

Gemcitabine-induced radiation recall phenomenon in 2 distinctive sites on the same patient

Lulu Zhang, MD, MPH,^a Raina Patel, MD,^b and Syed Mehdi, MD^c

^aDepartment of Internal Medicine, Albany Medical Center, Albany, NY; and ^bDepartment of Pathology, ^cDivision of Hematology-Oncology, Department of Internal Medicine, Stratton Veterans Affairs Medical Center, Albany, NY

Radiation recall phenomenon is an acute inflammatory reaction that develops in previously irradiated areas after administration of inciting agents systemically. The most common agents are anticancer drugs.¹ Gemcitabine, a fluorine-substituted deoxycytidine analog, is widely used as a chemotherapy medication. Its antitumor effect results from the blockade of DNA synthesis and DNA repair. It has been used in advanced pancreatic, non-small-cell lung, bladder, and ovarian cancers; soft-tissue sarcoma; and non-Hodgkin lymphoma.² It has occasionally been reported to cause radiation recall phenomenon.³ The time between radiation and recall may range from weeks to almost a year.⁴

Most other agents cause radiation recall dermatitis. However, gemcitabine seems to cause more internal organ damage, including myositis, typhlitis, pneumonitis, pleural effusion, tamponade, and brain necrosis.^{1,5} In most cases, withdrawing the offending agent and treatment with nonsteroid anti-inflammatory drugs or corticosteroid helps with symptoms. In a few cases, continuing gemcitabine with concomitant steroid therapy has been successful.^{6,7} Interestingly, rechallenging with the offending agent may not elicit the same symptoms.⁸ It is not possible to predict which patients will develop the reaction. However, prolonging the interval between the completion of radiotherapy and the initiation of chemotherapy may help minimize the risks.⁹ Here, we further review a case of both gemcitabine-induced radiation recall myositis and pseudocellulitis in the same patient and we provide details of relevant test results to help with diagnosis in the future.

Case presentation

A 66-year-old man with stage IIIa T3N1M0 squamous cell carcinoma of the right upper lung (Figure

1) and stage I T1N0M0 squamous carcinoma of the left supraglottic larynx, both diagnosed in August 2012, was treated with chemoradiation after undergoing a right anterior axillary thoracotomy with bilobectomy (upper and middle lobectomy) and en-bloc chest wall resection in August 2012. From October 1, 2012 to November 15, 2012, he received radiation treatment of 5,600 centigray (cGy) at 175 cGy per day fraction for 32 treatments to his supraglottic cancer, and 5,600 cGy at 200 cGy per daily fraction for a total of 28 treatments to the right chest wall. He also received concurrent weekly, low-dose carboplatin plus taxol, with carboplatin AUC 2 and paclitaxel 50 mg/m², for 2 weeks. The chemotherapy was then held because of odynophagia. He subsequently received adjuvant chemotherapy with cisplatin 60 mg/m² day 1 and gemcitabine 1,000mg/m² on day 1 and day 8, repeated every 3 weeks for 4 cycles, from December 12, 2012 to February 20, 2013.

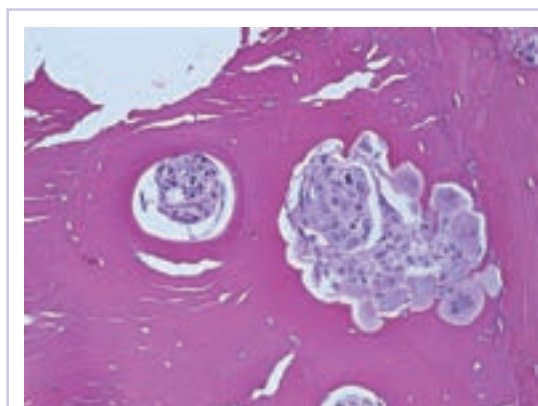


FIGURE 1 Poorly differentiated tumor invading chest wall cortical bone (H&E stain, 400x).

Accepted for publication November 18, 2013. Correspondence: Lulu Zhang, MD, MPH; Zhangl1@mail.amc.edu. Disclosures: The authors have no disclosures. JCSO 2014;12:188-190. ©2014 Frontline Medical Communications. DOI 10.12788/jcso.0044.

One week after finishing chemotherapy (104 days from last radiation therapy), the patient developed severe pain in his neck, throat, and right shoulder, which led to his being hospitalized. His right shoulder pain was sharp and aggravated by any movement. He had noticed neck swelling with skin redness and had brown-greenish thick secretions in his throat with dysphagia and odynophagia. He also experienced a 1-day fever, with a temperature maximum of 100.8 °F. He denied any muscle weakness, numbness, chills, dysuria, or diarrhea. He had a past medical history of diabetes mellitus type 2 and hyperlipidemia. He had been on rosuvastatin for his hyperlipidemia since 6 months before presenting, with normal creatine phosphokinase peak in October 2012. He had no history of autoimmune disorder, thyroid disease, or muscle disease.

A physical examination revealed a temperature of 100.8 °F, a heart rate of 116 beats per minute, and diffuse neck swelling with skin erythema (Figure 2). Although the exam did not reveal any swelling around the right shoulder, it showed exquisite tenderness to light touch around the whole right shoulder area, right arm, and right lateral chest. The patient had about 10 degrees of passive range of motion with the right shoulder in flexion, extension, and abduction, but no rotation was possible; there was zero degrees of active range of motion. The patient's sensation remained intact, and his pulses and arm circumferences were symmetrical. Other test results included: white blood count, 14.2 K/mm³ (normal range, 4.4-10.7); neutrophil, 81%; creatine phosphokinase peak, 683 units/L (21-232); erythrocyte sedimentation rate, 120 mm/hr (0-20); creatine phosphokinase, 16.72 mg/dl (0-0.8); HbA1C or glycated hemoglobin, 7.9% (less than 5.7%); thyroid-stimulating hormone, 1.59 uIU/ml (0.35-5.50); antinuclear antibody, negative. A venous duplex scan of the right upper extremity showed no evidence of deep venous thrombosis at the upper arm involving axillary, distal subclavian, or brachial veins.



FIGURE 2 Neck and chest wall dermatitis, after radiation therapy. The lump on the chest was the port used for chemotherapy.

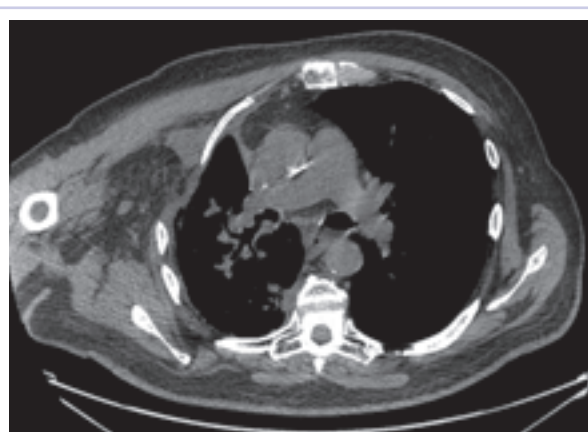


FIGURE 3 A computed-tomography scan of diffuse fat stranding of right chest wall after radiation (March 2013).

The patient was diagnosed with aspiration pneumonia and was started on piperacillin and tazobactam injection 3.375 g every 8 hours. His fever and leukocytosis were resolved. But the pain in his right shoulder with decreased range of motion did not improve after 4 days of treatment with piperacillin-tazobactam. A computed-tomography scan of the chest showed diffuse fat stranding of the right chest wall (Figure 3), which raised the suspicion of radiation recall phenomenon. Given the concern of concomitant pneumonia, he was started on naproxen 500 mg twice a day instead of steroids. His pain improved after 1 day of naproxen. His shoulder active range of motion increased to 40 degrees in all directions after 2 days of treatment and to 80 degrees in all directions after 4 days. He was given methylprednisolone 125 mg intravenously once after finishing the antibiotic, and was discharged on prednisone 40 mg daily, taken orally for 1 week. He was able to move his right shoulder with full range of motion after 1 week. The swelling in the neck decreased significantly after 2 weeks

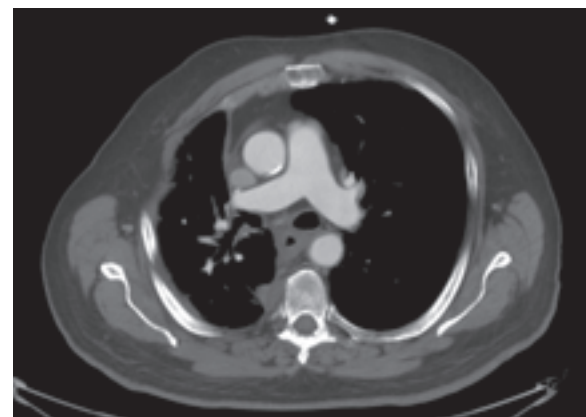


FIGURE 4 A computed-tomography scan shows improved inflammation of chest wall after steroid treatment (May 2013).

tapering treatment. A repeat CT scan of the chest also showed improvement (Figure 4).

Gemcitabine-induced radiation recall phenomenon is a rare but real disease entity. It may mimic many other inflammatory or infectious diseases. It is important to bear this diagnosis in mind when a patient develops symptoms in a previously irradiated area. Anti-inflammatory or corticosteroid treatments remain the mainstay therapy with good responses.

References

1. Friedlander PA, Bansal R, Schwartz L, Wagman R, Posner J, Kemeny N. Gemcitabine-related radiation recall preferentially involves internal tissue and organs. *Cancer*. 2004;100:1793-1799.
2. Katzung BG, Masters SB, Trevor AJ. *Basic & clinical pharmacology*, 12 e. Chapter 54. McGraw-Hill: AccessMedicine. <http://bit.ly/1e8jsF4>.
3. Fogarty G, Ball D, Rischin D. Radiation recall reaction following gemcitabine. *Lung Cancer*. 2001;33:299-302.
4. Jeter MD, Janne PA, Brooks S, et al. Gemcitabine-induced radiation recall. *Int J Radiat Oncol Biol Phys*. 2002;53: 394-400.
5. Eckardt MA, Bean A, Selch MT, Federman N. A child with gemcitabine-induced severe radiation recall myositis resulting in a compartment syndrome. *J Pediatr Hematol Oncol*. 2013;35:156-161.
6. Squire S, Chan M, Feller E, Mega A, Gold R. An unusual case of gemcitabine-induced radiation recall. *Am J Clin Oncol*. 2006;29:636.
7. Lock M, Sinclair K, Welch S, Younus J, Salim M. Radiation recall dermatitis due to gemcitabine does not suggest the need to discontinue chemotherapy. *Oncology Lett*. 2011;2:85-90.
8. Biswas J, Dutta S, Sharma S, Choudhury KB. Gemcitabine-induced radiation recall phenomenon in a post-operative and post-radiotherapy case of peri-ampullary carcinoma during adjuvant chemotherapy. *J Cancer Res Ther*. 2012;8:439-441.
9. Burris HA, Hurtig J. Radiation recall with anticancer agents. *Oncologist*. 2010;15:1227-1237.