Clinical–Pathological Conference: Case 1

Ilana Kaplan · Sonal S. Shah ·
Zoe Nicolaou-Ioannou · Dan M. Fliss

Received: 13 June 2010 / Accepted: 9 July 2010 / Published online: 24 July 2010
© Humana 2010

Clinical Presentation

A healthy 37-year-old female noticed a loose 2nd maxillary molar, which became progressively worse over several weeks. A course of antibiotics was prescribed by her dentist without improvement. She then visited an oral surgeon, and a decision to extract the tooth was taken, since all supporting bone seemed to have been lost. A panoramic radiograph showed partial opacification of the sinus floor which was interpreted as a possible sign for sinus mucocoele (Fig. 1a).

Immediately following extraction, an oro-antral communication was observed, with a mass of pale, soft, gelatinous tissue protruding through. A sample of the tissue was submitted for histopathological examination and CT scans were ordered. Coronal CT scans exhibited a mass occupying the right maxillary and ethmoidal sinuses, and protruding into the right nasal space and pterygomaxillary fossa. Destruction of the bony walls and septa were evident at the level of the maxillary and ethmoidal sinuses,

as well as thinning of the orbital floor and erosion of the pterygoid plates (Fig. 1b).

Differential Diagnosis

The differential diagnosis for this case was primarily based on two components: the radiographic presentation and the gelatinous gross surgical appearance. The coronal CT scans showed an expansile lesion that occupied the right maxillary sinus and ethmoid sinus and caused destruction of right-sided nasal structures. This presentation is consistent with an aggressive benign lesion or a low-grade malignant lesion. The gelatinous gross appearance was highly suggestive of a lesion or tumor with a prominent myxoid or mucinous component. Therefore, the most likely clinical diagnoses included the following entities: sinus mucocoele, sino-nasal myxoma, intestinal-type adenocarcinoma, chondromyxoid fibroma, chordoma, a myxoid variant of several types of soft tissue sarcomas, and finally osteogenic and chondrosarcoma.

Mucocoele is the most common expansile lesion of the paranasal sinuses. True sinus mucocoeles are very rare and when they occur, 90% of cases involve the frontal and ethmoid sinuses. There is no gender predilection and they occur in all age groups. Mucocoeles present radiographically as homogeneous opacification of the involved sinuses and can cause extensive bone destruction through pressure resorption. The radiographic presentation of our case is most consistent with this diagnosis. In addition, mucocoeles have a gelatinous gross appearance, since they result from the accumulation of mucous secretions due to impaired drainage caused by blockage of the ostium.

Sino-nasal myxoma is a benign lesion with aggressive clinical behavior. Generally, this is a tumor of the jawbones and rarely occurs in extra-gnathic locations. In cases involving the sino-nasal tract, the maxillary sinus is most

I. Kaplan (✉)
Institute of Pathology, Tel-Aviv Sourasky Medical Center,
6 Weitzman St, Tel Aviv, Israel
e-mail: ig_kaplan@012.net.il

S. S. Shah
Department of Oral and Maxillofacial Pathology,
Radiology, and Medicine, College of Dentistry,
New York University, New York, NY, USA

Z. Nicolaou-Ioannou
Private Oral and Maxillofacial Surgery, Limassol, Cyprus

D. M. Fliss
Department of Otolaryngology, Head and Neck Surgery,
Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel

Fig. 1 **a** A preoperative panoramic radiograph showing partial opacification of the right maxillary sinus with erosion of the sinus floor. **b** Coronal CT scans exhibiting a mass occupying both right maxillary and right ethmoidal sinuses, protruding into the right nasal cavity and pterygomaxillary fossa. Destruction of the bony walls and septae are evident at the level of the maxillary and ethmoidal sinuses, as well as thinning of the orbital floor and erosion of the pterygoid plates

frequently involved with secondary extension into the nasal cavity and the orbit. There is no gender predilection and this lesion is most frequently seen in patients in the 2nd or 3rd decades of life. The gross appearance is generally unencapsulated, multinodular, soft, and gelatinous. Myxomas present radiographically as expansile, infiltrative tumors.

Sino-nasal intestinal-type adenocarcinoma (ITAC) is a locally aggressive tumor with a 5-year survival rate of around 40%. This tumor is significantly more common in men than women and occurs over a wide age range. ITAC is most frequently associated with the ethmoid sinus, followed by the nasal cavity, and finally the maxillary sinus. Long-term occupational exposure to wood dust and leather is considered a major etiologic factor. Interestingly, sporadic cases tend to affect women more than men and occur

more frequently in the maxillary sinus. These tumors, particularly the mucinous type, often have a myxoid or gelatinous gross appearance.

Chondromyxoid fibroma is a benign cartilaginous tumor that may occur in the craniofacial bones and paranasal sinus. This lesion tends to be more common in men and the mandible is the most common location. Symptoms include pain and loosening of the teeth. The radiographic presentation varies from a well-defined, round radiolucent lesion to a large, ill-defined lesion.

Chordoma is derived from the notochord and generally is found in the spheno-occipital and sacrococcygeal areas. Tumors of the spheno-occipital region may involve the posterior nasal cavity, sphenoid sinus, nasopharynx and skull base. Rare cases of primary chordomas arising in the sino-nasal tract have been documented. There is a peak incidence in the 6th decade of life. Sino-nasal chordomas generally grow slowly, infiltrate locally, tend to recur, and rarely metastasize.

Although rare, almost all types of sarcomas can occur in the sino-nasal tract. Many of the soft tissue sarcomas have myxoid variants that would be consistent with a gelatinous gross appearance. Myxoid rhabdomyosarcoma, myxoid fibrosarcoma, myxoid leiomyosarcoma, and myxoid liposarcoma are the most commonly occurring soft tissue sarcomas in the sino-nasal region. All of these can present radiographically with sinus opacification and extensive bone destruction, similar to our case. However, the majority of these sarcomas tend to occur in older adults, whereas our patient was a 37-year-old female.

Myxoid fibrosarcoma tends to occur in the lower extremities but may be found in the nasal cavity and paranasal sinuses. There is no gender predilection and all age groups may be affected. However, most patients are diagnosed in the 5th and 6th decades of life. Radiographically, bone destruction is a characteristic feature. Grossly, myxoid fibrosarcomas are often multinodular and gelatinous in consistency.

Myxoid leiomyosarcoma of the sino-nasal tract most likely arises from the smooth muscle walls of blood vessels. This tumor may occur over a wide age range and has no gender predilection. Interestingly, leiomyosarcomas of the sino-nasal tract have a greater frequency of occurrence after radiation treatment, and in general tend to occur more often in immunocompromised patients. Sinus opacification and bone erosion are the typical radiographic presentation of sino-nasal leiomyosarcomas. Leiomyosarcomas with extensive myxoid changes present with a gelatinous gross appearance.

Osteosarcoma and chondrosarcoma are distinctly uncommon in the paranasal sinuses. Rare cases of myxoid chondrosarcomas have been described in the sino-nasal tract. These cases are typically seen in adults over the age

of 35. Myxoid chondrosarcomas are generally low-grade in the head and neck and consequently are slow-growing and painless. A correct diagnosis is often difficult because the stroma may be prominently myxoid, presenting as a myxoma or chondromyxoid fibroma.

Diagnosis and Discussion

The tissue received at biopsy showed a fairly cellular tumor, with strands and small clusters of cells in a loose myxoid matrix. The morphology of the cells varied between spindle, round-ovoid and occasionally stellate, with sparse eosinophilic cytoplasm and poorly defined cell margins. The nuclei were uniform, with fairly condensed chromatin and only rare nucleoli visible. Atypia was not evident and mitotic figures were rare. The myxoid background material seemed to be concentrated around the clusters of cells, and was dissected by thin strands of collagen fibers, creating a lobular appearance in some areas. Vascularity was minimal, composed of only rare capillary size vessels. (Figs. 2, 3).

The features of the resection specimen received later were identical except for some increased cellularity in the periphery of the sample, and will therefore not be described separately.

A comprehensive battery of immunostains was performed, including: vimentin, S-100, cytokeratins A1/A3, CK14 and 18, EMA, CEA, SMA, MSA, calponin, desmin,

CD34, NSE, chromogranin, synaptophysin, p63, c-Kit, Ki67 and Bcl-2. The tumor cells were strongly and diffusely positive for vimentin only, and negative for all the other stains (Fig. 4). Ki67 was low and positive in only 2–3% of the tumor cells.

In the following paragraphs the list of the relevant differential diagnosis of myxoid low grade tumors will be discussed, and narrowed down to a final diagnosis on the basis of the given results of immunostains.

Odontogenic or sino-nasal myxomas share many of the microscopic and staining features with the present tumor; they are composed of bland stellate or spindle cells in abundant myxoid matrix, with varying amounts of collagen fibers. Mitotic activity is absent or low and immunostains are typically positive only for vimentin, while negative for S-100, muscle markers and GFAP. The diagnosis of myxoma was ruled out in the present case because the tumor was relatively cellular with a high proportion of round to oval cells rather than spindle or stellate-shaped cells. Furthermore, the clustering of cells seen in the present case is not a feature of odontogenic or sino-nasal myxoma.

Pleomorphic adenomas (PA) are benign neoplasms predominantly originating in either major or minor salivary glands, but may also occur in other sero-mucinous glands such as those found in sinus or nasal mucosa. They may also present macroscopically as mucinous-gelatinous masses. These tumors are usually slow-growing, encapsulated or well circumscribed, and only rarely encroach on palatal or maxillary bone, unless a transformation to

Fig. 2 Multiple microscopic sections showing a respiratory type epithelial lining and a fairly cellular tumor, with strands and small clusters of cells in a loose myxoid matrix (**a–d**). (Hematoxyline and Eosin, original magnifications $\times 20$ – $\times 200$)

Fig. 3 The cells' morphology varies between spindle, round-ovoid and occasionally stellate, with sparse cytoplasm, poorly defined cell margins, uniform nuclei and no evident atypia. The cellularity is increased in the periphery of the sample (b). Vascularity is minimal,

composed of only rare capillary size vessels (c). The myxoid background material is concentrated around the clusters of cells (d) (Hematoxiline and Eosin, original magnifications $\times 20$ – $\times 200$)

Fig. 4 Strong and diffuse positivity for Vimentin in the tumor cells (immunostaining with vimentin, original magnification $\times 200$)

carcinoma has occurred. There was no microscopic evidence of a malignant transformation. Thus, the aggressive behavior of the present tumor was inconsistent with PA. In addition, negative staining with S-100, CK's, SMA, calponin and p63, which are typically positive in PA, were helpful in rejecting the diagnosis of PA.

Chondromyxoid fibroma (CMF) is a benign primary bone tumor characterized by lobulation and a myxoid or chondroid matrix with spindle cells often concentrated at the periphery of the lobules. S-100, SMA, MSA, Desmin, h-caldesmon and calponin are usually positive. CMF was

ruled-out on the basis of the negative results of these markers in the present case.

Ossifying fibromyxoid tumor (OFMT) is usually a benign solitary soft tissue tumor, although a subgroup which is locally aggressive and may even metastasize has been reported. This tumor is characterized by an acellular (pseudo)capsule, lobulated architecture, myxoid matrix, monotonous oval or round cells in a lace like configuration, intra-lesional fibrous septa and a peripheral rim of lamellar bone. In the subgroup with aggressive behavior, increased cellularity, atypia and mitotic figures have been described. Characteristic immunostaining results in OFMT include negative cytokeratin, positive S-100 in up to 70% of cases, variable results for MSA, SMA, desmin and GFAP, and negative for CD34. Although some of the microscopic features were similar, the lack of atypia, low mitotic activity, and IHC pattern were considered inconsistent with the aggressive variant of OFMT, while the destructive nature was incompatible with the benign variant. Although in the resection specimen some sections contained bone trabeculae at the periphery, these were considered to be part of the bone in the surrounding anatomic structures such as the sinus walls invaded by the tumor mass. Lack of positive stain for S-100, although not conclusive, was helpful in addition to the other morphologic considerations in rejecting the diagnosis of OFMT.

Chordoma is a malignant neoplasm located along the midline axis with a typical gross appearance of ill-defined gray-white gelatinous masses. Microscopically it is characterized by lobules separated by fibrous septa, myxoid matrix, and cords of cells with small nuclei and abundant vacuolated cytoplasm. Some cells are large with multiple vacuoles (physaliferous cells). Occasional epithelioid or spindle cells and bizarre cells have been described. Characteristic immunostains in chordoma include positivity for cytokeratins, EMA, S-100 and vimentin. The lack of large vacuolated cells as well as the negative stains for CK and EMA ruled out chordoma in the present case.

Low-grade fibromyxoid sarcoma (LGFMS) is a slow-growing, locally aggressive tumor, metastasizing only late in the disease course. Microscopically it is characterized by bland spindle fibroblasts, arranged in a whorled pattern in a myxoid-to- collagenized matrix. Mitosis is scant. Thin-walled arcaded blood vessels are typically present within the tumor mass. LGFMS stains positive for vimentin and is about 30% positive for EMA, while S-100 is typically negative. Cytogenetic changes diagnostic for LGFMS include t (7; 16) (q34; p11). The tumor presented was not predominantly composed of spindle cells and lacked the typical vascular pattern, which in addition to immunostaining results helped to rule out LGFMS.

Myxoid liposarcoma (MLS) is a tumor of older adults, microscopically well-circumscribed or encapsulated, lobulated, and exhibits variable cellularity with characteristic lipoblasts in a myxoid matrix. Mitoses are rare. The vasculature typically presents a Crow's feet pattern. MLS is typically negative for cytokeratins, positive for S-100 in 40% of cases and negative for MSA, SMA, CD34, GFAP and desmin. The tumor presented was infiltrative rather than encapsulated or well circumscribed, and lacked lipoblasts as well as Crow's feet vessels; therefore, the diagnosis of MLS could be ruled out.

Myxofibrosarcoma (Myxoid malignant fibrous histiocytoma) (MFS) is a locally aggressive tumor of older adults, characterized microscopically by infiltrative margins, spindle or stellate cells in a hypocellular myxoid matrix, cytological atypia, pseudolipoblasts containing acid mucin, and curvilinear vessels. MFS are usually vimentin positive, may be SMA or CD34 positive and negative for cytokeratins, S-100, MSA, GFAP and desmin. The present tumor lacked cytological atypia, pseudolipoblasts and curvilinear vessels, thus ruling out the possibility of MFS.

After excluding the other possible diagnoses and considering the radiographic, clinical, and microscopic presentation, a final diagnosis of extra-skeletal myxoid chondrosarcoma; low-grade (EMC) was rendered.

EMC is a rare and unique soft tissue tumor comprising less than 2.5% of soft-tissue sarcomas. First defined by Enzinger and Shiraki in 1972, it has a prominent myxoid

morphology, with a relatively protracted course and a better prognosis than chondrosarcomas of bone [1]. EMC occurs over a wide age range, with the majority of cases over age 35. The most common locations are the proximal extremities and limb girdles, followed by distal extremities, trunk and rarely in other locations [2]. Microscopic characteristics of EMCs include a multi-nodular architecture and cords or strands of small cells in a myxoid matrix. The cells are ovoid or spindle, with an eosinophilic cytoplasm and may exhibit hyperchromatic nuclei. Large atypical or rhabdoid cells, focal hyaline cartilage and cellular spindle cell areas resembling fibrosarcoma have all been described in individual cases but are uncommon features. The cellularity of EMC was described as low in 70% of cases, and the mitotic count is generally low, with 61% of cases showing less than 1 mitosis/10 HPF, and the remaining less than 2/10 HPF [3]. Using immunohistochemistry, the only marker which has been consistently positive in the majority of cases is vimentin. There is a wide variation in reports for other markers; the most frequently positive at least focally are S-100, neuroendocrine markers (NSE, synaptophysin and chromogranin) in a subgroup of patients and PGP9.5. Cytokeratins, EMA, smooth muscle actin, muscle specific actin, desmin and GFAP are rarely positive [2, 3]. Occasional cases showed some BCL-2 or c-kit positivity.

In recent years, cytogenetic studies of EMC identified 2 recurrent chromosomal aberrations: t(9;22)(q22;q12) resulting in EWSR1-NR4A3 fusion gene, and t(9;17)(q22;q11) resulting in RBP56-NR4A3 fusion gene. The latter is seen in the subgroup of cases with neuroendocrine differentiation. Other abnormalities such as trisomies 7, 8, 12, 18, 19, and 22, as well as structural rearrangements in 1q, 2q, 3q, 4q31, 6q have also been observed but are not diagnostic for EMC [2, 4, 5]. The EWSR1-NR4A3 fusion gene activates the PPARG nuclear receptor gene, and this may have clinical relevance as several PPARG agonists have been developed and are presently at various stages of clinical trials [4].

Electron microscopic analysis showed intracisternal microtubules and prominent mitochondria in EMC. Although EMC and myxoid chondrosarcoma of bone have some overlapping light microscopic features, there are distinctive differences in ultra-structure and cytogenetics, as well as in clinical behavior; these differences allow the differentiation between the two entities [6].

Only 16 cases of EMC involving the head and neck have been identified in the literature between 2000 and 2010, of which 6 cases have been reported to be nasal or sino-nasal, similar to the present case. Head and neck EMC occurred in a wide age range of 10–88 years (mean = 44 years). There were no obvious gender differences, with a 9: 8 M: F ratio, including the present case (Table 1).

Information on outcome was available for only half of the cases, and follow-up was uniformly short (9 months–3 years). Within these limitations, only 2 cases reported recurrent disease and none of the patients died of disease, thus confirming that EMCs of the head and neck are low-grade malignancies with a relatively protracted clinical course.

A retrospective study of EMC from 2 referral centers showed 82, 65, and 58% survival at 5, 10 and 15 years, respectively. A subgroup of patients in this study were treated by chemotherapy, but the response to chemotherapy was poor; thus, these results emphasize that adequate surgery is the primary and most important treatment modality in EMC [7]. However, complete surgical eradication of large malignancies in the head and neck region may not always be possible. In spite of this, the small number of reported sino-nasal EMC cases in the literature appear to have a relatively indolent course.

With the diagnosis of EMC, the patient underwent a right extended maxillectomy via Weber–Ferguson incision, including the excision of the pterygoid muscle and plates and an anterior and posterior ethmoidectomy. The maxillary

defect was reconstructed with an obturator and the inferior orbital wall was reconstructed with titanium mesh. A Dacryorhinocystotomy (DCR) was performed at the end of the procedure. The resection specimen showed an infiltrative invasion pattern, with microscopic features identical to those in the biopsy described previously. Neuroendocrine differentiation which may be a feature in some ECM was not evident in the present case. BCL-2 and c-kit which have occasionally been described in chondroid tumors were negative as well [8]. The frozen sections performed on samples from the tumor bed during surgery were negative, however, in the final surgical specimen some of the margins were involved. All lymph nodes in the neck dissection were tumor free. The surgical treatment was therefore followed by radiotherapy (70 cGy). The patient recovered well from these procedures and has received a denture-obturator. The cosmetic result was satisfactory to the patient, and functional results were fairly good, although she has had recurrent episodes of staphylococcal infection at the resection site, and has been under repeated antibiotic treatment. There was no sign of recurrence at 18 months post-operatively, and follow-up continues.

Table 1 Extraskelatal myxoid chondrosarcoma of the head and neck region, 2000–2010

Source	Tumor location	Gender/age	FU	Outcome
Diek A et al. Oncology 2009;23(8):718–21	Supra-clavicular	M, 49	1 year	AWD
Willems SM et al. Histopathology 2008;52, 465–474	Neck	M, 32 years	N/A	N/A
O'Brien J et al. Br J Neurosurg 2008;22(3):429–32	Cerebellopontine angle	F, 26 years	N/A	N/A
Kim YJ et al. Korean J Radiol 2007; 8(5): 452–5	Nasal, Ethmoidal Sinus	M, 10 years	N/A	N/A
Nakazora S et al. Oncol Rep 2006;16(1):115–8	Clavicle	M, 48 years	N/A	N/A
Betz CS et al. HNO 2007;55(1):51–5	Nasal septum	F, 88	<1y	Early rec., FOD after 2nd surgery
Saint-Blancard P et al. Rev Med Interne 2006;27(2):160–2	Neck, infra-hyoid, with LN involvement	F, 67	N/A	N/A
Ceylan K et al. Eur Arch Otorhinolaryngol 2006;263(11):1044–7	Maxillary & Ethmoidal sinuses, nasal cavity	F, 35	9 m	
Kotil K et al. J Neuroncol 2005;75(2):169–72	Intra-dural	M, 40	26 m	FOD
Cummings TJ et al. Clin Neuropathol 2004; 23(5):232–7	Jugular foramen	M, 63	N/A	N/A
Acero J et al. Int J Oral Maxillofac Surg 2003;32(3):342–5	Infra-temporal fossa	F, 22	3 y	FOD
Jerome-Marson V et al. Ann Pathol. 2003;23(3):253–7	Nasal cavity	M, 67	N/A	N/A
Algros MP et al. Ann Pathol. 2003;23(3):253–7	Sphenoidal sinus	F, 71	N/A	N/A
Im SH et al. J Korean Med Sci 2003;18:301–7	Intra-cranial	M, 48	3 y	FOD
Gonzalez- Lois C et al. Acta Neurochir (Wien) 2002;144(7):735–40	Intra-cranial	F, 17	18 m	Multiple rec.'s
Wadhwa N et al. Diagn Cytopathol 2000; 22(6):3839	Sphenoidal sinus	M, 44	16 m	FOD
Present case	Maxilla, maxillary & ethmoidal sinuses and nose	F, 37	18 m	FOD

AWD alive with disease, FOD free of disease, N/A information not available, Rec recurrent disease

References

1. Enzinger FM, Shiraki M. Extraskeletal myxoid chondrosarcoma. An analysis of 34 cases. *Human Pathol.* 1972;3:421–35.
2. Hisaoka M, Hashimoto H. Extraskeletal myxoid chondrosarcoma: updated clinicopathological and molecular genetic characteristics. *Pathol Int.* 2005;55(8):453–63.
3. Oliveira AM, Sebo TJ, McGrory JE, et al. Extraskeletal Myxoid Chondrosarcoma: a clinicopathological, immunohistochemical and ploidy analysis of 23 cases. *Mod Pathol.* 2000;13(8):900–8.
4. Filion C, Motoi T, Olshen AB, et al. The EWSR1/NR4A3 fusion protein of extraskeletal myxoid chondrosarcoma activates the PPARG nuclear receptor gene. *J Pathol.* 2009;217:83–93.
5. Subramanian S, West RB, Marinelli RJ, et al. The gene expression profile of extraskeletal myxoid chondrosarcoma. *J Pathol.* 2005; 206:433–44.
6. Antonescu CR, Argani P, Erlandson RA, et al. Skeletal and extraskeletal myxoid chondrosarcoma: a comparative clinicopathologic, ultrastructural, and molecular study. *Cancer.* 1998;83(8): 1504–21.
7. Drilon AD, Popat S, Bhuchar G, et al. Extraskeletal myxoid chondrosarcoma. *Cancer.* 2008;113(12):3364–71.
8. Daugaard S, Christensen LH, Hgdall E. Markers aiding the diagnosis of chondroid tumors: an immunohistochemical study including osteonectin, bcl-2, cox-2, actin, calponin, D2-40 (podoplanin), mdm-2, CD117 (c-kit), and YKL-40. *APMIS.* 2009;117(7):518–25.