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CASE REPORT

Gemcitabine-Induced Rectus Abdominus Radiation Recall

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ABSTRACT

Context Radiation recall has been described in the context of gemcitabine chemotherapy. However, this phenomenon has been largely limited to skin.

Case report We hereby report a case of radiation recall dermatitis and myositis occurring on gemcitabine monotherapy, five months after completing chemoradiation for locally advanced pancreatic cancer. Radiation recall resolved spontaneously with withdrawal of gemcitabine.

Conclusions This is the second case report that describes gemcitabine-induced radiation recall in rectus abdominus muscles after gemcitabine-based radiation therapy. Given the wide use of gemcitabine following chemoradiation for pancreatic cancer, providers should be aware of this potential complication.

INTRODUCTION

Pancreatic cancer is the fifth leading cause of cancer-related deaths in both men and women [1]. Less than 10% of newly diagnosed pancreatic cancers achieve 5-year survival. This grim prognosis is largely related to the advanced nature and unresectability of the tumor at the time of diagnosis. The median survival, with treatment, of patients with locally advanced disease has been limited to less than 1 year while the median survival of patients with metastatic disease has typically ranged between 5 and 7 months [2].

Recent efforts have focused on increasing treatment efficacy of locally advanced pancreatic cancer by using newer combinations of chemotherapy and radiation. Gemcitabine, a nucleoside analogue with potent radiosensitizing activity, has been recently investigated with radiation in the treatment of this patient population. Encouraging median survivals compared to historical controls have been described; however, this has been at the expense of significant toxicity [3, 4, 5]. Crane *et al*. compared, in a retrospective study of 114 patients, the outcomes of locally advanced pancreatic cancers treated with either gemcitabine plus radiation to those treated with 5-flurouracil (5-FU) plus radiation [6]. Gemcitabine-based radiation was associated with a median survival of 11 months versus 9 months for the 5-FU-based radiation [6]. Toxicity requiring hospitalization more than 5 days occurred in 23% of patients receiving gemcitabine versus 2% of those receiving 5-FU [6]. M. D. Anderson Cancer Center (MDACC) also reported on the use of gemcitabine-based radiation in the neoadjuvant treatment of patients with locally advanced pancreatic cancer [7]. While the rate of successful resection was high at 73%, hospitalization rate secondary to chemoradiation occurred in 43% of patients due to gastrointestinal and hematological toxicities [7].

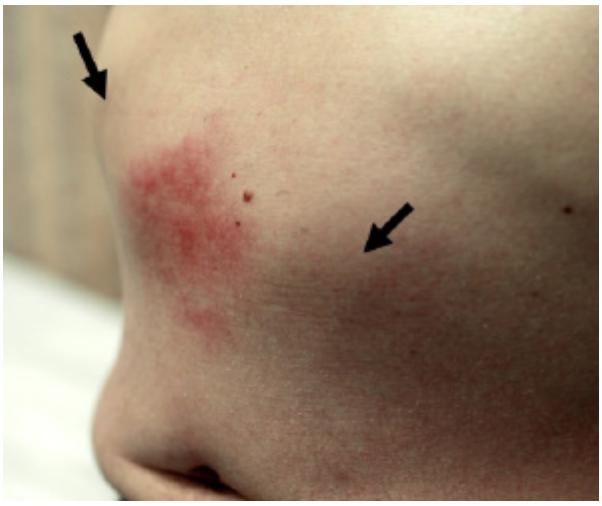

Figure 1. Well demarcated radiation recall dermatitis with evidence of rectus abdominis swelling (arrows).

While gastrointestinal toxicities have been commonly reported with gemcitabine-based radiation in patients with pancreatic cancer, recall myositis has been previously reported only once in this setting [8]. We hereby report the second case of gemcitabine-induced radiation recall rectus abdominus myositis in a patient previously treated with gemcitabine-based chemoradiation.

CASE REPORT

A 52-year-old Caucasian man with history of chronic alcoholism and recurrent pancreatitis presented with persistent abdominal pain radiating to the back for two months. Upon further investigation he was found to have locally advanced pancreatic cancer with encasement of the mesenteric vessels (clinical stage T3N0M0). The diagnosis of adenocarcinoma of the pancreas was confirmed by computerized tomography (CT) guided biopsy. The patient did not have any personal or family history of dermatitis, myositis, or any skin disorder or muscular disorder. He was an active smoker of 1 pack per day and had quit drinking 5 years prior to this presentation. He denied any chemical exposures and had just retired from a technician job at a manufacturing company. His medication included fentanyl patch, oxycodone, gabapentin, and amitriptyline. These medications were introduced early on in his treatment for pain control (at the time of initiation of chemoradiation).

The patient was treated on a clinical protocol with continuous intravenous infusion (i.v.) of 5-FU (200 mg/m^2/day for 5 days a week), weekly i.v. gemcitabine over 30 minutes at 200 mg/m^2, and concurrent radiation therapy (1.8 Gy/fraction/day for a total of 50.4 Gy). The clinical target volume (CTV) for radiation included the gross tumor volume (GTV, defined by CT) expanded by 1.5 cm in all directions. An additional margin of at least 1 cm was added to the CTV for set up error and patient movement to constitute the planning target volume (PTV). An isocentrically-mounted linear accelerator with 18 MV photon energy was used to administer radiation. Chemoradiation was well tolerated without any major toxicities or delay in therapy. Post chemoradiation CT scans revealed a significant decrease in his pancreatic mass in association with a marked decrease in serum CA 19-9 levels. He received further consolidation chemotherapy with intravenous gemcitabine at 1,000 mg/m^2/week over 30 minutes for 3 weeks every 4 week-cycle. During his fifth cycle of systemic chemotherapy he developed an erythematosus rash overlying a tender mass in the epigastrium (Figure 1, obtained after informed consent). No new medications, including topical ointments or creams, were introduced at the time of or prior to the development of these symptoms. There was no history of any prior chemical, mechanical, or thermal insult to the rectus abdominus area. A CT scan of the abdomen revealed an enlarged left and right rectus abdominus with areas of heterogeneity (Figure 2b) in comparison to baseline CT (Figure 2a). An ultrasound guided-biopsy failed to reveal any evidence of metastasis. This clinical inflammatory process (myositis and dermatitis) was attributed to gemcitabine-induced radiation recall. Gemcitabine was withheld and complete resolution of rectus abdominus myositis and overlying dermatitis followed. No other interventions such as glucocorticoids or anti-inflammatory drug use were implemented. Repeat CT scans

confirmed complete resolution of the previously described abnormalities (Figure 2c). The patient was not challenged with any further gemcitabine therapy. He progressed within 2 months from his last gemcitabine dose with the development of liver metastases. He was treated on a phase I clinical trial with capecitabine, docetaxel, and cisplatin for a period of 6 months with eventual disease progression. During this period, he did not experience any further episodes of radiation recall dermatomysositis. He succumbed to his disease shortly after progressing on combination chemotherapy.

DISCUSSION

Radiation recall is a phenomenon whereby radiation therapy followed by treatment with various drugs, such as chemotherapeutic agents, antitubercular drugs, tamoxifen, or exposure to ultraviolet light induces an inflammatory reaction in previously irradiated sites [9, 10, 11]. These reactions are most often cutaneous but have also been reported in other sites such as the lung, oral mucosa, intestine and central nervous system [12, 13, 14]. The exact mechanism of radiation recall is not known. Kitani *et al*. suggested that radiation therapy depletes the stem cells in the field of treatment rendering the irradiated tissue sensitive to future insults such as chemotherapy [15]. However, this theory remains largely unsubstantiated. Other theories include drug hypersensitivity and vascular damage as inducing factors. These, among others, have been reviewed elsewhere [16, 17].

Radiation recall reactions following gemcitabine was first described in the previously irradiated skin of a patient with breast cancer after two weeks from starting systemic gemcitabine therapy [18]. Multiple other cases of gemcitabine-induced radiation recall cutaneous reactions have been described since. However, gemcitabine-induced radiation recall in non-cutaneous sites have been rarely reported. One case of

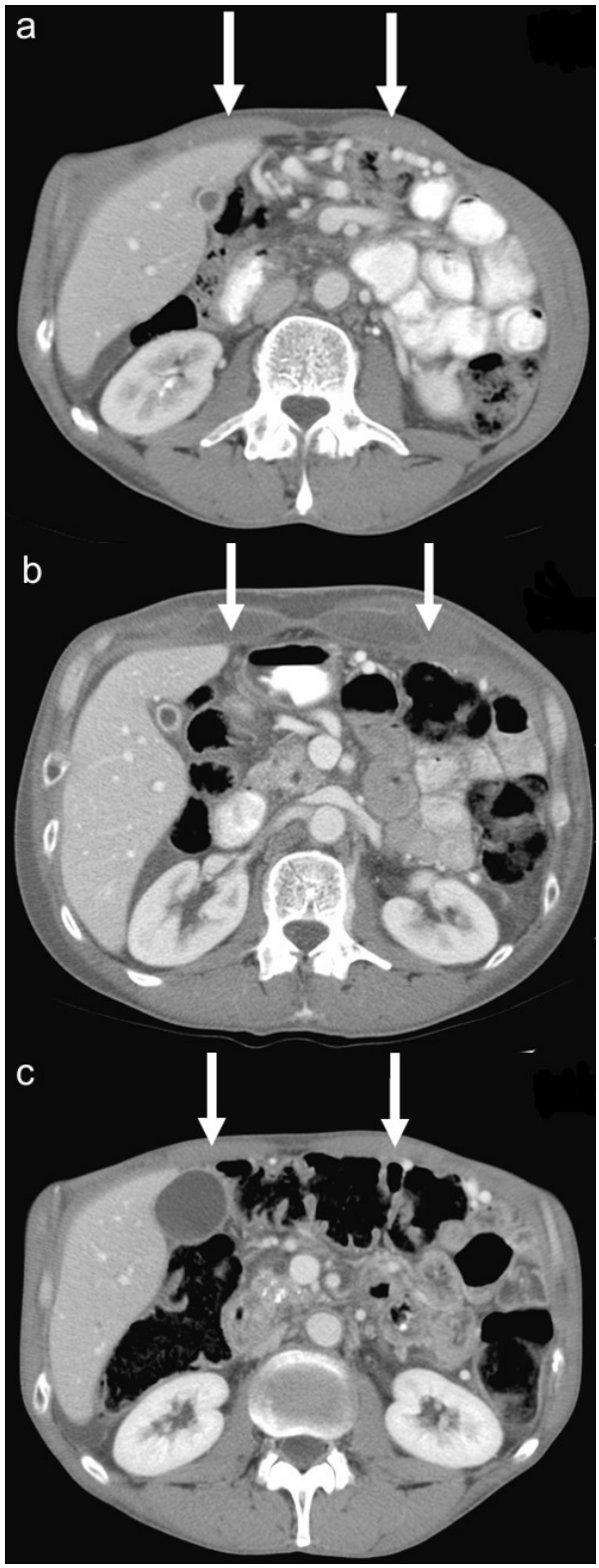

Figure 2. CT scan of the abdomen upon completion of chemoradiation (**a.**), at the time of radiation recall rectus abdominis myositis (**b.**), and after gemcitabine withdrawal (resolution of inflammatory process) (**c.**). White arrows point to the rectus abdominis (notably enlarged on picture **b.**)

gemcitabine-induced radiation recall dermatitis and myositis of the upper thorax has been described in a patient with non-small cell lung cancer [19]. Another case series reported on 6 patients with gemcitabine-induced radiation recall in the central nervous system, gastrointestinal tract, lymphatic, and musculoskeletal systems [20]. This same case series included a case of radiation induced myositis in the rectus abdominus area after 5-FU based radiation therapy. Gemcitabine in these cases was given in i.v. 1,000 mg/m^2 weekly regimens. The time between initiation of radiation and recall phenomenon ranged from 3 weeks to 8 months from the time gemcitabine was started [20].

Recently, Friedlander *et al*. reported on a case of rectus abdominus gemcitabine-induce radiation recall after gemcitabine-based chemoradiation for pancreatic cancer [8]. This reaction occurred after 3 months from completion of radiation therapy and resolved with corticosteroid treatment [8]. In our case, we observed radiation recall in the skin and rectus abdominus 5 months after the completion of chemoradiation and 4 months from initiation of consolidation gemcitabine therapy. This reaction resolved completely within 4 weeks from discontinuation of gemcitabine. The onset of our reaction was more delayed than the average of 56 days reported with prior gemcitabine radiation recall cases [8]. It is unclear if this reaction was primed by an exceptionally aggressive gemcitabine-based chemoradiation schedule. With gemcitabine being increasingly incorporated in both chemoradiation and chemotherapy of patients with locally advanced pancreatic cancer, oncologists and radiation oncologists should be aware of the possibility of such delayed reactions.

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Keywords gemcitabine; Myositis; Pancreatic Neoplasms; Radiotherapy

Abbreviations CTV: clinical target volume; GTV: gross tumor volume; PTV: planning target volume

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