Gemcitabine-related radiation recall in a patient with pancreatic cancer

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Radiation recall refers to inflammatory reactions triggered by chemotherapeutic agents and develops cutaneously in the previously irradiated areas. Such agents include anthracyclines, taxanes and capecitabine. Radiation recall related to gemcitabine has been reported in lung and breast cancer. Similar phenomenon associated with gemcitabine, the only FDA-approved drug for pancreatic cancer, is rarely reported. We report a patient with inoperable pancreatic cancer who developed gastrointestinal bleeding secondary to radiation-recall related to gemcitabine and review literature. A 57-year-old white male with unresectable pancreatic cancer received capecitabine in combination with radiation therapy followed by capecitabine alone given over approximately a 3-month time period. Computed tomography re-evaluation demonstrated a new liver lesion. The patient was then treated with gemcitabine and irinotecan. On day 15 of cycle 1, he reported progressive worsening of weakness and fatigue, and melena. Physical examination revealed hypotension (84/47 mmHg) and heme-positive stool on rectal examination. He denied aspirin or non-steroidal anti-inflammatory drug use. Chemotherapy was held. Hematocrit was 20% (previously 33%). He was transfused with 3 units of packed red blood cells. An esophago-gastro-duodenal examination was performed which showed antritis and duodenitis consistent with radiation therapy. A single site of oozing was injected with epinephrine. The diffuse gastritis was aggressively treated with proton pump inhibitors. The patient's hematocrit eventually stabilized and was 30% at discharge. Gemcitabine was not resumed. Radiation recall from gemcitabine is rare, but can potentially arise in any site that has been previously irradiated. Gemcitabine should be added to the list of drugs known to cause radiation recall. Treating physicians must be aware of this potential toxicity from gemcitabine either given concomitantly or followed by radiation. We suggest discontinuing gemcitabine if radiation recall is observed. Further studies are warranted into the pathogenesis of this unique phenomenon.
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Introduction

Radiation recall refers to inflammation developing in previously irradiated areas that subsequently are exposed to an inciting agent, including cytotoxic agents [1]. Such agents include anthracyclines, taxanes, dacarbazine, hydroxyurea, 5-flourouracil (5-FU), capecitabine, oxaliplatin and gemcitabine [1–10]. The reaction often manifests as a dermatitis, and can include maculopapular eruptions, vesicle formation and skin desquamation [11]. Internal organs and muscle are less commonly affected [12]. The reaction may occur days to weeks following exposure to the inciting agent. Rare cases of recall events have been reported 15 years after radiation treatment, but usually occur within months after treatment [2]. In this case report, we present a patient who was treated for locally advanced pancreatic adenocarcinoma, and developed a radiation recall presenting as diffuse gastritis and duodenitis while receiving gemcitabine after prior treatment with radiation and capecitabine. The clinical presentation of diffuse gastritis and duodenitis, and biopsy indicating radiation toxicity, we believe is consistent with a radiation recall phenomenon. We also reviewed previously reported cases of radiation recall reactions attributed to gemcitabine in patients with pancreatic cancer [12,13], and found that the most of these reactions manifested as non-dermal and involved the inflammation of internal tissue or organs. This differs from the classic dermatitis reported in the majority of cases of radiation recall attributed to gemcitabine in patients with breast and lung cancer, and other cytotoxic agents [10,14–18]. Potential etiologies for this observed difference with gemcitabine are discussed.

Case report

The patient is a 57-year-old white male who presented in August 2004 with abdominal pain and was found to have a biopsy-proven, locally advanced, surgically unresectable pancreatic cancer arising in the uncinate process, encasing the superior mesenteric artery and abutting the

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superior mesenteric vein. An endoscopic ultrasound confirmed this mass (35×32 mm) with invasion and complete obliteration of the superior mesenteric vein, as well as two enlarged peripancreatic lymph nodes.

The patient received a total radiation dose of 50.4 Gy at 1.8 Gy/day over 5.5 weeks with concomitant capecitabine (1600 mg/m^2/day in two divided doses Monday–Friday) on a study approved by the institutional review board [19]. Computed tomography image-based three-dimensional treatment planning was utilized to optimize radiation treatment planning by minimizing the radiation dose to surrounding normal tissues while ensuring adequate dose to the target volume (see Fig. 1). Anatomical structures, including the stomach, liver and kidneys, were contoured for dose–volume histogram analysis. The intestines were contoured as entire contents of the peritoneal cavity, exclusive of other named structures, to allow for organ motion. Approximately 16.5% of the total volume of the intestines received 30 Gy, while 6.9% received 45 Gy, with less that 2% receiving the maximum dose of 50.4 Gy. The portion of the intestines receiving 30 Gy or more was located entirely within the duodenum. Approximately 5.5% of the total volume of the stomach received 30 Gy, while less than 1% received 45 Gy, which was the maximum dose.

Capecitabine was administered concurrently during radiation at escalating doses from 850 mg/m^2 twice daily (b.i.d.) Monday–Friday. After chemoradiation therapy, he had a partial response, but remained unresectable. Capecitabine (2000 mg/m^2 p.o. b.i.d. for 14 days q 21 days) was administered [19]. Restaging after 3 cycles (9 weeks) demonstrated a new liver lesion.

This patient was then treated with gemcitabine given as a 24-h continuous infusion followed by irinotecan as a continuous infusion over 24 h given every 2 weeks on a clinical protocol approved by the institutional review board [20]. On day 15 of cycle 1, he reported progressive worsening of weakness and fatigue over the past week. He reported also some melena, but denied any bright red blood per rectum or hematochezia. He denied nausea, vomiting or abdominal pain. He also reported hypotension with blood pressure as low as 84/47 mmHg during the last week at home. Upon evaluation, the patient was found orthostatic. The abdomen was soft, non-tender and non-distended. Rectal examination revealed heme-positive stool. Laboratory data revealed hematocrit 20% compared with 33% 1 week ago. He denied aspirin or non-steroidal anti-inflammatory drug (NSAID) use.

Chemotherapy was held and a work-up for gastrointestinal bleed was performed. He was transfused with 3 units of packed red blood cells and a gastrointestinal consult was obtained. An upper endoscopy was performed which showed antritis and duodenitis consistent with radiation therapy (see Fig. 2). This suggested a recall reaction to the radiation triggered by gemcitabine. A single site of oozing was injected with epinephrine. Following this procedure, no further evidence of active gastrointestinal bleeding was noted. Upon discharge his hematocrit was 30%. He was not re-challenged with gemcitabine.

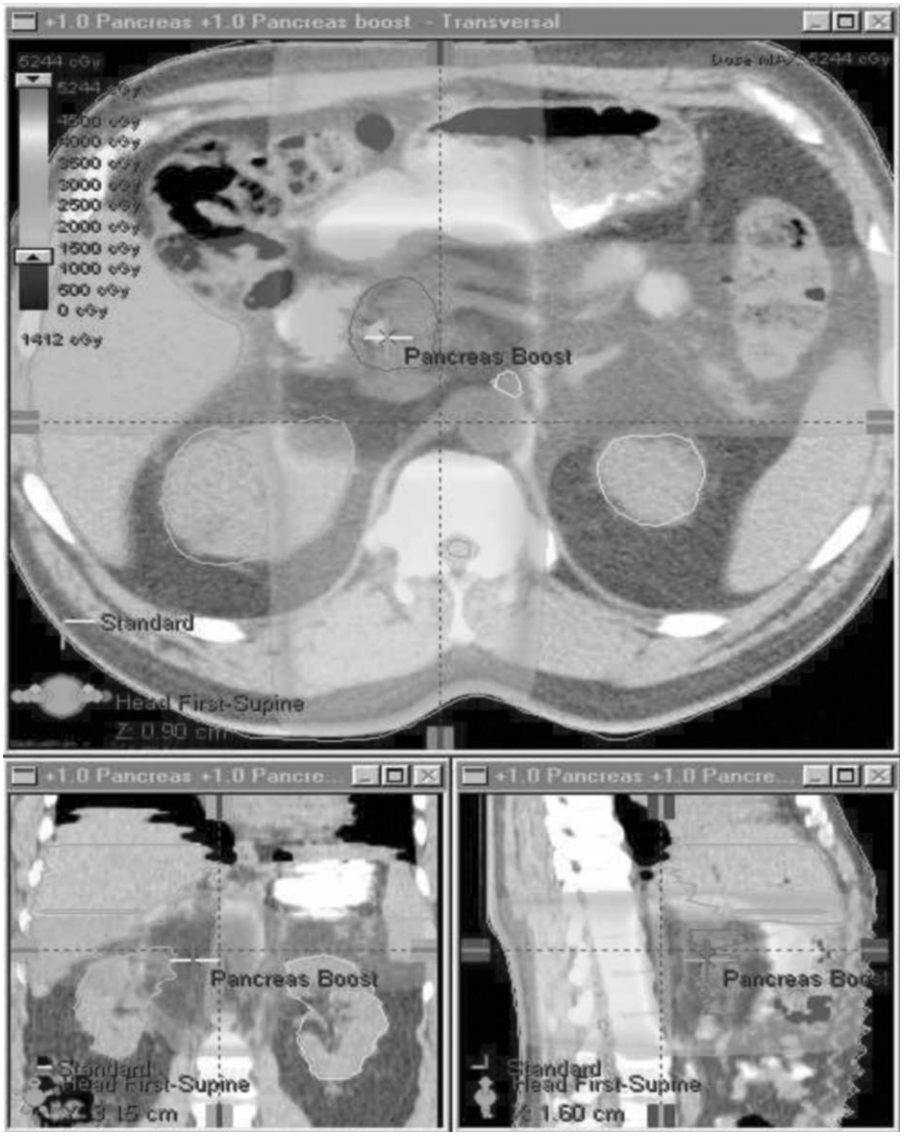
Discussion

Our case is the first case of gastrointestinal bleeding as the manifestation of gemcitabine-associated recall. The literature review suggests that radiation recall reactions due to gemcitabine affect internal tissue/organs disproportionately to that noted with other common agents [12,13]. The exact etiology of this recall is not known, but may be either secondary to altered pharmacodynamics of gemcitabine, lowering of the inflammatory threshold in irradiated tissue, or as a result of vascular damage.

Radiation recall phenomenon is defined as the recalling of an effect that is similar to an acute radiation reaction in an area of previous irradiation. This recall effect is seen in patients who have received previous radiation followed by a 'recall' medication, typically an antineoplastic [1,11]. Multiple drugs have been described as potential recall-triggering medications, including taxanes (paclitaxel and docetaxel), anthracyclines (doxorubicin and idarubicin), cytarabine, bleomycin, capecitabine, vinblastine, etoposide, methotrexate, trimetrexate, edatrexate, etoposide, melphalan, dacarbazine, oxaliplatin, dactinomycin, hydroxyurea, and gemcitabine [1–10].

We performed a literature search using PubMed with 'gemcitabine' and 'radiation recall' used as search terms to review prior cases of radiation recall attributed to gemcitabine. We found many cases of gemcitabine-related recall reactions in the literature [10,14–18], of which only two had pancreatic cancer [12,13]. The characteristics of these cases are summarized in Table 1. In this case report, we presented a patient being treated for locally advanced pancreatic adenocarcinoma who developed antritis and duodenitis that was attributed to a gemcitabine-induced radiation recall reaction. He received capecitabine as a radiosensitizer that concluded about 15 weeks previously. No such manifestations occurred during or after the radiation until gemcitabine was administered. In comparison to our patient, the published reports manifested as myositis in the rectus abdominus muscles while being treated with gemcitabine after the completion of chemoradiation to the pancreatic bed [12,13]. The choice of radiosensitizer differed as the former received gemcitabine [12] and the later received infusional 5-FU [13] with the same dose of radiation (50.4 Gy in 28 fractions). This implies that radiation recall can occur in patients who either receive

Fig. 1



Three-dimensional treatment plan with color wash dose distributions identifying dose delivered to tumor volume and surrounding normal anatomical structures.

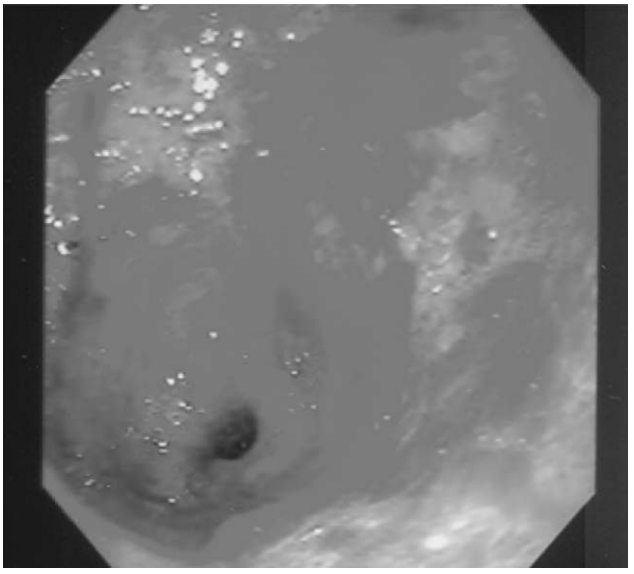
gemcitabine with concurrent radiotherapy or pre-/post-radiation. The time between initiation of radiation and recall of the radiation phenomenon ranged from 9 weeks to 2 months from the time gemcitabine was initiated. The usual dosage of gemcitabine in these cases was 1000 mg/m^2 given on a weekly basis [12,13], except in the present study the patient received a prolonged infusion of gemcitabine over 24 h [20].

Similar recall reactions have also been reported in patients with other solid malignancies, including breast carcinoma, non-small cell lung carcinoma, ovarian carcinoma and bladder carcinoma [10,14–18]. Although radiation recall reactions affiliated with the taxanes and anthracyclines develop in the skin in more than 60% of cases [2,3], the literature points out that only 30% [13] of cases associated with gemcitabine manifest as dermatitis. Approximately 70% of the cases involved inflammation in internal tissue or organs [13]. Reported sites include the central nervous system, gastrointestinal tract, and lymphatic and musculoskeletal systems [12,13]. The reason for this observed difference between the other cytotoxics and gemcitabine is not clear. It may be related to the underlying etiology of radiation recall reactions, including radiation-induced alterations of the pharmacodynamics of the chemotherapeutic agent, changes in

epithelial stem cells and idiosyncratic drug hypersensitivity reactions [21,22].

The exact pathogenesis for radiation recall phenomenon remains unclear. Some investigators have suggested that it may be the result of vascular damage, epithelial stem cell sensitivity or drug hypersensitivity [21–24]. One proposed mechanism suggests a lowering of the inflammatory threshold in irradiated tissue, which leads to a non-immune inflammatory reaction upon exposure to certain drugs. Gemcitabine is a deoxycytidine analog which undergoes phosphorylation in a stepwise fashion by the enzyme deoxycytidine kinase (dCK), first to the 5′-monophosphate form (dFdCMP) by dCK, then to the 5′-diphosphate (dFdCDP) and 5′-triphosphate derivatives (dFdCTP). dFdCDP is an inhibitor of ribonucleotide reductase, which results in decreases in the four physiologic deoxyribonucleotide triphosphates: dATP, dCTP, dGTP and dTTP. dFdCTP is incorporated into DNA by DNA polymerase and results in inhibition of DNA synthesis. The cytotoxicity of this compound is related to the di- and triphosphate forms [25]. Radiation induces injury to exposed cells, most likely with changes to the intracellular expression and activity of various proteins. It is possible that radiation exposure alters the expression or activity of dCK or cytidine deaminase in a subset of patients, which leads to the altered pharmacodynamics of gemcitabine resulting in a radiation recall event. As such, perhaps a relatively short interval between the completion of radiation therapy and the initiation of chemotherapy would facilitate the development of inflammatory changes.

Fig. 2



Endoscopic findings consistent with radiation recall syndrome in a patient with pancreatic cancer while on gemcitabine therapy.

The toxicity of concurrent gemcitabine and radiotherapy for locally advanced pancreatic cancer has been well documented [26], but the radiation recall in this set of population is either rare or, we believe, under-reported. With the increasing use of gemcitabine in other solid tumors (such as breast, lung, etc.) that may also include radiotherapy during the treatment, it is prudent that this phenomenon associated with gemcitabine be well known to clinicians involved in the care of these patients. This is of utmost importance in cases of pancreatic cancer as gemcitabine still is the only FDA-approved chemotherapeutic agent in this setting.

When evaluating radiation-related reactions, it is important to differentiate radiation recall from radiation sensitization and 'impaired healing of an ongoing skin reaction' [11]. Radiosensitization refers to the increased effectiveness of radiation due to the activity of precipitating agents. In animal models, radiosensitization occurs with inciting agents administered up to 3 days after radiotherapy [13]. Reactions occurring within 7 days after the completion of radiotherapy should be categorized as sensitization. It has been proposed that for a reaction to be labeled radiation

Table 1 Characteristics of pancreatic cancer patients who developed radiation recall due to gemcitabine

Patients [reference]	Dose of gemcitabine (mg/m^2)	Radiotherapy time	Radiotherapy dose (Gy/fractions)	Interval from radiotherapy to chemotherapy (weeks)	Time until recall (weeks)	Recall manifestations	Treatment	Outcome	Rechallenge
52/F [12]	1000 × 1, then 750 weekly × 9 months	Concurrent with 5-FU continuous infusion	50.4/28	3	9	Myositis in rectus muscle, SQ fat stranding	Ibuprofen	Recovered	Yes, but no recurrence of recall
62/M [13]	1000 weekly × 3 q 28 days	Concurrent with biweekly gemcitabine	50.4/28	5.5	8	Myositis in rectus muscle	Steroids	Recovered	NA
57/M	125 over 24 h q 2 weeks	Concurrent with capecitabine p.o.	50.4/28	13	15	Upper gastrointestinal bleeding manifested as antritis and duodenitis	Proton pump inhibitors, blood transfusion	Recovered	No

NA: not available.

recall, any acute radiation-related changes in the skin must be resolved [13].

Treatment of the recall reaction consists of discontinuing gemcitabine, initiating steroid therapy, supportive therapy and/or NSAIDs. Proton pump inhibitors can often ameliorate symptoms as they did in our patient. Most of these patients, including ours, have a full recovery.

In conclusion, radiation recall from gemcitabine chemotherapy is rare, but can potentially arise in any site even not previously irradiated. Treating physicians must be aware of this potential toxicity from gemcitabine and radiation, and discontinue the gemcitabine if radiation recall is observed. Reports of radiation recall seem to raise more questions than answers and we feel further studies are warranted into the pathogenesis of this unique phenomenon. Additional reports of radiation recall reactions associated with gemcitabine should be helpful to further understand this interesting phenomenon and further studies are warranted.

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