Radiation-Induced Fibrosarcoma After Radiotherapy for Osteosarcoma in the Mandibular Condyle

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Abstract: With recent improvements in survival duration after cancer treatment, it is becoming increasingly important to study treatment-related morbidity and mortality. Radiation-induced sarcomas in the irradiated field are well-known potential late sequelae of radiotherapy. These tumors are biologically aggressive. In the case described here, a radiation-induced fibrosarcoma appeared at 20 years after initial surgery, radiotherapy, and chemotherapy for an osteosarcoma of the mandibular condyle. Radiation-induced fibrosarcoma is relatively rare in the head and neck region. The details of this case are presented, and diagnostic and management considerations are described.

Key Words: Osteosarcoma, mandibular condyle, radiation-induced sarcoma, fibrosarcoma

Radiation therapy is an important treatment in the management of head and neck tumors, but its ability to induce neoplasms is well known. A radiation-induced tumor was first described by Frieben in 1902, only 7 years after the discovery of x-rays, after a patient underwent irradiation for a squamous cell carcinoma in the skin of one hand. 1 Although different sites and types of cancers have been reported after radiotherapy, the skin and the thyroid are the most commonly involved sites in the head and neck, and squamous cell carcinoma is the most commonly reported histological type. Radiation-induced sarcomas (RISs) are rare and were reported to account for 12% of lesions in patients exposed to radiation. 2

Osteosarcoma is a highly malignant bone tumor originating from the osteogenic mesenchymal matrix, and the cells can form osteoid, osseous, cartilaginous, and fibrous tissues. Although osteosarcomas constitute 40%–60% of all bone tumors, only 10% of these tumors occur in the head and neck region, and osteosarcoma in the mandibular condyle is rare. 3 The reported 5-year survival rates for patients with osteosarcoma of the jaw are 27%–84%. 4, 5

We report a case of radiation-induced fibrosarcoma that appeared at 20 years after initial surgery, radiotherapy, and chemotherapy for an osteosarcoma of the mandibular condyle. The aim of this case report is to improve understanding of the clinical behavior and biological aggressiveness of a radiation-induced fibrosarcoma in this site.

CLINICAL REPORT

A 38-year-old woman presented to an otolaryngologist with swelling and pain in the left temporomandibular joint (TMJ) that had been present for 5 months. She was diagnosed with a temporomandibular disorder and did not undergo treatment. After 4 weeks, she had trismus and increased swelling and pain at the site of the TMJ, at which time she was referred to our department.

She had a history of pyelonephritis that was treated with antibiotics 4 years previously, while the family history showed nothing in particular. The general condition of the patient was unremarkable. Local examination showed diffuse swelling and tenderness at the site of the TMJ, left facial nerve paralysis, mental nerve paralysis, and trismus. An intraoral examination revealed no lesion. An orbitoramus projection revealed that the left mandibular condyle was absorbed by a tumor (Fig. 1A). Computed tomography (CT) revealed tumor formation at the site of the TMJ, involving absorption of the mandibular condyle, masseter, pterygoid muscle, and parotid gland (Fig. 1B). Workups for regional lymph node and distant metastases were negative. A sample was taken from the center of the tumor mass in the TMJ using a needle biopsy. The histopathological findings showed spindle cell proliferation with only minimal amounts of osseous matrix. The histopathological diagnosis was fibroblastic osteosarcoma (Fig. 1C,D). The patient was diagnosed with fibroblastic osteosarcoma of the mandibular condyle. Surgical resection of the tumor was performed with segmental mandibulectomy from the left first premolar to the mandibular condyle and surrounding soft tissue of the TMJ.

At 5 months after the initial operation, follow-up CT and bone scintigraphy revealed tumor recurrence at the left zygomatic bone. The patient underwent an additional extended resection, followed...
by radiotherapy and chemotherapy. The inner limit of the resection was the pterygoid process, the upper limit was the zygomatic bone, and the lower limit was under the oral mucosa. External-beam radiation from parallel opposing portals was given to an 8 × 8-cm field focusing on the left zygomatic bone 5 times per week in 2-Gy/day fractions, up to 74 Gy. The treatment was continued for 8 weeks. Chemotherapy was performed after the radiotherapy and consisted of 2 courses of doxorubicin (20 mg/body/day for 6 days) and aclacinomycin (20 mg/body/day for 5 days). Total doses of these agents were doxorubicin 240 mg and aclacinomycin 200 mg of doxorubicin (40 mg/body/day for 6 days) and aclacinomycin (20 mg/body/day for 5 days). Follow-up CT and bone scintigraphy after these treatments revealed no recurrence at this site.

At 14 months after the initial surgery, the patient was referred with dysphasia, and a metastatic fibroblastic osteosarcoma was detected in the right ischial bone. The patient received radiotherapy and chemotherapy. External-beam radiation from parallel opposing portals was delivered to the right ischial bone 5 times per week in 2-Gy/day fractions, up to 70 Gy. The treatment was continued for 7 weeks. Chemotherapy was performed after the radiotherapy and consisted of 2 courses of cisplatin (140 mg/body/day for 1 day) and aclacinomycin (20 mg/body/day for 5 days). Total doses of these agents are cisplatin 280 mg and aclacinomycin 200 mg. Follow-up then ensued for 20 years, during which time there was no local recurrence or distant metastasis.

At 20 years after the initial surgery, the patient complained of pain and swelling from the left temporal bone to the occipital bone. CT showed a tumor with absorption of the sphenoid bone and the occipital bone (Fig. 2A). Positron emission tomography revealed high density on the pituitary fossa (SUV\text{max} = 12.7), left temporal bone (SUV\text{max} = 10.0), and occipital bone (SUV\text{max} = 14.7), with tumor invasion of the left temporal lobe (Fig. 2B). A needle biopsy was performed, and a histopathological examination showed fibrosarcoma (Fig. 2C, D). The patient received chemotherapy with cisplatin (60 mg/body/day for 1 day), 5-fluorouracil (500 mg/body for 5 days), and methotrexate (30 mg/body/day for 1 day). However, the RIS was uncontrollable with this chemotherapy regimen. Three months later, the patient died from a brain metastasis.

![FIGURE 2. A, A computed tomography scan at 20 years after the resection of the original tumor showed a radiation-induced sarcoma that involved the left temporal bone, sphenoid bone, and occipital bone. B, Positron emission tomography revealed high density on the pituitary fossa (SUV\text{max} = 12.7), left temporal bone (SUV\text{max} = 10.0), and occipital bone (SUV\text{max} = 14.7), with tumor invasion of the left temporal lobe. C, D, The pathologic findings demonstrated a fibrosarcoma. Hematoxylin-eosin staining, original magnification ×100 (C), ×400 (D).](https://example.com/figure2.jpg)

**DISCUSSION**

In this report, we describe a patient with an osteosarcoma in the left mandibular condyle who underwent initial surgical resection of the primary tumor and additional resection, chemotherapy, and radiotherapy for a recurrent tumor. Although a distant metastasis appeared in the right ischial bone, that lesion was well controlled by chemotherapy and radiotherapy. After 20 years, a fibrosarcoma occurred in the same anatomic site irradiated during the treatment of the primary tumor. This aggressive tumor led to the patient’s death.

A diagnosis of radiation-induced tumor formation requires the following criteria to be met: (1) documented history of irradiation at the site, (2) new malignancy arising within the irradiated field, (3) histological distinction between the new tumor and the original primary lesion, and (4) a latent period of 5 years or longer between the irradiation exposure and the development of the new malignancy.

Our case satisfied all of these criteria, and the tumor was therefore considered to be a RIS. Sarcoma tumorigenesis is an effect of prior radiotherapy at doses ranging from 16 to 112 Gy, and a total dose of 55 Gy or above increases the risk. The median latency period of RIS development was reported to be 10 years (range, 2–50 years). The most common histological subtype of RIS is malignant fibrous histiocytoma (36.4%), followed by angiosarcoma (18.2%), liposarcoma and soft tissue osteosarcoma (9% each), and leiomyosarcoma (7%).

The pathogenesis of RIS is still unclear. The double-stranded DNA damage induced by ionizing radiation is thought to cause genomic instability, which could be an etiologic factor resulting in malignancies. A RIS tends to occur at the edges of the radiation field, where the doses of radiation are sufficient to permanently alter the ability of cells to perform repair functions. In an investigation of the genetic changes in RISs, alterations in the p53 and Rd genes were implicated. Mutations of the p53 gene were analyzed using the polymerase chain reaction single-strand conformation polymorphism method on paraffin-embedded tumor specimens from 24 patients with RISs. Direct sequencing of the SSCP products showed a total of 58 p53 mutations in 88% of the RIS patients, whereas only 20% of patients with sporadic sarcomas showed p53 mutations. These findings suggest that RISs may occur through p53 gene mutations.

In the present case, we treated the radiation-induced fibrosarcoma using chemotherapy (cisplatin, 5-fluorouracil, and methotrexate), but this treatment was unable to control the tumor. The standard chemotherapy regimen for a RIS (doxorubicin, cisplatin, ifosfamide, and high-dose methotrexate) has only been established for osteosarcoma and malignant fibrous histiocytoma. However, the extent of radiotherapy and/or chemotherapy is limited by the amount of radiation previously received, which can leave surgical resection as the only treatment for a RIS.

RISs exhibit biologically aggressive behavior, and local recurrence and distant metastases are frequent. The prognosis of a RIS is poor. In our case, the radiation-induced tumor rapidly occurred in the temporal bone and occipital bone. Despite receiving chemotherapy, the patient died at 3 months after detection of the tumor. The reported 5-year overall survival rates for patients with a RIS are less than 30%. The reasons for such a poor prognosis include delays in diagnosis caused by the unreliability of clinical examinations, proximity of the tumor to major neurovascular structures, limited treatment options because of the danger of irradiating a previously irradiated field and the relatively poor sensitivity of these tumors to chemotherapy, and host immunosuppression caused by the first tumor and/or its treatment.

The risk factors for tumorigenesis are multifactorial and can include genetics, environmental exposure, drugs, chemotherapy, and radiation. A large number of patients with cancer can be potentially cured or palliated by radiation, and concern regarding RIS
Lipostructure in Parry-Romberg Disease

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Abstract: Parry-Romberg syndrome is a disease characterized by progressive hemifacial atrophy. Multiple surgical procedures have been used to improve the facial volume and contours of patients with this disease, including alloplastic, silicone, or collagen implants; lipofilling; and pedicled or free-flap transplants. The present case describes the successful application of lipostructure to treat a woman with Parry-Romberg syndrome affecting the left side of her face.

Key Words: Parry-Romberg syndrome, lipostructure, facial augmentation, facial atrophy

Parry-Romberg syndrome, or progressive hemifacial atrophy (PFH), is characterized by self-limiting, progressive atrophy of the subcutaneous fat on one side of the face. The disease, which more frequently affects the left side of the face, variably involves the associated skin, muscle, and bone. The skin covering the affected area is thin, shows signs of atrophy, and has a typical, yellow-brownish color. The affected muscle remains functional but has a diminished consistency; bone involvement can manifest as maxillary or mandibular hypoplasia, with the degree of hypoplasia correlating to the duration of the tissue atrophy. The loss of lashes and hair is another common finding in patients afflicted with this disease. The morphologic abnormalities associated with Parry-Romberg syndrome are usually manifest during the first and early second decades of life and may progress for up to 10 years before becoming stable. Although the pathogenesis of this disease is unclear, it is more common in women than in men.

The most appropriate treatment modality for these patients can be determined based upon the observations noted during their clinical examination. Regardless of the specific modality chosen, treatment involves augmentation of the atrophied region and restoration of facial symmetry to provide great psychological and emotional benefits to the patient. The use of autologous fat grafts, alone or in combination with other surgical methods, offers a practical treatment of the condition. Alternatively, the injection of biomaterials, such as alloplastic materials, silicone, or collagen, also provides practical solutions. Other treatment methods include pedicled or free-flap grafts. Regardless of the type of treatment selected, the treatment has to be performed on adult patients, when disease progression has arrested. The present case report describes the use of the lipostructure technique for the treatment of Parry-Romberg disease.

PATIENT AND METHODS

A 33-year-old woman presented with a history of PFH, characterized by left facial atrophy of the subcutaneous tissues that began when the patient was 10 years old. The condition appeared to have been stable since she was 15 years old. Objective clinical examination indicated moderate soft tissue deficits affecting the zygomatic, buccal, mental, cheek, and orbital regions of her left face without significant alteration of the skin pigmentation (Fig. 1). A free-flap graft was originally presented as the best solution for soft tissue augmentation in this patient. However, she rejected this procedure because she desired a simpler, safer, faster, and less traumatic procedure. Therefore, she underwent a single session of lipostructure, using Coleman’s technique 6, to reconstruct the 3-dimensional planes of her face.

Through a small incision, a mixed solution (0.5% lidocaine in a 1:200,000 dilution of epinephrine in lactated Ringer solution) was infiltrated into the donor sites (abdominal and thigh regions). Fat grafts were subsequently harvested through the same incisions, using a 2-mm diameter, blunt tipped cannula that was connected to a 1-mL Luer-Lock syringe. The syringe was manipulated to provide light negative pressure while the cannula was advanced within the harvest site in order to collect the donor adipose tissue. After the