Lumbar Insufficiency Fracture: a Rare Complication after Radiochemotherapy for Gastric Cancer

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Introduction

Gastric cancer is the second most common cancer in the world (1). Surgery is the mainstay of treatment for localized ric adenocarcinoma. On the other hand, occurrence of frequent local and regional relapse after surgery have caused the rationale to offer additional therapies to patients especially with worse prognostic factors. The results of randomized Intergroup Study INT-0116, comparing the effect of postoperative chemoradiotherapy with surgery alone indicated that chemoradiotherapy after resection for gastric cancer significantly improved relapse-free and overall survival rates (2). Thereafter, adjuvant chemoradiation therapy has been increasingly recognized as a standard of care for high risk gastric cancer patients.

Insufficiency fracture is caused by the effect of normal or physiologic stress on bone with demineralization and decreased elastic resistance. These clinical situations are associated with reduced bone formation and increased bone resorption, resulting in bone loss (3). They are often observed in postmenopausal women, in patients with inflammatory arthritides such as rheumatoid arthritis or in patients who have had high doses of steroids (3-11). Radiotherapy can also contribute to the development of insufficiency fracture, although the precise pathogenesis is not well defined (3-6, 9-14). Pelvic insufficiency fractures are rare and there are well known late complications of pelvic radiotherapy for gynecologic malignancies and rectal cancer, while few cases with lumbar insufficiency fractures have been described after pelvic radiotherapy (3-7, 9-14). However, to our knowledge there are no published data about lumbar insufficiency fractures after chemoradiotherapy for gastric cancer. So, there is a difficulty in diagnosis and management, because of limited experience with this condition. Thus, we present three gastric cancer patients with lumbar insufficiency fractures occurring after adjuvant chemoradiotherapy regime. In addition the literature was reviewed.

Case series

Case 1

A 65-year-old male patient was admitted to the surgical unit with a 3-month history of gastric pain, rectal bleeding and nausea. Gastroduodenal endoscopy revealed an exophytic mass on the antrum of the stomach with central ulceration that was proven to be adenocarcinoma by biopsy. Physical examination, biochemistry and chest x-ray were normal. Computed tomography (CT) of the abdomen evidenced
thickening of the gastric wall with an increased density of perigastric fatty tissues. He underwent total gastrectomy and gastrojejunostomy with D2 lymph node dissection. Histopathological examination revealed neuroendocrine adenocarcinoma with subserosal invasion and the surgical margins were clear. Only one of the dissected 54 nodes showed lymph node metastases. He was staged as T3N1M0 and chemoradiotherapy was suggested in accordance to our institution protocol. The first course of chemotherapy (5-fluorouracil 425 mg/m²/day intravenous (i.v.) bolus D1-5 and leucovorin 20 mg/m²/day i.v. bolus D1-5) was given 6 weeks after surgery, and radiotherapy was started on the 28th day following chemotherapy. Concomitant chemotherapy (5-fluorouracil 400 mg/m²/day i.v. bolus and leucovorin 20 mg/m²/day i.v. bolus) was administered during the first 4 days and the last 3 days of radiotherapy. He was treated with conformal radiotherapy technique (Figs. 1-2). A total radiation dose of 45 Gy was given in 25 fractions, five days per week, with 4 MV photons to the tumor bed, anastomoses, stumps, and perigastric lymph nodes. Dose variation in the planning target volume (PTV) was kept within +7 and -5% of the prescribed dose in accordance with ICRU 50/62 recommendations. Dose volume histograms (DVH) were recorded for kidneys, liver, spinal cord. AP–PA fields were weighted slightly anteriorly to keep the spinal cord dose at 45-50 Gy or lower (Fig. 3). During the chemoradiotherapy, grade 1 nausea and vomiting and grade 2 hematologic toxicity according to NCI Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) were seen. Two cycles of 5-fluorouracil (425 mg/m²/day) and leucovorin (20 mg/m²/day) D1-5, were given one month apart, one month after the completion of radiotherapy.

After the 9th month of completion of postoperative RT, he was referred again with severe lumbar pain. Physical

Fig. 1. 3-D treatment plan for gastric cancer (axial image)

Fig. 2. The radiation fields cover the areas of lymph node drainage, gastric remnant, anastomosis, duodenal stump, and gastric bed structures.

Fig. 3. Dose volume histogram (DVH) for 3-D treatment plan
and neurological examinations were normal. Distant and locoregional recurrence were not detected at bone scan, chest and abdominopelvic CT. Therefore, lumbar magnetic resonance imaging (MRI) was performed. MRI revealed partial compression of the lower end-plate of the L1 vertebra which was in the radiotherapy field. There was no pathological signal in the vertebra corpus on T1-weighted images that signalled bone metastasis (Fig. 4).

After one month, a new lumbar MRI showed progression of the compression (Fig. 5). So, the final diagnosis was insufficiency fractures of lumbar vertebra as a result of radiotherapy and non steroidal anti-inflammatory drug naproxen (500 mg twice daily, peroral), zoledronic acid (once in 3 months) and calcium (once daily peroral) were prescribed to the patient. One year after the treatment, control MRI showed chronic compression fractures and a decrease in edema which was appropriate with significant regression (Fig. 6). He used zoledronic acid for 3 years. In his third year follow-up, his symptoms completely recovered and now only takes a calcium tablet per day.

**Case 2-3**

Two female patients 53 and 67-year-old respectively were referred to the surgical unit with a 2-month history of gastric pain, and anorexia. They underwent subtotal gastrectomy. Both of them were staged as T3N1M0 gastric adenocarcinoma and received chemoradiotherapy protocol
according to intergroup 0116 study. Radiotherapy was given with 3D conformal technique as stated above. They presented us with severe lumbar pain 17 months and 9 months after the completion of irradiation, respectively. Neither distant nor locoregional recurrence was observed at work-up. Lumber MRI’s were also correlated with insufficiency fractures. One of them received the same treatment (naproxen, zoledronic acid, calcium) as stated in detail above and she made remarkable progress and after 6 months had minimal discomfort. Four years after the treatment, she is still in follow-up without symptoms and medical treatment. The other patient received tramadol tab., calcium tab and calcitriol tab. because severe osteoporosis was also detected in bone density scan. Six months after the treatment, control MRI showed significant regression and her symptoms were recovered. However, she died due to heart failure in 4 years after the completion insufficiency fracture treatment.

Discussion

Radiotherapy can contribute to the development of insufficiency fractures, radio-necrosis, abnormality of bone growth and the development of secondary malignancy, although incidence of irradiation complications of mature bone is not high in the literature (15). Insufficiency fractures is one of the types of stress fractures in a bone already weakened by decreased mineralization and with insufficient elastic resistance to withstand normal physiological stress (8). The use of high-dose steroids, low body weight, inflammatory arthritides such as rheumatoid arthritis and women with postmenopausal state are also related with insufficiency fractures (3-7). It can be seen rarely after radiotherapy and the pathogenesis is not exactly known. Irradiation can kill osteoblasts, osteocytes, osteoclasts and leave acellular bone matrix. All of these reduce the functional and structural components of the bone tissue. In addition, vascular damage can cause progressive ischemic changes and injury to the periostic vasculature. At the end the bone structure is weakened and risk of insufficiency fracture is increased (21).

Chemotherapeutic agents, adriamycin, vincristine, and cisplatin alone may induce osteonecrosis, and used in combination with irradiation, the risk is even greater. Jenkins et al. reported that concurrent chemoradiotherapy might predispose to pelvic insufficiency fracture in cervix cancer (16). The results of a large randomized intergroup trial INT 0116 reported that postoperative chemoradiotherapy conferred a survival advantage compared with surgery alone, which has led to the regimen being adopted as a new standard of care in gastric cancer (2). Besides, it is well known that the incidence of acute toxicities are increased with this regimen. However, reports on late toxicity have been scarce thus far. There is no data that shows a radiochemotherapy regime in gastric cancer increases the risk of insufficiency fractures. The incidence and clinical course of pelvic insufficiency fractures after radiotherapy for rectal and gynecological cancer have been reported (3-7, 9-14). Clinical manifestations of insufficiency fracture usually have occurred approximately 1 year after completion of radiotherapy (12, 16, 17). The most common symptom of pelvic insufficiency fracture is pain which is severe and acute in onset, especially with motion (12, 17, 18). The pain can be localized to the low back, pelvis or abdomen, and accompanied hip or groin pain (19). Sometimes the pain may diffuse down the leg. Radicular symptoms also can be present.

Unfortunately, patients with insufficiency fractures can be misdiagnosed and often face mismanagement because it can mimic bone metastasis. So, differential diagnosis is crucial. Blood tests are normal except mild elevation in serum alkaline phosphatase levels (14). Conventional radiography has a low sensitivity and may be misleading. CT scan, MRI and bone scan can reveal radiological findings of insufficiency fractures. Bone window CT scan is the definitive diagnostic examination for showing fracture lines in many cases of insufficiency fracture (21). Bone scan shows increased radionuclide uptake in most of the cases, but is particularly useful in identifying sacral lesions especially classical H-shaped fractures (8, 13). On the other hand MRI is the high sensitivity examination for the characteristic edema of insufficiency fracture and also useful for evaluating bone marrow changes after irradiation (12). MRI generally reveals that the lesions have diffuse low signal intensity on T1-weighted images and diffuse high signal intensity on T2-weighted images due to edema, and enhancement by gadolinium is usually observed. Bone biopsies to rule out malignancy are not generally recommended due to low diagnostic efficiency and the high probability of osteonecrosis (7, 8).

Generally the recommended treatment for pelvic insufficiency fracture is conservative care. It usually consists of analgesics, physical therapy and mineral replacement (6, 7, 10, 20). These treatments achieve symptomatic improvement in a month and disappearance within 6-12 months (7, 19). Insufficiency fractures due to osteoporosis can be treated with estrogen, calcitonin, bisphosphonates, and vitamin D-3 (5). Pentoxifylline can be used in late soft tissue injury and in osteoradionecrosis of skin, oral cavity, external genitalia. Bese et al. showed that pentoxifylline can cause clinical improvement in the treatment of insufficiency fractures of pelvic bone (20).

To minimize the risk of insufficiency fractures, it is important to determine patients with high risk factors such as older age, lower body weight, and osteoporosis. These high risk individuals could be targeted for preventative strategies, such as bone mineral densitometry screening, and fall prevention. An effective agent bisphosphonate which has been shown to reduce osteoporosis and cancer induced bone loss, can be used for treatment of high risk patients (21). However, studies are required to determine that
biphosphonate reduce the risk of insufficiency fractures. In addition, irradiated volume, fractionation and dose might correlate with the risk of insufficiency fracture, as stated in the literature. So, multiple beam arrangement instead of antero-posterior beams by CT planning could decrease the irradiation dose received by bone. Also, the use of new radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) can reduce the volume and dose of irradiated lumbar bone as many studies showed that IMRT decreased radiation toxicity (22-24).

We have reported three cases with lumbar insufficiency fractures occurring after the adjuvant chemoradiotherapy regime in gastric cancer. Pelvic insufficiency fractures after radiotherapy for gynecologic and rectal malignancies are well known but uncommon and have been investigated in previous studies, whereas few cases with lumbar insufficiency fractures have been described after pelvic radiotherapy (6, 7, 10, 13, 14). Symptoms and the clinical course of our patients with lumbar insufficiency fractures are similar to the reports regarding pelvic insufficiency fractures. Onset of symptoms were 9 or 17 months after completion of chemoradiotherapy. Two of the 3 patients were women in postmenopausal status and the male patient was 67 years old. In all our patients, bone scans were normal where as MRI showed reduction in signal abnormalities of insufficiency fractures lesions and compression in the lumbar vertebra. They did not present any history of trauma, corticosteroid usage or medical illness. However, all patients were treated with anterior-posterior parallel opposing 3-D conformal techniques. Postoperative intergroup radiochemotherapy protocol for T3, T4 and node positive gastric cancer patients has been used in our clinic since January 2003. We have started to use 3D conformal radiotherapy since 2004 to decrease toxicity. In these patients all tolerance doses of organs at risk were in the acceptable limits. However, dose received by vertebrae in the treatment field was calculated for all 3 patients after the development of fractures and the mean dose for vertebra was 30.25 Gy (minimum dose: 2.38 Gy and maximum dose: 55.32 Gy). It has been reported that the risk of radiation-induced bone injury has been increased with the size of radiation field, orthovoltage energy, high fraction size, radiation doses exceeding 40 Gy and the tolerance dose for elderly pelvic bones is less than that of a young adult (20, 25). In the present report, patient characteristics such as age, postmenopausal status, osteoporosis and radiotherapy technique might have contributed to the occurrence of lumbar insufficiency fracture. All of the patients’ symptoms were improved with given treatment.

In conclusion, lumbar insufficiency fractures are very rare but can cause significant morbidity in patients treated with radiochemotherapy for gastric cancer and need to be treated appropriately. Insufficiency fractures in the lumbar vertebra are often overlooked especially in the elderly or postmenopausal woman, who have nonspecific back pain or often misdiagnosed as metastatic disease. Thus, clinical suspicion is necessary for accurate diagnosis because clinical management and expected outcomes are entirely different. Because this is a case report, it is difficult to draw a firm conclusion regarding the risk factors, clinical course and the management of lumbar insufficiency fractures. However, all these features are generally similar to pelvic insufficiency fractures. The risk of lumbar insufficiency fracture in the adjuvant treatment of gastric cancer may be reduced by preventive strategies and/or changing radiotherapy techniques such as using multiple beam arrangement by 3-D conformal planning or intensity-modulated radiotherapy (IMRT), especially in high-risk patients.

References