Osteosarcoma of the Maxilla: Rare Contralateral Cervical Lymph Node Metastasis

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Osteosarcoma (OS) is the most common non-hematopoietic primary malignant bone tumour, accounting for around 19% of malignant bone tumours. It often occurs in the metaphyses of long bones, such as the distal femur and proximal tibia). OS of the jaw is rare, accounting for only about 6% of all OS cases, and the incidence of cervical lymph node metastasis is extremely low, with only a few case reports and small retrospective studies documented in the literature, and OS of the maxilla with contralateral lymph nodes metastasis is even rarer, with no relevant reports to date. In this paper, the present authors report a rare case of contralateral cervical lymph node metastasis of maxillary OS after surgery with no documented ipsilateral involvement and analyse the clinical manifestations, imaging manifestations and treatment of this case in the light of relevant literature. Based on this special rare case, its value and inspiration for the clinical diagnosis and treatment of OS of the jaw are explored.

Keywords: *cervical lymph node metastasis, contralateral metastasis, osteosarcoma of the jaw*
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Osteosarcoma (OS) is the most frequent primary solid malignancy of bone, and its typical symptoms include localised pain, swelling and limited joint motion.[1] The disease is most common in adolescents[2] and tends to develop in the metaphyses of long bones.[3-10] Around 60% of patients are aged between 10 and 20 years,[6] and around 30%~50% of patients experience recurrence of OS. Sixty-eight percent of patients with localised OS survive for 5 years or more, but 20%~30% of them are metastatic or recurrent cases.[4,6,7] The aetiology is unknown, but genetic factors, rapid bone proliferation, radiation exposure and alkylating agent exposure are important factors.[1,3,5] On imaging, tumours may exhibit a variety of appearances including sclerotic, laminated and the classic sunburst patterns.[1,11-13] In addition, OS is characterised by aggressive local invasiveness and a strong capacity to metastasise, predominantly to the lungs,[3,14-16] and to a lesser extent the bones. Haematogenous spread is common, whereas lymph node metastasis is rare,[17,18] with the incidence of the latter ranging from 1.4% to 2.3% in OS,[9,16] but the risk is higher in older patients.[16] Despite the low incidence of lymph node metastasis in OS, its prognosis is relatively poor.[16]

OS of the jaw (JOS) is relatively rare, accounting for approximately 6%~7% cases of all OS,[2,10,13] 6% of tumours of the jaw and less than 1% of all malignant head and neck tumours.[8,11] Unlike other cases of OS that tend to occur in children and adolescents, JOS mainly affects people in their thirties and forties[8,12,13,17] and is most commonly found in the mandible,[2,13] with no notable sex predilection.[10,11,17,18] Patients with JOS present early with swelling (85%~95.5%), pain, oedema, ulcers and tooth mobility, while a few present with cachexia as the first symptom.[12,18] JOS, which tends to recur locally,[11] is unpredictable in its response to chemotherapy, and the role of radiotherapy is limited.[1,10,13] Early radiographs of JOS show a widened periodontium and mandibular neural tube, and more aggressive tumours may exhibit sleeve-like root resorption

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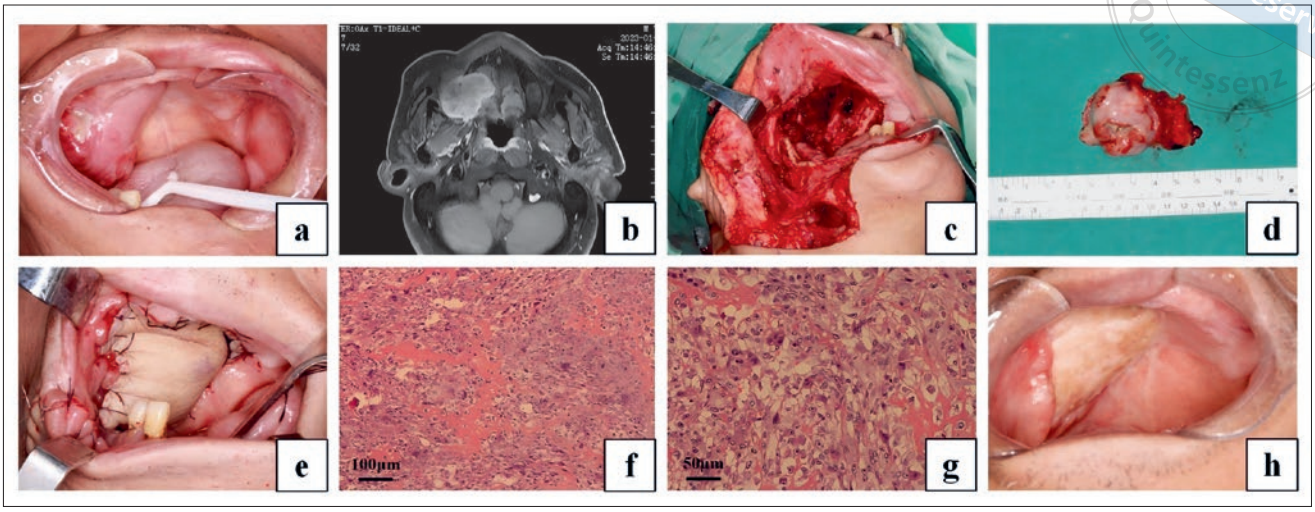

Fig 1a to h Clinical, radiological, surgical and histopathological features of right maxillary OS and postoperative healing. Intraoral photograph of the patient shows masses on the right palate and maxillary gingiva **(a)**. MRI reveals a right palatal tumour involving the right maxillary sinus and nasal cavity **(b)**. Post-maxillectomy pathology suggests a conventional OS **(c and d)**. An anterolateral thigh free flap was chosen for right maxillary bone defect repair during surgery **(e)**. Histopathological findings of the primary site **(f and g)**. Intraoral photograph showing good healing of the repair flap **(h)**.

or tooth subluxation. Periosteal reaction can be seen at the edge of JOS, and the closer the periosteum is to the tumour or the higher the malignancy degree of the tumour is, the more prominent the periosteal reaction is, which manifests itself as a laminated or sunburst pattern.[18] JOS usually has a low metastatic rate and occurs in more advanced stages of the disease, with fewer distant metastases and a relatively high survival rate.[1,10-12] The 5-year survival rate can reach 77%.[2,8] The incidence of mandibular OS metastasis is only 2.6%,[11] and maxillary OS metastasis is even rarer. Meanwhile, lymph node metastasis of maxillary OS mostly occurs in the same side, whereas contralateral metastasis is complicated and needs to break through more tissue barriers, which is extremely rare and has not been reported yet.

The present paper reports a rare case of contralateral cervical lymph node metastasis of maxillary OS after surgery with no documented ipsilateral involvement to provide diagnostic aid to clinicians. The Institutional Review Board of the School & Hospital of Stomatology, Wuhan University granted approval for the retrospective analysis (WDKQ2020-A954).

Case presentation

The patient sought medical treatment in January 2023 for a right palatal mass (Fig 1a). The mass measured 4 × 5 cm and was moderately painful and firm in consistency, and the tongue exhibited normal mobility. The patient had taken oral anti-inflammatory medication with no significant improvement. Then, the patient experienced decreased vision in the right eye and headache. MRI revealed a markedly enhancing abnormal signal, which showed a right palatal tumour involving the right maxillary sinus and nasal cavity (Fig 1b). Immunohistochemical staining revealed aberrant high expression of P53, focal weak expression of MDM2, negative expression of CDK4 and a low Ki-67 proliferation index (Fig 2). Combined with the biopsy findings, it confirmed the diagnosis of a malignant osteogenic tumour in the right palate. The patient subsequently underwent right total maxillectomy under general anaesthesia, and the defect was repaired with an anterolateral thigh free flap during the same period (Fig 1c to e). Although the patient did not undergo a right cervical lymph node dissection, the right submandibular gland as well as two lymph nodes on the superficial surface of the submandibular gland were removed during surgery to ensure that there was enough space in the neck to accommodate the vascular pedicle of the anterolateral thigh free flap. Microscopic examination (Fig 1f) revealed a hypercellular tumour with an infiltrative growth pattern and abundant formation of osteoid matrix. Under higher magnification (Fig 1g), markedly atypical spindle-shaped tumour cells were observed, featuring enlarged, hyperchromatic nuclei and readily identifiable pathological mitoses. The tumour cells were directly associated with the production of eosinophilic osteoid, findings consistent with conventional OS. The postoperative pathologic findings

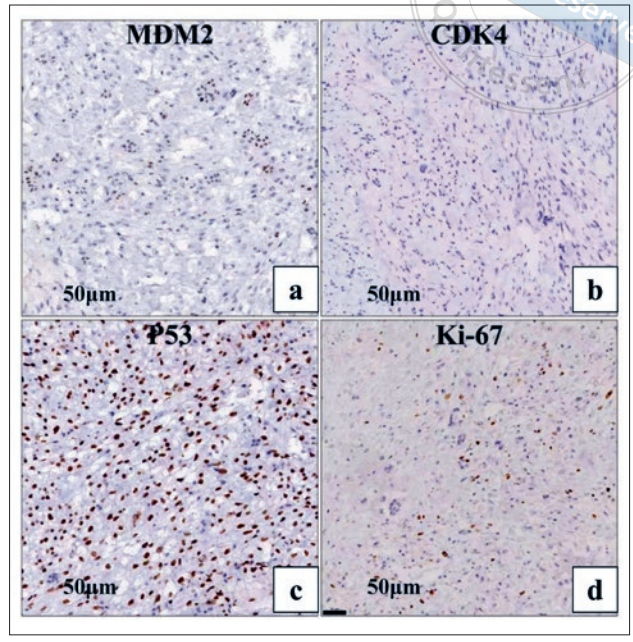

Fig 2a to d Immunohistochemical findings of the primary tumour showing focal weak MDM2 expression, negative CDK4 expression, diffuse strong P53 positivity and low Ki-67 proliferation index. MDM2: tumour cells exhibited focal weak positive expression and the proportion of positive cells was low **(a)**. CDK4: tumour cells showed negative expression **(b)**. P53: tumour cells displayed diffuse strong positive expression, with the proportion of positive cells exceeding approximately 80%, which represented a pattern of aberrant accumulation **(c)**. Ki-67: tumour cells presented scattered weak positive expression with a low proliferation index, indicating weak proliferative activity of the tumour cells **(d)**.

confirmed a diagnosis of conventional OS, and no metastatic cancer was found in the two lymph nodes sent for examination. The patient underwent postoperative radiation therapy (the high-risk area was given a dose of 60 to 66 Gy and the low-risk area a dose of 50 to 54 Gy) and recovered well after 22 months (Fig 1h). Local recurrence of the tumour was found 7 months after surgery; as a result, the right nasal base and part of the flap tissue were removed in a secondary surgical procedure, and no metastasis was found in the ipsilateral and contralateral lymph nodes during the same period.

Fifteen months after the second surgery, the left side of the patient's neck was palpable with obvious lymph node enlargement, and MRI showed that the signal in the right maxillary area was uniform, the boundary was clear, there were no abnormal nodules, bone destruction, invasive changes or signs of recurrence, the volume of lymph nodes in the left neck region II was larger than normal and the signal was increased, there was no central necrosis and the surrounding tissues were not significantly invaded (Fig 3a). In the contrast-enhanced mode of colour Doppler ultrasound, the enlarged lymph node presents as slight hyperperfusion, from the periphery to the centre, rapid wash-in and rapid wash-out, suggesting metastatic lymph node enlargement; as a result, the patient was readmitted to hospital. Given the rarity of cervical lymph node metastasis in JOS, the enlarged lymph node in the superior deep cervical region was first removed and quickly biopsied during the operation, confirming OS lymph node metastasis (Fig 3b to d), and then dissection of the left modified radical lymphatic nodes was performed immediately after (Fig 3e and f). Microscopic examination showed partial effacement of the lymph node architecture by tumour tissue, with neoplastic cells arranged in nests (Fig 3g). At higher magnification (Fig 3h), the morphological features of the metastatic cells were similar to those of the primary tumour, confirming the diagnosis of lymph node metastasis of OS. The postoperative pathological result also showed that the remaining lymph nodes (6 left submandibular and submental lymph nodes, 8 left deep superior cervical lymph nodes, 19 left deep middle cervical lymph nodes and 9 left deep lower cervical lymph nodes) were free of tumour metastasis.

Discussion

Most cases of OS present with osteoblastic, osteolytic or mixed appearances on imaging, without characteristic features; thus, a biopsy specimen is usually required to confirm the diagnosis.[12] In this case, computed tomography examination in late January 2023 showed a probable neoplastic lesion. Pathology examination in February showed round or polygonal tumour cells with obvious cellular heterogeneity, bone matrix formation around the cells and occasional calcification focus within the tumour, which led to the diagnosis of conventional OS; MRI examination in September 2023 showed probable OS recurrence, pathological examin-

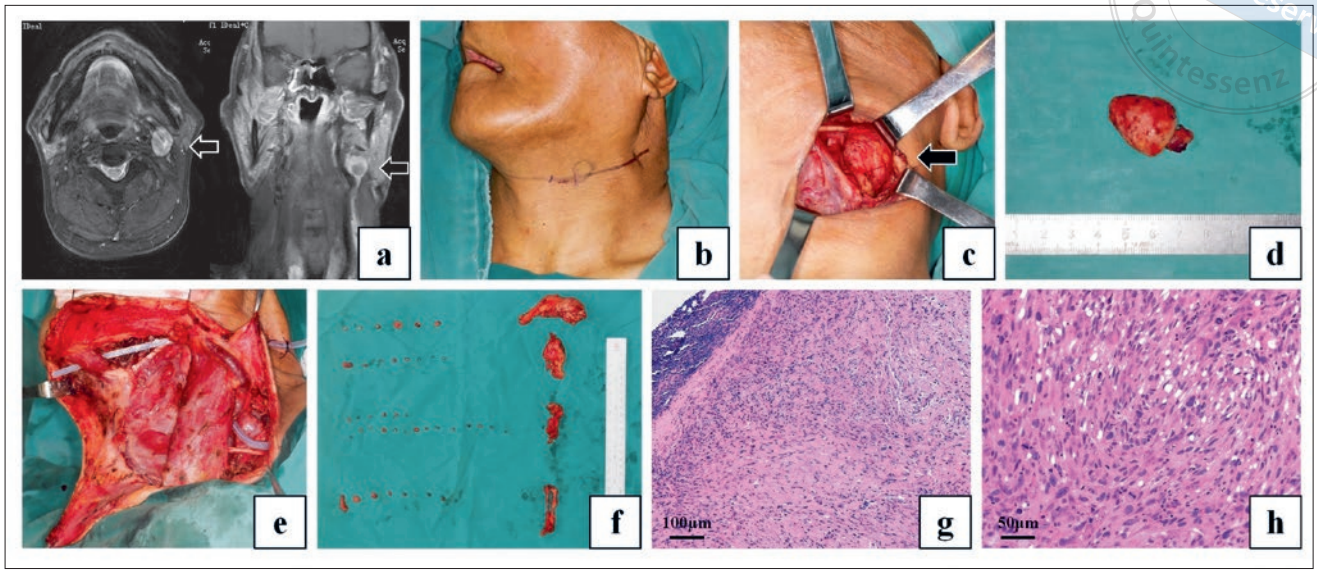

Fig 3a to h Imaging, surgical management and histopathological confirmation of contralateral cervical lymph node metastasis of OS. MRI shows lymph nodes enlargement in the left cervical region II **(a)**. Neck mass exploration was performed, and two superior deep cervical lymph nodes were removed and sent for quick frozen-section examination during the operation, which indicated recurrence **(b to d)**. Dissection of the left modified radical lymphatic nodes was performed subsequently **(e and f)**. Histopathological findings for the cervical region **(g and h)**.

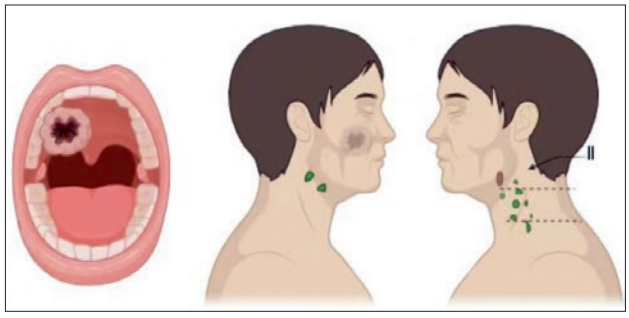

Fig 4 Schematic diagram of the metastasis process.

ation showed atypical spindle cells forming bone matrix directly and invasive growth of the tumour, identifying it as the recurrence of OS; colour Doppler ultrasound examination in September 2024 suggested metastatic lymph node enlargement; and the biopsy specimen showed OS metastases in the cervical lymph nodes, with karyokinesis visible. The metastasis process is shown in Fig 4.

Compared to ipsilateral lymph node metastasis in JOS, contralateral metastasis is extremely rare. The present case serves as an example of this. The primary tumour was located in the right maxilla. Despite the occurrence of local recurrence, ipsilateral cervical lymph node metastasis was never identified throughout the clinical course; instead, an isolated metastatic focus emerged in the left side of the neck level II. This unusual presentation prompted speculation regarding the underlying mechanism. MRI showed a clean primary site, an isolated metastatic deposit and the absence of a connecting pathway, which supported the diagnosis of a discrete metastatic event rather than contiguous spread.

Lymphatic drainage in the head and neck region is predominantly ipsilateral under physiological conditions; however, certain midline or paramedian structures possess lymphatic networks that may drain to bilateral or contralateral nodal basins due to anatomical variations and the existence of crossing lymphatic channels. The initial surgical intervention and subsequent reconstruction may have altered the normal lymphatic anatomy. The patient underwent a right total maxillectomy with reconstruction using an anterolateral thigh free flap. Although the patient did not undergo a right cervical lymph node dissection, the right submandibular gland as well as two lymph nodes on the superficial surface of the submandibular gland were removed during surgery to ensure that there was enough space in the neck to accommodate the vascular pedicle of the anterolateral thigh free flap. This iatrogenic disruption could have obstructed or diverted the ipsilateral lymphatic drainage pathways. Such an alter-

ation might have subsequently redirected lymphatic flow, potentially facilitating the spread of recurrent tumour cells to the contralateral nodal basin.

The possibility of "skip metastasis" must be considered, wherein tumour cells bypass the primary echelon lymph nodes and metastasise directly to more distal or contralateral nodes. Although this phenomenon has a low reported incidence[21] and is more frequently described in malignancies such as melanoma or papillary thyroid carcinoma, the aggressive tumour biology observed in this case could plausibly explain such aberrant behaviour. Consequently, this mechanism cannot be ruled out.

Contralateral cervical lymph node metastasis is extremely rare and easily overlooked. This case describes the rare situation in which OS of the maxilla develops contralateral cervical lymph node metastasis but ipsilateral lymph node metastasis does not occur, and reviews the clinical, imaging and pathological features of JOS with a strong emphasis on lymph node metastasis, which provides a valuable reference for the diagnosis and management of analogous cases. Therefore, it is recommended that for patients with maxillary OS, particularly those with primary tumours situated near the midline or with a history of extensive surgery that may have altered regional lymphatic drainage, bilateral neck involvement should be incorporated into the routine protocol for long-term follow-up and radiological surveillance. This heightened vigilance facilitates the early detection of aberrant lymph nodes, enabling timely intervention.

Conclusion

Contralateral cervical lymph node metastasis from maxillary OS is extremely rare and may occur even in the absence of ipsilateral nodal involvement. This case highlights the need for long-term and bilateral cervical surveillance in patients with maxillary OS, particularly after extensive surgery that may alter lymphatic drainage patterns.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Drs Jia Jun SONG and Ren Xiu FAN contributed to the investigation and manuscript draft; Drs Ren Xiu FAN, Liang MAO and Zi Li YU contributed to the manuscript review and editing; Drs Lei CHEN, Si Rui MA and Jun JIA contributed to the study supervision and manuscript revision. All authors gave final approval and agreed to be accountable for all aspects of the work.

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