Metastatic Embryonal Carcinoma in the Maxillary Gingiva

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Abstract. *Gingival metastases from embryonal carcinoma are very rare and often associated with widespread disease and poor prognosis. Because of their indistinct clinical appearance, they may be difficult to discriminate from more frequent gingival hyperplastic or reactive lesions. The case of a 35-year-old man who presented with a swelling in the left maxillary gingiva, extending from the first premolar to the second molar is reported. This medical history revealed that, 2 years previously, he had been diagnosed with a testicular mixed germ cell tumor (GCTs), for which he had undergone right inguinal orchidectomy and chemotherapy, leading to complete remission. Histology revealed a metastatic embryonal carcinoma. Imaging of the chest and abdomen showed this was the only site of metastasis. He is currently undergoing chemotherapy and responding well. This case draws attention to the multiple diseases that may present as gingival masses and stresses the difficulty of making a correct diagnosis. It is emphasized that in some mixed cases of testicular GCT it may be the more aggressive component that metastasizes, without being clearly apparent.*

About 1% of all oral cancers are metastases from primary tumors elsewhere in the body, and may be located in the soft tissues as well as in the jaw bones. Almost all types of malignancy may metastasize to the mouth. Although no particular malignancy appears to favor spread to the oral cavity, some primary tumors are found more frequently than others. For instance, primary lung tumors and breast cancer are more likely to give rise to oral metastases (1).

The metastatic spread of tumors of the germ cell line to the oral cavity is extremely rare; there are very few reports of the metastatic spread of testicular tumors to the oral cavity (2-5) and that of seminoma, although rare, has been reported (6-13), mainly to the jaw bones. Some cases have also been reported of embryonal carcinoma metastasizing to the oral cavity (3, 14).

Testicular germ cell tumors (GCTs) are a heterogeneous group of tumors with diverse histopathology and clinical behavior. They originate from the male gonad and are classified into two broad categories, namely seminoma and non-seminomatous germ cell tumor (NSGCT).

Seminoma is the commonest type of testicular germ cell tumor, accounting for approximately 50% of cases (15-17). There are two types of seminomatous tumor: (1) classic seminoma and its variants and (2) spermatocytic seminoma. In addition, seminoma is a recognizable component in a large proportion of mixed testicular germ cell neoplasms (16).

Non-seminomatous GCTs comprise embryonal carcinoma, yolk sac tumor, immature or mature teratoma, choriocarcinoma and other rare trophoblastic tumors. These tumor types are often seen together in various combinations, referred to as mixed GCTs, which may also include seminoma. The expressions "non-seminomatous GCT" and "mixed GCT" are usually used interchangeably in daily clinical practice.

We present a very rare case of a mixed GCT comprising a seminomatous component and an embryonal carcinoma component that, after two years, metastasized to the oral cavity in the form of its more aggressive component, embryonal carcinoma. We discuss immunohistochemical features and clinical and histological differential diagnosis of this difficult-to-recognize tumor.

Case Report

A 35-year-old man presented with a month-long history of a swollen mass at the left maxillary gingiva. Clinically, intraoral examination revealed soft tissue swelling, resembling a periodontal pyogenic abscess, a pyogenic granuloma-like tumor, or a hyperplastic reactive lesion. The lesion was located on the left buccal gingiva and vestibule and measured approximately 2.0x2.0 cm. The exophytic growth, in the region of the first premolar and second

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Key Words: Gingival metastasis, germ cell tumor, testicular tumor, embryonal carcinoma.

Table I. *Immunohistochemical findings of the current case.*

Antibody	Supplier	Dilution	Clone	Antigen retrieval
HCG	DAKO	1:400	βHCG	n.p.
PLAP	DAKO	1:40	8A9	Citrate pH=6
PANCYTOKERATIN	YLEM	1: 50	AE1/AE3	//
AFT	DAKO	1:200	Alpha fetoprotein	//
CD20	DAKO	1:200	L26	//
VIMENTIN	VENTANA	1: 400	Monoclonal	//
CD30	DAKO	1:50	BerH2	//
EMA	DAKO	1:50	E29	n.p.

HCG: Human chorionic gonadotropin; PLAP: placental alkaline phosphatase; AFT: alpha fetoprotein; n.p.: not performed.

molar, was associated with pain and bloody necrotic tag. The overlying tissue was edematous and erythematous. Extra oral head and neck examination showed no evidence of lymphadenopathy or other diseases. The patient's medical history included a right inguinal orchidectomy with adjuvant chemotherapy for stage 1 mixed GCTs 2 years previously. Radiologically, the chest was clear. Abdominal examination revealed no mass or organomegaly, and tumor marker levels of alpha-fetoprotein (AFP), the β subunit of human chorionic gonadotrophin (βhCG) and lactic dehydrogenase (LDH) were within the normal range.

A biopsy was performed and the results of histological examination of the tissue specimen showed the mass to be a metastatic embryonal carcinoma. The patient subsequently began a chemotherapeutic regime. Consolidation radiotherapy was not indicated; the patient is still undergoing chemotherapy and is doing well.

Histologically, the cells were arranged in a solid nodular pattern separated by thin fibrovascular trabeculae, rich in T-cell lymphocytes (Figure 1). Individual tumor cells were large, uniform, round to polygonal, with hyperchromatic nuclei, and slightly eosinophilic to clear cytoplasm. The nuclei contained one or more prominent nucleoli. Frequent mitoses were visible (Figures 2 and 3).

Materials and Methods

The excised biopsy specimens were fixed in 10% buffered-formalin and paraffin embedded; 5μ sections were stained with haematoxylin-eosin. For immunohistochemistry, the avidin-biotin complex (ABC) method was applied (17). Sections were deparaffinized with xylene for 15 min before rehydration through graded alcohols to water. Antigen retrieval was performed on the slides by placing them in a bath of 10 mM citric acid (pH 6) and boiling for 16 min using an autoclave.

A panel of monoclonal antibodies was used for the following markers (Table I): alpha-fetoprotein (AFP), (1:200 Dako), human chorionic gonadotropin (HCG) (1:400 Dako), placental alkaline phosphatase (PLAP) (1:40 Dako) pancytokeratin (1:50 Ylem), vimentin (1:400 Ventana), epithelial membrane antigen (EMA) (1:50 Dako), CD20 (1:200 Dako) and CD30 (1:50 Dako). Of the above antibodies, for HCG and EMA sections, antigen retrieval was not performed.

Table I lists the immunohistochemical antibodies, their sources and dilutions. Appropriate controls were tested simultaneously. The immunohistochemical reactivity was evaluated and graded as follows: − (negative), no staining; + (positive), focally positive staining of a limited number of cells; and ++ (intensely/strongly positive), focally or diffusely positive staining of numerous cells.

The tumor cells were negative for AFP, HCG, PLAP, pancytokeratin, vimentin, EMA, and CD20, and strongly positive for CD30 (Figure 4)

Discussion

Gingival metastases may sometimes be the first manifestation of widespread metastatic disease and thus particular attention must be paid to gingival lesions associated with atypical clinical symptoms and/or signs. Metastatic tumors are very rare in the oral cavity and may resemble benign lesions, such as pyogenic granuloma, periodontal abscess, or inflammatory hyperplastic lesions. The clinical appearance in our case was of a gingival mass that could have been misdiagnosed as a hyperplastic lesion associated with a tooth or as a reactive process; it was associated with pain and bleeding, rather common symptoms. In rare cases, the patients may complain of paresthesia, which develops relatively quickly (18, 19). It is clear that in many cases diagnosis can be difficult and requires a careful history to be taken, particularly the patient's remote medical history, as well as a biopsy for histological diagnosis.

Pathological diagnosis is also challenging from the morphological standpoint because of the different growth patterns and variants of embryonal carcinoma that exist. At microscopic examination, embryonal carcinoma displays variable growth patterns, including solid, syncytial, acinar, tubular, or papillary arrangement (20). Marked anaplasia, numerous mitoses including abnormal forms, and cellular overlapping are characteristic. The neoplastic cells are polygonal, undifferentiated and epithelial in appearance, with large vesicular and empty-looking nuclei and a thick, distinct

nuclear membrane. The cytoplasm is usually abundant and finely granular with no distinct cell border. Despite these variable growth patterns, embryonal carcinoma cells retain their cytological features; thus the key to differential diagnosis is to concentrate on cytological details of the tumor cells. In doubtful cases, immunohistochemical staining can help to make a correct diagnosis.

Differential diagnosis is principally *versus* seminoma or yolk sac tumor. The anaplastic variant of spermatocytic seminoma, because of its relatively monomorphic appearance and nuclear prominence, can frequently be misinterpreted as embryonal carcinoma. Yolk sac tumor may have a papillary and glandular pattern similar to that of embryonal carcinoma, and also have foci of both tumour types; in this case CD30 and AFP may assist with differentiation.

Immunohistochemically, we ran tests for AFP, HCG, PLAP, pancytokeratin, vimentin, EMA, CD20, and CD30. We found positivity only for CD30, whereas markers that have been reported as positive in other studies were negative in our case: embryonal carcinomas have commonly been reported to be positive for cytokeratins (21-23) but negative for EMA, which should help in distinguishing a metastatic embryonal carcinoma from a somatic carcinoma.

CD30, a sensitive marker for embryonal carcinoma (24-26), stains no other GCT, including seminoma and yolk sac tumor. However, it has been reported that CD30 expression can be lost in metastatic embryonal carcinoma after chemotherapy (27). This did not occur in our case, but chemotherapy might also in our opinion explain the loss of the immunohistochemical profile in some metastatic forms.

Embryonal carcinoma generally occurs in the 20-30 year age range and, although considerable progress has been made in its treatment, it is more aggressive than other germ cell tumors (28). The rate of progression differs with the histology; all germ cell tumors have the propensity to metastasize. Lymphatic spread is common to all testicular tumors; sequential spread, initially involving the retroperitoneal, para-aortic and subsequently the mediastinal and supraclavicular lymph nodes, is typical. Hematogenous spread is also possible, primarily to the lungs, but also to the liver, brain and skeleton.

Staging of these tumors takes into account the TNM system of classification plus levels of prognostically important tumor-specific serum markers, including HCG, AFP, and lactate dehydrogenase. Serum levels of the liver enzyme LDH reflect tumor turnover (29).

At initial presentation, our case was stage 1, and the patient underwent right inguinal orchidectomy with adjuvant chemotherapy. This is the traditional management protocol for mixed germ cell tumor at clinical stage I (localized disease). It is reported that adjuvant chemotherapy achieves a cure rate above 90% (30).

To conclude, we report a case of testicular tumor metastizing to the oral cavity, of which very few cases have been reported to date. Clinically, differential diagnosis must exclude numerous diseases that may present as a gingival mass, such as hyperplastic reactive lesion, pyogenic granuloma, periodontal abscess, or inflammatory conditions, and a careful medical history is recommended to achieve correct diagnosis. Biopsy and histological examination, supported by immunohistochemistry, are fundamental in defining the nature of the lesion precisely. Oral metastases are usually evidence of widespread disease and the prognosis is often poor, therefore a careful follow-up and a full understanding of this type of metastasis, as well as of other malignancies, may be helpful from both the clinical and the prognostic standpoints.

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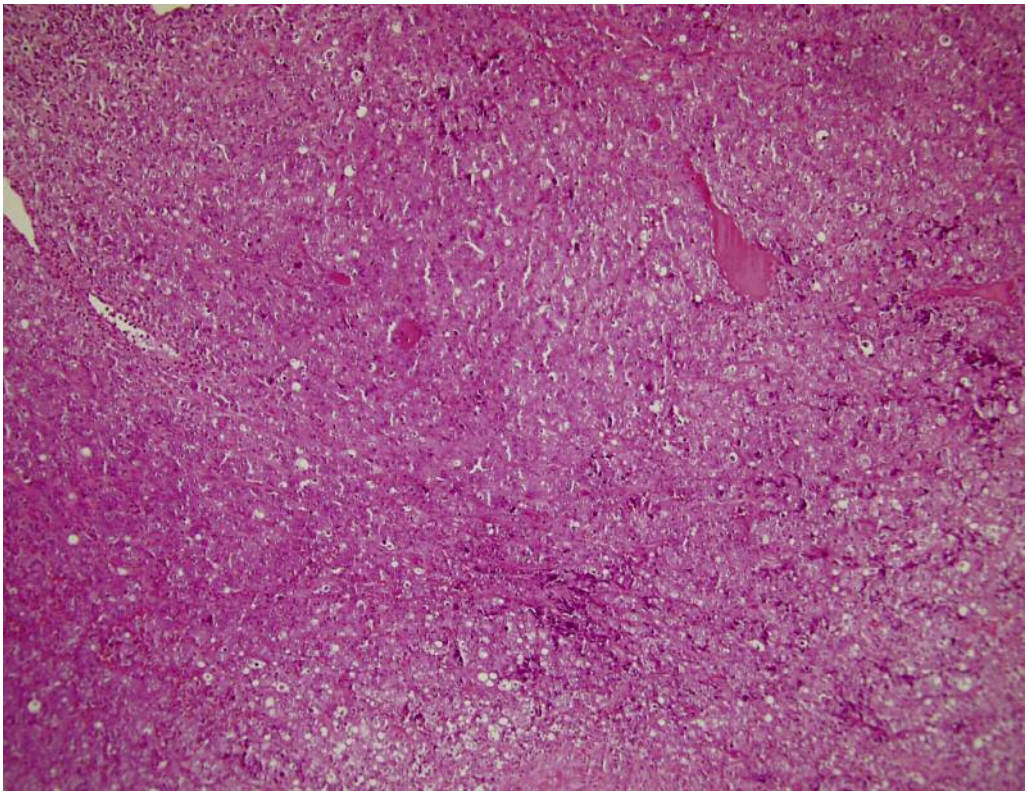

Figure 1. *The tumor shows a solid pattern separated by thin fibrovascular trabeculae (hematoxylin and eosin stain, original magnification x150).*

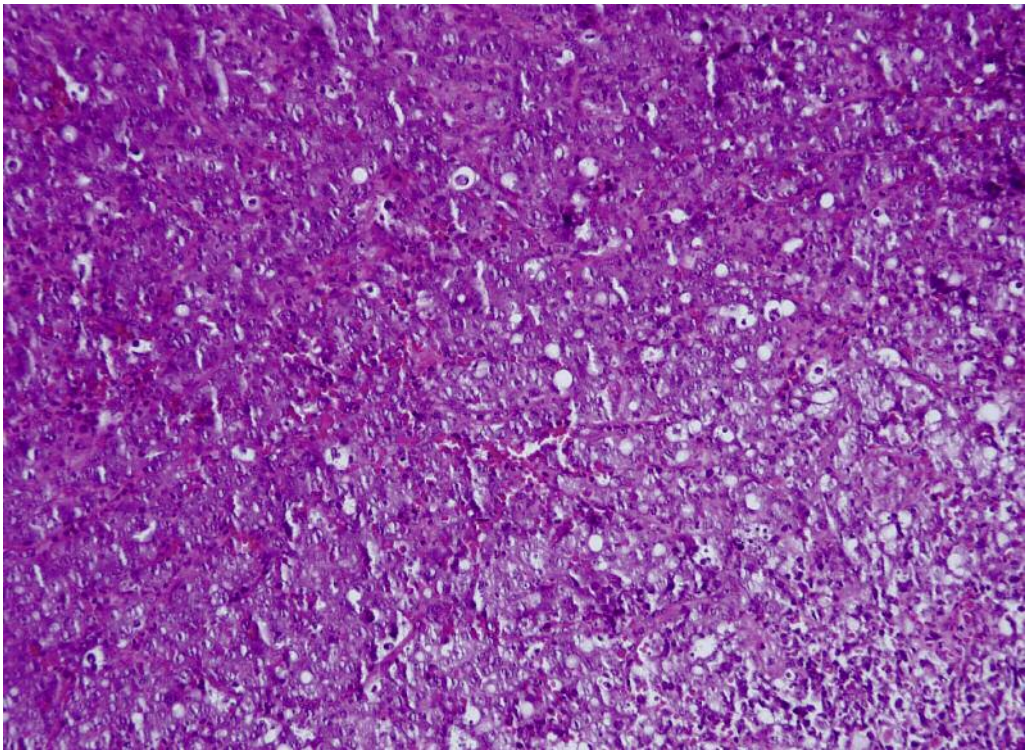

Figure 2. *Individual tumor cells are large, uniform, round to polygonal, with hyperchromatic nuclei, and with slightly eosinophilic to clear cytoplasm (hematoxylin and eosin stain, original magnification x150).*

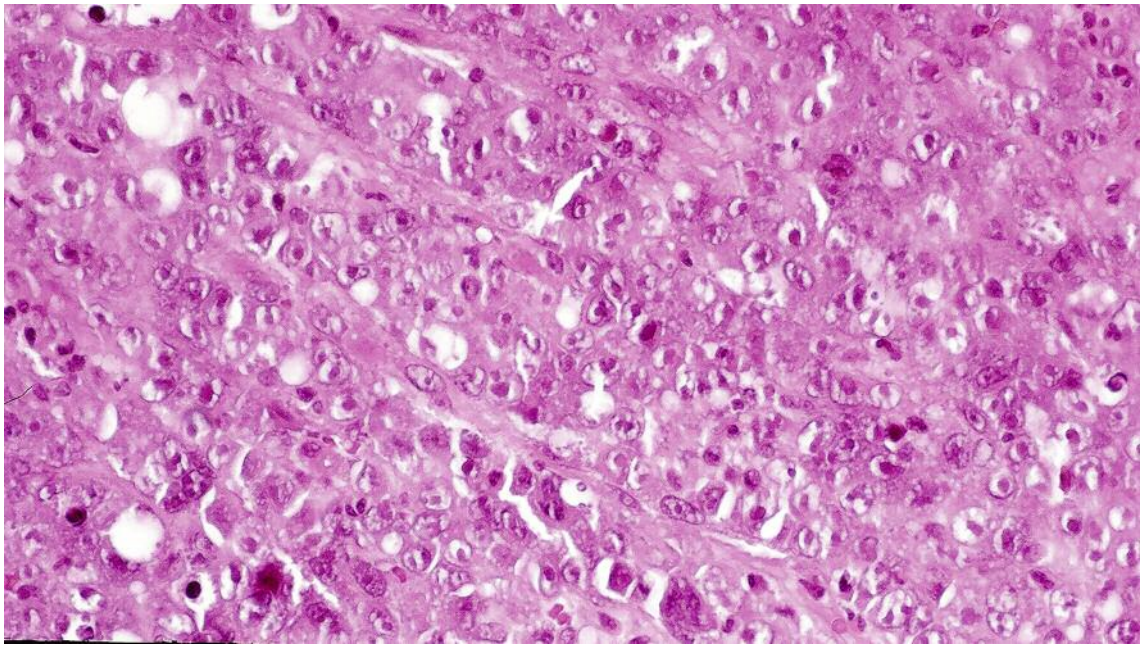

Figure 3. *The nuclei contain one or more prominent nucleoli. Frequent mitoses are visible (hematoxylin and eosin stain, original magnification x200).*

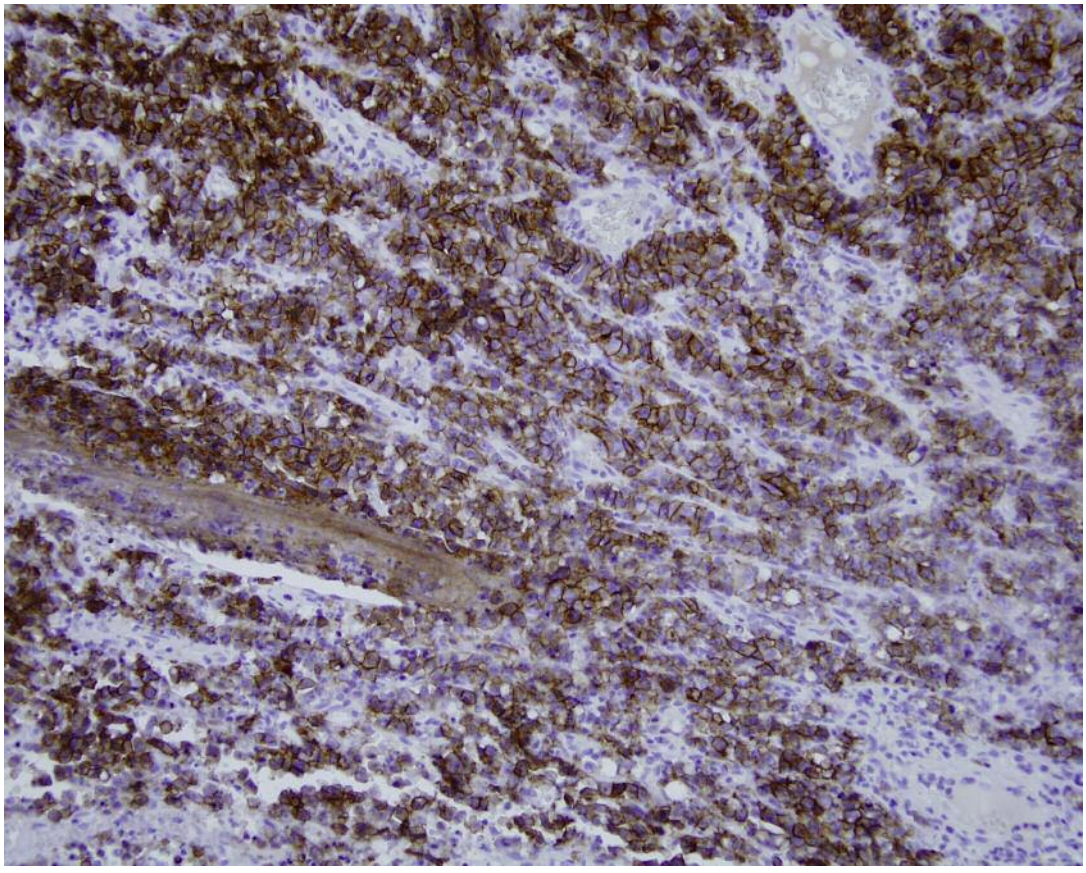

Figure 4. *Immunohistochemically shown strong membrane positivity for CD30 (original magnification x150).*

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Received November 9, 2007
Revised December 18, 2007
Accepted January 9, 2008