



TUMORS OF THE GNATHIC SYSTEM WITH MULTIPLE HISTOGENETIC CHARACTERISTICS

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ABSTRACT

Background: There is a great confusion in the scientific literature regarding tumors composed of tissues with different histogenetic and molecular characteristics. Diagnosis of a neoplasm composed of more than one tumoral tissue can be extremely challenging, so is the treatment. Methods: This is an attempt, illustrated with several examples of these types of tumors from the gnathic system, to gain a better understanding of this issue. Conclusions: As the best of our knowledge, this is the first report of a collision tumor between a sarcomatoid carcinoma and so called keratocystic odontogenic tumor. It is critical to understand these types of tumors, for correct diagnosis, staging and treatment.

Keywords: Tumors, Orofacial, Histogenetic, Collision, Combined tumors

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Contribution/ Originality

This paper contributes to the understanding of complex tumors that are usually difficult to diagnose and treat. A tumor with more than one histogenetic characteristic constitutes a challenge for the medical profession.

1. INTRODUCTION

Occasionally, elements of diverse histogenetic and molecular characteristics are noted within one tumoral mass. Diagnosis of a neoplasm composed of more than one tumoral tissue can be extremely challenging, so is the treatment. Shuch, et al. [1] there is a great confusion in the scientific literature regarding this topic. Sarcomatoid carcinoma, carcinosarcoma, mixed tumor, collision tumor, hybrid tumor, combined tumor, tumor transformation, biphasic tumor, tumor with metaplasia, etc, are often misclassified. This is an attempt to gain a better understanding of this issue.

2. LITERATURE REVIEW AND CASES

In the gnathic system, these unusual events may represent:

1-Tumor collision which is characterized by the presence of two different histogenetic lesions, apparently unrelated, which coexist in the same anatomic location and are not mixed at interface. Some hypotheses try to explain this phenomenon:

A second malignancy in the same area of a tumor, may occur after radiotherapy, however, collision tumors in immuno-competent individuals are very rare [2].

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- a) The first tumor produces micro environmental changes, facilitating the development of the second neoplasm [3, 4].
- b) Some collided tumors are metastases from other sites [3-5].
- c) The collision is coincidental.

2- Tumors with biphasic differentiation such as sarcomatoid carcinoma (SC) which represents a carcinoma with a sarcomatous component [6]. The carcinomatous and the sarcomatoid component are intermixed. It has been published, based on X-chromosome inactivation pattern and TP53 mutation studies, that in some sarcomatoid carcinomas both elements, epithelial and mesenchymal, arise from the same cell, and that the initial malignancy is a carcinoma which suffers sarcomatous transformation, keeping the mutation profile of the initial epithelial malignancy [7]. Sarcomatoid carcinomas are truly carcinomas, which have lost several of their epithelial characteristics and underwent mesenchymal differentiation. These tissues have the same genotype but express multi-phenotypic differentiation. Therefore, immunochemistry has a little value, making the final diagnosis difficult [5].

This category includes sarcomas with epithelial differentiation such as biphasic synovial sarcoma.

Theories for explanation of biphasic tumors:

- a) The epithelial and mesenchymal components arise from the same cell.
- b) The sarcomatoid component of sarcomatoid carcinoma may arise from a clone with lack of differentiation originated from the initial carcinoma [1-3]. Conversely, the epithelioid component of these sarcomas may arise from a cell with lack of differentiation originated from the original sarcoma.
- c) A mutagenic factor may interact with the tumoral tissue inducing a different type of tumor [8, 9].
- c) A growth factor produced by one tumor, may induce the development of the other [10].

A case of a mandibular sarcomatoid carcinoma associated with a collision keratocystic odontogenic tumor is described below and illustrates these two types of hybrid neoplasms.

Sarcomatoid carcinoma (SC) is highly malignant neoplasm that contain cells with properties of epithelial and mesenchymal tumors. It is an extremely rare and aggressive entity.

Keratocystic odontogenic tumor is a destructive, cystic odontogenic condition with 30% recurrence rate. The typical clinical/radiographic presentation of KCOT is that of an expansive, radiolucent, multilocular lesion, usually located on the posterior mandible and often associated with a non-erupted tooth. Based on the KCOT genetics and behavior, WHO classified this lesion as a tumor.

A 90 year old male presented, with generalized weakness, to the Oral and Maxillofacial Surgery Clinic, for evaluation of a recently appeared mandibular nodule. His medical history was relevant for prostate carcinoma treated years before, and believed to be in remission, diabetes and hypertension.

Upon oral examination, a pedunculated lesion with dark reddish discoloration, protruding from the edentulous alveolar ridge of the anterior mandible was seen. This mass bled easily and measured 1.2 cm. There was no expansion of the cortical bone and no extension to the floor of mouth was identified. The patient stated that the lesion appeared a few days previously. (Figure # 1) Panoramic radiography revealed an edentulous patient with 1.5 cm radiolucency on the anterior mandible. Basic laboratory tests were within normal limits. Incisional biopsy was performed. Six weeks later, the lesion had increased substantially in size. About two months after the lesion was first noticed, the tumor dimensions were enormous. (Figure # 2).

Computed tomography scan showed a destructive 5.0 cm lesion with a large soft tissue component and extension to the floor of the mouth. (Figures # 3 A-B)

The incisional biopsy exhibited sheets of malignant cells; most of them spindle, with hyperchromatism, pleomorphism, and atypical mitotic figures. The malignant cells were immunoreactive for pankeratin and p53. (Figures # 4-5) No reactive for p40, ERG, SMA, CD163, CD31 and S100. Multinucleated cells were also noted. There was no transition of the surface epithelium into the malignant tumor, nor was there keratin production. An intact keratocystic odontogenic tumor (KCOT) was identified, colliding with the spindle cell proliferation. (Figure # 6) Other association, besides collision, between the KCOT and the malignancy was not identified histologically. A diagnosis of sarcomatoid carcinoma and collision with keratocystic odontogenic tumor was rendered.

The patient was treated by wide excision, marginal anterior resection and radiation therapy. A percutaneous Endoscopic Gastrostomy tube for nutrition was placed. The prognosis is extremely poor.

3-Transformed tumor. A third category is that of a neoplasm that suffers complete transformation into a tumor with a different type of tissue, a totally different genotype.

The exact mechanism of the tumor's transformation is unclear. Gulbranson, et al. [11] the theories are:

- 1- There were two pre-existent cells types in the area.
- 2- They differentiated from a common oligopotential cell.
- 3- A known theory states that these cases originate as a tissue modification, due to severe chronic environmental stimuli [11]. The cells of a tumor show plasticity when they are exposed to tumor factors.

As an example, a case of an odontogenic carcinoma which underwent change into a leiomyosarcoma is shown. The clinical diagnosis of this case was pyogenic granuloma, located in the area of a molar extracted due to an "apical cyst" (Fig # 7) Initial histology exhibited a large population of proliferating epithelial neoplastic cells showing an odontogenic pattern. Hyperchromatism, pleomorphism and mitosis were seen. A diagnosis of odontogenic carcinoma was rendered. (Fig # 8 A) Almost immediately after the surgical treatment, the tumor recurred with a different histopathology. Spindle and pleomorphic, mesenchymal-looking cells. Immunohistochemistry showed: EMA (epithelial membrane antigen) negative, pankeratin: negative. Desmin (Muscle marker): was strongly positive in large bizarre cells supporting the diagnosis of myoblastic differentiation. (Fig # 8 B) No identifiable odontogenic tissue was found in numerous sections examined.

Final diagnosis: Rhabdomyoblastic differentiation of an odontogenic carcinoma. This tumor differed from carcinosarcoma and sarcomatoid carcinoma because the mesenchymal and carcinomatoid components, were never intermixed. The initial tumor was a carcinoma and the recurrence was a sarcoma.

4- Malignization: a benign condition, a tumor or a cyst, gives origin to a malignant neoplastic change. The occurrence of a malignancy arising from the lining of odontogenic cysts is well known. The accepted theory is that there is oncogenic multi-potentiality within the odontogenic epithelium. [12-14] a case of squamous cell carcinoma clearly arising in keratocystic odontogenic tumor (KCOT) (Figures # 9,10) is also shown in this article.

5- Combined tumor (carcinosarcoma) is a condition that exhibits a mixture of morphologic, molecular, histopathological and genetic characteristics of more than one tissue, within the same topographical area and shows different tumoral tissues admixed among them [6]. They are composed of a carcinoma and a sarcoma and they are classified as carcinosarcomas.

The theories that explain the formation of combined tumor are:

- a) They may arise from the same pluri-potential cell. However, in some cases, different tissues are derived from different precursor cells [6].
- b) The stem cell hypothesis which states that tumors originate from stem cells of the area. They differentiate in diverse progenies of cells that are able to form various types of tissues and intermixed tumors [3].

Combined tumors can also be benign. Mixed tumors are combined tumors. Odontogenic tumors develop according to the phases of odontogenesis. Inductive influences of odontogenic epithelium over mesenchymal tissue and vice versa are occurring during the process. [14, 15] this reciprocal influence is believed to be the cause of mixed tumors of odontogenic origin. There are several reports of association between benign odontogenic tumors and between tumors and cysts. (Figure # 11A-11B).

Salivary, and other glands, may suffer genetic rearrangements, as a consequence, a common cell origin from epithelial or mesenchymal component, gives rise to the other, by metaplasia of a sub clonal cell. The same viral infection, HPV, has been found in both epithelial and sarcomatous elements of mixed tumors of the genital area, suggesting metaplasia [14, 15].

3. CONCLUSIONS

Diagnosis of a neoplasm composed of more than one tumoral tissue can be extremely challenging, so is the treatment. There is a great confusion in the scientific literature regarding the classification of tumors with elements of diverse histogenetic and molecular characteristics and they are often misclassified. This is an attempt, illustrated with several examples of these types of tumors from the gnathic system, to gain a better understanding of this issue.

One of the cases represents a sarcomatoid carcinoma, which at the same time, is a collision tumor. While, sarcomatoid carcinoma is already a very rare event, its presentation together with another tumor displaying different cytogenetic and molecular characteristics, makes this case even more bizarre. The radiologic, clinical, and microscopic findings of unusual hybrid and complex tumors is always a challenge.

The prognosis of a collision tumor is determined by the higher-grade element and therefore, it should be treated as the most aggressive component. Due to the relatively less aggressive nature of the KCOT, this condition was treated as sarcomatoid carcinoma. The prognosis is poor. As the best of our knowledge, this is the first report of a collision tumor between a sarcomatoid carcinoma and a keratocystic odontogenic tumor. It is critical to understand these types of tumors, for correct diagnosis, staging and treatment

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Tumors of the Gnathic System with Multiple Histogenetic Characteristics.

Illustrations



Fig-1. -Case 1- Initial clinical presentation of sarcomatoid carcinoma collided with KCOT
Source: Dr K Friedman



Fig- 2.- Case 1- Clinical presentation after a few weeks. The mass has grown enormously
Source: Dr K Friedman

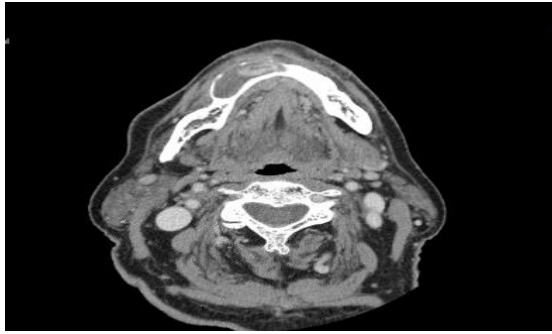


Fig-3A. Case 1-Computed tomography scan showed a destructive 5.0 cm lesion with a large soft tissue component and extension to the floor of the mouth

Source: Dr K Friedman

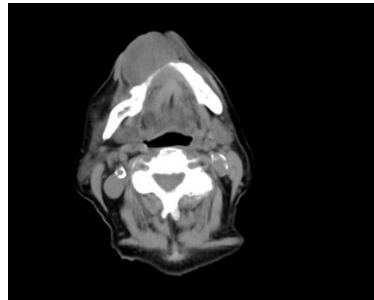


Fig-3A. Case 1-Computed tomography scan showed a destructive 5.0 cm lesion with a large soft tissue component and extension to the floor of the mouth

Source: Dr K Friedman

Case-1. Computed tomography scan showed a destructive 5.0 cm lesion with a large soft tissue component and extension to the floor of the mouth

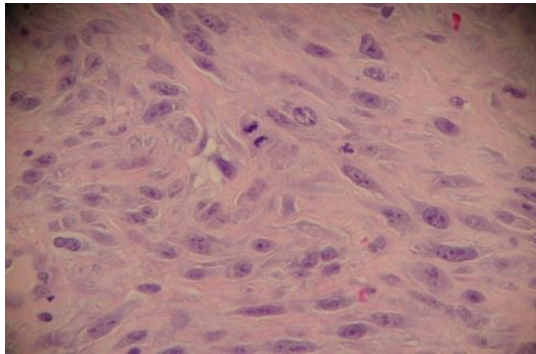


Fig-4. case 1- H&E 40X sarcomatoid carcinoma. Spindle atypical cells. Mitosis.

Source: Dr K Friedman

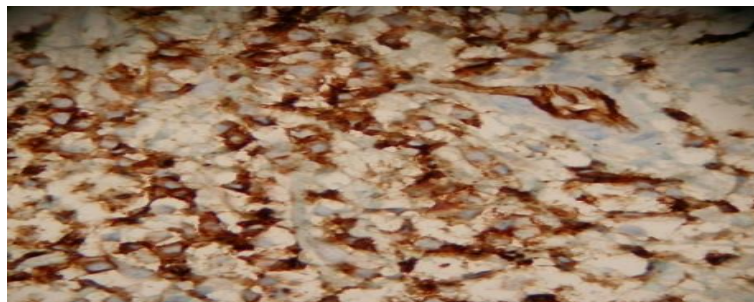


Fig-5. -Case 1- The malignant cells were immunoreactive for pankeratin and p53.

Source: Dr K Friedman

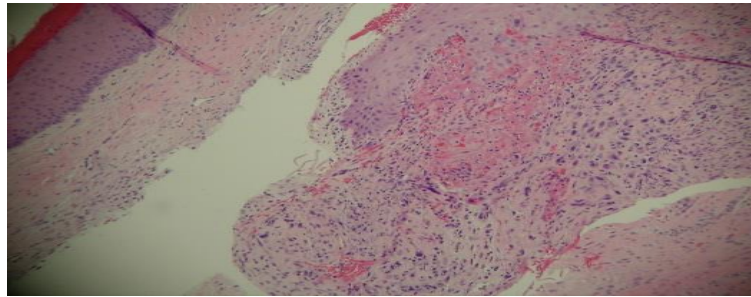


Fig-6. – Case 1 - H&E 40X Collision between KCOT and sarcomatoid carcinoma
Source: Dr I Velez



Fig-7. Case 2 - Initial clinical presentation of odontogenic carcinoma. The molar was extracted due to “an apical cyst”. Clinical diagnosis: pyogenic granuloma
Source: Dr Velez

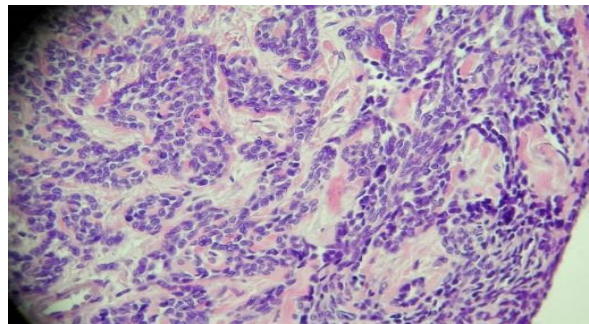


Fig-8A. Case 2-H&E 40X. Initial histology. Large population of proliferating epithelial neoplastic cells that display an odontogenic pattern. Hyperchromatism, pleomorphism and mitosis. Malignant odontogenic tumor.
Source: Dr Velez

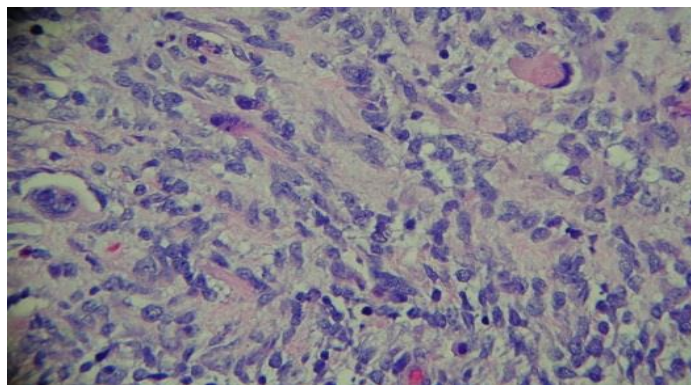


Fig-8B. Case 2- H&E 40X. Spindle undifferentiated cells with pale cytoplasm intermixed with anaplastic areas showing extremely hyperchromatic and large nuclei suggestive of skeletal muscle. Bizarre mitotic figures are seen. Immunohistochemistry proved rhabdomyoblastic differentiation
Source: Dr Velez



Fig-9. -Case 3- Large multilocular radiolucency with expansion and cortical compromise
Source: Dr Velez

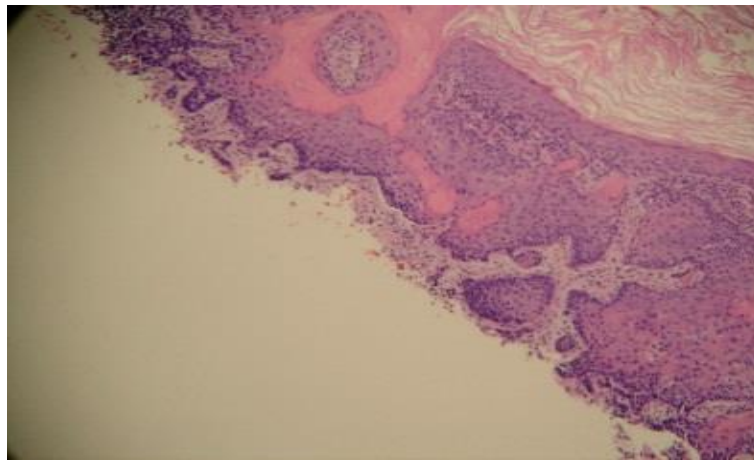


Fig-10. Case # 3-Proliferation of squamous cell carcinoma and invasion of epithelium originated on a KCOT
Source: Dr Velez

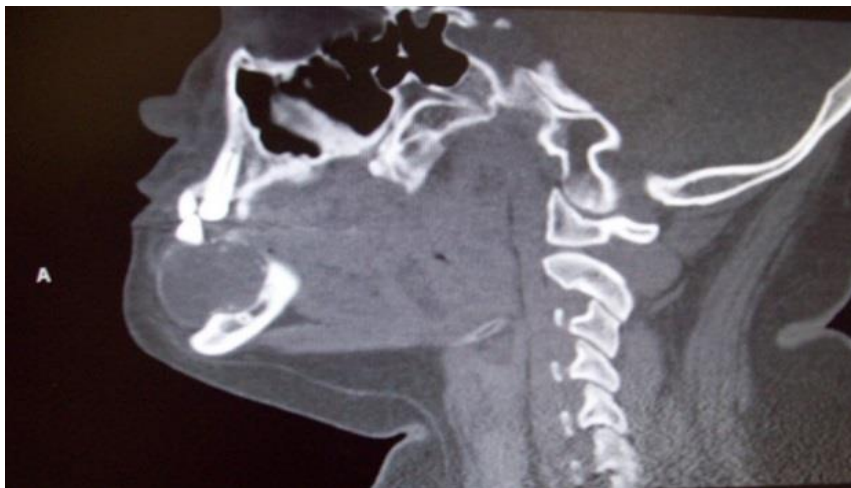


Fig-11A. Case 4-
Source: Dr Velez

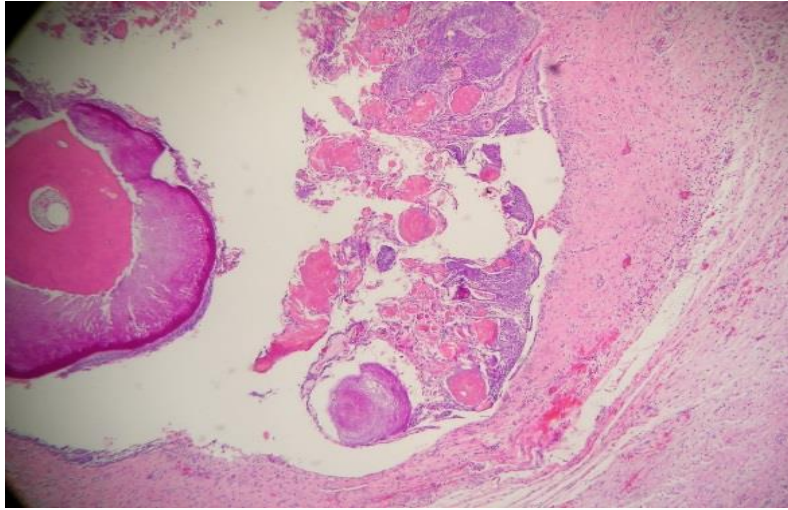


Fig-11B. Case 4- CT scan and histology, H&E -40X, of a mixed odontogenic tumor: calcifying odontogenic cystic tumor associated with odontoma.

Source: Dr Velez

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