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Case Report

Ewing's Sarcoma of Mandible: Practical Approach to a Challenging Case

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Keywords
Ewing sarcoma · Sarcoma of the head and neck · Multidisciplinary team

Abstract
As a rare entity, sarcomas of the head and neck are challenging cases. In this paper, we represent a unique case of Ewing sarcoma of mandible, serving as an example of multidisciplinary team importance in a developing country.

Introduction

"Diffuse endothelioma of bone" was the phrase used by James Ewing in 1920 for describing a bone tumor in a 14-year-old girl. The tumor was first considered as osteosarcoma, but later its unique structure, distinguishable cellular morphology, and prominent radiosensitivity led Ewing to see it as a unique entity, even hypothesizing an endothelial-cell origin [1]. The malignancy that bears Ewing's name, "Ewing's sarcoma," was first diagnosed more than 70 years later when the most common chromosomal translocations, i.e., t 11–22 and t 21–22, were detected [2].

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Ewing sarcoma (ES) had been classified to Ewing's family of tumors (EFT), along with ES of the thoracic region (Askin tumor), primitive neuroectodermal tumor, and extraosseous ES, based on their common chromosomal translocation and morphological features [2, 3]. Also, in favor of their same mentioned characteristics, they are thought to be formed from the same cell of origin, which is in doubt [3–5]. Recently, our understanding of these tumors has changed significantly: undifferentiated round-cell sarcomas with CIC rearrangement, BCOR alterations, or gene fusions involving non-ETS partner genes are classified separately from ES [6].

With the second place among primary bone malignancies in children and forth in adults, ES accounts for 4–15% of all primary bone tumors and 1% of all malignant tumors in children [2, 7]. ES peak incidence occurs in 10- to 20-year-old adolescents and young adults, and it occurs quite infrequently in people over 30 years and children under the age of five years. Men are more at risk than women, with a male-to-female ratio of 1.5 to 1 [2, 8].

The origin of ES is uncertain; however, the tumor is thought to be derived from neuroectodermal cells. Immature reticular and undifferentiated bone marrow mesenchymal cells have also been considered as tumor sources [9]. ES is mainly common in flat and long bones such as the pelvis, femur, tibia, and fibula [4]. The mandible is affected more frequently than the maxilla, representing just 0.7% of all sites [10]. Generally, ES is characterized by fast progression and a susceptibility for metastasis to distant organs, most commonly the lungs and bones, and should be evaluated in the differential diagnosis when an undifferentiated round-cell tumor is discovered in an adult soft tissue. ES has a better prognosis than many sarcomas, and a patient's cure is achievable [7]. Such primary lesions in the head and neck region had a better prognosis than other primary sites. On the other hand, management of jaw lesions is a challenge as functional impairment and facial disfigurement may affect the quality of life [11]. In the following case report, we represent a young Iranian woman with mandibular ES, who benefited from multidisciplinary treatment decision-making for her rare condition.

Case Description

A 28-year-old female patient with good general health was referred to the department of oral and maxillofacial surgery because of pain and swelling in her left lower jaw region for the past 3 months. There had been no previous trauma. She had no prior oncological history, and her medical and dental backgrounds were unremarkable. The examination showed a firm and fixed lesion, which had tenderness in palpation. No loose teeth and lymphadenopathy were detected.

Initial presentation in spiral computed tomography (CT) scan was a bone lesion in the left mandibular condyle and angle with a thick irregular periosteal reaction. CT imaging also revealed soft-tissue components with deep extension to lateral pterygoid muscle and superior extension into the left infratemporal fossa. There was no evidence of cervical lymphadenopathy (Fig. 1).

After an incisional biopsy, the histopathology report revealed neoplastic tissue consisted of "uniform small round cells" with round nuclei. Neoplastic tissue necrosis and deteriorated bony trabeculae invaded by the neoplasm were observed. The reported pathological features, malignant small round tumor cells with extended necrosis, were suggestive for ES/primitive neuroectodermal tumor and osteosarcoma (small-cell variant). Immunohistochemistry (IHC) was done for diagnosis confirmation, reporting small tumor cells which were positive for vimentine and MIC-2 (or CD99) and negative for SATB-2, Pan CK, CD45, or TLE-1. The Ki67 value was 12–15%. Based on the morphological features, immunohistochemical, and molecular findings, ES was verified. In Iran, performing PCR to detect chromosomal translocation is not feasible due to the costs and the patient avoided doing it despite oncologist's request.

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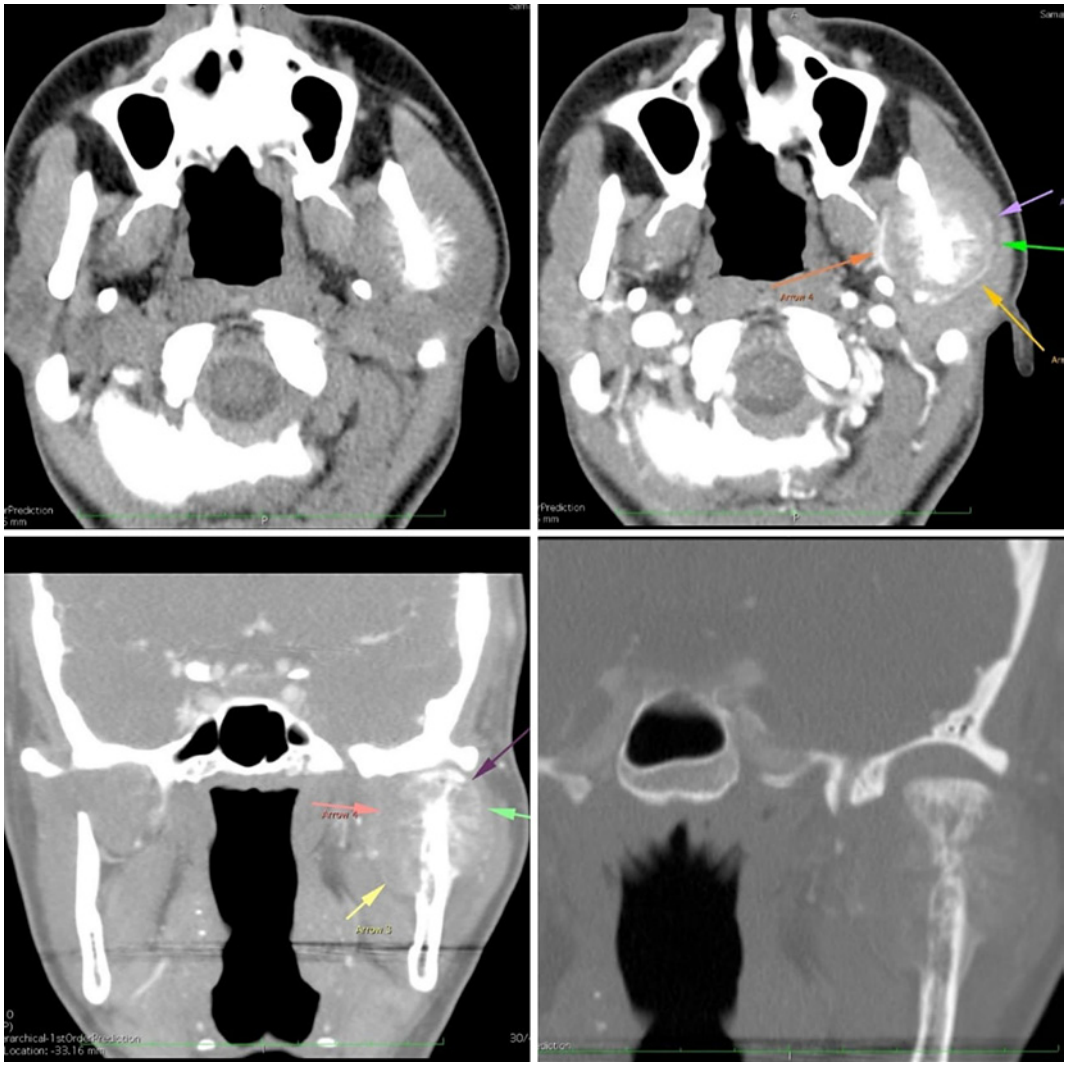

Fig. 1. Initial presentation in the spiral CT scan was bone lesion in the left mandibular condyle and angle with a thick irregular periosteal reaction. It also revealed soft-tissue components with deep extension to lateral pterygoid muscle and superior extension into the left infratemporal fossa.

A multidisciplinary (MDT) conference that consisted of a clinical oncologist, otorhinolaryngologist, oral and maxillofacial surgeon, radiologist, and pathologist was held for this rare medical condition, and the team recommended a complete workup, including magnetic resonance imaging (MRI) of the face, bone marrow aspiration and bone marrow biopsy, chest CT, and whole-body bone scan (WBBS). Bone destruction in the left mandible and a big enhancing soft-tissue mass (4 × 4 × 4.2 cm) around the ramus with masticator space involvement were detected in MRI. No other evidence of disease was reported in other staging modalities.

For this patient, the induction chemotherapy was recommended by MDT at the first step, using a vincristine, doxorubicin hydrochloride, and cyclophosphamide/ifosfamide and etoposide (VAC/IE) regimen which was administered for 9 weeks to shrink the tumor and increase the probability of a complete surgical resection. Interim assessment were carried out in order to restage the tumor following four cycles of chemotherapy, yielding the following results: (1) a zone of abnormally increased radiotracer activity in the left mandible was discovered in WBBS consistent with patient's history of ES. Other parts of the patient's skeleton were found

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to be normal, (2) spiral lung CT was normal, and (3) spiral contrast CT of the face and neck revealed soft-tissue edema in the left side of the face and thickening of the mandible bone.

A left sided marginal mandiblectomy was performed. The surgically removed specimen was pathologically identified as a 3.5 × 3 × 2.5 cm ES with closed surgical margins. It was also revealed that the neoplasm had spread to adjacent fibro-muscular tissue.

As a result of the patient's pathology having closed margins, adjuvant external beam radiation therapy (EBRT) was initiated (50.4 Gy in 28 fx). After the last EBRT session, additional 11 cycles of chemotherapy (VAC/IE × 11 cycles) was administered for the patient.

In terms of patient follow-up, PET-CT 1.5 years after the initial diagnosis was performed, with the results showing no evidence of local recurrence or distant metastases; but a year after completing treatment, the new onset of left facial swelling was observed. Following the recurrence of symptoms, an incisional biopsy and IHC panel revealed the presence of round blue cells, indicating ES.

A restaging CT scan of the lungs and the head and neck area revealed a small number of nodules in the lungs that were suspicious for lung metastases, along with changes in the primary site of the tumor in the left mandibular body and an abnormal soft-tissue mass lesion growing over the zygomatic arch that was suggestive of recurrence in the superior margin of the initial mass lesion, respectively (Fig. 2). In WBBS, zones of abnormal increased radiotracer activity in the left mandible, left temporomandibular joint, left maxilla-frontal region were detected.

After the confirmation of the ES recurrence, salvage chemotherapy (including topotecan + cyclophosphamide regimen) was recommended by MDT until disease progression, along with partial locoregional response after 4 months of chemotherapy, based on the head and neck CT scan, and fever, diarrhea, and neutropenia as its adverse events. Eight months later, new onset of facial swelling, lacrimation, and severe pain during the chemotherapy course led to the spiral head and neck CT scan with and also without contrast. Evidence of irregularity and lytic sclerotic changes in the anterior aspect of the left temporal bone and greater wing of left sphenoid bone and a soft-tissue component of about 18 × 14 mm in the lateral aspect of the left orbit were found. After contrast injection, the mass was markedly enhanced. There was another focal irregular soft-tissue enhancing mass-like lesion about 43 × 13 mm in the soft tissue of the left temporal region with extension to the infratemporal fossa adjacent to the involved temporal bone. These findings mainly were compatible with the second recurrence. Contrast-enhanced MRI better delineated the extent of recurrent infiltrative mass in this patient: completely obliterating left infratemporal space, extending into the left orbit but with no intracranial extension signifying progressive local disease (Fig. 3). Also, more than ten intraparenchymal nodules up to 11–12 mm in all pulmonary zones, suggesting lung metastasis, were reported in a spiral lung CT scan (Fig. 4). The patient had no respiratory symptoms.

The MDT conference was reheld with the goal of making the best decision to improve treatment efficiency and quality of life in such a complicated situation, and eventually, reirradiation was recommended for this palliative setting. Surprisingly, a dramatic clinical response occurred in the second week of radiotherapy, leading to RT dose escalation (55.8 Gy total dose to the primary site, in 31 fx), although with palliation intent. Three months later, the asymptomatic patient went under re-evaluation. MRI of the face and neck revealed only a 1 × 2 cm enhancing mass in the left masticator space and infratemporal area, compatible with 80% response based on RECIST criteria in the radiologist report. The lung CT scan, still growing in the size of metastatic lung nodules, showed ongoing progressive metastatic disease (Fig. 5), but MDT did not recommend any treatment as the young palliative patient never experienced any pulmonary symptoms. WBBS was normal. Eight months after the last EBRT session, fortunately, the patient has no symptoms either in the face or lungs yet, regardless of disease progression in the recent lung CT scan. Last MRI of the face and neck shows stable disease. She is referred for rehabilitation and best supportive care.

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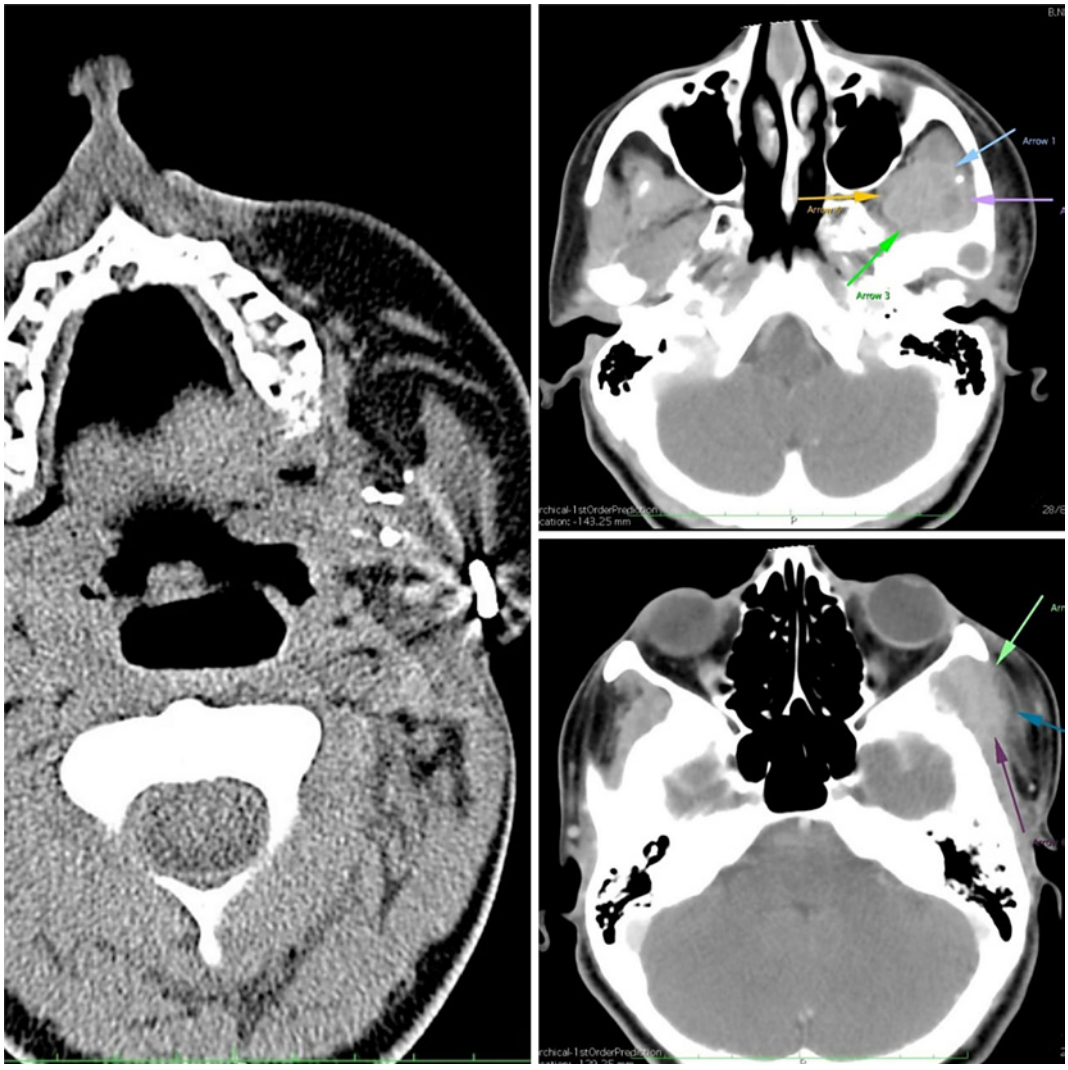

Fig. 2. Restaging CT scan of the face and neck showing a local recurrence.

Discussion

Overall, ES is defined by its aggressiveness, fast growth, and the presence of little blue round tumor cells in its microscopic view. It most typically affects the long and flat bones, with the head and neck being uncommon sites of involvement [12]. Based on a systematic review by Margaix-Muñoz et al. [7], the mandible, accounting for two-thirds of all the head and neck ES lesions (69%), is the most frequent location of the tumor in this region.

The first symptoms of ES in the oral cavity (which can be identical to dental infections) may include swelling, pain, and paresthesia. Thus, the possibility of misdiagnosis of mandible ES as periodontal infection would be high in the majority of instance [7, 11]. The first symptoms, in this case, were pain and swelling in the left lower posterior jaw region; however, because of its quick growth, further diagnostic procedures were done, leading to the identification of ES.

Chemotherapy is usually given first, followed by surgery and/or radiation as local therapy for ES treatment. Following the abovementioned treatments, further adjuvant chemotherapy, with or without radiation, will be administered [13]. The 5-year survival rate of patients has risen as a result of multidisciplinary strategies that include effective local and systemic

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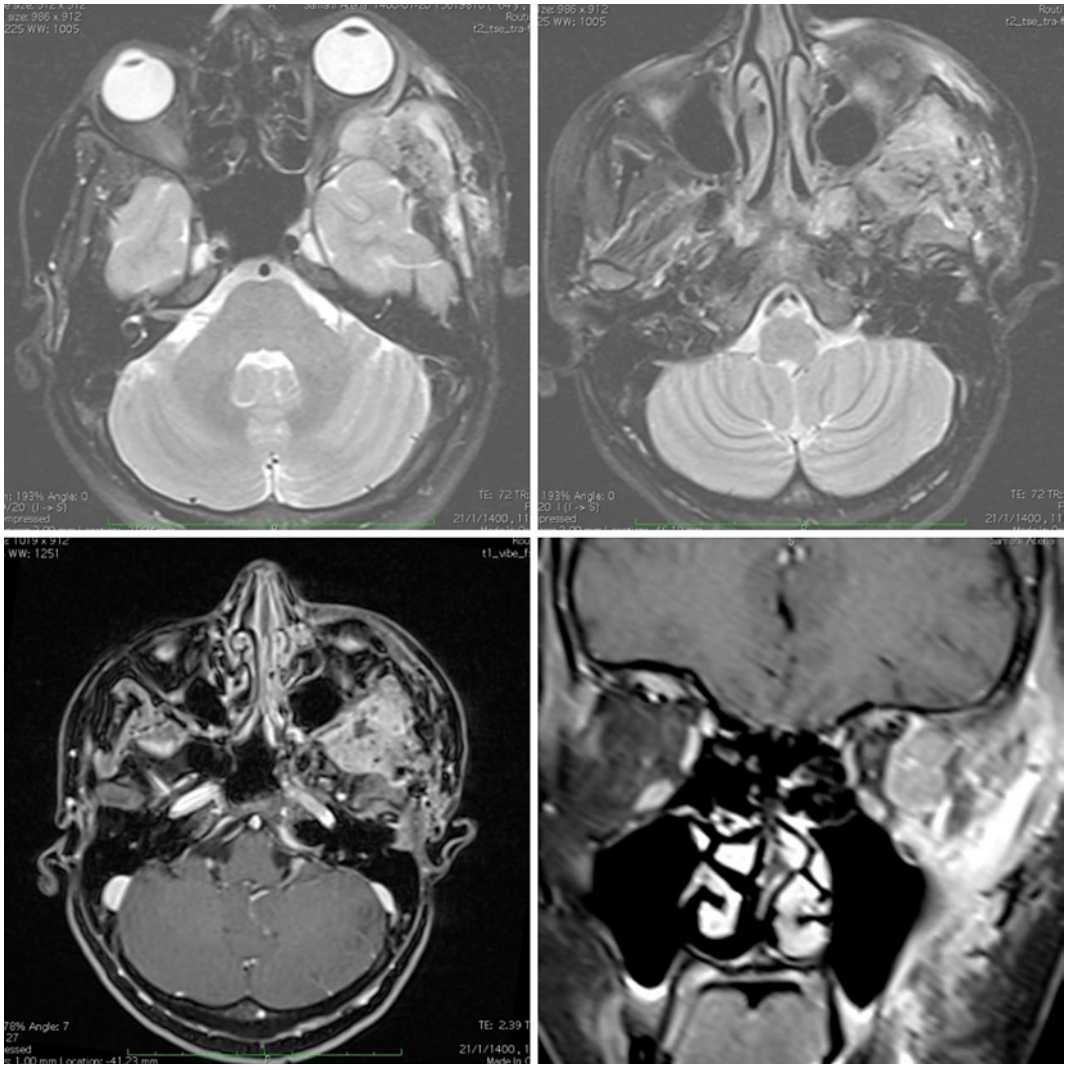

Fig. 3. MRI of the face and neck region, revealing progressive local disease.

treatment [14]. So, due to specific pathology and location in this patient, none of the local therapy (surgery and radiotherapy) or systematic treatment (multi-agent cytotoxic chemotherapy) should be compromised. Most modern treatment plans utilize initial (induction or neoadjuvant) chemotherapy followed by local treatment and additional chemotherapy.

Based on an America's guideline, the National Comprehensive Cancer Network (NCCN), the current standard treatment as prior multi-agent chemotherapy for ES includes VAC/IE for at least 9 weeks before local therapy [13]. In this case, the aforementioned treatment was used to restrict the tumor and raise the chances of a full surgical excision. Primary multi-agent chemotherapy could be longer than 9 weeks in patients with metastasis [13].

Depending on variables related to the patient and tumor, like tumor location, ease of resectability, and the therapies' morbidity, both surgery and radiation could be performed as local control. The decision between these two options is debatable and requires more research. Based on one of the latest analysis by the Children's Oncology Group, the probability of local failure was reported to be more with RT than with surgical resection, but the choice between these treatments did not affect event-free survival (EFS), overall survival, or distant failure. These data support surgical resection when required, while RT remains a viable option for

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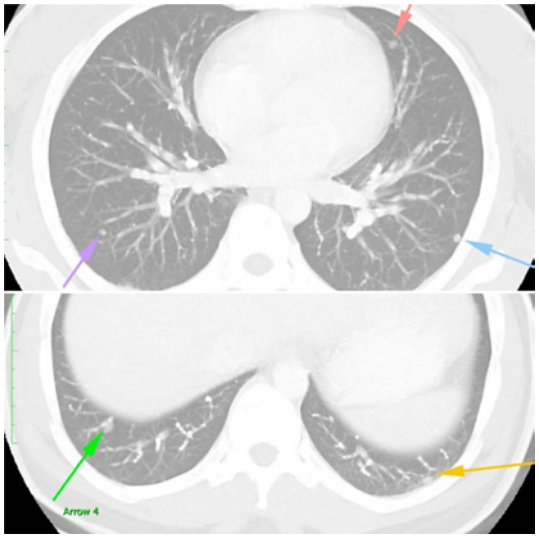

Fig. 4. Spiral lung CT scan showing lung metastasis.

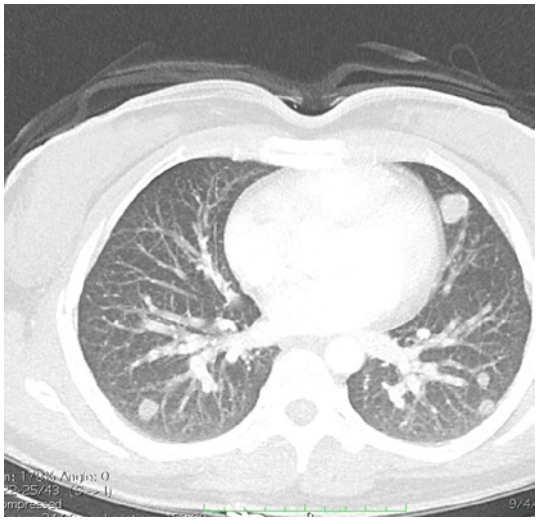

Fig. 5. Last lung CT scan signifying progressive lung metastases.

specific individuals [15]. On the other hand, the results from an analysis of 1,058 patients with localized nonmetastatic ES revealed an increased local failure and decreased EFS in patients having RT versus surgery, with/without radiation [16]. This would be more challenging when it comes to the head and neck region. Beyond challenges of facial surgery in young patients in the aspect of cosmetic and functional features, nonsurgical local control is generally preferred in patients with the skull and facial bone tumors due to the probability of clinically significant functional loss in order to achieving negative margins. On the other hand, due to the close vicinity to critical and radiosensitive organs such as the eyes, brainstem, spine, etc., EBRT and also establishing ideal portal margins in it without substantially impairing the functioning of these organs would be challenging [10, 17, 18]. In this case, surgical resection was taken in order to local control. As a result of the patient's pathology having closed margins, adjuvant EBRT was initiated.

Regardless of the surgical margin situation, it is strongly recommended that adjuvant chemotherapy be administered for 28–49 weeks following local control, depending on the regimen and dose of drugs used [1, 19, 20]. In the present case, a total of 11 cycles of chemotherapy with VAC/IE were administered to the patient as postoperative adjuvant therapy.

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Despite other risk factors such as tumor size (>80 mm), histologic response (greater than 90% necrosis), and other criteria, metastatic cancer at the initial diagnosis is the most prominent poor prognostic factor in ES. Metastasis mostly happens in the lungs, bones, and bone marrow [21, 22]. Cotterill et al. [22], in retrospective research on the predictive risk factors for ES, found that patients without early metastatic ES had a superior 5-year EFS than those with (22% vs. 55%). They also found that a later recurrence, after 2 years following initial diagnosis, was linked to a better prognosis than early ones [22]. Local and/or distant recurrence occurs in 30–40% of ES patients, and it is associated with a quite poor prognosis [23]. More than 70% of all relapses are early, with two-thirds of those occurring in distant locations, mostly the lungs and bones. Also, patients with widespread initial illness are more prone to experience distant recurrence, whereas those with localized disease are more likely to developing local recurrences [20].

In our presenting case, the results of PET-CT, 1.5 years after the initial diagnosis, revealed no evidence of local recurrence or distant metastases; but a year after completing treatment, which is more than 2 years from diagnosis, the new onset of left facial swelling was observed, indicating ES relapse based on incisional biopsy and IHC panel. Eight months later, new onset of facial swelling, lacrimation, and severe pain and findings in the spiral head and neck CT scan, with and also without contrast, were compatible with the second recurrence. Also, intraparenchymal pulmonary nodules in the spiral lung CT scan were suggestive for lung metastasis.

Here, we discussed a unique case of primary ES of mandible with a practical clinical approach, focusing on multidisciplinary decision-making. MDT discussion before the initiation of treatment is required to formulate the best approach for chemotherapy, radiation delivery, surgical technique, and mode of reconstruction.

Statement of Ethics

Ethical approval is not required for this study in accordance with national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contribution

Study concept and design: Zahra Keshtpour Amlashi (Z.K.A.), Abdolazim Sedighi Pashaki (A.S.P.), Seyed Alireza Javadinia (S.A.J.), and Mohammad Saeid Ahmadi (M.S.A.); acquisition of data: Fateme Sheida (F.S.) and Ahmad Ameri (A.A.); drafting of the manuscript: Leila Moaddab Shoar (L.M.S.), Mohammad Hadi Gharib (M.H.G.), and Z.K.A.; critical revision of the manuscript for important intellectual content: Omid Soltaninia (O.S.), Farhad Farahani (F.F.), and Rohollah Abbasi (R.A.)

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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