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Case Report

Docetaxel Induced Myositis

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Abstract

Taxane chemotherapeutic agents are widely used in the treatment of both early and advanced stage breast cancer and in other solid tumors over the last three decades. Though taxanes have a well-documented side effect profile ranging from myelosuppression to fluid retention to neurosensory toxicity, a further side effect causing a myositis has been increasingly documented in the literature with no clear underlying pathophysiology. This case describes a 65 year old African American female with estrogen receptor (ER) and progesterone receptor (PR) positive invasive ductal breast carcinoma who was receiving adjuvant docetaxel and cyclophosphamide. Prior to her fourth cycle she presented with severe thigh pain and inflammation with laboratory findings demonstrating an elevated creatinine phosphokinase (CPK), erythrocyte sedimentation rate (ESR) and aldolase. In addition her magnetic resonance imaging (MRI) was notable for heterogeneous, patchy enhancement involving multiple muscles with a distribution consistent with multifocal myositis. She was worked up extensively and found to have no underlying predisposition or other causative agent to result in this disabling inflammatory myositis. She responded well to a course of corticosteroids and the offending agent was not reintroduced. As Anthracycline/Taxane combination chemotherapies have become the cornerstone of adjuvant and neoadjuvant treatment of breast cancer, we are beginning to see rare side effects of these therapies documented in the literature. This is the seventh case report documenting this association in the literature despite its extensive clinical usage. This case shows a rare side effect of myositis and demonstrates the need for further studies to demonstrate a definitive association. This can be explained either on the basis of its rare nature or underreporting due to its lack of known association.

Keywords: Docetaxel; Myositis; Cancer

Introduction

Docetaxel is a well-established chemotherapy agent and was first FDA approved in 1999 in the treatment of non-small cell lung cancer. It was later found to be effective in treating prostate, head and neck, gastric and breast cancer [1]. Despite being a very potent chemotherapeutic agent, its efficacy is often restricted by some debilitating adverse effects. In majority of the clinical trials, docetaxel related sideeffects include myelosuppression, fluid retention, edema and neurosensory toxicity [2]. Myositis, which is inflammation of the skeletal muscle, is a side effect that has rarely been reported in the setting of docetaxel use. We would like to discuss this rare side effect to highlight the rare toxicities of anticancer drugs. We would also like to discuss the role of steroids in this setting.

Case Presentation

We report a case of a 55 year old African American woman with past medical history of hypothyroidism, diabetes type II, and stage I left breast cancer who presented with intractable bilateral thigh pain and swelling. She was diagnosed with stage I, Estrogen receptors/ Progesterone receptors (ER/PR) negative, human epidermal growth receptor 2 (HER2) negative (Triple-negative), invasive ductal breast carcinoma following breast conserving surgery and sentinel lymph node biopsy in August 2015. One month later she was started on adjuvant chemotherapy with a plan for four cycles of Docetaxel 75 mg/m^2 IV and Cyclophosphamide 600 mg/m^2 IV every 21 days. Eighteen days after her third cycle of Docetaxel and Cyclophosphamide the patient presented to our emergency department with one week of persistent bilateral thigh pain and swelling mainly involving the medial aspect of her thighs, not relieved by oral pain medications including oxycodone. She denied any fevers or chills. No changes were made to any of her medications in the last few months prior to this presentation. Physical exam was significant for bilateral thigh edema and tenderness to light touch. She had decreased active range of motion of both hips and difficulty ambulating due to the severe pain. There were no skin lesions. Her neurological exam displayed intact sensation with normal power and reflexes. Laboratory findings included an erythrocyte sedimentation rate (ESR) of 92 (normal range: 0–24 mm/hr), creatinine phosphokinase (CPK) of 300 (normal range: 30–135 U/L) which later peaked at 978. Her aldolase was elevated to 30.3 (normal range: ≤ 8.1 U/L). There were no leukocytosis or electrolytes abnormalities. Thyroid-stimulating hormone (TSH) was within normal range. Workup of rheumatologic diseases including antinuclear antibody (ANA), double stranded DNA (ds-DNA), anti-Smith, rheumatoid factor (RF), cyclic citrullinated peptide (CCP), anti-Ro (SSA) and anti-La (SSB), ribonucleoprotein (RNP), and Scl 70 were unrevealing. Differential diagnosis at that time included lower extremity deep venous thrombosis (DVT), bone metastasis, soft tissue infection, osteomyelitis and drug induced myopathies. Her statin medication was stopped. Duplex Ultrasound ruled out DVT. Femur and pelvis x-rays showed no radiographic evidence of osseous

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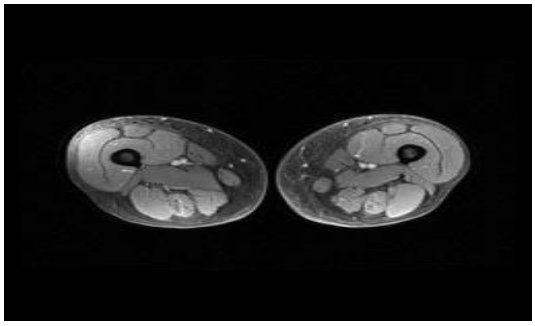

Figure 1: Axial T1-weighted FAT SAT image illustrating increase uptake of contrast, indicative of diffuse inflammation and muscle edema.

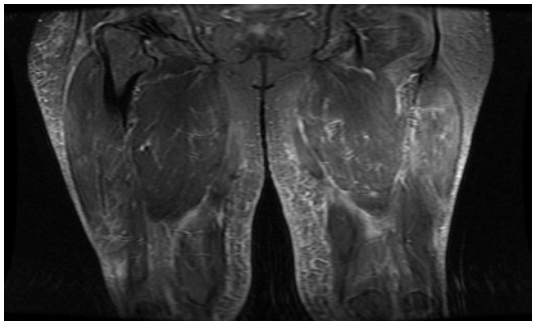

Figure 2: Coronal short tau inversion recovery (STIR) image showing increased fluid signal of the left thigh, compatible with myositis.

metastatic disease or avascular necrosis of the hip joints. Pt was not given antibiotic therapy due to lack of evidence of an active infection. A computerized tomography (CT) of the thighs however did show skin thickening and subcutaneous edema which was further evaluated with magnetic resonance imaging (MRI). This demonstrated heterogeneous, patchy enhancement involving multiple muscles within the anterior compartment of the right thigh (Sartorius muscle and Rectus Femoris muscle), the posterior compartment of the right thigh (Semi-Tendinous muscle), the medial compartment of the left thigh (Abductor Longus), as well as the anterior compartment of the left thigh (Rectus Femoris). The distribution was consistent with multifocal myositis. Associated edema was also seen. The commencement of Docetaxel and Cyclophosphamide was the only significant factor that could have led to this acute myositis, with docetaxel being the likely etiology. Treatment for Docetaxel induced myositis with Prednisone 60mg for 5 days was initiated. Within 24 hours a substantial improvement of pain, tenderness, swelling, and range of motion was noticed. Subsequently, a tapering regimen of Prednisone was prescribed with complete resolution of her pain and a down trending CPK. She did not complete her fourth cycle and was started on adjuvant breast radiation. A repeat CT scan four months later demonstrated near complete resolution of the previously seen abnormalities (Figure 1,2).

Discussion

As Anthracycline/Taxane combination chemotherapies have become the cornerstone of adjuvant and neoadjuvant treatment of breast cancer, we are beginning to see rare side effects of these therapies documented in the literature. The toxicity profile of Docetaxel includes hematologic toxicity (most commonly neutropenia), cutaneous toxicity, neurologic toxicity, arthralgia, myalgia, and capillary-leak syndrome [3]. Arthralgias and myalgias, while not noted as common side effects in early trials are now commonly reported, and in one such study arthralgias and myalgias were reported by 87% of patients undergoing sequential anthracycline/taxane based chemotherapy [4]. This study did not differentiate between paclitaxel and docetaxel, though these side effects tend to be reported more with paclitaxel [5]. In this study myositis was also reported only after paclitaxel and not observed with docetaxel. Sensory neuropathy has been noted with docetaxel and even proximal muscle weakness can develop but is likely neuropathic in origin and CPK levels will be normal [6].

To identify docetaxel as the etiology of our patient's myositis we carefully reviewed the broad differential that an acute myositis poses and investigated potential etiologies. Dermatomyositis (DM) or polymyositis (PM) was taken into consideration but ruled out given her acute presentation and that she did not present with muscle weakness which is documented in over 90% of patients with DM and PM [7] She also had a negative ANA, anti-Smith, anti-Ro (SSA) and anti-La (SSB), and ribonucleoprotein going against an idiopathic inflammatory myositis [8]. Though this patient is diabetic, the clinical course was not in keeping with a diabetic amyotrophy given the unilateral onset, the elevated CK and MRI findings and her rapid recovery [9]. Sensorimotor polyneuropathy as part of a paraneoplastic syndrome was felt to be unlikely again given her clinical presentation of leg edema and elevated muscle enzymes. Her absence of sensory or autonomic manifestations was also against this diagnosis. Pyomyositis was also ruled out given this lack of systemic symptoms and MRI findings inconsistent with this diagnosis [10]. Statin induced myositis was a distinct possibility given this was part of our patient's home medications. Statins, along with several other drugs can initiate an inflammatory myopathy however though this is one of her home medications, it is unlikely to cause a myositis given she had been taking it for several years and her symptoms resolved promptly with the initiation of steroid treatment [11]. Though she does have a history of hypothyroidism which can be associated with myalgia and elevated CK her TSH was within normal range [12]. After ruling out the various differentials we concluded that docetaxel was likely the offending agent causing this patient's myositis. This is a side effect that can be easily overlooked by physicians particularly in the setting of other existing causative factors. However, it is treatable and we should have a higher index of suspicion when monitoring patients on Taxane therapies. Our patient responded well to treatment with prednisone and months later she continues to be asymptomatic. On review of documented cases of this adverse effect, immunosuppressant agents are the main stay of therapy. Most cases demonstrated good response with steroids, however some patients required other agents such as Plaquenil and Methotrexate and even IVIG was successful for refractory cases [13-18].

Conclusion

This case shows a rare side effect of myositis and demonstrates the need for further studies to demonstrate a definitive association. This is the seventh case report documenting this association in the literature despite its extensive clinical usage. This can be explained either on the basis of its rare nature or underreporting due to its lack of known association.

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