Clinico-Pathologic Conference: Case 2

Camilla Kragelund · Shabnum Meer ·
Lars Pallesen · Jesper Reibel

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Clinical Presentation

A 19 year old Caucasian male was referred to an Oral and Maxillofacial surgeon diagnosed with chronic pericoronitis, and amoxicillin, metronidazole, and ibuprofen had been prescribed. According to the patient a swelling in the mandible had persisted for 3 weeks, however, the patient's father suspected that it had been present for about 3 months. The patient's chief complaint was impaired mouth opening and pain in occlusion which hampered food intake. Furthermore, the patient experienced paresthesia localized to the tip of the tongue. The medical history showed no general symptoms nor recognized systemic diseases. No daily drug intake and no known allergies to medication. The patient smoked 20 cigarettes daily for 2 years.

Physical examination demonstrated enlargement of the right submandibular lymph node. Assessment of the oral cavity showed a 3 × 3 cm elevated soft tissue lesion in the lower right retromolar area in conjunction with the 2nd molar. There were tooth impressions into the overlying mucosa, but no ulcerations and no obvious signs of infection

(Fig. 1). Radiographic examination revealed an impacted lower right 3rd molar and a slightly diffuse radiolucent area localized to the ascending ramus (Fig. 2). A malignant neoplasm was suspected and a biopsy was taken (Fig. 3).

Differential Diagnoses

The history of the fairly large, ill-defined, non-corticated, highly proliferative intrabony lesion with no association to the impacted tooth, and showing dilatation of the inferior alveolar nerve canal with localized paresthesia suggests a non-odontogenic soft tissue malignancy. Even though there is spread to regional lymph nodes the lesion appears to have broken out of the bone into the soft tissue mitigating against surface mucosal origin, excluding the possibility of a carcinoma. Furthermore, the retromolar area is a site often associated with more sinister lesions. The intrabony tumors considered in the differential diagnosis include eosinophilic granuloma, intrabony salivary gland malignancies, plasmacytoma/myeloma, non-Hodgkin's lymphoma, Ewing's sarcoma/PNET, malignant non-odontogenic sarcomas such as malignant peripheral nerve sheath tumors (MPNST) and rhabdomyosarcoma, especially in a young adult.

Eosinophilic granuloma usually presents in children or young adults, as a single intra-osseous lucency in the mandible, and often with an associated soft tissue swelling with or without ulceration. There may be metastasis to regional lymph nodes. The histology is well recognised and the diagnosis confirmed with CD1a and S100 immunopositivity supported by the ultrastructural demonstration of Birbeck granules. The two main *intrabony salivary malignancies* often seen in the retromolar area and which may present with trismus include *mucoepidermoid carcinoma* and *acinic cell*

C. Kragelund (✉) · J. Reibel
Department of Oral Medicine, Section of Oral Pathology,
School of Dentistry, University of Copenhagen, 20, Norre Allé,
2200 Copenhagen N, Denmark
e-mail: ckra@sund.ku.dk

S. Meer
Division of Oral Pathology, Faculty of Health Sciences,
University of the Witwatersrand, Johannesburg, South Africa

L. Pallesen
Department of Oral and Maxillofacial Surgery, School of
Dentistry, University of Copenhagen, Copenhagen, Denmark

Fig. 1 Intraoral swelling of the retromolar area with tooth impressions of the overlying mucosa

Fig. 3 The lesion after incision of the oral mucosa and before biopsy

Fig. 2 Radiograph of the right mandibular ramus showing an impacted lower 3rd molar and a slightly diffuse radiolucent area localized to the ascending ramus

carcinoma. The most likely source for most intraosseous salivary malignancies is odontogenic epithelium. In contrast to the salivary gland counterparts however, intrabony variants occur slightly more commonly in middle age and in females.

Plasmacytoma is a unifocal monoclonal neoplastic proliferation of plasma cells that usually arises in bone, with infrequent soft tissue extension. Common in males and although they have been reported in young adults, they are seen more in older individuals. Radiographically there

is often a unilocular radiolucency with no sclerotic borders or a fairly ragged radiolucency similar to that of myeloma. Immunohistochemical studies demonstrate a monoclonal plasma cell infiltrate. Whilst a *B-cell non-Hodgkin's lymphoma*, especially *Burkitt's lymphoma* is included in the differential diagnosis, there is no history of immunosuppression and even though 50–70% of endemic Burkitt lymphoma present in the jaws of young males, this form of Burkitt's lymphoma is extremely uncommon in the Danish population. Unifocal *acute lymphoblastic lymphoma* is usually diffuse in its presentation.

Ewing's sarcoma/PNET is a distinctive primary malignant tumor of bone showing features consistent with neuroectodermal origin. It displays a male predominance, occurs in young adults and the vast majority of patients affected are white. Though not common in the jaws, it is more common in the mandible. Ewing's sarcoma constitutes 6–8% of all primary malignant bone tumors representing the third most common malignant osseous neoplasm after osteosarcoma and chondrosarcoma.

Although the *aggressive fibromatoses* including *myofibroma* and *desmoplastic fibroma*, which are benign or graded as borderline “malignancies”, may present as solitary rapidly enlarging and destructive intrabony masses with trismus within the head and neck region, commonly in the mandible and especially in young adults, the presence of paresthesia and regional metastasis precludes these lesions from the differential diagnosis. However, within the same spectrum of disease the *low-grade myofibroblastic sarcoma* remains a strong possibility. This rare malignancy of low-grade potential presents clinico-pathologically in a manner similar to both the aggressive myofibromatoses and low-grade adult fibrosarcoma.

Thus the favoured differential diagnosis is that of a non-odontogenic soft tissue sarcoma. Even though *central*

osteogenic sarcoma and *MPNST* have to be considered in the differential diagnosis, these sarcomas seldom show regional metastasis. *MPNST* may occur in young adults and although they may present as ill defined lucencies, causing dilatation of the mandibular canal they occur more commonly in the setting of neurofibromatosis. Sarcomas that are known to show regional lymph node metastasis include rhabdomyosarcoma, alveolar soft part sarcoma, clear cell sarcoma, epithelioid sarcoma and synovial sarcoma. Based on the highly proliferative, rapidly enlarging nature of this intrabony retromolar lesion showing destruction, paresthesia and regional spread to lymph nodes in a young adult male, the most common and likely diagnosis is that of *rhabdomyosarcoma*.

Diagnosis and Discussion

Light Microscopy

Histological examination of hematoxylin and eosin (H&E) stained sections showed areas of a myxoid stroma with small, ovoid tumor cells with dark nuclei and sparse cytoplasm. These areas were surrounded by elongated tumor cells with vesicular nuclei arranged in a dense, cellular fascicular pattern. 6 mitotic figures per HPF were registered in the cellular areas, some of them with an atypical appearance. Scattered in the cellular areas were large round or polygonal cells with abundant eosinophilic cytoplasm some of which had hyperchromatic, eccentrically placed nuclei—rhabdomyoblast-like cells. No cross-striations were found. Focally, collagen fascicles and areas of necrosis were seen (Figs. 4, 5).

Fig. 4 Small, ovoid tumor cells with dark nuclei and sparse cytoplasm in a myxoid stroma

Fig. 5 Cellular area with abundant mitotic figures, some of them with an atypical appearance. Elongated tumor cells with vesicular nuclei and one large round rhabdomyoblast-like cell with abundant eosinophilic cytoplasm and a hyperchromatic, eccentrically placed nucleus

Immunohistochemistry

Tumor cells showed strong positive cytoplasmic reaction for desmin and nuclear reaction for MYF4 (myogenin) (Figs. 6, 7). WT1 also showed a positive reaction. Vimentin and smooth muscle actin showed scattered positivity in tumor cells whereas S100 was negative. All antibodies used were obtained from Dako, Glostrup, Denmark.

Genetics

Analysis for genetic translocations of FKHR (alveolar rhabdomyosarcoma), EWSR (Ewing tumor), and SYT

Fig. 6 Desmin in tumor cells showing strong cytoplasmic reaction. Note the large rhabdomyoblast-like cells

Fig. 7 MYF4 in tumor cells showing strong nuclear reaction

(synovial sarcoma) showed no abnormalities. The final diagnosis was embryonal rhabdomyosarcoma (RMS) according to the 2002 WHO classification [1].

Radiographic Assessment

Magnetic resonance imaging (MRI) revealed a soft tissue tumor measuring 4 (anteroposterior) × 3.2 (mediolateral) × 3.5 (craniocaudal) cm infiltrating the right medial pterygoid muscle and the anterior part of the right masseter muscle. The tumor extended between the tongue and the medial part of the mandible.

Treatment

The patient initiated curative chemotherapy 3 weeks after the first biopsy. This comprised 4 courses of vincristine, dactinomycin, and isophosphamide. The patient tolerated the chemotherapy well. The treatment was monitored by (18)F-fluorodeoxyglucose positron emission tomography (PET/CT) and MRI showing that the tumor responded satisfactorily. After 3 months of treatment there were no symptoms or abnormal intra-oral findings recorded. Another biopsy was taken and the histological findings showed reactive changes only (fibrosis and muscle atrophy). The patient was subsequently treated with 5 additional courses of chemotherapy (vincristine and isophosphamide) combined with intensity modulated radiotherapy. At present, 6 months after the diagnosis, the patient is treated on an outpatient basis.

RMSs are relatively rare tumors, and except for the pleomorphic subtype, they occur most frequently in children [2]. They are rare in adults [1]. In order to get an overview of published cases of intra-oral RMSs in adults a literature search was performed on PubMed with search terms [RMS] and

[adult] and [oral]. Only cases and case series published in English of intra-oral RMSs in adults (≥ 18 years) with clear clinical information (gender, age and clinical localization of the tumor) and with defined histological criteria, which were supported by immunohistochemistry or genetic analysis were included. 18 cases fulfilled the inclusion criteria and were all published from 1995 or later [3–12]. The cases were 12 males (67%) and 6 females with a mean age of 40.2 years (range 19–78 years) and 32.2 years (range 18–41 years), respectively. The intra-oral location of the tumors was described as associated to bone in 11 cases (mandible: 3, maxilla: 6, palate: 2) and to soft tissue in 7 cases (cheek: 4, tongue: 1, sub-mandibular gland: 1, not specified: 1). Histological subtypes included 8 embryonal (mean age 30.9 years), 4 embryonal of the spindle cell subtype (mean age 37.3 years), 3 alveolar (mean age 27.7 years), 2 pleomorphic (mean age 77.5 years), and 1 described as a sclerosing, pseudovascular subtype (41 years). The literature search supports the assumption that there is a slight male predominance of RMS in adults. The age range is wider among the males as compared to the females. The localization of the tumors can be associated to bone and soft tissue, but there is no clear support of any predominant site. The mean age of the pleomorphic RMS is higher than that of the other histological types.

The etiology of RMSs has been associated to genetic translocation of the FKHR gene in alveolar RMS [1]. A single case reported a possible radiation-induced RMS [3]. Soft tissue swellings should be biopsied and/or referred to a specialist. If a malignant lesion is suspected the patient should be biopsied or referred according to the national guidelines. As in the present case, RMSs may be misapprehended as what appears to be a common reactive lesion.

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References

1. Parham DM, Barr FG. Embryonal rhabdomyosarcoma. In: Fletcher CDM, Unni KK, Mertens F, editors. World health organization classification of tumours. Pathology and Genetics. Tumours of soft tissue and bone, vol. 146. Lyon France: IARC-Press; 2002. p. 146–52.
2. Kaatsch P. Epidemiology of childhood cancer. *Cancer Treat Rev*. 2010;36(4):277–85.
3. Goosens V, Van den Berghe I, De Clercq C, Casselman J. Radiation-induced mandibular adult spindle cell rhabdomyosarcoma. *Int J Oral Maxillofac Surg*. 2008;37(4):395–7.
4. Rubin BP, Hasserjian RP, Singer S, Janecka I, et al. Spindle cell rhabdomyosarcoma (so-called) in adults: report of two cases with emphasis on differential diagnosis. *Am J Surg Pathol*. 1998;22(4):459–64.
5. Pavithran K, Doval DC, Mukherjee G, et al. Rhabdomyosarcoma of the oral cavity—report of eight cases. *Acta Oncol*. 1997;36(8):819–21.

6. Lin J, Yip KM, Chow LT. Pleomorphic rhabdomyosarcoma of the submandibular salivary gland. *Otolaryngol Head Neck Surg.* 1997;116(4):545–7.
7. Furlong MA, Mentzel T, Fanburg-Smith JC. Pleomorphic rhabdomyosarcoma in adults: a clinicopathologic study of 38 cases with emphasis on morphologic variants and recent skeletal muscle-specific markers. *Mod Pathol.* 2001;14(6):595–603.
8. Mentzel T, Katenkamp D. Sclerosing, pseudovascular rhabdomyosarcoma in adults. Clinicopathological and immunohistochemical analysis of three cases. *Virchows Arch.* 2000;436(4):305–11.
9. Franca CM, Caran EM, Alves MT, et al. Rhabdomyosarcoma of the oral tissues—two new cases and literature review. *Med Oral Patol Oral Cir Bucal.* 2006;11(2):E136–40.
10. Chi AC, Barnes JD, Budnick S, et al. Rhabdomyosarcoma of the maxillary gingiva. *J Periodontol.* 2007;78(9):1839–45.
11. Chen SY, Thakur A, Miller AS, et al. Rhabdomyosarcoma of the oral cavity. Report of four cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1995;80(2):192–201.
12. Nascimento AF, Fletcher CD. Spindle cell rhabdomyosarcoma in adults. *Am J Surg Pathol.* 2005;29(8):1106–13.