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Case Report

# Primary undifferentiated high-grade pleomorphic sarcoma/malignant fibrous histiocytoma arising from the mandible

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ABSTRACT

A patient who had a primary undifferentiated high-grade pleomorphic sarcoma/malignant fibrous histiocytoma that apparently arose in the mandible, but showed uncertain differentiation on histopathological examination, is described. Our regimen, a combination of pre- and postoperative chemotherapy and surgical resection, produced a good outcome.



## 1. Introduction

Sarcomas arising in the oral region have a much lower incidence than epithelial tumors, accounting for 1.8% of all primary malignant oral tumors surveyed in Japan [1]. Undifferentiated sarcoma accounts for only 0.1% of sarcomas in the oral cavity [1]. Histopathologically, this tumor shows diverse features; standard treatment has not yet been established. In this article, a patient who had an undifferentiated high-grade pleomorphic sarcoma/malignant fibrous histiocytoma that apparently arose in the mandible, but showed no specific line of differentiation on histopathological examination, is described.

## 2. Case report

An 8-year-old boy was admitted to our hospital because of pain and bleeding of the right mandibular deciduous molar region and swelling of the right buccal region. His medical and family histories were not relevant to the current disorder. Facial findings revealed an elastic hard mass in the right buccal region (Fig. 1A). There were no abnormalities of the facial skin, but trismus was present. An exophytic region with gingival hyperplasia at the region was found (Fig. 1B).

Computerized tomography (CT) scans revealed osteolytic changes and a mass measuring about 4 cm in diameter in the right side of the mandible. The inside of the lesion showed a relatively low, heterogeneous density (Fig. 2A and B). Radiographic findings suggested osteomyelitis, but that was considered unlikely because of mild inflammation. The clinical diagnosis was a suspected tumor in the right mandible.

A few days later, a biopsy was performed under general anesthesia to make a definite diagnosis. Histologically, the tumor was markedly cellular with the proliferation of spindle tumor cells arranged in fascicular and storiform patterns, intermingled with occasional giant cells with bizarre nuclei (Fig. 3A–C). Mitotic figures were commonly seen within the tumor (approximately 10/high-power fields (HPFs)), along with the focal areas of necrosis and hemorrhage. The tumor showed no specific line of differentiation including matrix production, such as bone and cartilage. Furthermore, immunohistochemical examination showed no specific differentiation (Table 1). However, the diagnosis of synovial sarcoma was ruled out by the facts that the tumor was essentially a bone tumor on the imaging survey and that the fusion genes (SYT-SSX1 and SYT-SSX2), which are cytogenetically specific markers for synovial sarcoma, were not detected by reverse transcription polymerase chain reaction (RT-PCR) on tumor samples (data not shown). Although the definite pathological diagnosis was unable using limited biopsy specimen, the tumor fell under the category of undifferentiated high-grade pleomorphic sarcoma/malignant fibrous histiocytoma of indeterminable

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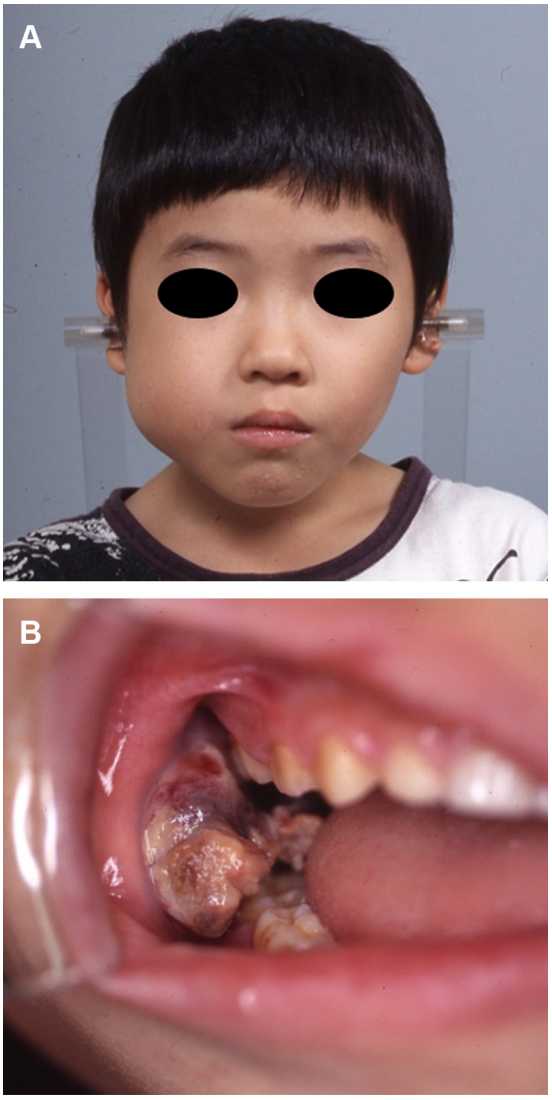


**Fig. 1.** Facial and oral findings at the initial visit. The patient's cheek is swollen, and oral examination shows an exophytic region with gingival hyperplasia at the distal gingiva of the right mandibular deciduous molar region.

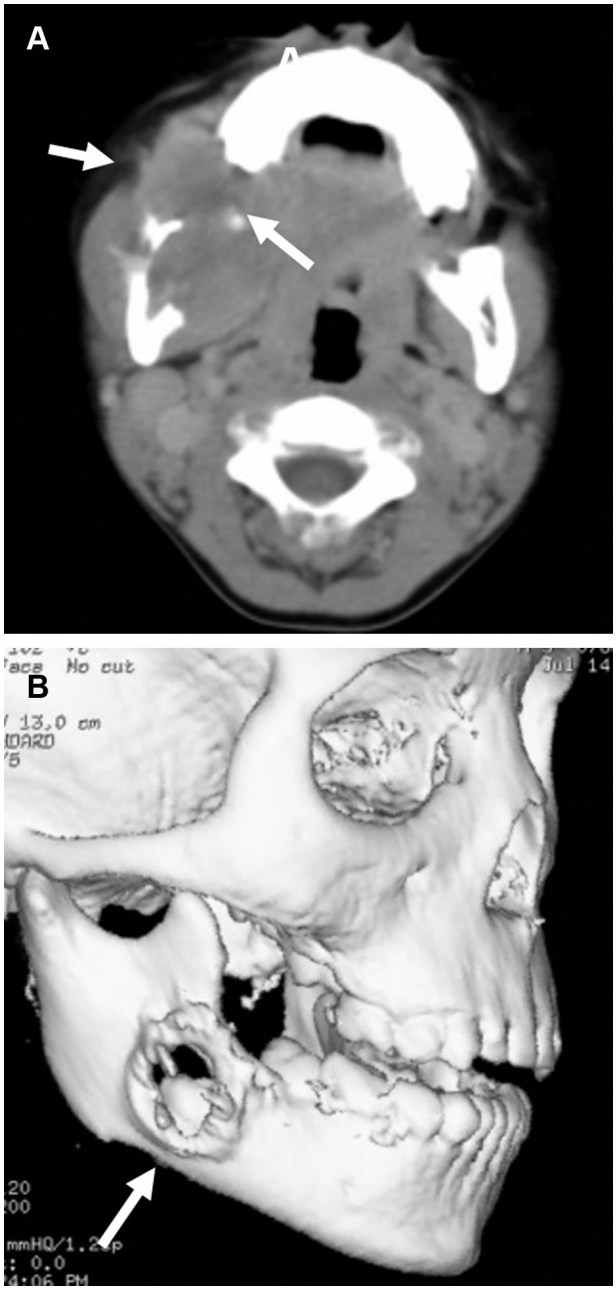


**Fig. 2.** Axial (A) and 3-dimensional (B) CT images. Osteolytic changes and a mass measuring about 4 cm in diameter are found in the right side of the mandible (arrows).

differentiation based on the histopathological and molecular pathological findings.

The patient was transferred to the Department of Pediatrics of our hospital to undergo chemotherapy. He was given ifosfamide plus etoposide (IE therapy), followed by one course of chemotherapy with vincristine, actinomycin D and cyclophosphamide (VAC therapy) (Fig. 4). A month after the therapy, the mass associated with destruction of the right side of the mandible had markedly shrunk to about 2.5 cm × 2.2 cm on CT scans. There was no enlargement of the cervical lymph nodes on either side. The patient subsequently received three courses of VAC therapy, for a total of four courses of VAC therapy. The CT scans showed that the tumor had decreased. Since there was no evidence of distant metastasis to the chest or abdomen, the tumor was resected by right mandibular segmentectomy under general anesthesia 1 month after chemotherapy. The resected mandible was reconstructed with a vascularized rectus abdominis musculocutaneous flap. During the operation, intermaxillary fixation was placed on the deciduous molars of the unaffected side using a multi-bracket appliance and bite splint fabricated before surgery. After surgery, the contour of the face and the occlusion were favorably maintained. The occlusion was retained by intermaxillary fixation for 3 days after surgery. A functional appliance (bionator) was applied for 7 months after surgery.

The resected specimen, measuring 6.5 cm × 5.0 cm × 3.2 cm, included the right mandibular bone and the surrounding muscle tissue. The second deciduous molar and the first molar, as well as the surrounding oral mucosa, were also included in the specimen. On the cut surface, an ill-demarcated soft mass, measuring 2.5 cm × 1.5 cm × 1.0 cm in size, was located in the mandible, with the destruction of cortical bone and extending directly to the submucosa (Fig. 5A). Histologically, the tumor cells had almost disappeared and were replaced by fibrosis. The residual tumor cells were seen scattered at the periphery of fibrosis, with backgrounds of edema and hemorrhage, which underwent marked degenerative change with hyperchromatic, irregularly shaped nuclei (Fig. 5B and

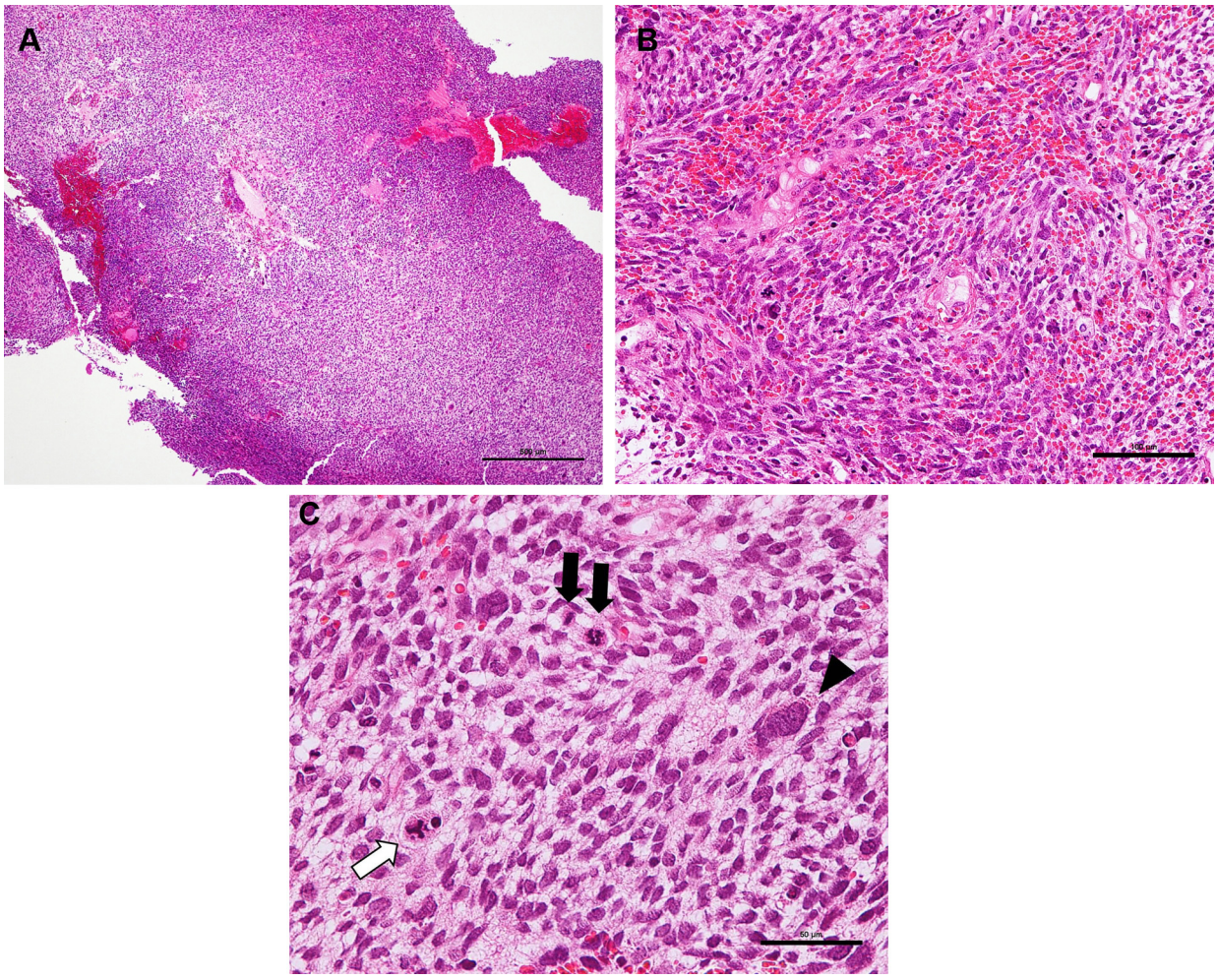


**Fig. 3.** Histopathological examination: low power (A), (B) and high power view (C). (A) The tumor was highly cellular with focal necrosis and hemorrhage. (B) The tumor is cellular with proliferation of spindle-shaped cells with pleomorphism (20×, hematoxylin and eosin stain (HE)). (C) At high power, spindle-shaped cells with atypical nuclei are intermingled with occasional giant cells with bizarre nuclei (arrow head). Mitotic figures (arrows) are frequently seen with focal atypical mitosis (white arrow) (40×, HE).

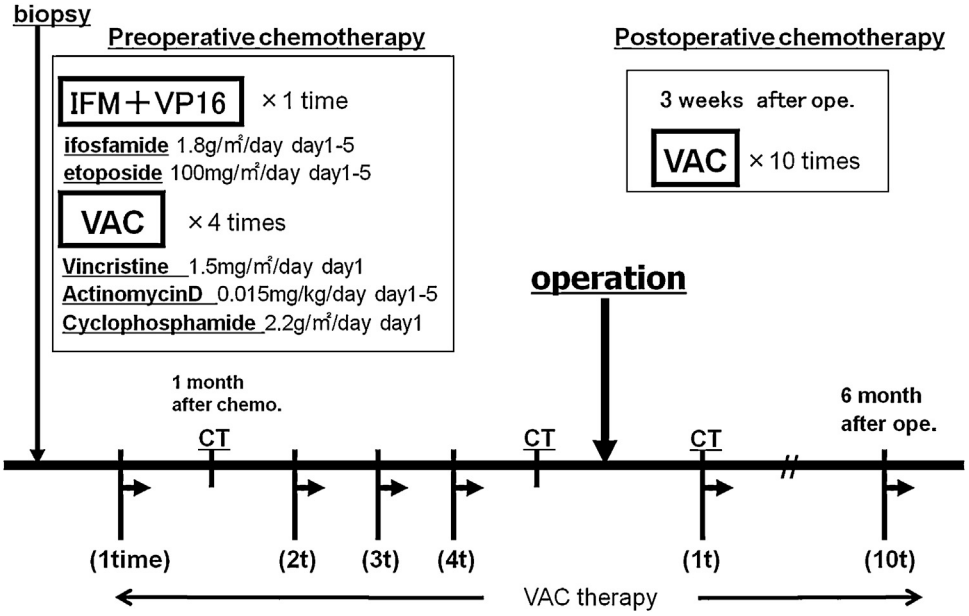


**Fig. 4.** The timeline of chemotherapy (each scale mark is 1 month).

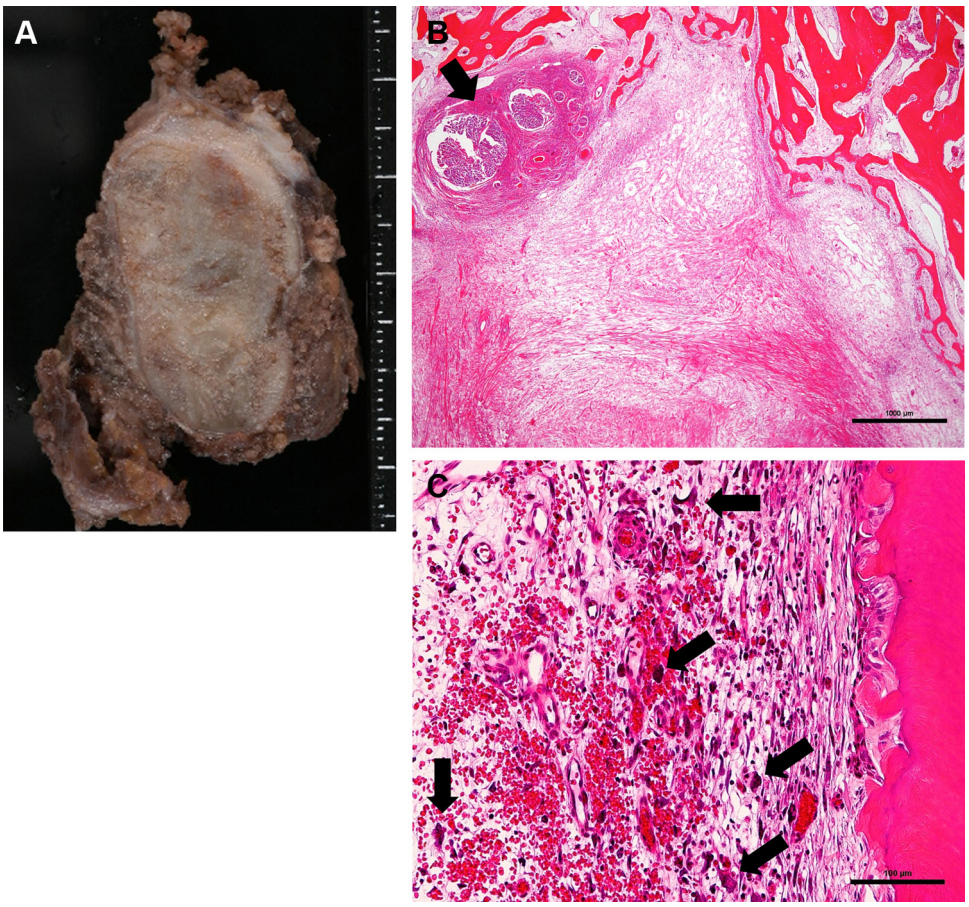


**Fig. 5.** (A) The resected specimen of the mandibular tumor measuring 6.5 cm × 5.0 cm × 3.2 cm includes the right mandibular bone and the surrounding muscle tissue. On the cut surface of the resected specimen, an intraosseous tumor of the mandibular bone shows a fibrous appearance with an expansile and destructive growth pattern. (B) The tumor is replaced by fibrosis with destruction of the mandibular bone with involvement of the inferior alveolar nerve (arrow) (2×, HE). (C) At the periphery of fibrosis, degenerative tumor cells with atypical nuclei (arrows) observed rescattered with hemorrhagic and edematous backgrounds (20×, HE).

**Table 1**
Immunohistochemical examinations of the tissue obtained at biopsy.

| Immunohistochemical examination | Findings |
|---|---|
| Cytokeratin (AE/AE3) | (−) |
| Cytokeratin (CAM5.2) | Focal+ |
| Epithelial membrane antigen | (−) |
| Vimentin | Focal+ |
| Desmin | (−) |
| Myoglobin | (−) |
| Muscle-specific action (HHF35) | (+) |
| Smooth muscle actin (1A4) | (−) |
| Caldesmon | (−) |
| Calponin | (−) |
| S100 protein | (−) |
| GFAP | (−) |
| NSE | (−) |
| CD99 | (−) |
| CD56 | Weak+ |
| c-Kit | (−) |
| HMB45 | (−) |
| BCL-2 | (+) |
| CD45(LCA) | (−) |
| CD3 | (−) |
| CD20 | (−) |
| CD34 | (−) |
| CD31 | (−) |
| Factor VIII-related antigen | (−) |
| D2-40 | (−) |

C). The surgical cut-end of the specimen was negative for tumor cells.

A month after surgical resection, VAC therapy was resumed. For 6 months after surgery, a total of 10 courses of chemotherapy were delivered and the treatment was completed (Fig. 4). At 7 years and 8 months after surgery, CT scans revealed no signs of local recurrence and the patient showed no evidence of distant metastases to the cervical lymph nodes or lung. His maxilla–mandibular relationship was favorable, and the occlusion of the remaining teeth had been maintained using the oral functional appliance (Fig. 6).

## 3. Discussion

Primary high-grade sarcoma rarely arises in the mandibular bone of children. The histological appearance of the tumor was spindle cell like and the pleomorphic morphology was without any specific line of differentiation, which causes difficulty in making pathological diagnosis. In general, histological typing of high-grade sarcomas is often problematic on a biopsy specimen due to intratumoral heterogeneity and undeterminable differentiation status that is often observed in sarcomas. In such instances, the final pathological diagnosis should be made through extensive histological and immunohistochemical examination of surgical specimens. In the present surgical specimen, no additional useful information for pathological diagnosis was obtained, because most of the tumor cells had disappeared by effective preoperative chemotherapy.

According to the World Health Organization (WHO) classification of tumor of bone (2013) [3], differential diagnosis of

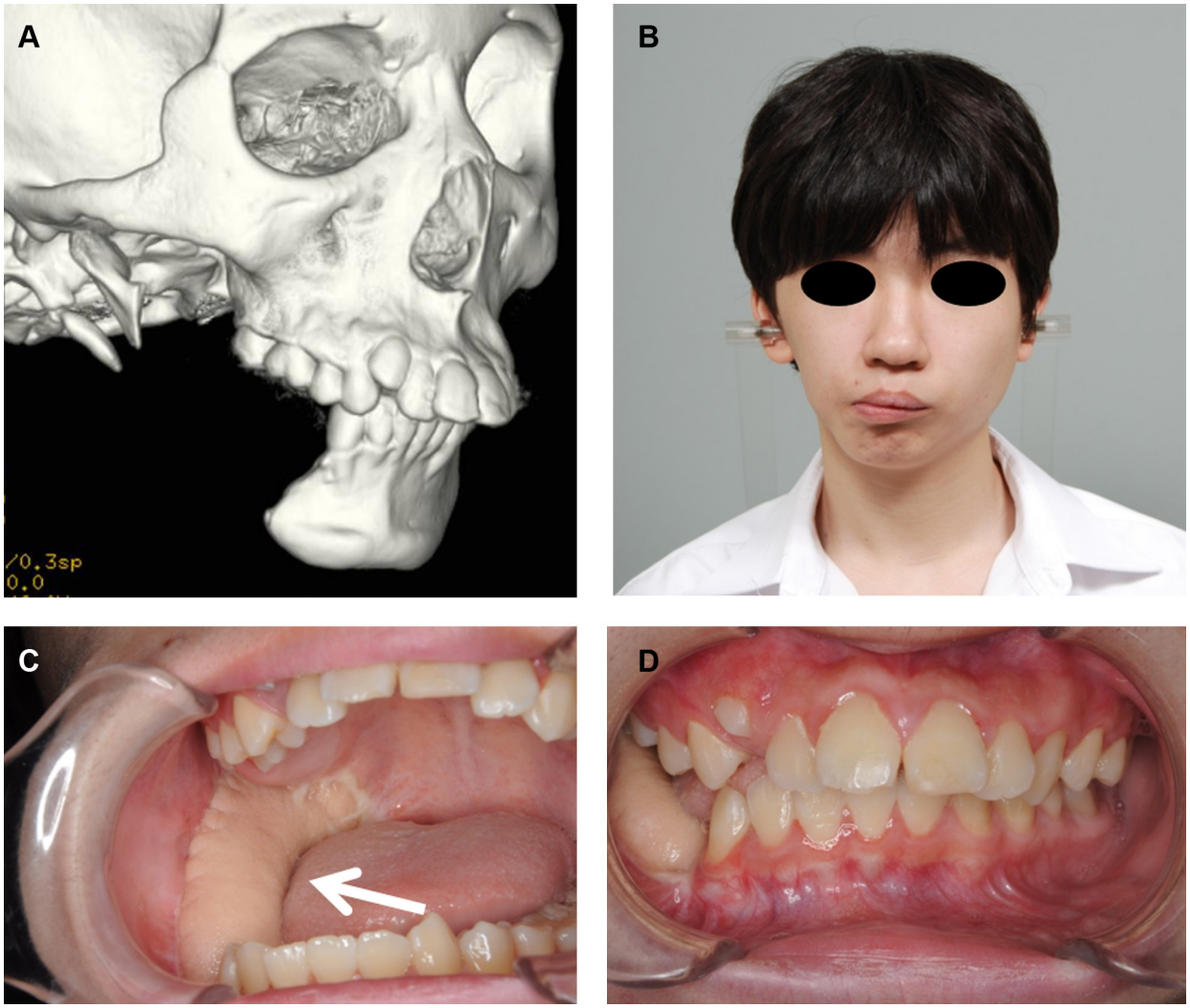


**Fig. 6.** CT image, facial and oral photographs at 7 years and 8 months after surgery. (A) Signs of local recurrence and obvious deformity of the mandible are not seen on the three-dimensional (3D)-CT image. (B) No distinct deformity of the face is found. (C) The reconstructed region in the mandible using a rectus abdominis musculocutaneous flap (arrow). (D) The occlusion has been kept stable.

the present tumor includes spindle-shaped cell and pleomorphic sarcomas such as osteosarcoma (both osteoblastic and fibroblastic subtypes), leiomyosarcoma, undifferentiated high-grade pleomorphic sarcoma, undifferentiated high-grade pleomorphic sarcoma/malignant fibrous histiocytoma and malignant peripheral nerve sheath tumor (MPNST). Although rare, synovial sarcoma, a soft-tissue tumor that shows epithelial differentiation, has been reported as a primary arising from the bone [2]. In this case, monophasic synovial sarcoma was also added to the differential diagnosis because the spindle-shaped cells of the tumor showed weak positivity for both vimentin and cytokeratin. However, it was excluded by negativity for tumor-specific fusion gene SYT-SSX by using RT-PCR. Notably, aberrant expression of the cytokeratin was sometimes observed in sarcomas, which is unrelated to true epithelial differentiation [4]. Immunohistochemically, the tumor showed positivity for HHF35, one of the muscle markers; however, leiomyosarcoma was also excluded by negativity for other smooth muscle markers. Coexpression of vimentin and HHF35 may suggest potential myofibroblastic differentiation, which is occasionally seen in osteosarcoma and undifferentiated pleomorphic sarcoma. Although tumors of the fibrogenic group often show myofibroblastic phenotype, no possible high-grade sarcoma was listed in the classification. MPNST is diagnostically a problematic tumor that often lacks expression of neurogenic markers. However, it is almost unlikely by absence of symptoms suggesting neurofibromatosis 1. Finally, osteosarcoma may also be ruled out, because no evidence of neoplastic bone formation was noted despite pretherapeutic imaging analyses and extensive histological examination of the surgical specimen. In conclusion, the present tumor is exclusively classified as undifferentiated high-grade pleomorphic sarcoma arising from the mandible.

A standard chemotherapy for sarcoma has not been established in childhood except for osteosarcoma, Ewing sarcoma and rhabdomyosarcoma because of the small number of cases. However, the Intergroup Rhabdomyosarcoma Study (IRS) Group reported that VAC therapy was effective for not only rhabdomyosarcoma but also undifferentiated sarcoma [5].

In this case, the patient was given one course of IE therapy, which is effective for sarcoma, while confirmation of the pathological diagnosis was awaited. As the final diagnosis, this tumor was likely a high-grade undifferentiated sarcoma derived from the jaw in childhood, which cannot be classified into any categories. Consequently, VAC therapy was chosen as an induction chemotherapy. We suspected that the VAC therapy was likely to be effective for this tumor

whose biological nature was similar to Ewing's sarcoma, showing marked cellular growth with frequent mitotic figures within the tumor.

The IRS in the United States reported a disease-staging classification based on tumor site, histologic type and pre- and postoperative findings. Treatment has been evaluated to produce the best outcomes and is now considered standard [6–9]. Thus, this case was treated according to 'Group 3' in the IRS Postsurgical Grouping Classification [8]. The treatment protocol requires postoperative radiotherapy. This patient did not receive radiotherapy for four reasons: (1) the tumor was completely resected by surgery, with no evidence of metastasis to regional lymph nodes; (2) the patient responded well to preoperative chemotherapy; (3) there was a risk of development of a secondary cancer; and (4) a disturbance of jaw growth could occur. Late complications occur in 77% of patients with IRS II and III tumors of the head and neck (excluding orbital lesions) [10,11].

Recently, microsurgery is being performed more frequently in children. Nakatsuka et al. reported that the safety and reliability of microsurgery have been established in children [12]. The fibula-free flap technique for reconstruction of the mandible has been reported to have advantages such as providing adequate length, reliable shape, low donor morbidity and a distant location from the mandible to facilitate a multi-team approach. However, hard-tissue reconstruction of the mandible was not performed this time, and a rectus abdominis musculocutaneous flap was used for reinforcement of the defect after the mandibular segmentectomy. The reasons why hard-tissue reconstruction was not performed is that there is no evidence to demonstrate that growth will occur in a reconstructed mandible using the fibula bone as reported by Bidra et al. [13]. Furthermore, we think that the vertical defect in the reconstructed mandible and the long waiting time before starting dental implant placement and functional bone stimulation are major problems in such a young patient [14]. Actually, we think that the space occupied by the mandibular segmentectomy has been maintained by the soft tissue of the rectus abdominis musculocutaneous flap, and the deviation of the mandible on the unaffected side has been minimized using a functional appliance. In future, we are considering the use of the fibula to repair bone defects in adolescence.

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