Gemcitabine Induced Radiation Recall Myositis: Report of Two Cases

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ABSTRACT

Radiation recall phenomenon can appear as dermatitis, pseudocellulitis, panniculitis or myositis after the administration of certain drugs and develop in the skin and soft tissue at previously irradiated sites. Several drugs are associated with the radiation recall and gemcitabine is one of them. Gemcitabine-related radiation recall preferentially involves internal organs and can also be observed at the fibromuscular tissue in the radiation portal. Herein, we report two cases with gemcitabine induced radiation myositis. One patient with non-small cell lung carcinoma, and the other one with pancreatic carcinoma developed myositis in the previously irradiated site after administration of gemcitabine based chemotherapy.

Key Words: Radiation recall, Gemcitabine, Myositis, Side effect

ÖZET

Gemsitabine Bağlı Radyasyon "Recall" Myoziti: İki Olgu Sunumu

Radyasyon 'recall' fenomeni, ışınlama alanında radyoterapi sonrası uygulanan çeşitli ilaçlara bağlı olarak cilt ve yumuşak dokuda, dermatit, psödoselülit, pannikülit veya myozit olarak ortaya çıkabilen bir klinik tablodur. Gemsitabin radyasyon 'recall' ile ilişkili bilinen ajanlardan biridir. Gemsitabine bağlı radyasyon 'recall' genellikle iç organlarda gözlense de radyoterapi alanı içindeki kas dokusunda da izlenir. Küçük hücreli dışı akciğer kanseri ve pankreas kanseri tanılarıyla radyoterapi uygulanan ve Gemsitabine bağlı radyasyon 'recall' myoziti gelişmiş iki olgu sunularak literatür eşliğinde tartışılmıştır.

Anahtar Kelimeler: Radyasyon recall, Gemsitabin, Myozit, Yan etki

INTRODUCTION

Radiation recall is a rare and infrequently reported adverse effect of radiotherapy (RT). Although skin has been the major site of radiation recall toxicity, the recall reaction may occur in previously irradiated sites such as mucous membranes in the upper respiratory tract, lung, muscles, and gastrointestinal tract.

D'Angio et al.[1] have first described radiation recall dermatitis in 1959 as an Actinomycin D potentiated X-ray effect. The recall is triggered by the administration of certain drugs and occur within days to years after the exposure to ionizing radiation.[2,3] Gemcitabine (GEM), a nucleoside analogue with potent radiosensitizing activity, has been recently investigated with radiation in the treatment of pancreatic cancer, non-small cell lung cancer (NSCLC) and other solid tumors. Most of the radiation recall reactions attributed to GEM affect internal organs, rather than dermis.[4] Almost all the radiation recall myositis reactions reported in the literature have been related to GEM. Although a rare complication, treating physicians must be aware of this potential, and sometimes morbid side effect.

Herein, we present two cases with myositis consistent with a radiation recall reaction induced by GEM and report the clinical course, and treatment options in the light of the current literature.

CASE 1

A 42 year-old caucasian female presented to her surgeon with elevated levels of CA 19-9 which is incidentally found during a routine check-up. Abdominal MRI revealed a mass at the pancreatic tail. The patient underwent pancreatosplenectomy and lymph node dissection, and pathological examination confirmed the diagnosis of a moderately differentiated pancreatic ductal adenocarcinoma of 3.5 cm diameter in the corpus-cauda of the pancreas. Microscopically peripancreatic fat tissue invasion, perineural invasion and lymphovascular invasion were present with negative surgical margins, and none of five peripancreatic lymph nodes were involved. The patient was diagnosed with T2N0M0 carcinoma of the pancreas, and was referred to our department for postoperative RT. We treated the tumor bed and regional lymph nodes to a total dose of 45 Gy in 1.8 Gy fractions using conformally shaped four fields of 18 MV photons. The patient tolerated the treatment well, no acute side effects of the gastrointestinal tract, skin and soft tissue were observed during RT.

The patient received continuous 5-FU infusion concomittantly with RT, followed by 4 cycles of adjuvant GEM 1250 mg/m^2/week, 3 weeks in every 4-week-cycle. One month after the last cycle of GEM chemotherapy she developed a tender mass, pain and swelling of the abdominal wall muscles in the areas of the previous radiation fields. Abdominal MRI revealed diffuse edema and inflammation of the muscles of the anterior and right abdominal wall which was consistent with myositis (Figure 1). Her pain was moderate and scored 4-5 out of 10 with Visual Analogue Scale (VAS).[5]

The patient is diagnosed with radiation recall myositis and treated with corticosteroids (CS) and nonsteroid antienflammatory drugs (NSAID's). Gabapentin was used to ease the neuropathic pain. Her pain and edema of the abdominal muscles regressed in a week and the clinical and radiologic findings disappeared in one month time, and medications were stopped. The patient is followed 38 months after the diagnosis without any evidence of disease.

CASE 2

A 67 year-old caucasian female presented with coughing and dyspnea. CT scan of the thorax revealed a mass at the left upper lobe and lingula which caused total atelectasis and bronchial obliteration without pathologic mediastinal lymph nodes. After fiberoptic bronchoscopic biopsy she was diagnosed with NSCLC. PET-CT detected a FDG avid mass directly invading the mediastinum in the left upper lobe and ipsilateral N2 lymph nodes were also involved. She was diagnosed with stage IIIB NSCLC and received 62Gy curative RT with 3-D conformal technique to the FDG avid sites. No concurrent chemotherapy was administered during RT. The patient tolerated RT well without any skin or soft tissue reaction. Following RT, GEM 1200 mg/m^2 1-8 days and Carboplatin AUC 5.5 1 day / 30 days in 3 cycles was initiated. A dose reduction was done after first cycle because of the intolerance of the patient, and GEM dose was reduced to 800 mg/m^2. The patient complained of severe fatigue, muscle and joint pain, and chemotherapy was discontinued after third cycle. After the completion of systemic therapy, CT scan of the thorax revealed partially

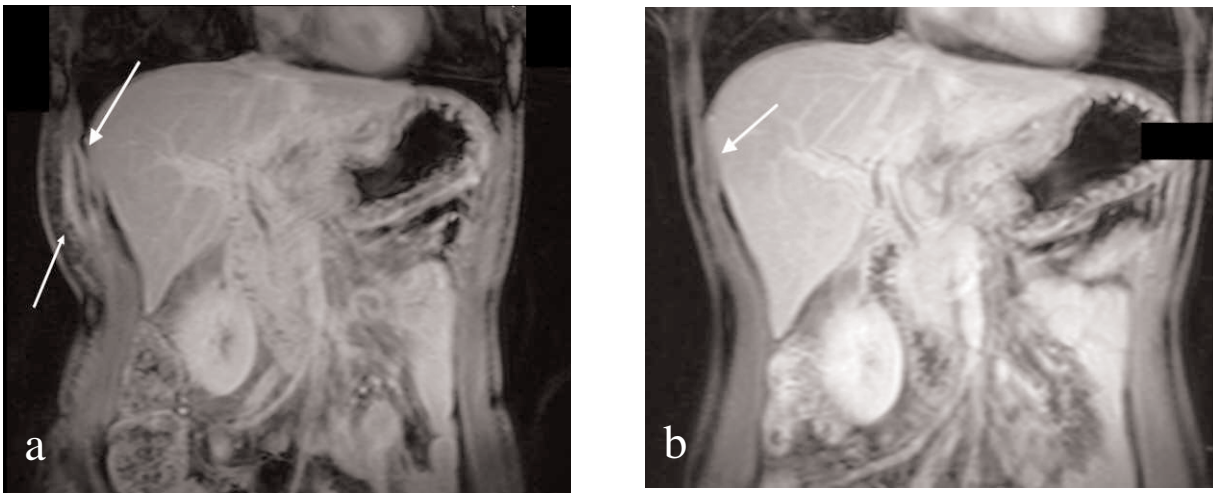

Figure 1. MR scan of the abdomen showing muscle edema and thickening with contrast fixation (white arrows) in the radiation portal **(a)** 4 months after radiation, and **(b)** one months after symptomatic treatment with complete regression

regression of the left upper mass, and total regression of atelectasis. Two weeks after the last cycle of chemotherapy she presented with a painful swelling on her left breast and chest wall extending to her axilla. She described a burning pain and her left arm and shoulder movements were reduced because of the pain. The pain was scored 7-8 with VAS. There were no erythema or pigmentation of the skin and the soft tissue on the irradiated areas were swollen. CT scan of the thorax was repeated and left sided pectoral and paraspinal muscles at the previously irradiated sites were found thickened from 1 cm to 3 cm (Figure 2). MRI showed a dramatical muscle edema and soft tissue reaction at the left breast and subcutaneous soft tissue with heterogenous contrast fixation, consistent with myositis. CS and NSAID's, as well as opioids and antihistaminics were prescribed for recall reaction but they did not have any effect. After two months from the onset of the symptoms CS-induced diabetes emerged and the CS treatment was stopped. Although there was a spontaneous regression of pain, the VAS was still 5-6. Superoxide dismutase (SOD), pentoxifylline, Vitamin E 800 mg per day and selenium tablets were prescribed for the recovery of radiation injury. Gabapentin was tried to resolve neuropathic pain but again without any effect. Topical lidocaine 5% pomade was found effective in exacerbated pain attacks. Thorax CT and MRI were repeated in every two months and revealed that tumor was under control but myositis findings were stable. Four months after the first symptom of recall, the patient was able to handle the pain without analgesics and her pain level regressed to 3-4 according to VAS. There was no change in patient's physical examination such as tenderness and swelling of the muscles except the pain level. She has had nine months of follow-up with recall myositis and she continued using SOD, pentoxifylline, Vitamin E and selenium. Her pain intensity regressed totally, but she still has difficulties in moving her left shoulder. Sixteen months after the diagnosis of NSCLC, she is still metastates-free and with radiologically stable local disease. Her broncoscopy was repeated because of the postobstructive pneumonia, and multipl broncoscopic biopsies were reported as inflammatory changes without malignant cells.

DISCUSSION

In the last half century, radiation recall reactions have been reported in the literature and most of the cases are examples of radiation recall dermatitis which mimic acute radiation reaction of the skin. In the last ten years, radiation recall reactions were seen in the unconventional areas such as central nervous system, gastrointestinal tract, lung and musculoskeletal systems.[6,7]

Gemcitabine is a newly developed drug which is very effective on solid tumors and has a potentiated radiosensitizing activity. Due to the increasing use of GEM, increasing numbers of recall phenomenon

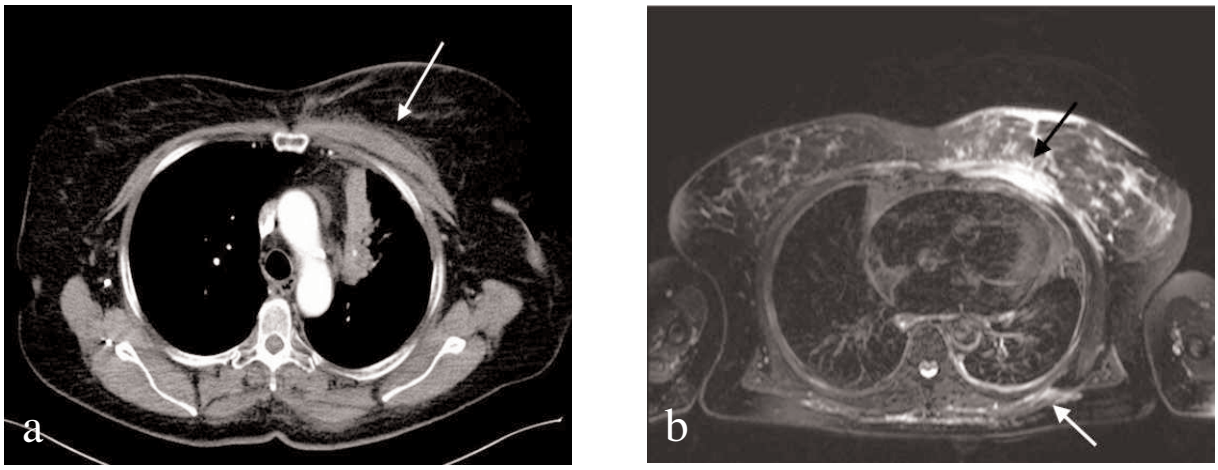

Figure 2. CT scan **(a)** and MR scan **(b)** of the thorax showing marked thickening of the pectoral and dorsal paraspinal muscles.

have been reported.[4,6] Seventy percent of GEM induced radiation recall reactions effect internal organs and muscle tissue is effected more often.[4] We performed a literature search using PubMed to find previously reported cases of GEM induced radiation recall myositis and found eleven cases.[4,6,8-15] Seven cases with NSCLC, and one case with bladder cancer were treated with palliative intent, 3 pancreatic cases were treated with curative intent.

In all these cases total radiation dose, dose per fraction and treatment technique seem to play an important role in the severity of the myositis reactions. Welsh et al.[8] treated the sacrum to a total dose of 45 Gy in 2.5 Gy fractions in a patient with metastatic bladder cancer. To protect the neobladder, opposed two lateral fields were utilized. Therefore gluteal muscles, where the myositis developed, bilaterally received a greater dose per fraction. Fogarty et al.[9] treated the mediastinum of a lung cancer case palliatively and delivered 36 Gy in 12 fractions via ap-pa portals. Myositis involved the posterior chest wall. The symptoms of myositis settled on a tapering dose of oral CS and NSAID's over a 6 week period and cessation of chemotherapy. There was however persistent subcutaneous fibrosis in the reaction area causing limitation of movement in the neck and right shoulder. Miura et al.[10] reported two cases of myositis, where ap-pa portals were used and myositis was seen in the 50 Gy isodose line. Our findings are consistent with those cases in terms of the severity of the reactions. We retrospectively contoured the muscles where recall reactions developed, and calculated doses to these structures using dose volume histograms. The anterior abdominal wall muscles of our pancreatic case received a mean dose of 14.8 Gy (range, 1.6-20.6 Gy), whereas the right lateral abdominal wall muscle received a mean dose of 29 Gy (range, 6.6-35.3 Gy). When recall symptoms appeared, the patient complained more pain at her right abdominal wall. The median dose to the abdominal muscles was low in this case and she recovered from myositis in one month time with simple symptomatic-analgesic medication. In contrast, in the other patient the tumor was located close to the chest wall. Therefore, pectoral muscle and dorsal wall received the full dose of the radiation. Mean pectoral and dorsal paraspinal muscle doses were 63 Gy (range, 34- 66.74 Gy) and 62.2 Gy (range, 31.2-66.2 Gy), respectively. This patient had severe myositis and her symptoms slightly regressed despite CS, pentoxyphilline and antioxidant drugs.

These findings suggest that, in patients treated with two opposed fields the recall reactions were severe, necessitating long term medication, and sometimes leading to chronic morbidity, whereas in patients treated with multiple fields the severity of the reactions was mild, and symptomatic relief was achieved in a short period of time. Therefore using multiple fields and conformal techniques must be encouraged, especially in patients prone to receive GEM.

The relation between the recall and the dose of GEM has been investigated by Jeter et al.[6] They reported of six cases and concluded that if GEM is used in doses of 600 mg/m^2 and higher, the possibility of radiation recall may also rise. All patients

with recall myositis reported in the literature[4,6,8-15] and our patients in the current study received 1000 mg/m^2 or more of GEM, supporting their findings.

Clinical course of the recall myositis differs from patient to patient and the unknown pathophysiologic mechanism does not dictate a spesific therapy. Withdrawal of the offending agent is recommended first, rechallenge with the same chemotherapy agent is debatable. Many patients are treated with topical CS and NSAID's.[3,4,6] In some cases with severe recall reaction not responding to CS and/or NSAID's, antioxidant drugs in a wide spectrum from tocopherol to SOD can be used.[16] Pentoxifylline which improves blood flow in patients with circulation problems by decreasing the viscosity of the blood[16] might be beneficial. For more aggressive approaches with severe tissue breakdown hyperbaric oxygen therapy may be considered.[17] Early physical therapy and rehabilitation are recommended to reduce chances of developing long-term disability secondary to muscle fibrosis.[18]

In conclusion, GEM is the leading agent to cause radiation recall myositis. Treating physicians must be aware of this potential toxicity of GEM either given concomittantly or followed by radiation. Conformal treatment techniques, using lower dose per fraction, and multiple fields are recommended to deliver lower doses to the soft tissue, even in the palliative cases treated with GEM. Muscle doses should be evaluated carefully. Recall reactions usually regress with cessation of responsible agent or with symptomatic therapy. However, some cases do not respond to symptomatic therapy and limitation of movements may develop with severe impairment of quality of life.

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