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Case Report

Gemcitabine-Induced Radiation Recall Myositis: Case Report and Review of the Literature

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Keywords
Breast cancer · Gemcitabine · Radiation · Bone metastasis

Abstract
Gemcitabine-induced radiation recall (GIRR) is a phenomenon wherein the administration of gemcitabine induces an inflammatory reaction within an area of prior radiation. We present the case of a 39-year-old female patient with metastatic breast cancer who experienced GIRR myositis 3 months following postoperative radiotherapy, with additional potential paraspinal myositis following ablative radiotherapy to the thoracic spine. A review of previously published cases of GIRR myositis was performed. The case and literature review describe the clinical course and presentation of GIRR, and highlight the importance of including radiation recall as part of a differential diagnosis when a patient undergoing chemotherapy experiences an inflammatory reaction at a prior site of radiation.

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Introduction

Radiation recall describes a well-known, but poorly understood phenomenon by which administration of chemotherapy or another systemic agent induces an inflammatory reaction within a previously irradiated field [1]. Radiation recall was first described in 1959, when it was found that latent effects of radiation, such as dermatitis, could be induced by actinomycin D [2]. Though clinically rare, since that time radiation recall has been observed for various other systemic agents and inciting factors [3]. While the recall phenomenon is most commonly reported as dermatitis, it has also been observed in other organs including the lung, intestine, and muscles [1, 4–6]. Gemcitabine has previously been implicated in radiation recall. When reported, it is noted to preferentially affect internal tissue and organs [7]. Herein we report a case of a 39-year-old woman with myositis that is clinically consistent with gemcitabine-induced radiation recall (GIRR) myositis. We also review reported cases of GIRR myositis and discuss the findings and implications.

Case Description

Events are outlined in the timeline (Fig. 1) and summarized below. In 2008, the 39-year-old patient was diagnosed with metastatic ER-negative, PR-negative, HER2-positive cancer. At initial presentation, PET scan demonstrated both regional lymph node involvement and osseous metastases. She was started on systemic therapy with Adriamycin and Cytoxan, followed by Taxol and Herceptin. Subsequent therapies included maintenance single-agent Herceptin, followed by Herceptin and lapatinib. By late 2011, her osseous disease showed complete radiologic response on PET scan, and she was offered local therapy to the primary tumor. In January 2012, she underwent a right mastectomy, with ypT2N1a disease, followed by postmastectomy radiation up to 50 Gy with a 10-Gy chest wall boost.

In late August 2012, she presented with a painful osseous lesion at the T12 vertebra and an impending pathologic fracture of the left distal femur. She underwent surgical stabilization of the femur with rod placement, followed by postoperative radiotherapy, 30 Gy in 10 fractions (Fig. 2a). T12 was treated with single-fraction stereotactic body radiotherapy (SBRT) up to 24 Gy.

In December 2012, gemcitabine (1,000 mg/m^2, days 1 and 8) and Herceptin were given in a 21-day cycle. In January 2013, she presented to the Emergency Department with leg swelling, shortness of breath, and pleuritic chest pain to the lower thorax. Physical examination noted left leg swelling and some mild effusion of the left knee. The ultrasound was negative for deep vein thrombosis (DVT), and the chest CT was negative for pulmonary embolism. Symptoms were attributed to a viral syndrome with associated pleurisy.

The patient's symptoms had worsened at the time of her reexamination by oncology on March 2013. PET scan showed increased FDG activity and edema in the left thigh that was thought to be consistent with postradiation inflammatory changes (Fig. 2b). MRI of the thoracic spine demonstrated paraspinal muscle fluid collections and a new T12 fracture, and chemotherapy was held. CT-guided biopsy of the paraspinal fluid collection was negative for abscess or malignancy. Although a T12 vertebroplasty improved the chest/back pain and her swelling, her leg pain persisted.

On March 19, 2013, gemcitabine and Herceptin were resumed with a 20% gemcitabine dose reduction. Within 2 days, she developed worsening leg pain and swelling, and required the use of a cane for ambulation. Repeat extremity ultrasound showed no evidence of DVT, but revealed marked, diffuse enlargement of the vastus medialis or rectus femoris muscles of the left thigh, suggestive of myositis. At that time, her providers noted that her symptoms appeared and worsened following each gemcitabine administration, but improved off chemotherapy. Given the temporal relationship and other negative evaluation, the patient's symptoms were attributed to GIRR from the prior palliative radiotherapy to the left femur. Gemcitabine was stopped, and she was started on dexamethasone and physical therapy. The patient required dexamethasone for relief of her symptoms until August 2013. After a slow taper, she regained leg function and was not rechallenged with gemcitabine.

Over the subsequent 3 years, she had received treatment with Herceptin, ado-trastuzumab, and eribulin/Herceptin without recurrence of the symptoms. Gait was described as normal at the most recent follow-up, and she was described as physically active, engaging in regular exercise. In retrospect, it is also possible that the exacerbation of pain and fluid collection within the paraspinal muscles of T12 seen in March of 2013 may have been related to recall myositis in that region.

Literature Review

A literature search was performed using the search terms "gemcitabine," "radiation," "recall," and "myositis" to compile known reports of GIRR myositis (Table 1, Table 2, Table 3). Twenty-one cases were identified as having myositis in a radiation port following gemcitabine treatment. Fractionated radiation doses ranged from 28 to 70.2 Gy.

The time interval between radiation and chemotherapy initiation ranged from 0 days to 4 months. The majority had chemotherapy more than 1 month after radiotherapy. The time between radiation and onset of recall symptoms varied from 4 weeks to 5.5 months. Only 1 patient had symptoms less than 1 month after radiation, 20 were ≥3 months, 10 were ≥4 months, and 7 were ≥5 months. All patients achieved at least partial improvement of their symptoms with discontinuation of gemcitabine, regardless of whether their treatment consisted of steroids (9 patients), NSAIDs (5 patients), analgesics (4 patients), or no treatment at all (2 patients). Out of the 9 confirmed patients who resumed chemotherapy following myositis, 5 patients underwent gemcitabine rechallenge, with only 1 patient requiring concomitant steroids for symptom control.

The patient described in the present report is consistent with other reported cases. The time intervals between chemotherapy, radiotherapy, and the onset of symptoms are within the range of the other cases. The current case of possible myositis at T12 was the only case associated with a single fraction of ablative radiotherapy. Interestingly, our patient had prior chest wall radiotherapy, but did not develop evidence of recall in that location. In review of the literature, this is consistent with other cases in which recall myositis did not appear in all prior sites of radiotherapy. Remote courses were less often affected by recall myositis. These findings are also consistent with prior reviews of radiation recall that suggest a possible relationship between the time interval from radiation to chemotherapy and the severity of recall symptoms [1, 3, 8]. However, such a correlation likely depends on the rela-

tionship between several factors, such as drug type, dosage, radiation location, radiation dosage, and timing of each treatment [3].

Discussion

Radiation recall is a delayed inflammatory response at a site of prior radiation [9, 10]. GIRR has been noted to have a predilection for soft tissue and internal organs, resulting in a less typical appearance of radiation recall. For example, GIRR has been documented to cause pseudocellulitis, acute ascending colitis, abdominal wall and subcutaneous fat stranding, optic neuritis, lymphangitis, rectal hemorrhage, brainstem radionecrosis, and myositis [5, 9, 11–13]. These atypical presentations highlight the importance of clinical awareness of GIRR.

The diagnosis of GIRR myositis is challenging, as it may appear similar to infection, thrombosis, or other sources of inflammation [14]. A few key signs may help distinguish this condition. Primarily, the inflammation is confined to a prior radiation portal. Furthermore, there is a temporal relationship between the timing of gemcitabine administration and appearance of symptoms [9]. Radiologic studies may be used to support the diagnosis of myositis with appearance of swelling and edema of the underlying musculature. They may also assist in ruling out other potential etiologies [15]. Because reported cases of myositis have been associated with elevated creatinine kinase and even compartment syndrome, appropriate recognition and treatment is essential to facilitate recovery and minimize morbidity [10, 16, 17]. Review of cases suggests that the most important factor for resolution is the discontinuation of gemcitabine, with the potential use of anti-inflammatory medications.

The mechanisms of action of radiation recall remain poorly understood. However, the varied presentations of GIRR, even within an individual's prior sites of radiotherapy, suggest that multiple factors influence both the appearance and severity of recall. Jeter et al. [11] proposed that the doses of gemcitabine of 600 mg/m^2 or higher may pose a higher recall risk. Others suggest that higher radiation treatment doses or shorter intervals between radiotherapy and chemotherapy may influence recall development [9]. However, these are not well-defined risk factors. With an increased use of gemcitabine across many tumor types, along with routine use of definitive and palliative radiotherapy, clinicians should be alerted to this possible complication.

We suspect that the exacerbation of pain at the site of T12 SBRT along with the MRI and biopsy findings are consistent with a focal recall myositis at that location. Our patient did not have further exacerbation of pain at that site with the dose-reduced gemcitabine. This suggests that the intervention with vertebroplasty may have affected the local environment. The underlying recall mechanism may also have differed from that in the leg. Radiation recall at an SBRT-treated site had been reported in the past, although the recall effect was induced by sorafenib and manifested itself in the form of dermatitis [18].

Due to its rare and unpredictable onset, radiation recall continues to be a poorly understood phenomenon. This is further complicated by the possibility that there are multiple mechanisms for different medications (gemcitabine, carboplatin, etc.) and/or types of recall (dermatitis, myositis, etc.). Current hypotheses for explaining radiation recall include sensitivity of descendants of cells that survive radiation, changes in local vasculature, and drug-

induced hypersensitivity reactions [1]. There is not enough evidence to support any definite mechanism [1, 9]. However, the drug-induced hypersensitivity hypothesis appears to best explain the characteristics of radiation recall. This hypothesis describes radiation recall as a nonimmune inflammatory reaction triggered by certain drugs at a site where the inflammatory threshold has been lowered by radiation. Prior radiation to a specific site may induce constant low-level expression of several inflammatory cytokines, including IL-1, IL-6, PGDF-β, TNF-α, and TGF- β [18]. Introduction of drugs such as gemcitabine may then lead to up-regulation of such inflammatory cytokines inducing the recall reaction [1]. This theory is further supported by the various clinical presentations of radiation recall, including the timing of onset, the lack of worsening reactions following rechallenge in some cases, and the induction of recall from noncytotoxic agents (such as simvastatin) [1, 8].

Conclusion

In conclusion, GIRR myositis is a rare, but significant reaction that may present like other conditions such as DVT or infection. As such, it should be part of the differential diagnosis when a patient on gemcitabine reports pain and swelling to a previously irradiated area, although other causes should be thoroughly investigated. In particular, GIRR myositis should be considered when there is a shorter time interval between the completion of radiation and the initiation of chemotherapy. Discontinuation of chemotherapy and possibly the use of anti-inflammatory medications are important steps to reduce symptoms and improve the patient's quality of life. In some cases, patients have been successfully rechallenged with gemcitabine, although that may not always be possible.

Statement of Ethics

The authors have no ethical conflicts to disclose. IRB approval was obtained.

Disclosure Statement

The authors declare that there is no conflict of interest.

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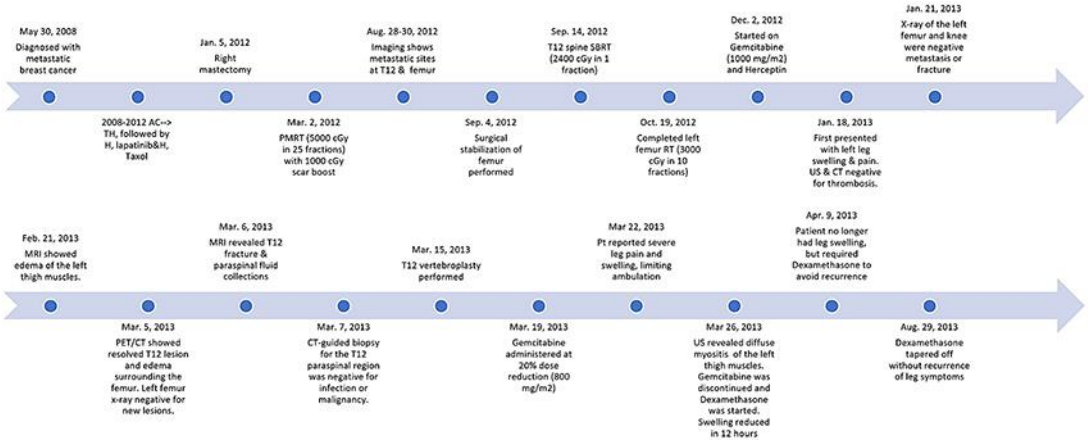

Fig. 1. Timeline of the case.

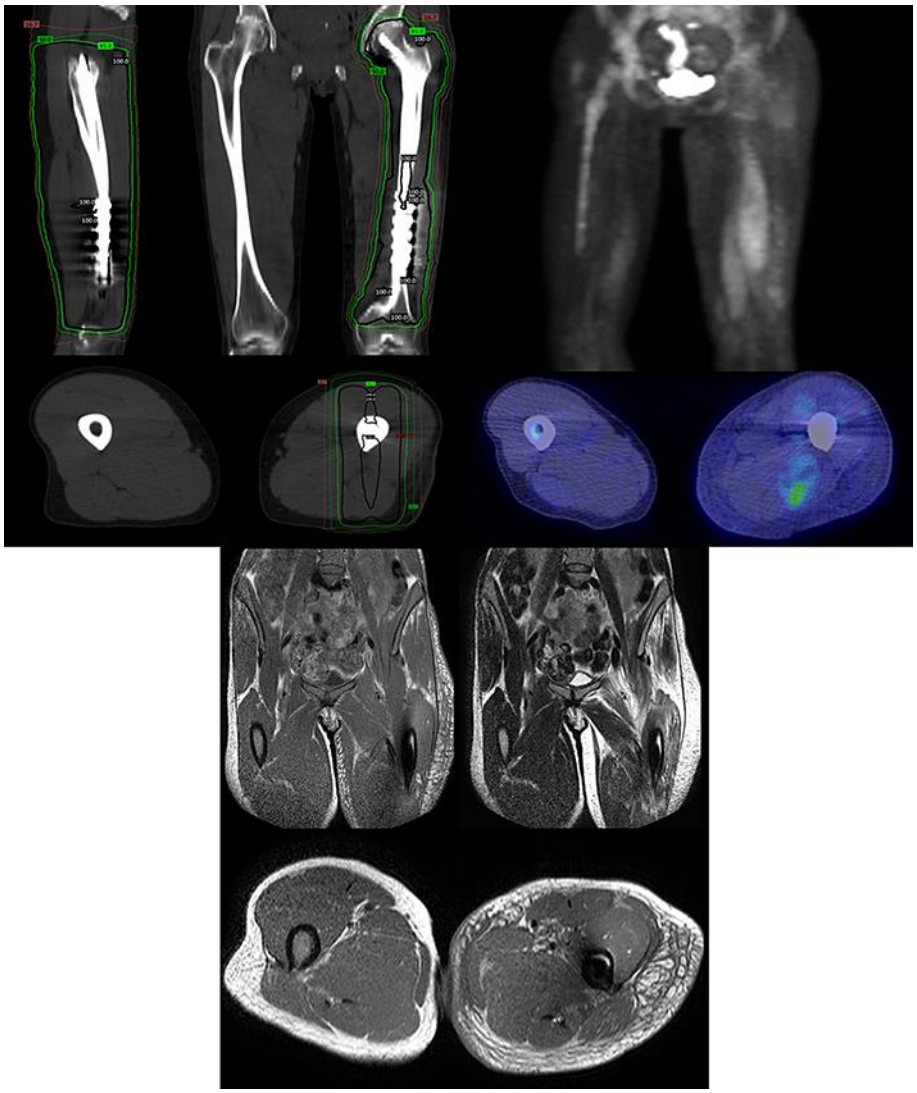

Fig. 2. Top left: radiation fields of the left femur, with sagittal (top left), coronal (top right), and axial (bottom) views. The isodose levels shown are 16.7, 50, 95, and 100%. Top right: PET/CT showing edema and increased FDG uptake of the left thigh, consistent with myositis, with front-facing 3D (top) and axial (bottom) views. Bottom: MRI showing edema of the left thigh, consistent with myositis, with T1-weighted coronal images (top left), T2-weighted coronal images (top right), and T1-weighted axial images (bottom).

Table 1. Collection of previous case reports of gemcitabine-induced radiation recall myositis

Author	Cancer type	Radiation location	Dose	CTx regimen	Time between RT and gemcitabine start	Time between RT completion and recall symptoms	Clinical symptoms/signs	Undergoing chemo at time of symptom onset?	Imaging findings (and modality)	Treatment	Outcome	Post-treatment CTx?
Alco et al. [19]	Pancreatic adenocarcinoma	Pancreas and regional lymph nodes	1.8 Gy × 25 (45 Gy)	Gemcitabine 1,250 mg/m^2/week, 3 weeks in 4 week cycle	0 (concurrent)	20 weeks	Tender mass, pain, and swelling of abdominal muscles	No (last dose 1 month before onset)	Edema and inflammation of the anterior and right abdominal wall muscles (MRI)	Corticosteroids, NSAIDs, and gabapentin	Symptom reduction in 1 week; clinical and radiologic findings resolved in 1 month	N/A
Alco et al. [19]	NSCLC	Left upper lobe and ipsilateral L2 lymph nodes	62 Gy total (fractions N/A)	Gemcitabine (1,200 m/m^2 for 1–8 days), and carboplatin (AUC 5.5 for days 1 and 30), for 3 cycles; gemcitabine reduced to 800 mg/m^2 after first cycle because of intolerance	N/A (CTx started after RT)	N/A (~104 days after starting CTx)	Pain and swelling of left breast and chest wall, with reduced ROM of arm and shoulder	No (last dose 2 weeks before onset)	Edema and soft tissue reaction at the left breast musculature and subcutaneous soft tissue (MRI)	Corticosteroids, NSAIDs, opioids, antihistamines, SOD, pentoxifylline, vitamin E, gabapentin, topical lidocaine and selenium	Meds did not affect myositis; pain reduced after 4 months, resolved after 9 months, with lasting reduced ROM	N/A
Delavan et al. [15]	Breast cancer	Left thigh	8 Gy × 1 (8 Gy) (4 years prior) 3 Gy × 13 (39 Gy) (4 months prior)	Gemcitabine (unknown dosage)	17 days	107 days	Increasing pain and swelling to the posterior left thigh, warm to palpation	No (last dose ~3.5 weeks before onset)	Increased signal intensity in the posterior thigh musculature (MRI)	Dexamethasone	Symptoms improved over 3 days, symptom free 1 week later	Not reported
Eckardt et al. [17]	Synovial sarcoma	Right forearm	3.5 Gy × 8 (28 Gy) preop, followed by 2 Gy × 10 (20 Gy) boost	Gemcitabine (900 mg/m^2 on days 1 and 8) and docetaxel (100 mg/m^2 on day 8) for 2 cycles at 21 and 28 days, respectively	5 days	40 days	Swelling of the right forearm with progressively worsening range of motion, compartment syndrome	No (last dose 7 days before onset)	Edema of the flexor compartment muscles, with layering fluid along the superficial fascia and between the muscles (MRI)	Dexamethasone	Patient required slow taper corticosteroids for multiple months; patient continues to have muscle edema and myositis on 1-year follow-up MRI.	No
Fakih [20]	Pancreatic adenocarcinoma	Pancreas	1.8 Gy × 28 (50.4 Gy)	Concurrent fluorouracil (2,000 mg/m^2/day for 5 days a week) and gemcitabine (200 mg/m^2 weekly) followed by adjuvant gemcitabine (1,000 mg/m^2/week for 3 weeks every 4-week cycle)	0 days (concurrent) ~21 days to initiation of adjuvant dose gemcitabine	~18 weeks	Erythematosus rash overlying a tender mass in the epigastrium	Yes	Enlarged left and right rectus abdominus with areas of heterogeneity (CT)	None, other than withholding gemcitabine	Complete resolution	Yes (capecitabine, docetaxel, and cisplatin)
Fogarty et al. [21]	NSCLC	Lung	3 Gy × 12 (36 Gy)	Gemcitabine (1,000 mg/m^2 on days 1 and 8) and carboplatin (AUC 5, day 1)	~3 months	~4.5 months	Posterior chest wall pain with localized tenderness, skin rash, elevated CK, ESR	Yes	Enhancement of the chest wall musculature consistent with nonspecific inflammatory change (MRI)	NSAIDS, oral steroids	Symptoms improved but persistent minor skin changes and subcutaneous fibrosis	Not reported

Table 2. Collection of previous case reports of gemcitabine-induced radiation recall myositis (continued)

Author	Cancer type	Radiation location	Dose	CTx regimen	Time between RT and gemcitabine start	Time between RT completion and recall symptoms	Clinical symptoms/ signs	Undergoing chemo at time of symptom onset?	Imaging findings (and modality)	Treatment	Outcome	Post-treatment CTx?
Friedlander et al. [7]	Pancreatic adenocarcinoma	Pancreas and regional lymph nodes	1.8 Gy × 28 (50.4 Gy)	Gemcitabine (40 mg/m^2 biweekly and concurrently with radiation, followed by 1,000 mg/m^2 weekly for 3 weeks per month)	39 days	3 months	Tenderness of rectus muscles, mild rash, elevated CK	Yes	Increased signal in the subcutaneous tissue of the anterior abdominal wall (MRI)	Corticosteroids	Complete resolution, no recurrence after steroid tapering	Not reported
Ganem et al. [22]	Squamous cell carcinoma of the lung	Pelvis	3 Gy × 11 (33 Gy)	Gemcitabine (1,000 mg/m^2 on days 1, 8, 15) and cisplatin (100 mg/m^2 on day 15)	1.5 months	5 months	Right buttock pain	Yes	Hypersignal and edema on gluteal soft tissue (MRI)	Oral opiates, antibiotics, steroids	Alleviation over the course of 3 months	Not reported
Graf et al. [16]	NSCLC and anal cancer, history of dermatomyositis	Pelvis	Not reported	5-FU and MMC given with pelvic RT for anal cancer, carboplatin and gemcitabine (dosage not given)	2 months	4 months	Erythema, swelling, warmth, and tenderness of the buttocks and groin area	Yes	High signal in the bilateral gluteal maximus, quadratus femoris, adductor magnus, obturator externus and right iliopsoas muscles (MRI), elevated CK	Prednisone and opiate analgesia	Gradual improvement with steroids	Not reported
Grover et al. [5]	Adenocarcinoma and neuroendocrine neoplasm, unknown primary	Left hip and left acromion	3 Gy × 10 (30 Gy)	Gemcitabine (1,250 mg/m^2) and carboplatin (AUC 5)	2 weeks	4 weeks	Worsening pain in left shoulder and hip	Yes	Soft tissue edema of the muscles adjacent to the left acromion and the left hip (MRI)	Narcotics	Pain resolved 5 months after radiotherapy	Gemcitabine therapy continued
Horan et al. [23]	NSCLC	Lung	3 Gy × 8 (24 Gy)	Gemcitabine (1,000 mg/m^2, weekly)	2 months	~13 weeks	Pain and swelling of the right pectoralis major, biopsy proven muscle necrosis	Yes	Thickening of right pectoralis major muscle (CT)	Analgesics	Symptoms gradually declined when gemcitabine was stopped	Gemcitabine re-challenge, no further symptoms
Jeter et al. [11]	Pancreatic adenocarcinoma	Pancreas	1.8 Gy × 28 (50.4 Gy)	Gemcitabine (1,000 mg/m^2 one dose; followed by 750 mg/m^2 weekly for 9 months)	3 weeks	3 months	Abdominal wall tenderness and erythema	Yes	Subcutaneous fat stranding and decreased density of rectus muscles in radiation portal (CT)	Ibuprofen	Symptoms responsive to ibuprofen	Gemcitabine re-challenge, no further symptoms
Lock et al. [24]	Hepatic adenocarcinoma	Liver	2.94 Gy × 15 (44.1 Gy)	Gemcitabine (1,000 mg/m^2 for days 1 and 8 for a 3-week cycle)	8 weeks	18 weeks	Abdominal discomfort with induration; overlying skin erythema	Yes	Enhancement of abdominal muscles with thickening (MRI)	Ibuprofen, vitamin E, and vitamin C	Gradual resolution over the course of 6 weeks	Gemcitabine was continued, reduction of symptoms
Miura et al. [25][a]	NSCLC	Right hip	2 Gy × 25 (50 Gy)	Concurrent cisplatin (80 mg/m^2 day 1) and vinorelbine (20 mg/m^2, days 1, 8, and 15) followed by gemcitabine (800 mg/m^2 biweekly)	1 month	3 months	Right thigh pain	N/A	Edema within right thigh muscles (MRI)	Analgesics	Gradual resolution of symptoms	Yes (unknown regimen)

Table 3. Collection of previous case reports of gemcitabine-induced radiation recall myositis (continued)

Author	Cancer type	Radiation location	Dose	CTx regimen	Time between RT and gemcitabine start	Time between RT completion and recall symptoms	Clinical symptoms/ signs	Undergoing chemo at time of symptom onset?	Imaging findings (and modality)	Treatment	Outcome	Post-treatment CTx?
Miura et al. [25][a]	NSCLC	Lung	2 Gy × 30 (60 Gy)	Concurrent cisplatin and (80 mg/m^2 day 1) and vinorelbine (20 mg/m^2, days 1 and 8) followed by vinorelbine (13 mg/m^2 biweekly) and gemcitabine (800 mg/m^2 biweekly)	3 months	5.5 months	Upper chest muscle pain	N/A	Enhancement of pectoralis muscles (MRI)	NSAIDs	Improvement of symptoms	Yes (gefitinib)
O'Regan et al. [10]	Hodgkin lymphoma	Chest	1.8 Gy × 22 (39.6 Gy)	4 cycles of gemcitabine, vinorelbine, and liposomal doxorubicin (unknown dosage)	2 months	5 months	Worsening bilateral anterior chest pain, pectoralis muscle necrosis by biopsy	No (last dose 2.5 weeks before presentation)	Diffuse bilateral swelling of the pectoral muscles with mild stranding of the adjacent subcutaneous fat (CT)	Analgesics	Complete resolution	Not reported
Patel et al. [26]	Nasopharyngeal carcinoma	Head and neck	70.2 Gy total (fractions N/A)	Gemcitabine (1,000 mg/m^2) and oxaliplatin (100 mg/m^2) every 2 weeks	N/A (CTx started after RT)	6 months	Bilateral neck pain and swelling with restriction of neck movement	Yes	Diffuse bilateral soft-tissue edema of the muscles in the cervical neck (MRI)	Dexamethasone	Symptoms worsened with tapering of dexamethasone/ low-dose prednisone started without recurrence.	Not reported
Pinson et al. [27][b]	NSCLC	Lung	3 Gy × 10 (30 Gy)	Carboplatin (AUC 5 on day 1) and gemcitabine (1,000 mg/m^2 on days 1 and 8), 3-week cycle	4 weeks	14 weeks	Skin erythema, upper chest muscle pain	Yes	Swelling of the pectoralis major and pectoralis minor (CT)	Ibuprofen	Complete resolution in 3 weeks	Not reported
Squire et al. [14]	NSCLC	Pelvis (left sacroiliac and left acetabulum)	3 Gy × 10 (30 Gy)	Gemcitabine (1,000 mg/m^2)	1 month	3 months	Tenderness and discomfort to left hip and buttock, elevated CK	Yes	Edema in gluteal muscles (MRI)	Oral prednisone	Symptoms worsened with tapering of prednisone and improved with increasing doses	Gemcitabine continued for 5 more months, symptoms controlled with prednisone
Welsh et al. [28]	Bladder cancer	Parasacral region	2.5 Gy × 18 (45 Gy)	Gemcitabine and cisplatin (unknown dosage)	4 weeks	5 months	Pain in bilateral superolateral gluteal regions	Yes	Band-like pattern of edema on gluteal region (MRI)	NSAIDs, prednisone	Complete resolution after 6 weeks, but with visible residual scar and muscular atrophy	CTx continued
Current	Breast cancer	Left thigh (femur)/ T12 vertebra	3 Gy × 10 (30 Gy)/ 24 Gy × 1 (24 Gy)	Gemcitabine (1,000 mg/m^2 for days 1 and 8) and herceptin (342 mg every 3 weeks)	54 days/ 79 days	3 months/ 5.7 months	Worsening leg pain and swelling/ Chest and back pain	Yes	Enlargement of muscles of the left thigh (US)/ T12 fracture and paraspinal fluid collections (MRI)	Dexamethasone/ T12 vertebroplasty	Progressive resolution of symptoms after 4-month course of dexamethasone/ Reduction of chest and back pain following vertebroplasty	Yes (herceptin)

[a] Paper is written in Japanese. [b] Paper is written in Dutch.