A mixed image in the maxillary sinus

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CLINICAL PRESENTATION

A 19-year-old male patient complaining of a diffuse swelling of 4 months' duration on the right side of his face was referred to our department. No palpable cervical lymph node was found, and patient's past medical history was noncontributory. Intraoral examination did not reveal any significant visual alteration in the right maxillary mucosa; however, a slight swelling in the maxilla, extending from the first to the third molars, could be noted during local palpation, demonstrating a hard consistency suggestive of bone cortical expansion (Figure 1A). There was no tooth mobility. Panoramic radiography revealed an irregular, ill-defined radiolucent image containing radiopaque foci on the right side of the maxilla and invading the maxillary sinus (Figure 1B). Computed tomography (CT) demonstrated a hypodense image containing small hyperdense foci. Axial sections revealed destruction of the posterior aspect of the maxillary sinus and of the lateral lamina of the pterygoid process, and coronal sections showed an infiltrative growth in the nasal cavity and the sagittal sections revealed orbital floor disruption (Figures 1C-E).

DIFFERENTIAL DIAGNOSIS

The nonspecific clinical features and the aggressive mixed radiographic presentation of the lesion led us to consider a broad range of lesions. Although central ossifying fibroma and a benign or malignant odontogenic tumor with hard tissue production were initially considered, malignant neoplasms, such as synovial sarcoma (SS), Ewing sarcoma family of tumors (ESFT), and osteosarcoma or chondrosarcoma, were considered more likely, given the destructive growth observed on the CT scan.

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Central ossifying fibroma is a benign neoplasm containing a fibrocellular stroma and variable amounts of mineralized structures and accounts for approximately 15.4% of all benign fibro-osseous lesions.[1] Although it can rarely present as multiple lesions, it is more frequently diagnosed as a solitary tumor, predominantly affecting females in their second to fourth decades of life and causing an asymptomatic swelling in the posterior region of the mandible.[1-3] In the current report, because of the painless growth of a lesion with a mixed radiographic appearance, central ossifying fibroma was initially considered. However, the infiltrative and destructive growth pattern of the tumor was not consistent with the well-demarcated features typically seen in central ossifying fibromas.

Similarly, the destructive growth of the tumor carrying a mixed radiographic appearance (feature used to exclude ameloblastoma and myxoma) made a benign odontogenic tumor highly unlikely, and we initially decided to consider only a malignant odontogenic tumor, such as ameloblastic fibrosarcoma (AFS) and odontogenic ghost cell carcinoma (OGCC), as a diagnostic option. OGCC more frequently involves the maxilla, whereas AFS is more common in the posterior region of the mandible, and both tumors may extend toward the maxillary sinus.[4,5] Adult males are the most affected, but some cases have been described in younger patients. A long-term persistent swelling followed by a rapid, painful growth is the most frequently described finding.[6-8] Radiographically, these tumors may appear as poorly defined mixed lesions, depending on the degree of dystrophic calcifications (i.e., AFS) and deposition of dentinoid material (i.e., OGCC). Because malignant odontogenic tumors can demonstrate an aggressive clinical course, we considered them a possibility.

SS is an aggressive high-grade neoplasm derived from undifferentiated mesenchymal cells and carries the specific t(X;18)(p11.2;q11.2) chromosome translocation.[9,10] SS is more frequently diagnosed in the extremities, whereas the head and neck region is affected in 3% to 10% of the cases, usually affecting males in their third to fifth decades of life.[10] Head and neck tumors usually present nonspecific clinical signs and symptoms, such as a progressive painless growth,[11] with calcifications being found in some cases.[12,13] Thus, because SS has been described in the

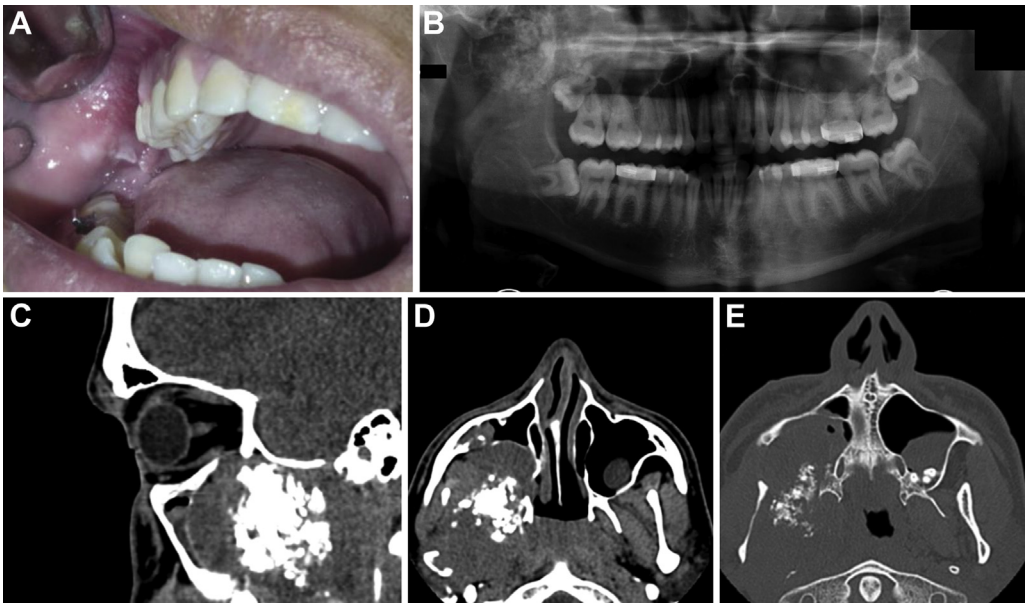

Fig. 1. Clinical and imaging features observed in this case. **A,** Intraoral examination did not show any evident alteration in the maxillary mucosa of the patient. However, palpation of the affected maxillary area demonstrated a slight cortical bone expansion. **B,** Panoramic radiography showed an ill-defined radiolucent image, with radiopaque foci invading the maxillary sinus. **C,** Soft-tissue window sagittal plane of computed tomography (CT) revealed the presence of hyperdense material inside the hypodense lesion that extensively obliterated the right maxillary sinus. Soft tissue **(D)** and hard tissue **(E)** window axial plane of CT scan showing the destruction of the posterior wall of the maxillary sinus, which is almost completely involved by the tumor.

paranasal sinuses,[12,14] it was also considered a diagnostic possibility in this case.

ESFT represents the third most common primary bone neoplasm, harboring the t(11;22) chromosomal translocation involving the *EWS* and *FLI-1* genes. Males are more affected in their first two decades of life and usually exhibit a painful swelling. The long bones, pelvis, and ribs are the most affected locations, but gnathic bone involvement is uncommon. Radiographically, a destructive radiolucent process with poorly defined borders is the main characteristic of this entity.[15,16] Although ESFT diagnosis in this case was supported by the patients' age, when gnathic bones are involved, the mandible is the most affected site, with the neoplasm only rarely affecting the maxilla and the maxillary sinus[17]; moreover, calcifications are not commonly found in ESFT.

Finally, osteosarcoma and chondrosarcoma are the two most common primary malignant bone tumors (excluding hematologic malignancies), and the involvement of the head and neck region has widely been documented.[18] Adult males are the most affected patients, with a rapidly growing painless swelling. Radiographically, osteosarcoma and chondrosarcoma usually cause cortical bone destruction, ranging from ill-defined radiolucent to variably mixed images, occasionally presenting the so-called "sun-ray" and "Codman triangle" findings.[18,19] The aggressive mixed radiographic features of this case led us to consider osteosarcoma and chondrosarcoma as the most likely diagnostic possibilities.

DIAGNOSIS

An incisional biopsy under local anesthesia was done, and microscopic examination revealed a malignant neoplasm comprising two cellular components. Epithelial cells were arranged in small foci and exhibited abundant eosinophilic cytoplasm with indistinct cell borders and round-to-ovoid nuclei. These epithelial nests were surrounded by pleomorphic spindle cells containing scarce cytoplasm and hyperchromatic nuclei organized in short bundles that predominated in the histologic sample. Scattered mitotic figures could be found, but necrosis was absent (Figure 2). Considering the two cellular components observed, microscopic diagnosis was highly suggestive of SS, but the immunohistochemical study was done to exclude other less likely possibilities, such as hemangioendothelioma, sinonasal hemangiopericytoma, rhabdomyosarcoma, ESFT, lymphoma, osteosarcoma, and melanoma. Diffuse positivity for vimentin was found in spindle cells, for TLE1, Bcl-2, and CD99 in both spindle and epithelial cells, and for AE1/AE3 and EMA in epithelial cells (Figure 3). The Ki67 proliferative index was higher than 40%, and reactions against S100, LCA, desmin,

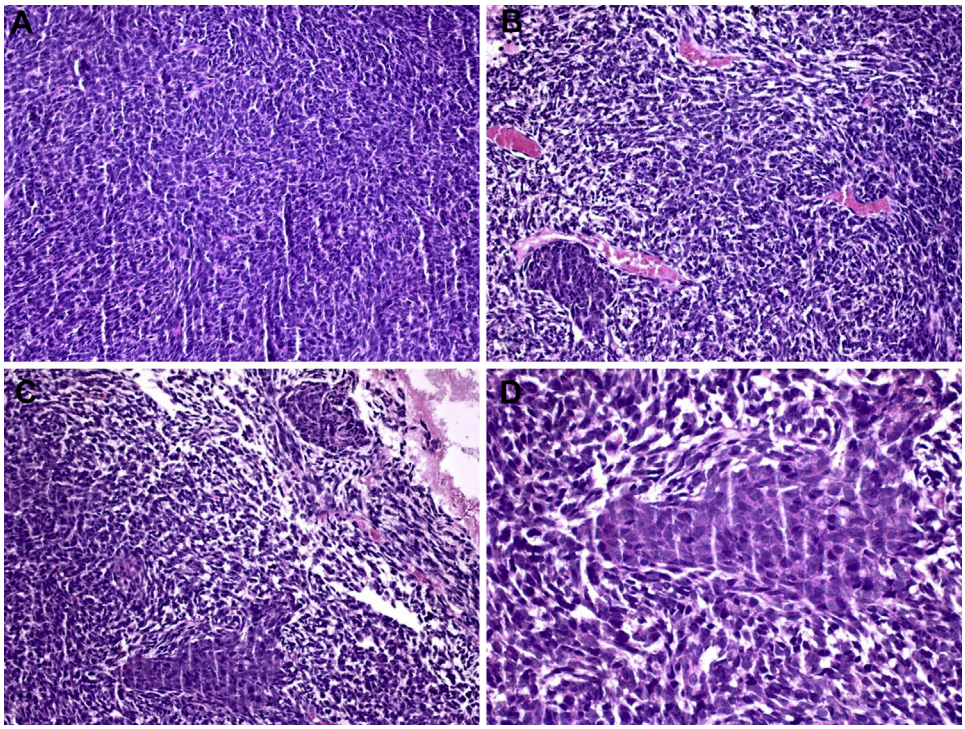

Fig. 2. Histopathologic findings of the neoplasm. **A,** The tumor was predominantly composed of hypercellular areas containing atypical spindle cells (hematoxylin and eosin [H&E]; ×200). **B,** Blood vessels were frequently observed throughout the specimen, demonstrating that the neoplasm was highly vascularized (H&E; ×200). **C,** Small islands of epithelial cells were distributed in the lesion (H&E; ×200). **D,** Epithelial cells demonstrated a more evident eosinophilic cytoplasm, with round to oval nuclei (H&E; ×400). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM02883.*

Fli-1, and CD34 were negative. Hence, the final diagnosis of biphasic SS was rendered.

MANAGEMENT

Treatment consisted of wide surgical removal of the tumor combined with adjuvant radiotherapy to a total dose of 70 Gy. At the 5-month follow-up, the patient was found to have developed lung and scalp metastases. Palliative chemotherapy with isophosphamide, doxorubicin, and epirubicin was applied. During follow-up, the patient exhibited local recurrence in the maxilla and died after 1 year of follow-up.

DISCUSSION

SS was first described in 1846 and named "synovial sarcoma" because of its microscopic resemblance to the developing synovium.[20] However, the tumor was later shown not to be derived from synovial tissues but possibly arising from undifferentiated mesenchymal cells. SS accounts for 5% to 10% of all soft tissue sarcomas, more commonly affecting the lower extremities of young adults, and has a slight male prodominance.[21-23] The head and neck region is affected in 3% to 10% of all cases, more frequently the hypopharynx,[10,12,22] and although rare, SS affecting the maxillary sinus has been reported.[12,14]

Head and neck SS is usually a painless, slow-growing tumor, which can cause different symptoms, such as dysphagia, hoarseness, and dyspnea, depending on the affected site.[12] As illustrated in this report, the presence of radiopacity caused by focal dystrophic calcification and, less frequently, bone formation are found in approximately 30% of SS and can be identified by using both conventional radiography and CT.[12,13]

SS may present different histologic variants. The monophasic subtype is entirely composed of spindle cells (or very rarely of epithelial cells), whereas the biphasic subtype is composed of both cell types.[10] Although the spindle and epithelial components are morphologically distinct, they are believed to be histogenetically related,[22] and this theory is supported by the expression of different markers in both populations. Poorly differentiated subtype has an increased degree of cellularity, with hyperchromatic, round, small atypical cells and higher mitotic activity, and may form rosette-like structures.[24] The present case showed a biphasic differentiation, but despite the presence of radiopacities seen in the panoramic radiographs and CT scans,

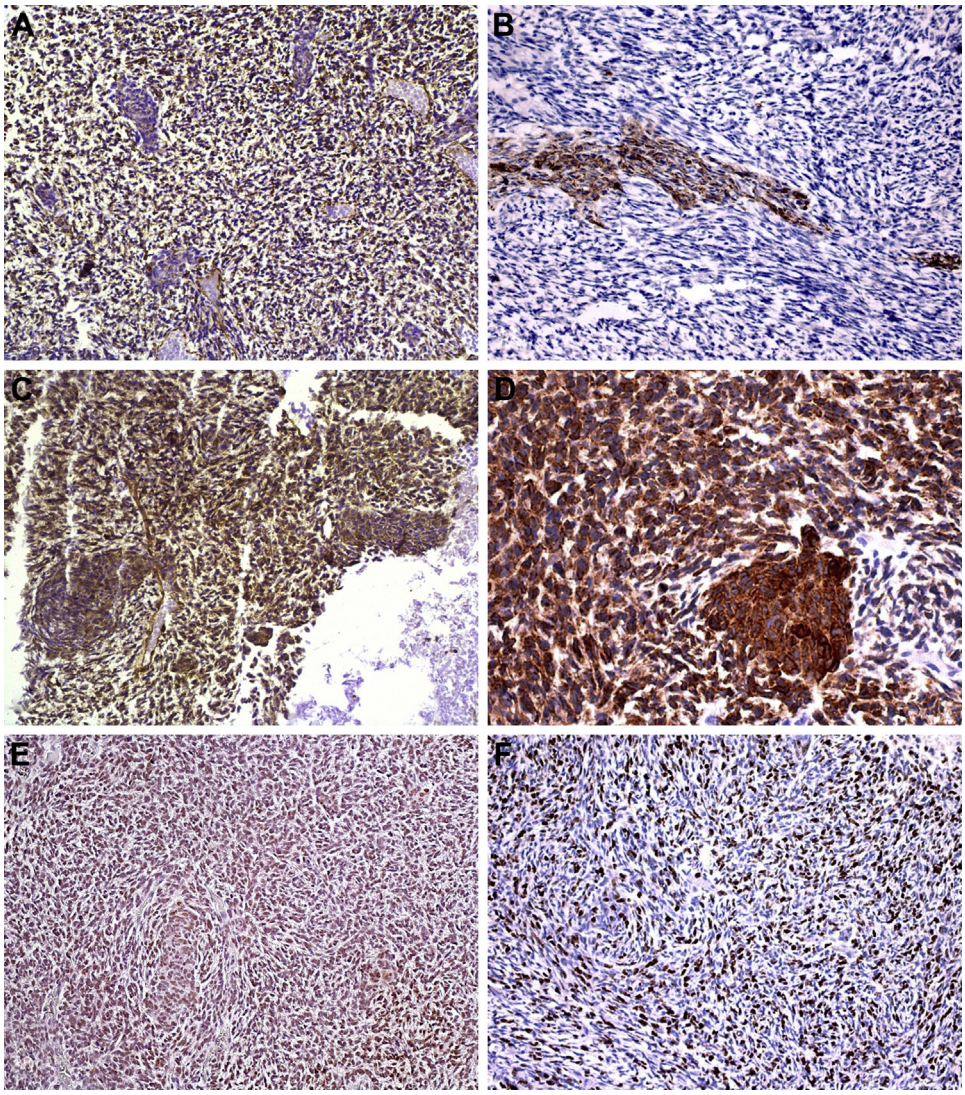

Fig. 3. Immunohistochemical features of the neoplasm. **A,** Vimentin was positive in the spindle cell component of the tumor (DAB [3,3′-diaminobenzidine]; ×100). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM02885*. **B,** AE1/AE3 reactivity was found only in the epithelial islands that were distributed in the neoplasm (DAB; ×200). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM02887*. **C,** CD99 positivity was present in both spindle and epithelial components (DAB; ×100). **D,** A strong cytoplasm positivity for Bcl-2 was also observed in both epithelial and spindle cells (DAB; ×100 X). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM02891*. **E,** TLE1 reactivity was diffusely obtained in the nuclei of the neoplastic cells (DAB; ×200). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM02893*. **F,** The tumor exhibited a proliferative index measured by Ki67 staining of approximately 40% (DAB; ×100).

calcifications were not found in our sample, possibly because of the small sample evaluated.

SS is positive for vimentin, Bcl-2, CK, EMA, CD99, and TLE1. Vimentin is more frequently found in spindle cells, but 15% to 30% of epithelial cells can also express this marker. Strong Bcl-2 positivity is frequently obtained in SS, whereas other differentials, such as hemangiopericytoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, and malignant mesothelioma, are usually Bcl-2 negative.[23-25]

CD99 is present in over 70% of the cases, staining positively both components of the tumor, including the poorly differentiated variants, but this marker can also be found in ESFT, rhabdomyosarcoma, and lymphoma.[23,24] TLE1 is a sensitive and specific marker for SS and can be helpful to distinguish it from other histologic mimics.[26] The immunohistochemical pattern of the present case is in accordance with the literature, as spindle cells were positive for vimentin and epithelial cells expressed AE1/AE3 and EMA. TLE1, Bcl-2,

and CD99 were expressed in both components of the tumor, and Ki67 was approximately 40%.

Chromosomal studies have demonstrated in more than 90% of SS the reciprocal translocation t(X:18)(q11,p11) involving the fusion of *SYT* gene with one of the three closely related genes, *SSX1*, *SSX2* or *SSX4*. In approximately one-third of the cases, this chromosomal translocation represents the sole cytogenetic abnormality of SS, but molecular studies have demonstrated the upregulation of a number of other genes.[21,27,28] In the present case, a molecular examination was not performed, but the microscopic features and the immunohistochemical panel were sufficient to confirm this diagnosis.

As exemplified in this report, wide surgical resection is the therapy of choice for head and neck SS, and radiotherapy has also been used as adjuvant therapy.[11,22] However, despite the improvements in the therapeutic protocols, 5-year and 10-year survival rates were shown to reach only 66% to 80.4% and 53% to 78.2% in recent large studies, demonstrating that SS of the head and neck is a very aggressive malignant entity.[10,22]

CONCLUSIONS

SS affecting the head and neck is uncommon and the involvement of maxillary sinus is even less frequent, but it must be considered in the differential diagnosis of aggressive tumors. Moreover, although rare, it is possible to find SS demonstrating radiopacities and hyperdense foci on conventional radiography and CT.

REFERENCES

1. de Noronha Santos Netto J, Machado Cerri J, Miranda AM, Pires FR. Benign fibro-osseous lesions: clinicopathologic features from 143 cases diagnosed in an oral diagnosis setting. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;115:e56-e65.
2. Ribeiro AC, Carlos R, Díaz KP, Gouvêa AF, Vargas PA. Bilateral central ossifying fibroma affecting the mandible: report of an uncommon case and critical review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2011;111:e21-e26.
3. Chang CC, Hung HY, Chang JYF, et al. Central ossifying fibroma: a clinicopathologic study of 28 cases. *J Formos Med Assoc*. 2008;107:288-294.
4. Zabolinejad N, Hiradfar M, Anvari K, Razavi AS. Ameloblastic fibrosarcoma of the maxillary sinus in an infant: a case report with long-term follow-up. *J Pediat Surg*. 2008;43:e5-e8.
5. Sun ZJ, Zhao YF, Zhang L, Li ZB, Chen XM, Zhang WF. Odontogenic ghost cell carcinoma in the maxilla: a case report and literature review. *J Oral Maxillofac Surg*. 2007;65:1820-1824.
6. Lai J, Blanas N, Higgins K, Klieb H. Ameloblastic fibrosarcoma: report of a case, study of immunophenotype, and comprehensive review of the literature. *J Oral Maxillofac Surg*. 2012;70:2007-2012.
7. Pontes HA, Pontes FS, Silva BS, et al. Immunoexpression of Ki67, proliferative cell nuclear antigen, and Bcl-2 proteins in a case of ameloblastic fibrosarcoma. *Ann Diag Pathol*. 2010;14:447-452.
8. McCoy BP, O'Carroll MK, Hall JM. Carcinoma arising in a dentinogenic ghost cell tumor. *Oral Surg Oral Med Oral Pathol*. 1992;74:371-378.
9. Lee YF, John M, Edwards S, et al. Molecular classification of synovial sarcomas, leiomyosarcomas and malignant fibrous histiocytomas by gene expression profiling. *Br J Cancer*. 2003;88:510-515.
10. Clair JM, Arshi A, Abemayor E, St. John M. Factors associated with survival in patients with synovial cell sarcoma of the head and neck. An analysis of 167 cases using the SEER (Surveillance, Epidemiology, and End Results) database. *Otolaryngol Head Neck Surg*. 2016;142:576-583.
11. Salcedo-Hernandez RA, Lino-Silva LS, Luna-Ortiz K. Synovial sarcomas of the head and neck: comparative analysis with synovial sarcoma of the extremities. *Auris Nasus Larynx*. 2013;40:476-480.
12. Rangheard AS, Vanel D, Viala J, Schwaab G, Casiraghi O, Sigal R. Synovial sarcomas of the head and neck: CT and MR imaging findings of eight patients. *Am J Neuroradiol*. 2001;22:851-857.
13. Wilkerson BJ, Crim JR, Hung M, Layfield LJ. Characterization of synovial sarcoma calcification. *AJR Am J Roentgenol*. 2012;199:W730-W734.
14. Salcedo-Hernandez RA, Silva LSL, Ortiz KL. Maxillary sinus sarcomas: epidemiological and clinicopathological experience of 25 years in a national reference cancer center. *Indian J Otolaryngol Head Neck Surg*. 2014;66:359-364.
15. Barnes L, Eveson JW, Reichart P, Sidransky D. *World Health Organization Classification of Tumors. Pathology and Genetics of Head and Neck Tumours*. Lyon, France: IARC; 2005.
16. Karimi A, Shirinbak I, Beshkar M, et al. Ewing sarcoma of the jaws. *J Craniofac Surg*. 2011;22:1657-1660.
17. Tajima S, Ohkubo A, Yoshida M, Koda K, Nameki I. Ewing's sarcoma family of tumors of the maxillary sinus: a case report of multidisciplinary examination enabling prompt diagnosis. *Int J Clin Exp Pathol*. 2015;8:960-966.
18. Pontes HA, Pontes FS, Abreu MC, et al. Clinicopathological analysis of head and neck chondrosarcoma: three case reports and literature review. *Int J Oral Maxillofac Surg*. 2012;41:203-210.
19. Paparella ML, Olvi LG, Brandizzi D, Keszler A, Santini-Araujo E, Cabrini RL. Osteosarcoma of the jaw: an analysis of a series of 74 cases. *Histopathology*. 2013;63:551-557.
20. Sabrazes J, Loubat E, de Grailly R, Magendie J. Synovial sarcomes. *Gaz Hebd Sci Med Bord*. 1934;55:754-762.
21. Pontes H, Pontes F, Silva T, et al. Diffuse swelling of the left side of the face. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2010;110:685-690.
22. Wushou A, Miao XC. Tumor size predicts prognosis of head and neck synovial cell sarcoma. *Oncol Lett*. 2015;9:381-386.
23. Pelmus M, Guillou L, Hostein I, Sierankowski G, Lussan C, Coindre JM. Monophasic fibrous and poorly differentiated synovial sarcoma: immunohistochemical reassessment of 60 t(X;18)(SYT-SSX)-positive cases. *Am J Surg Pathol*. 2002;26:1434-1440.
24. Subramaniam MM, Shuen CS, Petersson F. Poorly differentiated synovial sarcoma of the sphenoid sinus: report of the first case

and review of synovial sarcomas of the sinonasal tract. *Histopathology*. 2012;61:1232-1237.
25. Kottu R, Prayaga AK. Synovial sarcoma with relevant immunocytochemistry and special emphasis on the monophasic fibrous variant. *J Cytol*. 2010;27:47-50.
26. Foo WC, Cruise MW, Wick MR, Hornick JL. Immunohistochemical staining for TLE1 distinguishes synovial sarcoma from histological mimics. *Am J Clin Pathol*. 2011;135:839-844.
27. Cihak RA, Lydiatt WM, Lydiatt DD, Bridge JA. Synovial sarcoma of the head and neck: chromosomal translation (X;18) as a diagnostic aid. *Head Neck*. 1997;19:549-553.
28. Lu YJ, Birdsall S, Summersgill B, et al. Dual colour fluorescence in situ hybridization to paraffin embedded samples to deduce the presence of the der;Xt(X;18)(p11.2;q11.2) and involvement of either the SSX1 or SSX2 gene: a diagnostic and prognostic aid for synovial sarcoma. *J Pathol*. 1999;187:490-496.

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