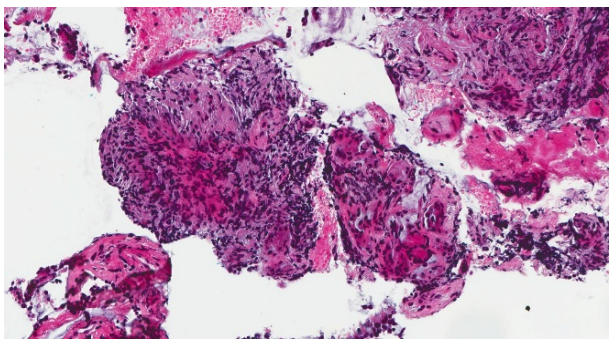

Figure 3. Left upper lung lobe needle core biopsy revealed presence of granulomatoid focus. Hematoxylin and eosin stain, 20x

Additional lab workup revealed normal c3 and c4, positive ANA 1:160, RF, and negative dsDNA, c-ANCA, p-ANCA, anti-smith, anti-RNP, anti-SSA, anti-SSB, anti-histone. Infectious workup including HIV, quantiferon gold, Histoplasma, EBV, CMV were negative. Paraneoplastic workup (anti-Hu/Ri/Yo) were negative. A bronchoscopy with biopsy of the mediastinal lymph nodes showed lung parenchyma with several focal granulomatoid areas. (Figure 3).

AFB culture, stain, bronchial, fungal cultures from the biopsy sample were negative. Patient's hospital course was complicated by the development of a complete right-sided Bell's palsy for which pulse steroids was started. Patient's ataxia, facial palsy, appetite gradually improved over a course of few days with administration of corticosteroids. Golimumab was discontinued as it was thought to be responsible for the constellation of her symptoms.

3. Discussion

TNF-α antagonists have been effective in treating inflammatory conditions such as RA, AS. Paradoxically many cases of sarcoidosis or sarcoid-like development in patients receiving TNF-α antagonist have been reported. Five TNF-blockers are approved by the USA Food and Drug administration (FDA) and are currently available: Infliximab, Etanercept, Adalimumab, Golimumab, and Certolizumab. [7] Infliximab, Adalimumab, and Etanercept have all been associated with the development of sarcoidosis suggesting a class effect. [1] The majority of these incidents have been attributed to Etanercept perhaps because it is a soluble TNF receptor blocker and it binds to transmembrane receptor with less avidity. [1] A review of literature revealed 52 cases where the use of TNF-α antagonists has led to the development of a sarcoid-like reaction. Among those cases 33 occurred with Etanercept, 12 with Infliximab and 7 with Adalimumab. [4]

The etiology of this paradoxical granulomatous formation in patients receiving TNF-α antagonist is not well understood. The matter is further complicated by the fact that these agents are also useful in treating sarcoidosis. [9] CD4 T-helper cells and alveolar macrophages are responsible for secreting IFN-γ and TNF-α which play a major role in maintenance of the granuloma. [1] There may be physiological crosstalk between TNF-α and IFN-α pathways. Type I IFN activity is upregulated during treatment with TNF antagonists. IFN-α can enhance the production of IFN-γ and IL-2. Expression of both cytokines are elevated in sarcoid T cells. IFN-γ along with TNF-α is strongly implicated in granuloma formation. [1] It is also postulated that the blunting of TNF-α with antagonists could introduce a cytokine imbalance which inadvertently activate specific T cells that can cause granuloma formation. [4]

Golimumab is a relatively newer drug belonging to the class of TNF-α antagonist. It is a fully human antibody raised against TNF-α and has been approved for the treatment of active RA, AS, and psoriatic arthritis. [7] Its efficacy in ulcerative colitis is still being investigated in clinical trial. It is intended for use in combination with Methotrexate for RA treatment, with and without Methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARD) and ⁄ or NSAID for PA

and AS. [7] The most common reported side effects are pain, edema, eczema at the injection sites, reactivation of herpes simplex, bacterial infection, lichenoid eruption, multiform erythema, lupus erythematosus, lymphoma.

4. Conclusion

The case we present here is the first case of Golimumab induced sarcoidosis per literature review. Further study will be needed to investigate the mechanism of action behind this paradoxical granulomatoid reaction in TNF-α antagonist recipient(s). Sarcoid like granulomatosis should be regarded as a known adverse effect of TNF-α antagonist, [8] including this newer drug Golimumab.

Acknowledgment

Special thanks to Dr. C. A. Curcio from the department of pathology for providing the biopsy slides and to the department radiology for providing the radiographic images.

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