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Case Report

A Case of Primary Osteosarcoma of the Mandible That Responded to Preoperative Chemotherapy: p16 as a Potential Prognostic Factor

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We report a case of mandibular osteosarcoma in a Japanese woman in her 70s who was p16-positive. Despite the rapid growth of the tumor, the patient responded well to chemotherapy and was then able to undergo surgery. Head and neck osteosarcoma (HNOS) is a very rare cancer, and although the importance of surgery has been pointed out, the effectiveness of chemotherapy is unclear. Resection margin negativity and response to chemotherapy have been reported as prognostic factors; another report assessed the effectiveness of the immunohistochemical expression of p16 protein as a predictor of response to chemotherapy.

Key words: head and neck osteosarcomas, tumor suppressor p16

Osteosarcoma is the most common primary malignant tumor of bone, with an incidence of 1-2 per million people per year [1]. Primary head and neck osteosarcomas (HNOS) are considered rare, accounting for less than 6% of the osteosarcoma cases [2].

The effectiveness of multidisciplinary treatment combining chemotherapy and surgery has been established for primary osteosarcoma of long bones [3]. Conversely, surgical resection is the first choice for the treatment of primary HNOS. However, the clinical benefit of adjuvant chemotherapy has not yet been clearly established.

A negative surgical margin has been established as a prognostic factor for primary HNOS [4]. Responsiveness to chemotherapy has also been reported as a prognostic factor [5]. Recently, immunohistochemical expression of p16 protein has been reported as an indicator of responsiveness to chemotherapy in mandibular osteosarcoma [6].

Here we report a case of osteosarcoma of the mandible in which multidisciplinary treatment with preoperative chemotherapy was markedly effective and surgery was successful despite rapid tumor growth. We present this case and discuss the literature regarding the relationship between p16 and HNOS.

Case Report

A 70-year-old woman visited the oral surgery department of a general hospital after noticing a swelling in the lower right gingival region. A computed tomography (CT) scan revealed a neoplastic lesion with bone destruction. A biopsy revealed osteosarcoma. She was referred to our hospital the following month.

Examination revealed an easily bleeding mass developing from the center of the lower-right jawbone (Fig. 1A). Contrast-enhanced CT revealed a soft mass with a maximum diameter of 45 mm with destruction of the right mandible. Contrast-enhanced magnetic

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resonance imaging (CE-MRI) similarly showed a soft tissue mass with right mandibular destruction. (Fig. 2A, B). Enlarged lymph nodes were observed in the right I, II, and IV areas.

Positron emission tomography (PET)-CT revealed a high accumulation of fluorodeoxyglucose (FDG) at the primary site (maximum standardized uptake value [SUV_{max}] = 12.3) and mild accumulation (SUV_{max} = 2.2) in the surrounding lymph nodes. No FDG accumulation suggesting obvious distant metastasis was observed.

The patient had no history of radiation therapy. The patient was diagnosed with primary osteosarcoma of the right mandible and right cervical lymph node metastasis. A treatment plan was formulated to perform an extensive resection and to consider post-surgical treatment based on the pathological diagnosis.

One week following the initial examination, the tumor was found to have spread rapidly and extensively (Fig. 1B). The decision was made to postpone the surgery and to initiate chemotherapy instead.

The standard regimen of preoperative chemotherapy for long-bone osteosarcoma is a triple-agent combination of methotrexate (MTX) with cisplatin (CDDP) and doxorubicin (DRX). In this case, however, on consultation with an orthopedic surgeon, dual drug therapy without MTX was selected, owing to the patient's age and poor organ function. The dose of each drug was reduced to 70% (CDDP: 80 mg/m^2 and DRX: 20 mg/m^2).

Immediately after the start of chemotherapy, the tumor began to shrink rapidly, and after three courses, the oral tumor had flattened dramatically (Fig. 1C). CE-MRI revealed that the overall tumor was markedly reduced in size, although an indistinct borderline mass

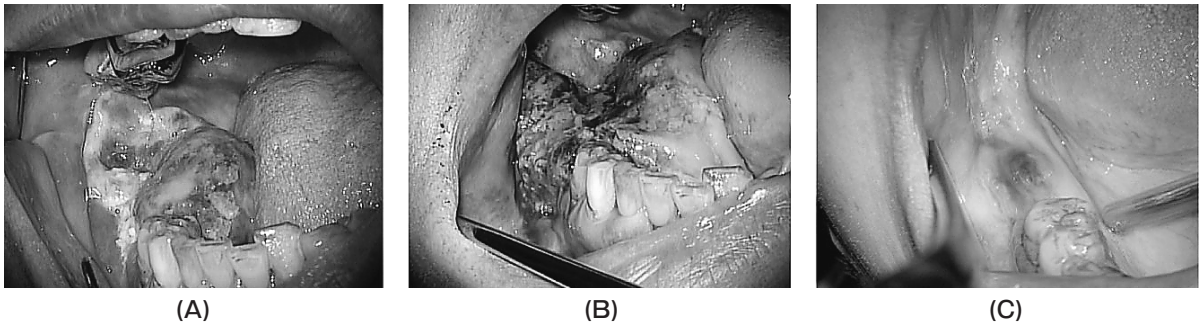

Fig. 1 Clinical course of the tumor. (**A**), At the initial examination, the tumor was approximately 3 cm × 5 cm and extended from the floor of the mouth to the gingiva and reticular triangle; (**B**), In just one week, the tumor had grown rapidly, completely replacing the remaining normal gingiva and floor of the mouth while also compressing the tongue; (**C**), After three courses of cisplatin and doxorubicin, the tumor had shrunk significantly.

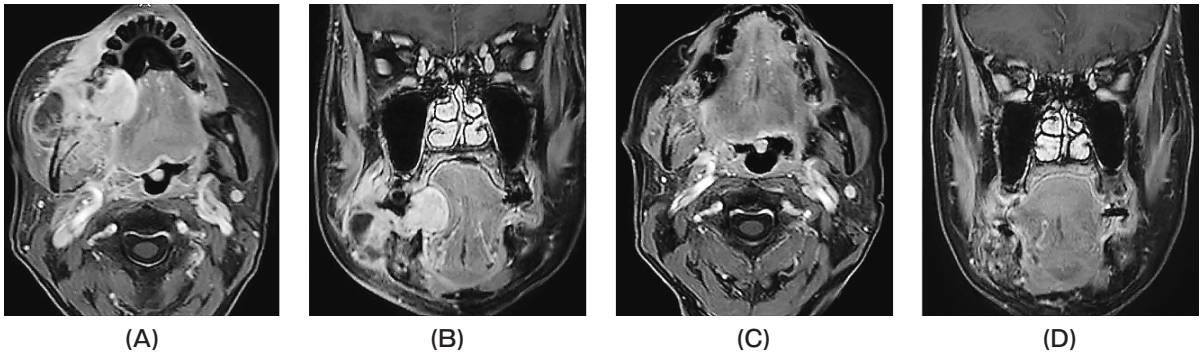

Fig. 2 Contrast-enhanced magnetic resonance imaging (MRI) findings before and after chemotherapy. (**A**, **B**), At the time of initial examination, the tumor appeared hypointense on T1-weighted MRI and heterogeneously hyperintense on T2-weighted MRI. The tumor was deviating from the tongue and the right masseter muscle; however, its borders were clear, suggesting that it was not directly invasive. The border with the medial pterygoid muscle was partially obscured; (**C**, **D**), Following three courses of chemotherapy, the primary site and cervical lymphadenopathy were clearly reduced, although some remained, as the images show.

remained, primarily within the mandible (Fig. 2C, D). After lymph node shrinkage was confirmed on CT and no findings suggestive of distant metastasis were observed, surgery was performed.

Mandibular segment resection, neck dissection (right I-V, left I), latissimus dorsi flap reconstruction, and tracheotomy were performed (Fig. 3). Although the chemotherapy visibly reduced the primary lesion, a mandibular zone resection was performed according to the pre-treatment degree of extension in order to adequately resect the inferior alveolar nerve and the medial pterygoid attachment. At the same time, parts of the platysma, parotid gland, and tongue were resected together to include the resection margin. The operation time was 11 h and 37 min, and the blood loss was 195 mL.

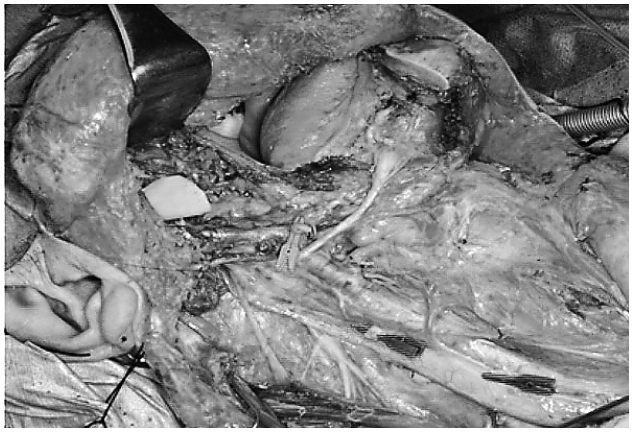

Fig. 3 The chemotherapy visibly reduced the primary lesion. However, mandibular segmental resection was performed to remove the inferior alveolar nerve, medial pterygoid attachment, and the extent of lesion development before chemotherapy. At the same time, parts of the platysma, parotid gland, and the tongue were resected together as a resection margin. The operation time was 11 h and 37 min, and the blood loss was 195 mL.

Histopathological examination led to a diagnosis of primary mandibular osteosarcoma (Fig. 4A, B). The surgical margin was negative, and the therapeutic effect was judged to be Grade 1. All the removed cervical lymph nodes were free of metastases. Evaluation of p16 by immunostaining showed that the tumor cells were extensively and highly positive (Fig. 4C).

Following surgery, four adjuvant chemotherapy courses with CDDP and DXR were given according to the chemotherapeutic protocol for long-bone osteosarcoma, after which the patient requested that treatment stop. At the 2-year and 10-month follow-ups after surgery, no evidence of recurrence was observed.

Discussion

Osteosarcoma is the most common primary malignant bone tumor, with an annual incidence of 1-2 per million people. HNOS are rare, accounting for only 2-10% of all osteosarcomas [2]. Differences in clinical features, such as age of onset and metastatic mode, have been elucidated between HNOS on the one hand and, on the other, common osteosarcomas of the extremities and pelvis. The most typical age of onset of common osteosarcoma is in childhood and adolescence [7], often presenting with distant metastases from an early stage [8], whereas the typical age of onset of HNOS is in the 30s to 40s and in elderly individuals [8]. Distant metastases are considered relatively rare in HNOS. A low occurrence of lymph node metastasis has been reported in both long-bone osteosarcoma and

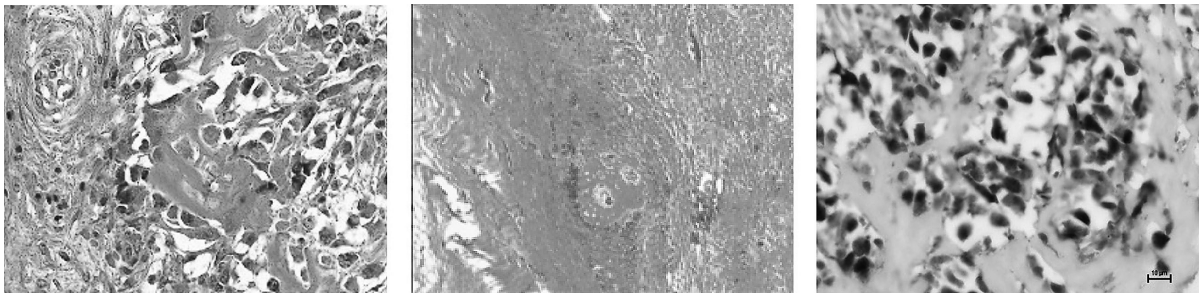

Fig. 4 (A), Large atypical cells with deposition osteoid were found in the osteosarcoma of the mandibular bone (hematoxylin and eosin [H&E]); (B), Cell density was low. Areas of scarring associated with bone matrix, atypical cell proliferation, and destruction of bone trabeculae by tumor cells were observed (H&E); (C), Pathological pictures of p16 immunostaining are shown. p16 accumulated mainly in the nucleus, with some weak staining in the sporophytes.

HNOS [9].

The basis of treatment for HNOS without distant metastasis is surgery. Among HNOSs, in which a safe margin is anatomically difficult to obtain, mandibular osteosarcoma can be resected relatively easily with a safe margin and has a relatively good prognosis [2]. In HNOS, prophylactic neck dissection is usually not necessary because lymph node metastasis is relatively rare [9]. Indeed, the present case was pN0, contrary to the preoperative diagnosis.

Considering other treatment options for osteosarcoma, the efficacy of postoperative radiation therapy of 60 Gy or more has been shown in cases with positive pathological margins [4]. High-quality evidence for the effectiveness of heavy ion beams in osteosarcoma treatment has not yet been established. However, their relatively high performance in unresectable trunk osteosarcoma has been reported, with 2- and 5-year survival rates of 58% and 33%, respectively, and 2- and 5-year local control rates of 73% and 62% [10]. The efficacy of heavy particle radiation therapy has been shown to increase with decreasing tumor volume [10]. Although there are few reports, heavy particle therapy may be effective for HNOS, in which tumor volume is smaller than in trunk osteosarcoma. In our patient's case, heavy particle therapy was also proposed, but she declined it.

Regarding chemotherapy, long-bone osteosarcoma shows many hematogenous metastases, and the efficacy of preoperative and postoperative adjuvant chemotherapy has been shown in randomized controlled trials, leading to its establishment as a standard treatment [3]. As a result, the 5-year survival rate, which was 15-20% with surgery alone, has increased significantly from 55% to 80% in recent years [11]. On the other hand, no randomized controlled trials evaluating chemotherapy for HNOS have been conducted. Two meta-analyses published in the 1990s, based on nonrandomized and retrospective studies, presented conflicting results [5,12]. Thus, the efficacy of chemotherapy for HNOS has not been established. However, a meta-analysis by Kassir *et al.* that showed chemotherapy had no effect did not take into account the status of the pathological specimen, which has recently been established as a prognostic factor; this limitation of that meta-analysis should be considered in interpreting its findings [12]. More recently, a multivariate analysis of a retrospective study with HNOS under the age of 75 showed that chemotherapy contributed significantly to reducing the risk of local recurrence, although it did not contribute to an improvement in overall survival [13]. Another retrospective study reported that chemotherapy did not directly contribute to an improvement in overall survival but contributed significantly to disease-free survival, to the reduction of the risk of distant metastasis, and to negative postoperative pathological margins [10]. Even for HNOS, which is said to have lower metastatic rates than long-bone osteosarcomas, chemotherapy is expected to improve the local control rate. In the present case, the rapid growth of the tumor made surgery as an initial treatment difficult; however, chemotherapy successfully reduced the tumor size and allowed for tumor removal while maintaining a safe margin. The majority of the tumor disappeared and the remnant portion that was resistant to treatment was resected; the pathological evaluation was grade 1. Chemotherapy was highly effective as adjuvant chemotherapy, although complete remission was not anticipated.

In HNOS, negative pathological margins have been established as independent prognostic factors [4,9]. Although there is no consensus on other prognostic factors, p16 protein expression has recently received attention as a predictor of response to chemotherapy in common long-bone primary osteosarcomas.

The G1 phase is a critical period in human somatic cells; it defines the progression of the cell cycle, and the failure of the checkpoint mechanism that controls the progression from the G1 to the S phase is a prerequisite for carcinogenesis. p16 protein acts as a negative regulator of the Rb pathway by inhibiting cyclin D and plays an important role in the regulation of the G1 cell cycle phase (the p16-pRb pathway). The intact p16-pRb pathway is thought to be essential for chemotherapeutic agents to effectively kill tumor cells; however, its mechanism of action remains to be elucidated. The expression of p16 protein is decreased in many cancers and is associated with sustained cell growth, and decreased p16 protein expression is reported to correlate with poorer prognoses of cancers [14]. A meta-analysis reported that p16 could be a predictor of chemotherapy response, although it did not directly correlate with overall survival or disease-free survival in long-bone osteosarcoma [15]. Similarly, p16 has been demonstrated as a predictor of chemotherapy response in primary osteosarcoma of the mandible [6]. The staining status of p16 is stable before and after chemotherapy

and surgery, and p16 can be evaluated not only before treatment but also in samples obtained during treatment [6]. Low levels of p16 are expected to predict a poorer response to chemotherapy. In this case, considering the patient's advanced age, MTX could not be administered and the doses of CDDP and DRX had to be reduced. Fortunately, chemotherapy was successful in shrinking the tumor, making surgery was possible; without successful chemotherapy, surgery was considered impossible. If p16 is established as an indicator of response to chemotherapy, it may play an important role in determining optimal treatment strategies for patients. Prioritizing alternative adjuvant therapies for patients who are expected to have low response rates to chemotherapy would reduce the burden on both medical staff and patients. The establishment of effective treatments and prognostic factors should be considered in HNOS, which is a rare cancer.

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