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Case Report

Ewing's sarcoma family of tumors of the maxillary sinus: a case report of multidisciplinary examination enabling prompt diagnosis

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Abstract: There have been approximately 10 reports in English literature of cases of Ewing's sarcoma family of tumors (EFT) arising in the maxillary sinus. In this location, some tumors mimic EFT, and are more frequently encountered. Herein, we present an additional case of an EFT originating in the maxillary sinus. The patient was a 15-year-old boy complaining of a non-tender swelling of the left cheek. Laboratory tests showed no abnormalities. Computed tomography and magnetic resonance imaging revealed a mass centered in the maxillary sinus with degeneration of the surrounding bones. Pathological examination along with flow cytometry and G-banding enabled the prompt diagnosis of EFT with the *EWS/FLI1* fusion gene. The patient is planned to undergo chemotherapy. An origin in the head and neck and the presence of the typical *EWS/FLI1*, in conjunction with an opportunity for immediate treatment, may predict a relatively better prognosis for EFT in our case.

Keywords: Ewing's sarcoma family of tumors, maxillary sinus, pathology, flow cytometry, G-banding

Introduction

The Ewing's sarcoma family of tumors (EFT) comprises the second most common malignant tumors of the bone or soft tissue in children, adolescents, and young adults [1, 2]; EFT includes several subsets of tumors: Ewing's sarcoma (ES) of the bone (ESB); extraosseous ES (EES); peripheral primitive neuroectodermal tumors of the bone (pPNET); and malignant small-cell tumors of the thoracopulmonary region, or Askin's tumor. All these tumors are known to be of neuroectodermal origin [3]. The degree of neural differentiation is considered in order to determine the histopathological subclassification of the EFT. Classical ES (ESB or EES) is characterized by minimal evidence of neural differentiation; pPNET shows evidence of neural differentiation. Since biological behavior, prognosis, and treatment are similar for all subsets of EFT, this histopathological subclassification may not correspond to clinical strategies [3].

Ewing's sarcoma family of tumors of the head and neck are rare and account for only 1% to 4% of all EFTs, as the extremities and the trunk are commonly affected sites [2, 4, 5]. In the head and neck region, the jaw and skull bones are typically the affected sites [6]. The head and neck is rarely involved as the primary site of the EES, an even rarer subset of ES [7]; ES of the maxillary and ethmoid sinuses, and the nose have been recognized as EES [7-9]. There have been approximately 10 English literature reports of EFT cases originating in the maxillary sinus [10, 11]. In this location, malignant lymphoma (ML) and rhabdomyosarcoma (RMS) are the representative differential diagnoses; reaching a definitive diagnosis of EFT is sometimes challenging [12].

Herein, we present a rare case of EFT originating in the maxillary sinus. Multidisciplinary examination facilitated a prompt diagnosis in this case.

Case report

A 15-year-old boy visited our hospital with the chief complaint of non-tender swelling of the left cheek; it was elastic hard on palpation.

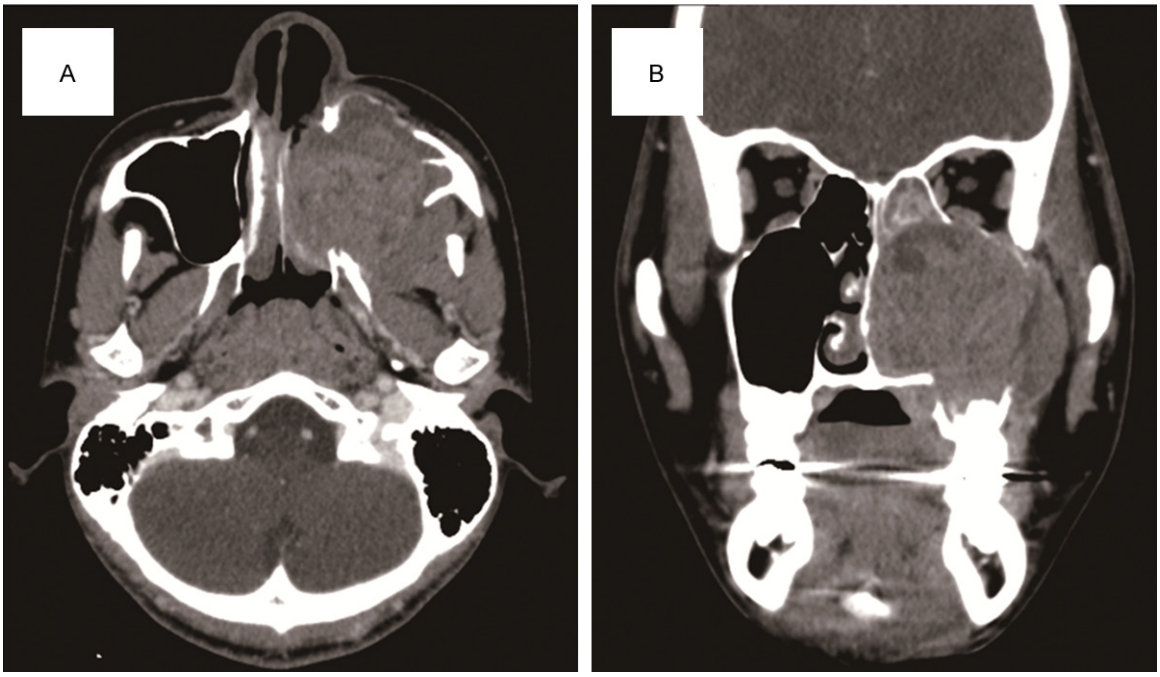

Figure 1. Computed tomography. Axial (A), and coronal (B) images. A visible mass is centered in the left maxillary sinus, causing degeneration in the surrounding bones. The mass shows soft tissue density and is sized 55 × 45 × 40 mm.

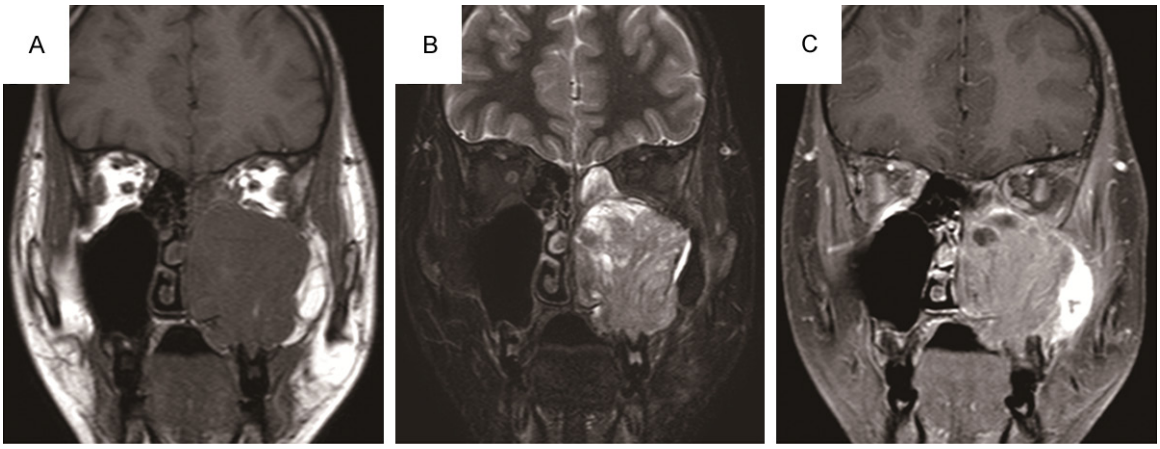

Figure 2. Magnetic resonance imaging. A. T1 weighted image revealing a mass with low intensity. B. Fat-suppressed T2 weighted image, exhibiting a mass with heterogeneously moderate to high intensity. C. Contrast-enhanced fat-suppressed T1 weighted image revealing a mass with moderate enhancement.

Laboratory tests showed no abnormalities. Computed tomography revealed a mass centered in the left maxillary sinus with destruction of the surrounding bones. Its density was nearly the same level as soft tissue and its size was 55 × 45 × 40 mm (**Figure 1A**, **1B**). No metastasis was identified. Magnetic resonance imaging using contrast material was promptly conducted; the T1 weighted image revealed a low-intensity mass (**Figure 2A**), which showed heterogeneously moderate to high intensity on the fat-suppressed T2 weighted image (**Figure 2B**). The contrast-enhanced fat-suppressed T1 weighted image displayed moderate enhancement (**Figure 2C**). On suspicion of malignancy, the subsequent biopsy was submitted to histopathological examination, cytopathological examination, flow cytometry (FCM), and G-ban-

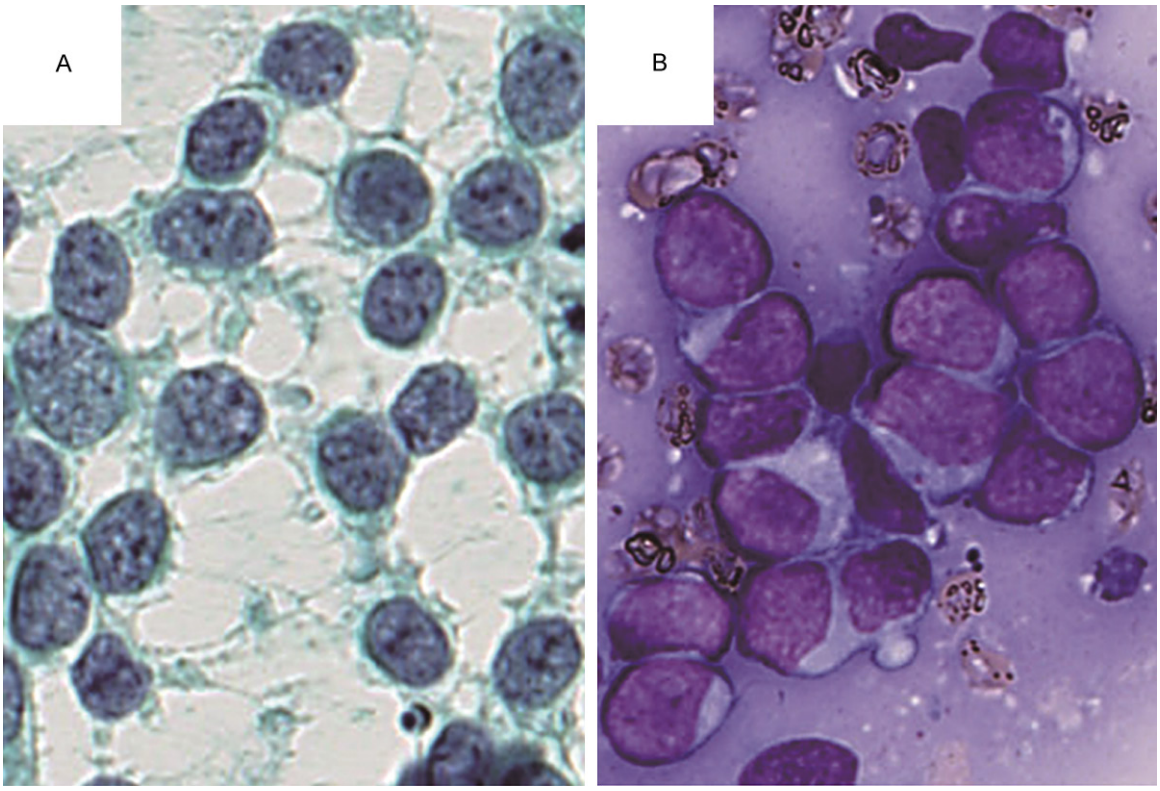

Figure 3. Imprint specimens for cytology. Papanicolaou (A), and Giemsa (B) staining. Monotonous proliferation of discohesive cells with high nuclear-to-cytoplasmic ratio is visible. The nuclei are moderately enlarged and filled with finely granular chromatin, and lack prominent nucleoli (× 600).

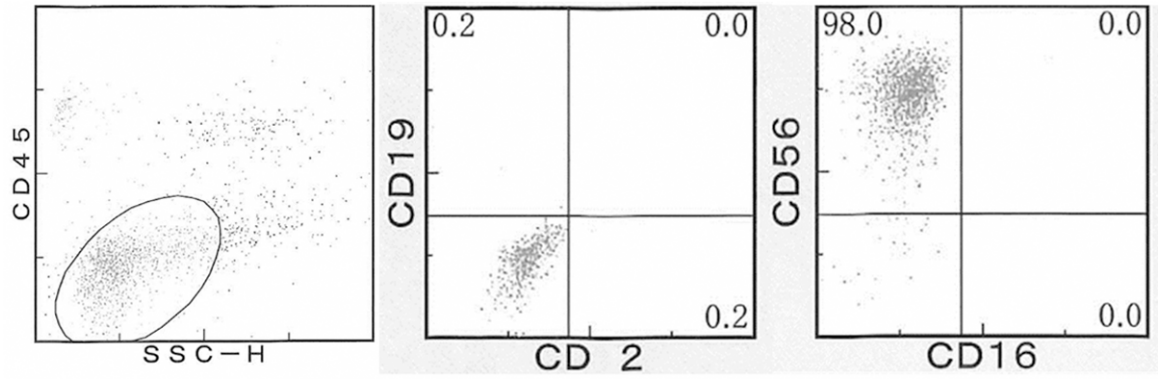

Figure 4. Flow cytometry. An abnormal cell population expressing CD56, and negative for CD45, is visible.

ding. First of all, imprint specimens for cytopathological examination were obtained. They demonstrated the monotonous proliferation of discohesive cells with high nuclear-to-cytoplasmic ratio. Nuclear enlargement was not conspicuous and the nucleus was filled with finely granular chromatin, without prominent nucleoli (**Figure 3A**, **3B**). The possibility of ML or RMS was provoked. Then, the FCM results revealed a CD45-negative abnormal cell population that was positive for CD56 (**Figure 4**). The possibility of ML was almost excluded; that of EFT was evoked. Immunohistochemistry (IHC) targeting for RMS and EFT was added to the histopathological examination. Routine hematoxylin and eosin (HE) stain along with IHC had been prepared. HE stain revealed the presence of monotonously proliferating small round cells

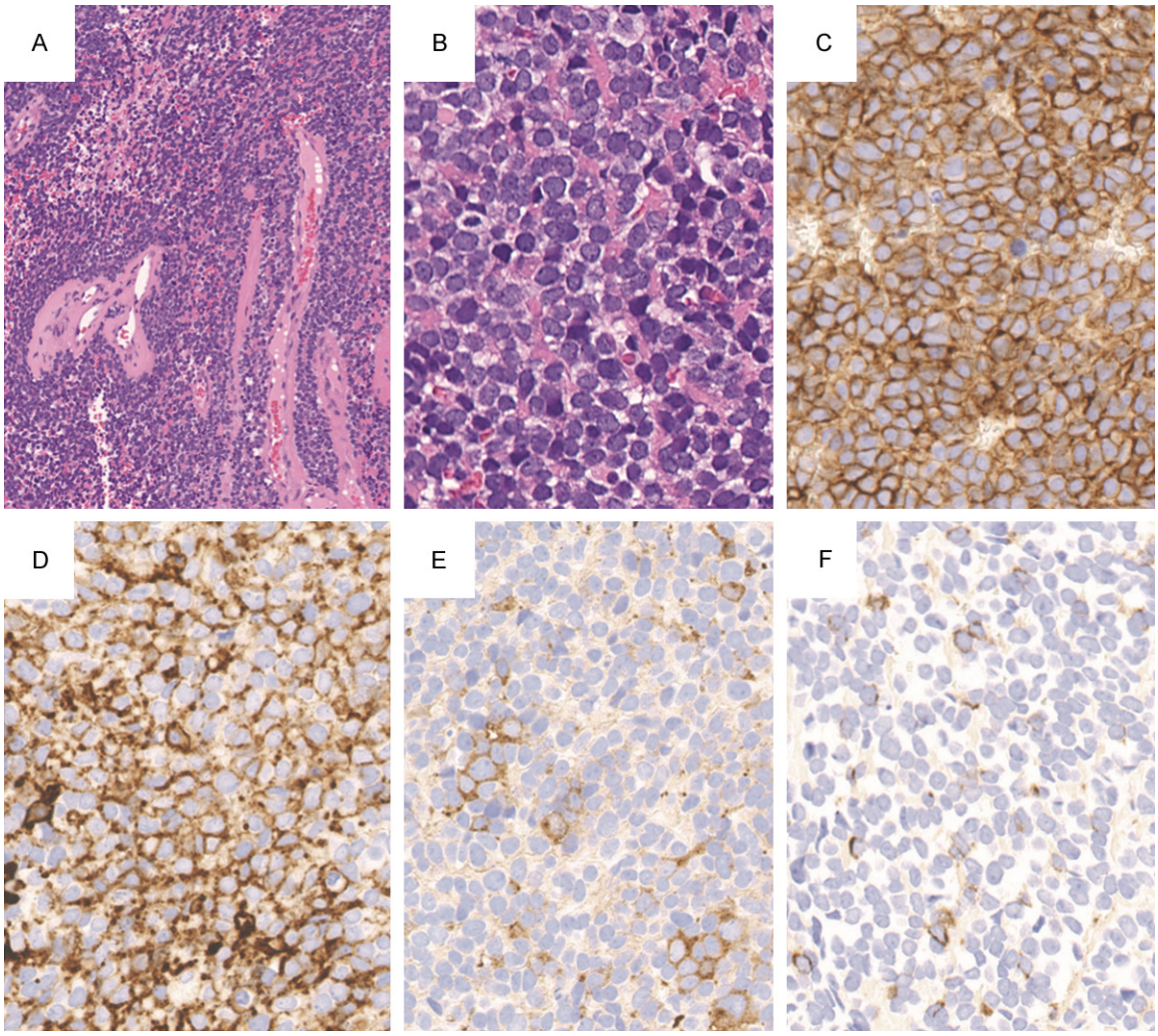

Figure 5. Histopathological and immunohistochemical findings. A. Low-power view revealing the monotonous proliferation of small round cells, with diffuse growth (hematoxylin and eosin, × 100). B. High-power view. Neural differentiation is not evident morphologically (hematoxylin and eosin, × 400). C. Immunopositivity for CD99 (× 400). D. Immunopositivity for CD56 (× 400). E. Focal positivity for synaptophysin (× 400). F. Focal positivity for pan-cytokeratin (AE1/AE3) (× 400).

with a diffuse growth pattern (**Figure 5A**). Neural differentiation was not evident morphologically (**Figure 5B**). Mitotic figures were seen occasionally; patchy necrosis was present. On IHC, the cells were positive for CD99 (**Figure 5C**) and CD56 (**Figure 5D**). Focal positivity for synaptophysin (**Figure 5E**) and pan-cytokeratin (AE1/AE3) (**Figure 5F**) was observed, while CD45, desmin, and S100 protein were negative. Consequently, EFT emerged as the most probable diagnosis. Subsequently, the results of G-banding showed a 43, XY, -9, -11, t(11;22)(q24;q12), -21 karyotype (**Figure 6**). This information confirmed the diagnosis of EFT. The patient was immediately referred to a cancer center specializing in the treatment of sarcomas with the intent of initiating chemotherapy.

Discussion

The differential diagnosis for EFT occurring in the sinonasal tract is broader than that occurring at other bones and soft tissue. Several tumors that comprise round cells arise in this location, among which EFT is relatively rare. Some of these tumors include RMS, olfactory neuroblastomas, small cell carcinomas, sinonasal undifferentiated carcinomas, NUT midline carcinomas, malignant melanomas and ML [13, 14]. In this case, considering the maxillary sinus origin and the patient's age, RMS and ML

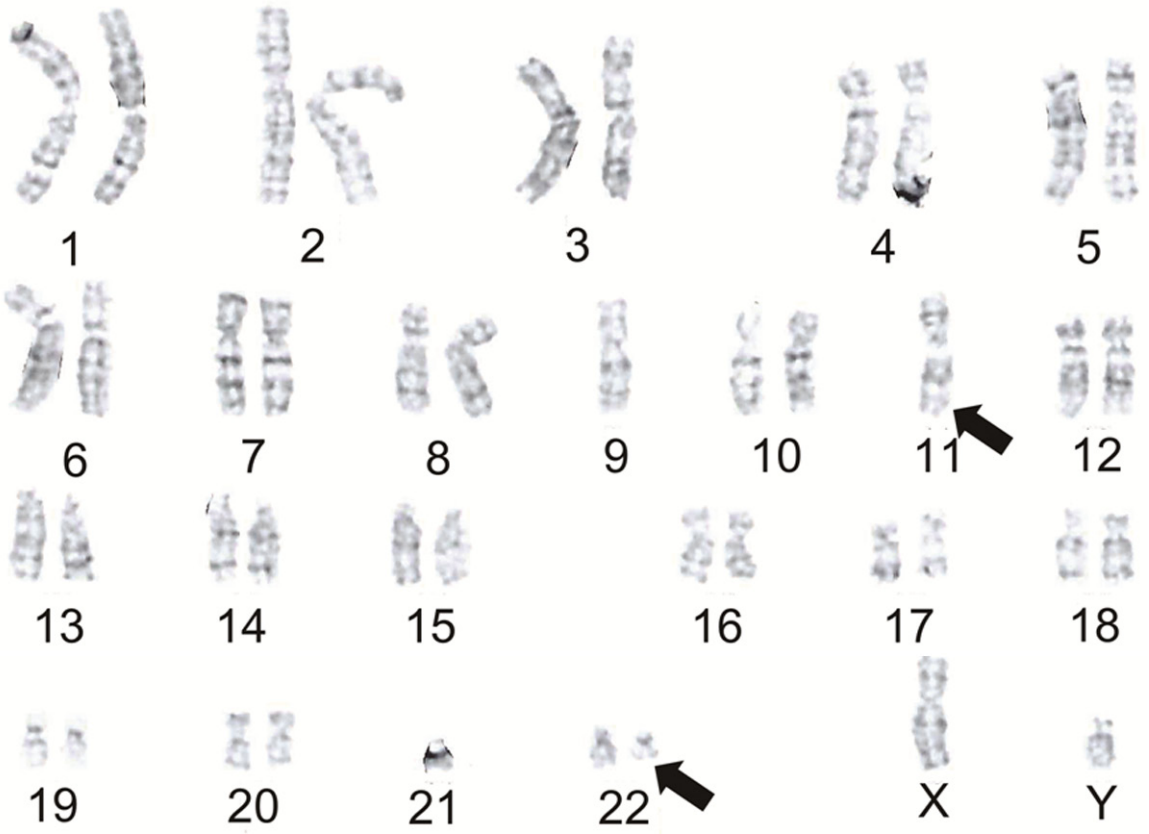

Figure 6. G-banding. A single karyotype is presented: 43, XY, -9, -11, t(11;22)(q24;q12), -21. Arrows indicate the chromosomes involved in the translocation.

were included in the differential diagnosis. The FCM results, which found no CD45-positive abnormal cell population facilitated in distinguishing the tumor from ML. On IHC, a CD99-positivity finding was insufficient for the EFT diagnosis, as some RMS and ML are immunoreactive for CD99 [15]. Furthermore, EFTs are occasionally positive for cytokeratin and/or neuroendocrine markers including CD56 and/or synaptophysin [12, 16]; there have been occasional reports of RMS that are immunopositive for these three markers [17, 18]. Despite these similarities, it is relatively straightforward to distinguish between EFT and RMS as the former is immunonegative for desmin, while the latter is immunopositive [12].

A majority of EFTs have t(11;22)(q24;q12) (*EWS/FLI1*), which corresponds to a fusion between the 5' end of the *EWS* gene (22q12) and the 3' end of the *FLI1* gene (11q24), the latter of which is a member of the ETS family of transcription factors [19]. A less common translocation is the t(21;22)(q22;q12) fusing the *EWS* to the *ERG* gene (21q22), which is also a member of the ETS family (*EWS/ERG*) [20]. Fewer than 1% of cases have t(7;22)(p22;q12) (*EWS/ETV1*) [21], t(17;22)(q12;q12) (*EWS/E1AF*) [22], t(2;22)(q33;q12) (*EWS/FEV*) [23], fusing the *EWS* gene with an ETS family gene, namely the *ETV1*, *E1AF*, and *FEV* genes, respectively. The detection of t(11;22)(q24;q12) alone did not confirm an EFT diagnosis, as it has also been observed in RMS [24]. In our case, morphological evaluation in conjunction with IHC became the basis for rendering a definitive diagnosis of EFT.

The EFT is a high-grade tumor, with local invasion and a strong tendency to metastasize; it was once considered to be a systemic disease. As it rapidly initiates the development of metastatic spread, systemic chemotherapy plays an essential role in treatment, whether or not metastasis is found at initial staging [25, 26]. With multidisciplinary approaches that use chemotherapy, radiotherapy, and surgery advances, the disease-free survival of EFT has

improved; the overall 5-year survival rate for localized EFT is 60% to 70% [27]. Following neoadjuvant chemotherapy, complete surgical resection with disease-free margins provides the best method to control local disease [5]. Because of the functional and cosmetic side effects of surgery of lesions in the head and neck, however, complete resection is occasionally inappropriate for EFT in the region [5]. In the present case, the patient was referred to a cancer center with the intent of initiating chemotherapy. The EFTs that originate in the head and neck region are known to be less aggressive and fatal than those occurring in other anatomic sites [28]. In addition, EFTs that harbor the *EWS/FLI1* fusion have been shown to have a better prognosis than those having less common translocations, independent of origin, stage, and size [29]. Therefore, our patient may pursue a relatively favorable clinical course among patients having various EFTs.

In conclusion, we have presented an extremely rare case of EFT arising in the maxillary sinus, which could be considered as extraskeletal ES. This anatomical location is predisposed to harbor some potential mimics of EFT, which are more frequently encountered than EFT. By conducting a multidisciplinary examination, we were able to confirm a timely, accurate diagnosis, thus enabling the patient to seek immediate treatment. An origin in the head and neck and the presence of the typical *EWS/FLI1*, in conjunction with an opportunity for immediate treatment, may predict a relatively better prognosis for EFT in our case.

Disclosure of conflict of interest

None.

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References

[1] Granowetter L, Womer R, Devidas M, Krailo M, Wang C, Bernstein M, Marina N, Leavey P, Gebhardt M, Healey J, Shamberger RC, Goorin A, Miser J, Meyer J, Arndt CA, Sailer S, Marcus K, Perlman E, Dickman P and Grier HE. Dose-intensified compared with standard chemotherapy for nonmetastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study. J Clin Oncol 2009; 27: 2536-2541.

[2] Obata H, Ueda T, Kawai A, Ishii T, Ozaki T, Abe S, Tanaka K, Tsuchiya H, Matsumine A, Yabe H and Japanese Musculoskeletal Oncology G. Clinical outcome of patients with Ewing sarcoma family of tumors of bone in Japan: the Japanese Musculoskeletal Oncology Group cooperative study. Cancer 2007; 109: 767-775.

[3] Carvajal R and Meyers P. Ewing's sarcoma and primitive neuroectodermal family of tumors. Hematol Oncol Clin North Am 2005; 19: 501-525, vi-vii.

[4] Vaccani JP, Forte V, de Jong AL and Taylor G. Ewing's sarcoma of the head and neck in children. Int J Pediatr Otorhinolaryngol 1999; 48: 209-216.

[5] Gradoni P, Giordano D, Oretti G, Fantoni M, Barone A, La Cava S, Ferri A, Sesenna E, Ferri T and Izzi GC. Clinical outcomes of rhabdomyosarcoma and Ewing's sarcoma of the head and neck in children. Auris Nasus Larynx 2011; 38: 480-486.

[6] Siegal GP, Oliver WR, Reinus WR, Gilula LA, Foulkes MA, Kissane JM and Askin FB. Primary Ewing's sarcoma involving the bones of the head and neck. Cancer 1987; 60: 2829-2840.

[7] Aferzon M, Wood WE and Powell JR. Ewing's sarcoma of the ethmoid sinus. Otolaryngol Head Neck Surg 2003; 128: 897-901.

[8] Boor A, Jurkovic I, Friedmann I, Plank L and Kocan P. Extraskeletal Ewing's sarcoma of the nose. J Laryngol Otol 2001; 115: 74-76.

[9] Coskun BU, Cinar U, Savk H, Basak T and Dadas B. Isolated maxillary sinus Ewing's sarcoma. Rhinology 2005; 43: 225-228.

[10] Li M, Hoschar AP, Budd GT, Chao ST and Scharpf J. Primary Ewing's sarcoma of the ethmoid sinus with intracranial and orbital extension: case report and literature review. Am J Otolaryngol 2013; 34: 563-568.

[11] Yamaoka M, Akiyama M, Yokokawa Y, Terao Y, Yokoi K, Kato T, Fukushima T, Sakurai H and Ida H. Multidisciplinary therapy including proton beam radiotherapy for a Ewing sarcoma family tumor of maxillary sinus in a 4-year-old girl. Head Neck 2013; 35: E386-390.

[12] Hafezi S, Seethala RR, Stelow EB, Mills SE, Leong IT, MacDuff E, Hunt JL, Perez-Ordonez B and Weinreb I. Ewing's family of tumors of the sinonasal tract and maxillary bone. Head Neck Pathol 2011; 5: 8-16.

[13] Wenig BM. Undifferentiated malignant neoplasms of the sinonasal tract. Arch Pathol Lab Med 2009; 133: 699-712.

[14] Stelow EB, Bellizzi AM, Taneja K, Mills SE, Legallo RD, Kutok JL, Aster JC and French CA. NUT rearrangement in undifferentiated carcinomas of the upper aerodigestive tract. Am J Surg Pathol 2008; 32: 828-834.

[15] Brinkhuis M, Wijnaendts LC, van der Linden JC, van Unnik AJ, Voute PA, Baak JP and Meijer CJ. Peripheral primitive neuroectodermal tumour and extra-osseous Ewing's sarcoma; a histological, immunohistochemical and DNA flow cytometric study. Virchows Arch 1995; 425: 611-616.

[16] Llombart-Bosch A, Machado I, Navarro S, Bertoni F, Bacchini P, Alberghini M, Karzeladze A, Savelov N, Petrov S, Alvarado-Cabrero I, Mihaila D, Terrier P, Lopez-Guerrero JA and Picci P. Histological heterogeneity of Ewing's sarcoma/PNET: an immunohistochemical analysis of 415 genetically confirmed cases with clinical support. Virchows Arch 2009; 455: 397-411.

[17] Bahrami A, Gown AM, Baird GS, Hicks MJ and Folpe AL. Aberrant expression of epithelial and neuroendocrine markers in alveolar rhabdomyosarcoma: a potentially serious diagnostic pitfall. Mod Pathol 2008; 21: 795-806.

[18] Mechtersheimer G, Staudter M and Moller P. Expression of the natural killer cell-associated antigens CD56 and CD57 in human neural and striated muscle cells and in their tumors. Cancer Res 1991; 51: 1300-1307.

[19] de Alava E and Gerald WL. Molecular biology of the Ewing's sarcoma/primitive neuroectodermal tumor family. J Clin Oncol 2000; 18: 204-213.

[20] Sorensen PH, Lessnick SL, Lopez-Terrada D, Liu XF, Triche TJ and Denny CT. A second Ewing's sarcoma translocation, t(21;22), fuses the EWS gene to another ETS-family transcription factor, ERG. Nat Genet 1994; 6: 146-151.

[21] Jeon IS, Davis JN, Braun BS, Sublett JE, Roussel MF, Denny CT and Shapiro DN. A variant Ewing's sarcoma translocation (7;22) fuses the EWS gene to the ETS gene ETV1. Oncogene 1995; 10: 1229-1234.

[22] Urano F, Umezawa A, Hong W, Kikuchi H and Hata J. A novel chimera gene between EWS and E1A-F, encoding the adenovirus E1A enhancer-binding protein, in extraosseous Ewing's sarcoma. Biochem Biophys Res Commun 1996; 219: 608-612.

[23] Peter M, Couturier J, Pacquement H, Michon J, Thomas G, Magdelenat H and Delattre O. A new member of the ETS family fused to EWS in Ewing tumors. Oncogene 1997; 14: 1159-1164.

[24] Thorner P, Squire J, Chilton-MacNeil S, Marrano P, Bayani J, Malkin D, Greenberg M, Lorenzana A and Zielenska M. Is the EWS/FLI-1 fusion transcript specific for Ewing sarcoma and peripheral primitive neuroectodermal tumor? A report of four cases showing this transcript in a wider range of tumor types. Am J Pathol 1996; 148: 1125-1138.

[25] Skubitz KM and D'Adamo DR. Sarcoma. Mayo Clin Proc 2007; 82: 1409-1432.

[26] Iwamoto Y. Diagnosis and treatment of Ewing's sarcoma. Jpn J Clin Oncol 2007; 37: 79-89.

[27] Dubois S, Gorlick R, Janeway KA and Marina N. Malignant bone tumors. In: Lanzkowsky P, editors. Manual of pediatric hematology and oncology. London, UK: Academic Press; 2011. pp. 739-758.

[28] Raney RB, Asmar L, Newton WA Jr, Bagwell C, Breneman JC, Crist W, Gehan EA, Webber B, Wharam M, Wiener ES, Anderson JR and Maurer HM. Ewing's sarcoma of soft tissues in childhood: a report from the Intergroup Rhabdomyosarcoma Study, 1972 to 1991. J Clin Oncol 1997; 15: 574-582.

[29] de Alava E, Kawai A, Healey JH, Fligman I, Meyers PA, Huvos AG, Gerald WL, Jhanwar SC, Argani P, Antonescu CR, Pardo-Mindan FJ, Ginsberg J, Womer R, Lawlor ER, Wunder J, Andrulis I, Sorensen PH, Barr FG and Ladanyi M. EWS-FLI1 fusion transcript structure is an independent determinant of prognosis in Ewing's sarcoma. J Clin Oncol 1998; 16: 1248-1255.