CASE REPORT

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Ewing's sarcoma/primitive neuroectodermal tumour occurring in the maxillary sinus*

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SUMMARY

A 12-year-old-boy complained of swelling of the left cheek. Fiberscopic examination revealed the presence of a soft reddish mass in the middle meatus of the left nostril. CT scan showed a large mass completely filling the left maxillary sinus. The lesion originated from the maxillary sinus and extended to the middle nasal meatus; bone destruction and invasion of the subcutaneous tissue of the cheek were noted. T2-weighted MRI images revealed a heterogeneous signal in the left maxillary sinus. Under general anaesthesia, biopsies were obtained through an intraoral incision. On pathology, atypical cells containing irregular nuclei with scanty cytoplasm were noted. The tumour cells were strongly positive for CD99 and reacted weakly with NSE however the cells were negative for synaptophysin, LCA and cytokeratin on immunohistochemical examination. Based on these findings, the tumour was diagnosed as a Ewing's sarcoma/primitive neuroectodermal tumour. The patient was treated with radiotherapy and combination chemotherapy; subsequently, the tumour's size decreased markedly. After 20 months of follow-up, the patient showed no evidence of local tumour growth or metastasis.

Key words: Ewing's sarcoma, primitive neuroectodermal tumor, maxillary sinus, CD99

INTRODUCTION

Ewing's sarcoma is a malignant neoplasm consisting of small round cells and is frequently found in the long bones of the limbs or the pelvis [1]. In contrast, only 2-3% of all Ewing's sarcomas are found in the head and neck area [2]. The mandible and the skull base are the two most common primary sites for Ewing's sarcoma in the head and neck region [3]. Recently, Ewing's sarcoma has been linked with soft tissue neoplasms originally described as primitive neuroectodermal tumours (PNET); thus, the term Ewing's sarcoma / primitive neuroectodermal tumour (ES/PNET) is currently favoured for this tumour family [4]. Furthermore, in the WHO classification, Ewing's sarcoma and PNET are labelled together under the rubric of EWS/PNET [3]. It is extremely rare for ES/PNET to occur in the nasal cavity and the paranasal sinuses; only 12 cases have been reported in the English literature to date (Table 1) [2, 5-14].

In this report, we describe a rare case of ES/PNET occurring in the maxillary sinus and discuss its clinical features.

CASE REPORT

A 12-year-old boy visited our hospital with a painless swelling of the left cheek of 2 months' duration after having been punched in the face by his brother. There was no history of rhinorrhea, nasal obstruction, epistaxis or facial paraesthesia. On initial clinical examination, the patient's general condition was good. On physical examination, an immobile and elastic soft mass was noted on the left cheek. A swelling of the left canine fossa was observed on examination of the oral cavity. Fiberscopic examination revealed a soft reddish mass located in the middle nasal meatus. On plain radiography of the paranasal sinuses, the left maxillary sinus was enlarged and completely opacified and the medial wall of the maxillary sinus was not clearly defined compared to the right maxillary sinus. The CT scan showed an enhancing soft tissue mass without calcification, which involved the entire left maxillary sinus and invaded the subcutaneous tissue of the left cheek. Destruction of the medial and lateral walls of the left maxillary sinus was also observed. However, the orbital contents and the cranial fossa were intact (Figure 1). The MRI showed a low-intensity mass on T1-weighted images and a heterogeneous high-intensity mass on T2-weighted images. The tumour was markedly enhanced by gadolinium.

A biopsy was performed under general anaesthesia through an intraoral incision. On histology, the tissue sample was found to contain small, round cells with large, round-to-ovoid nuclei and scant cytoplasm (Figure 2). Mitotic figures were occasionally seen. Immunostaining was positive for the MIC-2 gene product (CD99) (data not shown), weakly positive for NSE and negative for muscle, epithelial and leukocyte markers. The MIB-1-labeling index was 15%. Molecular studies using poly-

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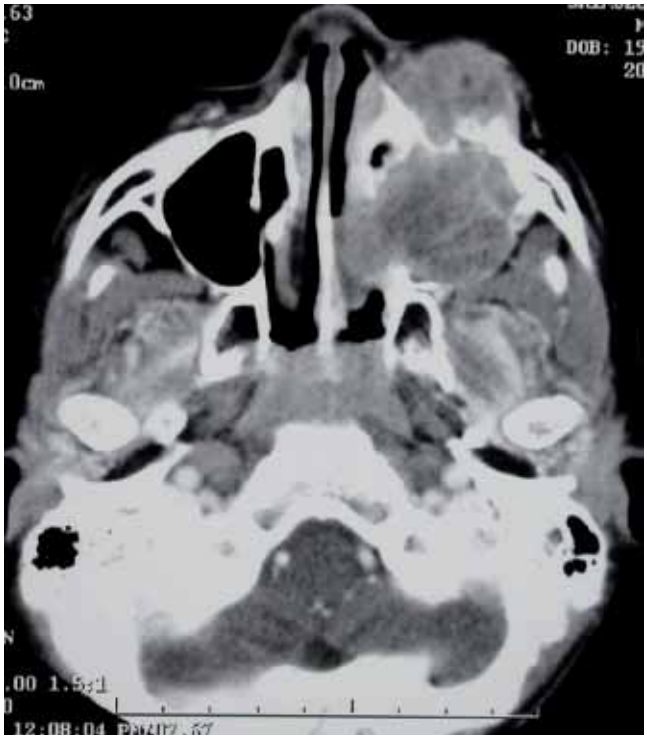

Figure 1. Axial CT images show an enhancing mass invading the left maxillary sinus, destroying the medial and lateral wall.

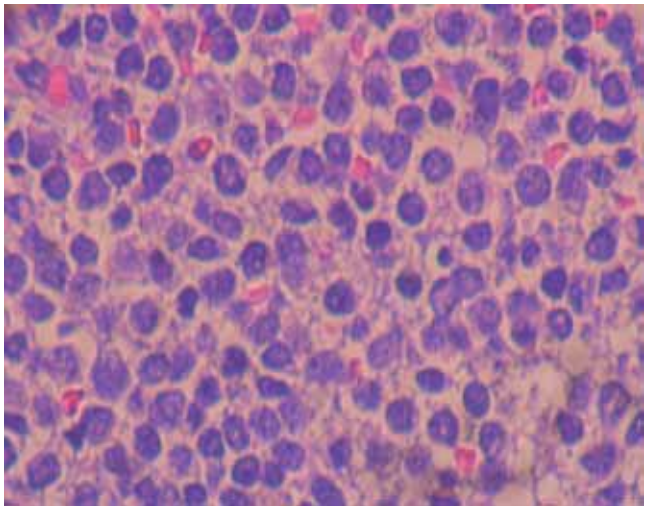

Figure 2. The tumour cells have large, round-ovoid nuclei and scant cytoplasm. Mitotic figures are occasionally seen.

merase chain reaction (PCR) analysis confirmed a chromosomal translocation between the EWS gene (22q12) and ERG gene (21q22). Among the many chromosomal changes, trisomy 8 was observed.

Taking into account the above, the tumour was diagnosed as ES/PNET. Intrathoracic and bone metastases were excluded following a CT scan of the chest and FDG-PET. Furthermore, microscopic examination of samples obtained from the iliac

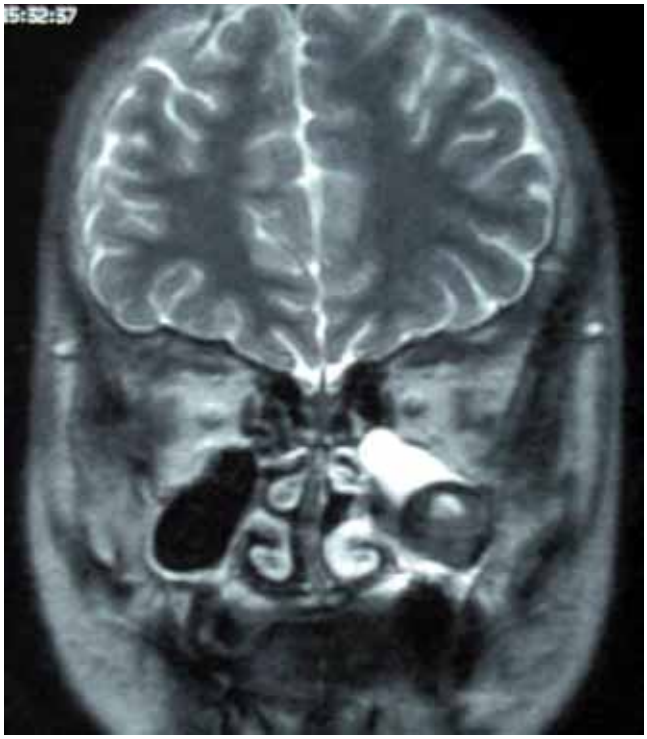

Figure 3. At the end of combined chemotherapy and radiotherapy, a decrease in tumour size can be seen on coronal MRI.

bone showed no evidence of bone marrow metastases. Taking into account the deformity that could be produced by surgery, the patient was initially treated with combined chemotherapy/radiotherapy. The chemotherapy consisted of vincristine, doxorubicin, cyclophosphamide, ifosamide, and etoposide given for 48 weeks. At week 12, the patient received radiation therapy for local control because the tumour size had not decreased by that time. In order to treat ES/PNET, a radiation dose above 40 Gy is considered necessary, while doses between 55 Gy and 60 Gy are usually given for definitive radiotherapy [15]. In this case, radiation therapy was stopped at 45 Gy due to severe dermatitis, stomatitis and pancytopenia. MRI performed after this treatment showed that the tumour had decreased markedly in size (Figure 3). At that time, the patient was offered surgical resection, but he declined.

The patient continues to be followed-up. At 20-month follow-up, the patient showed no evidence of local tumour growth or metastasis.

DISCUSSION

After osteosarcoma, ES/PNET is the second most frequent primary malignant tumour occurring in bone. However, it is rare for ES/PNET to be found in the head and neck region. The most common symptom in patients with ES/PNET is locoregional pain that does not completely disappear during the night [16]. When ES/PNET occurs in the maxillary sinus, the primary symptom is facial swelling, which is sometimes accompanied by facial pain due to inflammation of the maxillary sinuses and orbital involvement [17].

Table 1. All reported cases until June 2007.

Case/Gender/ Age in y	Chief Complaint	Location	Therapy	Metastasis	Duration	Recurrence
1[5]) /M/39	Epistaxis, Nasal obstruction, Malar pain	Middle turbinate	Craniofacial resection, RT	None	2 years	None
2[6]) /M/7	Diplopia	Nasal cavity, Ethmoid sinus, Orbita	Craniofacial resection, chemo	None	No record	No record
3[7]) /M/14	Mass at the nose	Ethmoid sinus, Nasal cavity, Cribriform plate	Craniofacial resection, chemo, RT	None	5 years	None
4[7]) /F/28	Mass at the nose	Nose	Partial rhinectomy, chemo, RT	None	2 years	None
5[8]) /F/11	Nasal obstruction	Maxillary sinus	Chemo, RT	Lung	10 months	Stable
6[9]) /F/57	Nasal obstruction, Headache, Anosmia	Nasal cavity, Maxillary sinus	Chemo, RT	Cervical LN, Bone	3 months	Died
7[10]) /M/19	No record	Nasal cavity	Denker operation, RT	None	9 months	None
8[11]) /F/20	Nasal obstruction, Epistaxis	Nasal cavity	Surgery, chemo, RT	None	1 year	None
9[2]) /F/14	Nasal obstruction, Epistaxis	Ethmoid sinus	Ethmoidectomy, chemo, RT	None	No record	No record
10[12]) /F/23	Nasal obstruction, Epistaxis	Maxillary sinus, Nasal cavity	Lateral rhinotomy, chemo, RT	None	59 months	None
11[13]) /F/9	Swelling of the maxilla	Nasal cavity, Ethmoid sinus, Orbita	Chemo	None	No record	No record
12[14]) /F/16	Swelling of the cheek	Maxillary sinus	Chemo, RT	None	1 year	None
Present case /M/12	Swelling of the cheek	Maxillary sinus	Chemo, RT	None	20 months	Stable

Although primary malignant tumours in the maxillary sinuses are rare in children, a tumour must be considered in the differential diagnosis when complete opacification of one sinus and bone destruction of the sinus walls are observed on radiographic examinations [(8)]. Rhabdomyosarcoma is the most frequent paediatric maxillary malignant tumour, followed by malignant lymphoma. However, on CT examination, rhabdomyosarcoma of the maxillary sinus presents as a poorly defined, non-homogenous soft-tissue mass that destroys adjacent bone [(18)]. Yasumoto et al. [(19)] reported that mucosal thickening with periantral soft tissue infiltration might suggest an early stage of malignant lymphoma of the maxillary sinus. The characteristic periosteal 'onion-skinning' reaction seen in the long bones is not common in maxillary sinus ES/PNET [(20)]. In the present case, the CT scan showed that the tumour had originated from the anterior wall of the maxillary sinus and had extended both posteriorly and anteriorly. Compared to the tumour's volume, the bone destruction of the anterior wall of the maxillary sinus seemed limited. These findings may be helpful in making the diagnosis of maxillary sinus ES/PNET by CT.

The definitive diagnosis of ES/PNET depends on histology and molecular genetic confirmation. ES/PNET is one of the group of neoplasms collectively referred to as "small round cell tumours of childhood", which include neuroblastoma, rhabdomyosarcoma, lymphoma, and the Ewing family of tumours [(21)]. On histology, these neoplasms have narrow sheets of poorly differentiated cells with uniform, round or oval nuclei and scant cytoplasm [(22)]. However, it is not easy to distinguish ES/PNET morphologically from other small round cell tumours. Immunohistochemistry is essential in order to make the diagnosis of ES/PNET; positivity to CD99 (MIC-2), with membranous accentuation, is considered to be characteristic of ES/PNET [(23)]. Although lymphoblastic lymphoma is also strongly immunoreactive to CD99 and has a membrane pattern that is similar to ES/PNET, lymphoblastic lymphoma is immunoreactive to leukocyte common antigen (LCA) (CD45), while ES/PNET is not [(15)]. Neuroblastoma is immunoreactive to NSE, S-100 and neurofilament protein [(7)].

Rhabdomyosarcoma is also immunoreactive to CD99, but the staining is usually focal, weak, and cytoplasmic [(15)]. In addition, rhabdomyosarcoma is immunoreactive to desmin and actin [(6)]. The present case demonstrated immunostaining that was weakly positive to NSE, but negative to LCA (CD45), cytokeratin, and synaptophysin.

PCR molecular analysis is also helpful for making the diagnosis of ES/PNET. About 85% of ES/PNETs show the characteristic chromosomal translocation between chromosomes 11 and 22, the t(11;22)(q24;q12) [(24)]. In about 10% of ES/PNETs, a vari-

ant translocation t(21;22)(q22;q12) is observed as in the present case [15]. In addition to reciprocal chromosomal translocations, trisomies 8 and/or 12 are observed in one-third to half of the cases [25]. Cases demonstrating the EWS/FLI1 fusion are reported to have a better prognosis than those with other variant gene fusions [26].

Local surgical control of the primary lesion in combination with systemic chemotherapy control of subclinical micrometastases is considered to be fundamental for the treatment of ES/PNET [17].

Alobid et al. presented the case of a 23-year-old woman with ES/PNET of the maxillary sinus [12]. The patient had a surgical resection, followed by chemotherapy and radiotherapy. This resulted in 59 months of disease-free follow-up, which is the longest follow-up of all reported cases (Table 1). On the other hand, Coskun et al. reported a case of maxillary sinus ES/PNET treated with chemotherapy and radiotherapy [14]. The patient had been followed for one year without recurrence.

In our case, surgical resection was recommended after combination chemotherapy and radiotherapy, but the patient declined surgery. The patient shows no evidence of local tumour growth; however, if his general condition permits, Cyberknife therapy might be considered as a treatment option, though its effectiveness has not yet been demonstrated.

In summary, we have described the case of a 12-year-old male with ES/PNET of the maxillary sinus. It is difficult to differentiate ES/PNET of the maxillary sinus from similar tumours, such as rhabdomyosarcoma, based on clinical and radiological examinations. Histological and immunohistochemical examinations are required to make the diagnosis. Although ES/PNET of the maxillary sinus is rare, when a patient presents with a unilateral maxillary lesion, the possibility of malignancies, including ES/PNET, must be considered and biopsies performed.

REFERENCES

1. Wilkins RM, Pritchard DJ, Burgert EO Jr, Unni KK. Ewing's sarcoma of bone. Experience with 120 patients. Cancer. 1986; 58: 2551-2555.
2. Aferzon M, Wood WE, Powell JR. Ewing's sarcoma of the ethmoid sinus. Otolaryngol Head Neck Surg. 2003; 128: 897-901.
3. Wenig BM, Prasad ML, Dulfuerov P, Fanburg-Smith JC, Kapadia SB, Tohmpson LDR. Neuroectodermal tumours. In: Barnes L, Eveson JW, Reichart P, Sidransky D, eds. World Health Organization Classification of Tumours. Pathology and Genetics of Head and Neck Tumours. Lyon: IARC Press, 2005; 65-66.
4. Batsakis JG, El-Naggar AK. Ewing's sarcoma and primitive neuroectodermal tumors; cytogenic cynosures seeking a common histogenesis. Adv Anat Pathol. 1997; 4: 207-220.
5. Pontius KI, Sebek BA. Extraskeletal Ewing's sarcoma arising in the nasal fossa. Light-electron microscopic observations. Am J Clin Pathol. 1981; 75: 410-415.
6. Lane S, Ironside JW. Extra-skeletal Ewing's sarcoma of the nasal fossa. J Laryngol Otol. 1990; 104: 570-573.
7. Howard DJ, Daniels HA. Ewing's sarcoma of the nose. Ear Nose Throat J. 1993; 72: 277-279.
8. Filiatrault D, Jequier S, Brochu P. Pediatric case of the day. Primitive neuroectodermal tumor (PNET) of the right maxillary sinus. Radiographics. 1993; 13: 1397-1399.
9. Toda T, Atari E, Sadi AM, Kiyuna M, Kojya S. Primitive neuroectodermal tumor in sinonasal region. Auris Nasus Larynx. 1999; 26: 83-90.
10. Csokani LV, Liktor B, Arato G, Helffrich F. Ewing's sarcoma in the nasal cavity. Otolaryngol Head Neck Surg. 2001; 125: 665-667.
11. Boor A, Jurkovic I, Friedmann I, Plank L, Kocan P. Extraskeletal Ewing's sarcoma of the nose. J Laryngol Otol. 2001; 115: 74-76.
12. Alobid I, Sprekelsen MB, Alos L, Benitez P, Traserra J, Mullol J. Peripheral primitive neuroectodermal tumour of the left maxillary sinus. Acta Otolaryngol. 2003; 123: 776-778.
13. Howarth KL, Khodaei I, Karkanevatos A, Clarke RW. A sinonasal primary Ewing's sarcoma. Int J Pediatr Otorhinolaryngol. 2004; 68: 221-224.
14. Coskun BU, Cinar U, Savk H, Basak T, Dadas B. Isolated maxillary sinus Ewing's sarcoma. Rhinology. 2005; 43: 225-228.
15. Bernstein M, Kovar H, Paulussen M, et al. Ewing's sarcoma family of tumors: current management. Oncologist. 2006; 11: 503-519.
16. Widhe B, Widhe T. Initial symptoms and clinical features in osteosarcoma and Ewing sarcoma. J Bone Joint Surg Am. 2000; 82: 667-674.
17. Infante-Cossio P, Gutierrez-Perez JL, Garcia-Perla A, Noguer-Mediavilla M, Gavilan-Carrasco F. Primary Ewing's sarcoma of the maxilla and zygoma: report of a case. J Oral Maxillofac Surg. 2005; 63: 1539-1542.
18. Latack JT, Hutchinson RJ, Heyn RM. Imaging of rhabdomyosarcomas of the head and neck. Am J Neuroradiol. 1987; 8: 353-359.
19. Yasumoto M, Taura S, Shibuya H, Honda M. Primary malignant lymphoma of the maxillary sinus: CT and MRI. Neuroradiology. 2000; 42: 285-289.
20. Siegal GP, Oliver WR, Reinus WR, et al. Primary Ewing's sarcoma involving the bones of the head and neck. Cancer.1987; 60: 2829-2840.
21. Cohn SL. Diagnosis and classification of the small round-cell tumors of childhood. Am J Pathol. 1999; 155: 11-15.
22. Wilson DJ, Dailey RA, Griffeth MT, Newton CJ. Primary Ewing sarcoma of the orbit. Ophthal Plast Reconstr Surg. 2001; 17: 300-303.
23. Stevenson AJ, Chatten J, Bertoni F, Miettinen M. CD99 (p30/32MIC2) neuroectodermal/Ewing's sarcoma antigen as an immunohistochemical marker: review of more than 600 tumors and the literature experience. Appl Immunohistochem. 1994; 2: 231-240.
24. Turc-Carel C, Aurias A, Mugneret F, et al. An evaluation of 85 cases of remarkable consistency of t(11;22)(q24:q12). Cancer Genet Cytogenet. 1988; 32: 229-238.
25. Maurici D, Perez-Atayde A, Grier HE, Baldini N, Serra M, Fletcher JA. Frequency and implications of chromosome 8 and 12 gains in Ewing sarcoma. Cancer Genet Cytogenet. 1998; 100: 106-110.
26. de Alava E, Kawai A, Healey JH, et al. EWS-FLI1 fusion transcript structure is an independent determinant of prognosis in Ewing's sarcoma. J Clin Oncol. 1998; 16: 1248-1255.

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