Gemcitabine-Induced Myositis in a Luminal B Breast Cancer patient: A Case Report

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ABSTRACT: Human epidermal growth factor receptor-positive breast cancer is an aggressive cancer which represents approximately a quarter of all breast cancers worldwide. Recent advances have led to the development of targeted therapies, such as trastuzumab (H), which have significantly improved prognosis. Such therapies are currently used alongside other chemotherapeutic agents, such as paclitaxel (P) and gemcitabine (G). The most common side effects of PGH combination therapy include thrombocytopenia and anemias. However, there have been no previous reports of myositis resulting from this combination. We report the case of a 54-year-old metastatic breast cancer patient on PGH therapy who developed muscle weakness. The patient was initially treated with trastuzumab, pertuzumab, and paclitaxel. However, pertuzumab was changed to gemcitabine due to severe diarrhea. After the fourth cycle of PGH, the patient presented with muscle weakness and creatine kinase levels of up to 6755 U/L. Magnetic resonance imaging of the femur and pelvis revealed diffuse bilateral myositis, suggesting a diagnosis of gemcitabine-induced myositis. The patient was placed on intravenous fluids and corticosteroids, which resolved her condition. To our knowledge, this is the first report of gemcitabine-induced myositis in a breast cancer patient. Further studies are needed to determine the underlying mechanisms of gemcitabine-induced myositis and develop preventative measures.

KEYWORDS: Breast cancer, gemcitabine, paclitaxel, trastuzumab, myositis, case report

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Introduction

Human epidermal growth factor (HER2) receptor-positive breast cancer presents aggressively with poor prognosis.[1] HER2 overexpression is seen in 25% to 30% of breast cancers (BC).[2] However, with the introduction of HER2-targeted therapy such as trastuzumab, outcomes of BC patients have significantly improved.[1] Combinations of such drugs with chemotherapeutic agents are commonly used in both metastatic and adjuvant settings.[1]

The major risk factor associated with trastuzumab is cardiac dysfunction, which can be observed in up to 4.1% of patients receiving adjuvant treatment.[1] However, incorporating anthracycline-free regimens reduces the risk of cardiac dysfunction and other side effects of trastuzumab.[1] Among those regimens, paclitaxel (P) and gemcitabine (G) in combination with trastuzumab (H) (PGH) has been shown to be well-tolerated with promising outcomes.[3] Previously reported side effects of PGH include granulocytopenia, thrombocytopenia, anemia, neuropathy, and infection.[1-3] Contrarily, chemotherapy-induced myositis is very uncommon, and reports of such cases are limited.[4] Previously published PGH trials have not reported myositis as a pertinent side effect. Hence, in this article we report the case of a 54-year-old metastatic BC patient who presented with PGH-induced rhabdomyolysis. An informed written consent was obtained from the patient for the publication of this manuscript and its accompanying figures. To the authors' knowledge, this is the first article describing myositis as a result of this combination.

Case Presentation

A 54-year-old female presented to the emergency department complaining of muscle stiffness, cramps, and difficulty walking for the past 3 days after receiving her fourth cycle of PGH. She is a known case of metastatic luminal B BC, which was initially treated with trastuzumab, pertuzumab, and weekly infusions of paclitaxel. However, pertuzumab was replaced with gemcitabine after 2 cycles due to complaints of severe diarrhea. The patient disclosed that she experienced similar symptoms in the past after every dose of the new regimen, which was subsequently followed with tea-colored urine. Upon physical examination, lower limbs had a motor score of 3/5 bilaterally with tenderness in the right thigh upon palpation.

Her lab results recorded a creatine kinase value of 4983 U/L which was on an upward trend, increasing to 6755 U/L after a couple of hours (Figure 1). She was administered 2 doses of morphine 3 mg upon admission, 3 hours apart, which relieved her pain. Further workup revealed mild hyponatremia at 133 mmol/l and mild hypocalcemia at 1.98 mmol/L. The remaining electrolyte levels were within normal range. Total white blood cell count was normal; however, the patient had a low lymphocyte count of

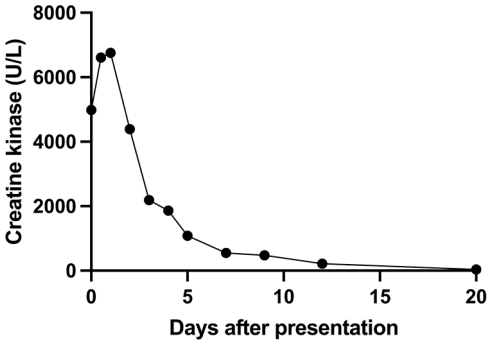

Figure 1. A graphical representation of the patient's creatine kinase levels after presentation.

0.42×10^9/L. In addition, lab results indicated an elevated erythrocyte sedimentation rate of 54 mm/hour, and her antibody panel came back negative. Furthermore, thyroid function tests revealed subclinical hypothyroidism with a thyroid-stimulating hormone level of 5.3 mU/L and a free thyroxine level of 20.4 pmol/L. Urine chemistry tests showed no excreted myoglobin. Levels of alanine transaminase and aspartate transaminase were also elevated at 98 and 96.6 U/L, respectively. Lastly, coagulation profile tests demonstrated a PT of 15.6 seconds and an INR of 1.2. Accordingly, a high degree of clinical suspicion was placed upon drug-induced myositis due to gemcitabine. We decided to place her under observation and refer her to our rheumatology, nephrology, and neurology departments.

The patient's condition deteriorated the following day when she developed new onset of bilateral lower limb heaviness and numbness over the tips of both feet. Nerve conduction study and electromyography showed electrodiagnostic evidence of mild length-dependent sensory-motor polyneuropathy and minimal features of irritative myopathy of the lower extremity's proximal muscle. Magnetic resonance imaging of the pelvis and femur was ordered promptly, which revealed findings suggestive of diffuse bilateral myositis and diffuse bone marrow replacing lesions, likely metastasis from her breast cancer (Figures 2 and 3).

Her chemotherapy was put on hold, and she began improving after receiving IV hydration and pulse corticosteroid therapy with 1 g of methylprednisolone daily for 3 days. One week after her initial presentation, the patient regained some mobility and was able to walk with support. She was later discharged and is currently continuing her chemotherapeutic regimen with a 30% reduction in gemcitabine dosage.

Discussion and Conclusion

Myositis may result from a wide spectrum of etiologies; however, chemotherapy-induced remains a rare entity. In the present study, we report the case of a luminal B BC patient who developed acute myositis after switching to a regimen containing gemcitabine. Although our patient was receiving a combination of chemotherapeutic drugs, she stated that her symptoms began after initiating gemcitabine. Hence, we believe that gemcitabine was the main culprit in this patient. Subsequent investigations ruled out any alternative causes of myositis.

Gemcitabine, a deoxycytidine analog, is one of the most promising chemotherapy agents against solid tumors, including non-small-cell lung carcinoma, pancreatic cancer, and BC.[5] The most reported side effects of PGH therapy include febrile neutropenia, thrombocytopenia, and anemia.[2] However, there have been no previous reports of PGH-induced myositis in the literature. Due to the patient receiving combination therapy, it is difficult to fully determine the specific drug which lead to the patient's presentation. It is high likely, however, that gemcitabine was the underlying factor, as mild symptoms of myopathy began with the first cycle of gemcitabine.

Gemcitabine-induced myositis is also an extremely rare occurrence. Most cases of gemcitabine-induced myositis are associated with radiation recall myositis, a phenomenon characterized by muscle lesions in previously irradiated areas.[6] However, emerging evidence is increasingly demonstrating a link between direct myotoxicity and gemcitabine without previous radiation therapy. For example, Chun et al. reported the case of a diabetic patient diagnosed with pancreatic adenocarcinoma.[7] After receiving his sixth cycle of gemcitabine monotherapy, the patient developed facial and right forearm swelling, which resolved after the cessation of gemcitabine. Contrarily, our patient presented with muscle heaviness and weakness.

To date, the mechanisms underlying gemcitabine-induced myositis remain unclear. Thrombosis, vasculitis, and microvascular proliferation can often be seen in affected muscle biopsies and may play a role in the development of the condition.[6] Increased inflammatory markers and muscle enzymes are commonly seen in patients, distinguishing myositis from edema.[6] Cases of gemcitabine-induced myositis are treated with drug cessation and corticosteroids, often resolving within 1 week of treatment.[8] Although previous studies do not highlight whether chemotherapeutic regimens can be resumed, PGH was continued in our patient, with a reduction in gemcitabine dosage. After 5 additional PGH cycles, the patient is tolerating the treatment well and has not reported recurrence of symptoms.

A major limitation of this case is the inability to confirm gemcitabine as the triggering agent. Reports of paclitaxel- and trastuzumab- induced myositis are very rare. Maeng et al. described the case of paclitaxel-related radiation recall myositis in a 57-year-old patient with recurrent cervical cancer.[4] Additionally, Sasaki et al. reported a case of fatal giant cell myositis and myocarditis after treatment with paclitaxel and carboplatin in a thymoma patient.[9] To the authors' knowledge, there have been no reports of paclitaxel-induced myositis in a BC patient. On the other hand, trastuzumab-related myotoxicity has been associated with dermatomyositis.[10,11] Our patient reported onset of muscle weakness after the patient's treatment regimen was switched from pertuzumab to gemcitabine. Furthermore, the patient did not have any skin symptoms, largely excluding trastuzumab as the causative agent. Collectively, we believe these findings suggest gemcitabine as the causative agent in the present case.

In this article, we presented the case of a 54-year-old metastatic BC patient undergoing PGH treatment who presented

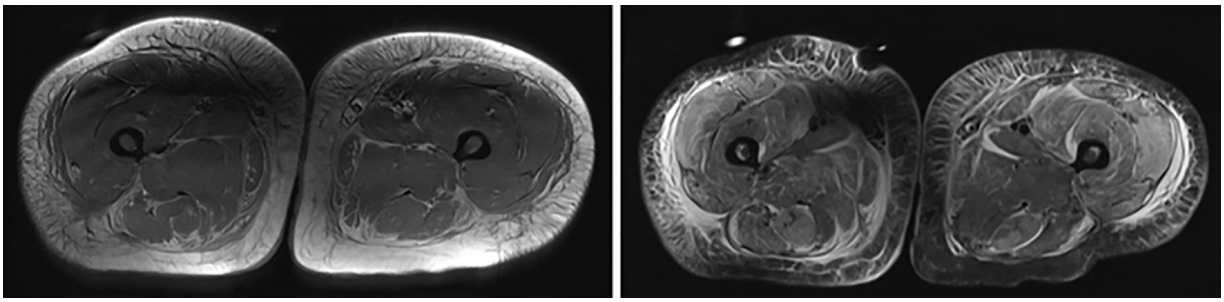

Figure 2. Axial MRI scan showing diffuse edema of all muscle compartments in both legs.

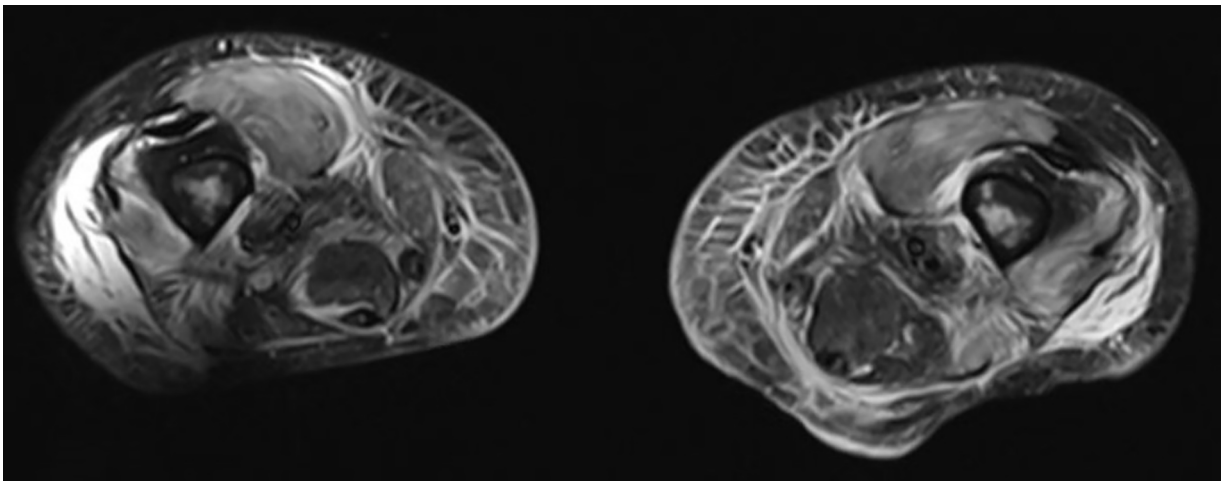

Figure 3. Axial MRI scan of the femurs showing bone marrow-replacing lesions suggestive of metastasis.

with muscle heaviness and weakness. Gemcitabine-induced myositis often presents as part of a radiation recall phenomenon. Direct gemcitabine myotoxicity, on the other hand, is exceedingly rare. To our knowledge, this is the first report of gemcitabine myotoxicity in a BC patient. Early recognition and treatment of this condition is crucial to limit debilitating complications. However, due to the limited nature of case reports, our findings are only suggestive, and conclusions should be drawn carefully. Further studies are needed to identify the true prevalence of gemcitabine-induced myotoxicity and its underlying pathophysiology.

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Author Contributions

SSA, TZA, AKH, and AS drafted the original version of the manuscript. AB, MAE, and DA critically revised the manuscript and were the supervising physicians for this patient.

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