Salivary gland malignancy with divergent differentiation: is it a teratocarcinosarcoma?

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Four poorly differentiated malignant lesions occurred in a 60-year-old Chinese male in the nasal cavity, submandibular gland, a lymph node in the neck, and the mandible. These malignant lesions developed within an 8-year period and each showed distinctive histological features. Among these malignant lesions, the neoplasm in the submandibular gland presented variegated histological and immunohistochemical (IHC) features and posed a diagnostic challenge in interpretation. Based on microscopic and IHC findings, we believe the diagnosis of teratocarcinosarcoma is justified for the submandibular neoplasm and the metastasis in the lymph node. The pathological features and diagnoses of these malignant lesions are discussed. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;104:82-8)**

Teratocarcinosarcoma is a rare neoplasm that mainly occurs in the nasal cavity and paranasal sinuses, with less than 50 cases reported in the literature.[1-8] Shanmugaratnam et al.[9] first described this lesion in 1983 under the term "teratoid carcinosarcoma." Heffner and Hyams[1] reviewed a series of similar tumors and further defined this entity under the term "teratocarcinosarcoma." Due to the variegated histological features of the neoplasm, the same entity was also reported under diagnoses such as malignant teratoma, teratocarcinoma, and blastoma.[1,10-17] Teratocarcinosarcoma seldom occurs outside the nasal and paranasal regions. However, a case has been reported to occur in the floor of the mouth; computed tomography (CT), magnetic resonance imaging scans, and intraoperative findings support origin from the oral cavity.[18] We present a case in which 4 poorly differentiated malignant lesions occurred in the nasal cavity, submandibular gland, a lymph node in the neck, and the mandible in a 60-year-old Chinese male. Among these malignant lesions, the neoplasm in the submandibular gland showed divergent differentiation histologically and immunohistochemically for a salivary malignancy. We think a diagnosis of teratocarcinosarcoma is justified for this lesion and discuss the diagnostic dilemma of this challenging case.

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CASE REPORT

A 60-year-old Chinese male with a chief complaint of swelling and dull pain in the anterior mandible came to the teaching hospital of Kaohsiung Medical University, Taiwan in May 2004. His past medical history revealed multiple malignant lesions. He had a history of smoking and alcohol consumption but denied a betel quid chewing habit. The only family history of significance was a son who died of nasopharyngeal carcinoma at age 18. We reviewed the hematoxylin-eosin stained microscopic slides of the previous malignant lesions, and further immunohistochemical (IHC) studies were performed on the available tissue sections of these malignant lesions. The entire case material was reviewed and also sent to the Armed Forces Institute of Pathology (Washington, DC) for an additional consultative opinion.

According to his medical record, the patient sought medical attention in 1996 for nasal obstruction and bloody discharge. Computed tomography revealed a nasal mass and an incisional biopsy was performed. Histological evaluation revealed sheets of hyperchromatic, epithelioid cells with focal areas of necrosis (Fig. 1, *A, B*). There was no keratin or ductal differentiation in this neoplasm, which was diagnosed as nonkeratinizing undifferentiated carcinoma, and the patient was treated with radiotherapy of 7020 cGy in 39 fractions,

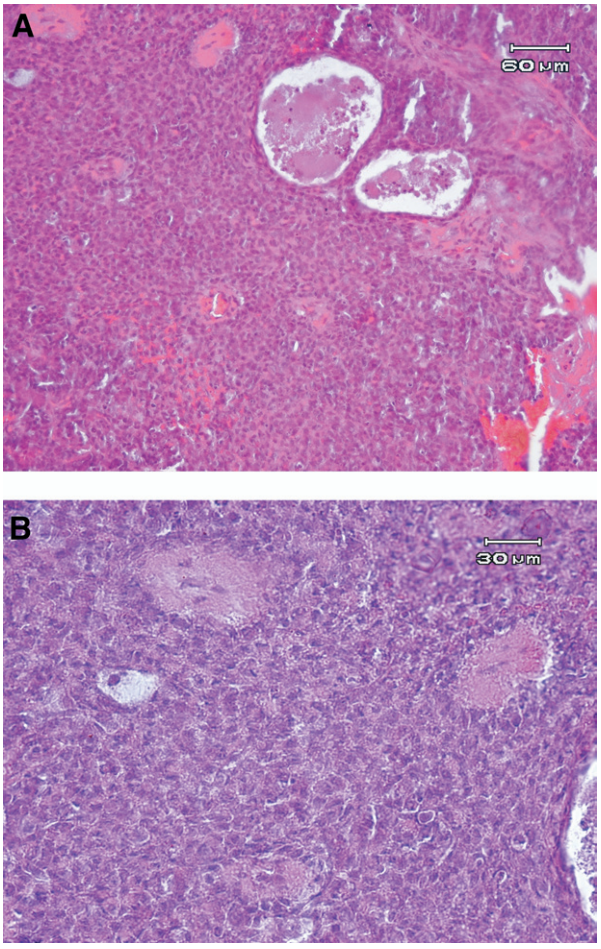

Fig. 1. The histology of the incisional biopsy of the nasal mass, showing sheets of polygonal, hyperchromatic epithelioid cells with focal areas of necrosis. **A**, Hematoxylin-eosin stain, original magnification ×10. **B**, Hematoxylin-eosin stain, original magnification ×20.

followed by surgical removal. He has been followed up every 3 months since then.

In 1999, the patient developed a tender swelling in the left submandibular gland. An incisional biopsy was performed and the histology revealed a neoplasm composed of primitive, hyperchromatic cells forming aggregates of epithelioid cells among loose, myxoid regions of plump cells and spindle cells (Fig. 2, *A*). These primitive, hyperchromatic cells showed a diversity of differentiation. There was squamous differentiation (Fig. 2, *B*) and duct formation (Fig. 2, *C*) in the areas of epithelioid aggregates. Some areas also appeared to have neuroectodermal differentiation with rosette formation (Fig. 2, *D*). Areas of necrosis and cystic degeneration in these epithelioid aggregates were often seen. No areas revealed possible preexisting benign mixed tumor despite extensive sampling. Without IHC study, this lesion was diagnosed as "carcinoma ex pleomorphic adenoma" in 1999, and the patient was treated with surgical excision. Immunohistochemical studies were performed following review of the hematoxylin-eosin stained slides in 2004. Positive staining for cytokeratin (Fig. 2, *E*, left), S-100, and CD56 (Fig. 2, *E,* right) was found in the epithelioid but not the spindle cells. Positive staining for vimentin was found in both epithelioid and spindle cells. Neuron-specific enolase (NSE) showed positivity in the epithelioid cells and in some spindle cells (Fig. 2, *F,* left); however, synaptophysin and chromogranin A were negative. Smooth muscle actin (SMA) showed scattered positive staining in the spindle cells (Fig. 2, *F*, right), but myogenin and desmin were uniformly negative in both the epithelioid and the spindle cell components.

Two years later in 2001, the patient was found to have a swollen lymph node in the left neck, and the histology of the excisional biopsy revealed a neoplasm consisting of primitive hyperchromatic cells arranged in alternating packed and loose regions, similar to the submandibular lesion (Fig. 3, *A*). Ductlike structures and rosette formation were occasionally seen (Fig. 3, *B*). In some areas, larger anaplastic cells were also identified (Fig. 3, *C*). Immunohistochemical testing for cytokeratin and vimentin were performed at the original institution, revealing focal positive staining in the tumor cells. A diagnosis of metastatic carcinoma was rendered and surgical excision was completed in 2001. Further IHC studies on this tissue sample were performed in 2004, and the results showed focal positive staining for cytokeratin (Fig. 3, *D*, left), CD 56 and S-100, and diffuse positivity for NSE (Fig. 3, *D,* right). In addition, scattered tumor cells stained for SMA, myogenin, (Fig. 3, *E,* left), and desmin (Fig. 3, *E,* right).

Three years later in May 2004, the patient appeared at the Dental Department of Kaohsiung Medical University complaining of pain and swelling in the anterior mandible. A CT scan showed a bony defect with cortical breakthrough in the anterior mandible (Fig. 4, *A*). The incisional biopsy showed a neoplasm composed of round, poorly differentiated, hyperchromatic cells with scanty cytoplasm (Fig. 4, *B, C*). Areas of necrosis were commonly seen, but no squamous, rosette, or ductlike structures could be identified. Immunohistochemical studies utilizing cytokeratin, LCA (leukocyte common antigen), NSE, synaptophysin, chromogranin, CD56, S-100, SMA, myogenin, and desmin were all negative, with only vimentin demonstrating positive staining. The lesion was diagnosed as poorly differentiated malignancy. The patient was treated with radiotherapy totaling 6000 cGy and 6 courses of chemotherapy. The patient was alive with disease at the most recent follow-up in June 2005.

DISCUSSION

This case is of interest in that multiple malignant lesions developed in the head and neck region within an 8-year period and each showed distinctive histological features. Whether a single primary neoplasm subsequently metastasized to other locations or more than one primary neoplasm occurred in this patient is probably subject to individual interpretation. In our opinion, we agreed with the original diagnosis of the nasal mass as nonkeratinizing undifferentiated carcinoma. The submandibular gland lesion shows no histological re-

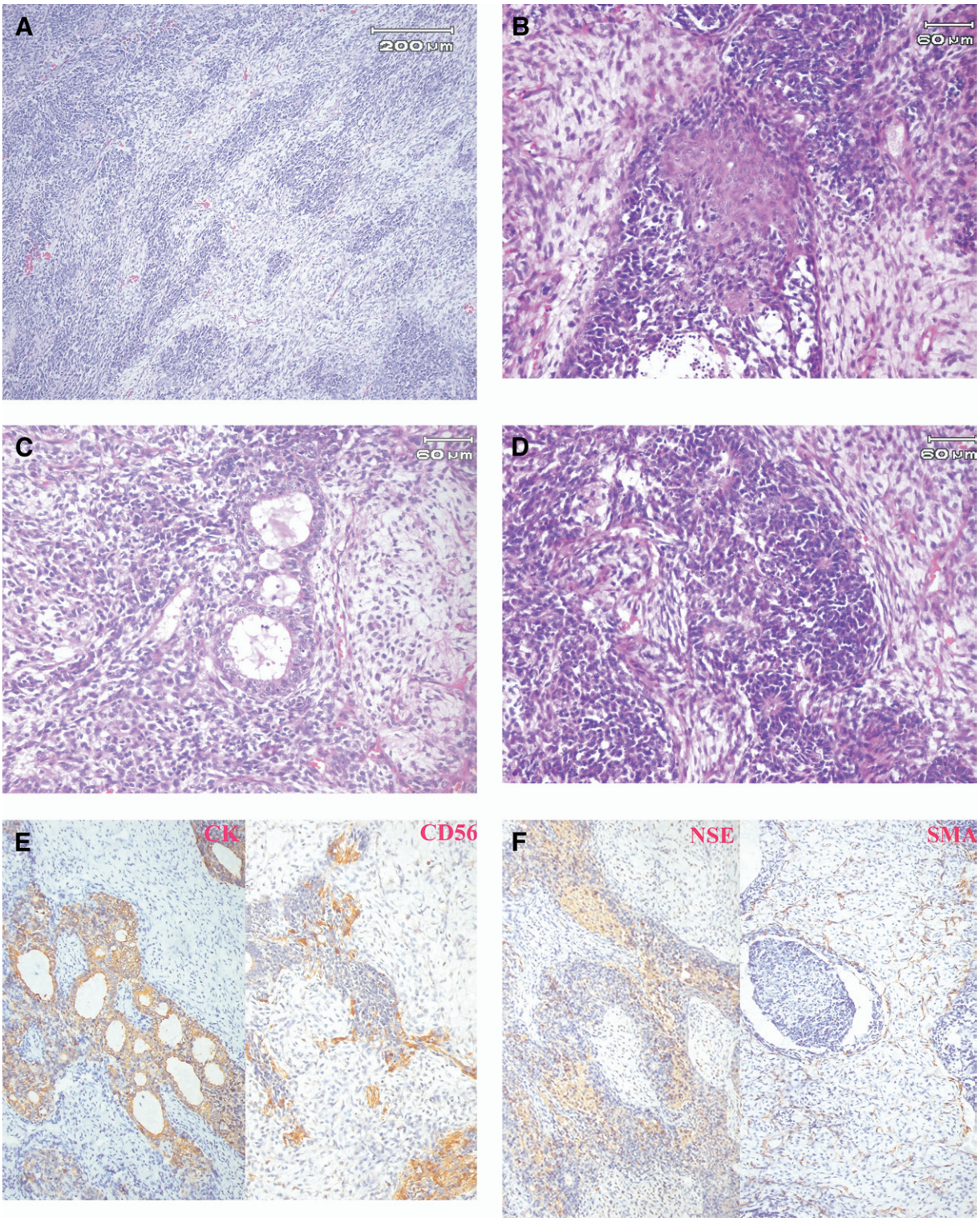

Fig. 2. The histology and immunohistochemical findings of the neoplasm in the submandibular gland. It was composed of primitive, hyperchromatic cells forming aggregates of epithelioid cells among loose, myxoid regions of plump and spindle cells. **A**, Hematoxylin-eosin stain, original magnification ×5. **B**, Squamous differentiation (hematoxylin-eosin stain, original magnification ×10). **C**, Ductal differentiation (hematoxylin-eosin stain, original magnification ×10). **D**, Rosette formation (hematoxylin-eosin stain, original magnification ×10). **B-D** were found in the aggregates of epithelioid cells. **E**, Immunohistochemical results showed positive staining for cytokeratin (left, original magnification ×5) and CD56 (right, original magnification ×5) in the epithelioid cells. **F**, Neuron-specific enolase showed positive results in the epithelioid cells and some spindle cells in the myxoid region (left, original magnification ×5); smooth muscle actin showed scattered positive staining in the spindle cells (right, original magnification ×5).

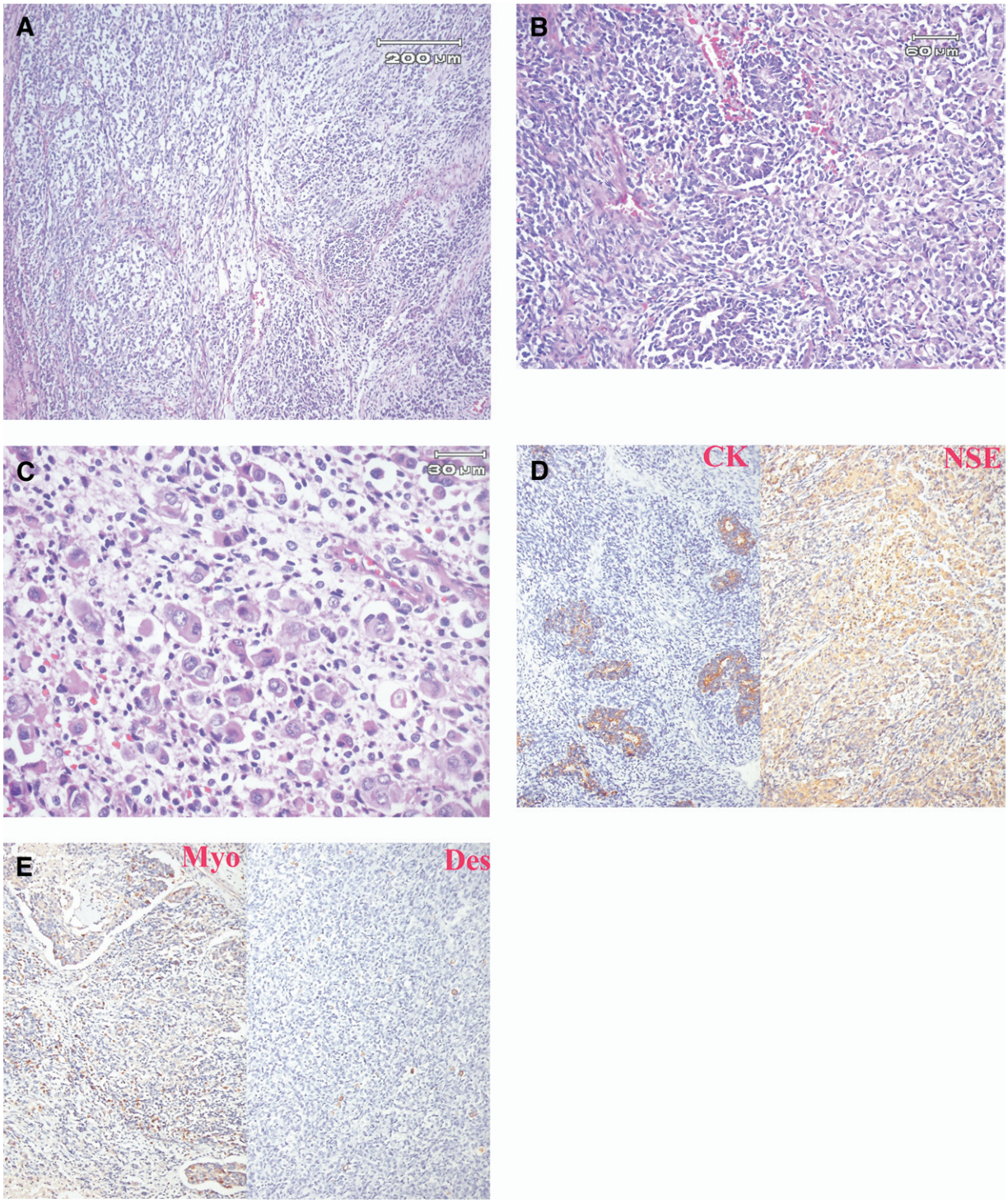

Fig. 3. The histology and immunohistochemical findings of the neoplasm in the lymph node. It was composed of primitive hyperchromatic cells (**A**) arranged in alternating packed and loose regions (hematoxylin-eosin stain, original magnification ×5) with (**B**) ductlike structure and possible rosette formation (hematoxylin-eosin stain, original magnification ×10). **C**, Larger, anaplastic cells were also found (hematoxylin-eosin stain, original magnification ×20). Immunohistochemical studies revealed (**D**) focal positive staining for cytokeratin (left, original magnification ×5), diffuse positivity for neuron-specific enolase (right, original magnification ×5), and (**E**) scattered positivity for myogenin (left, original magnification ×5) and desmin (right, original magnification ×5).

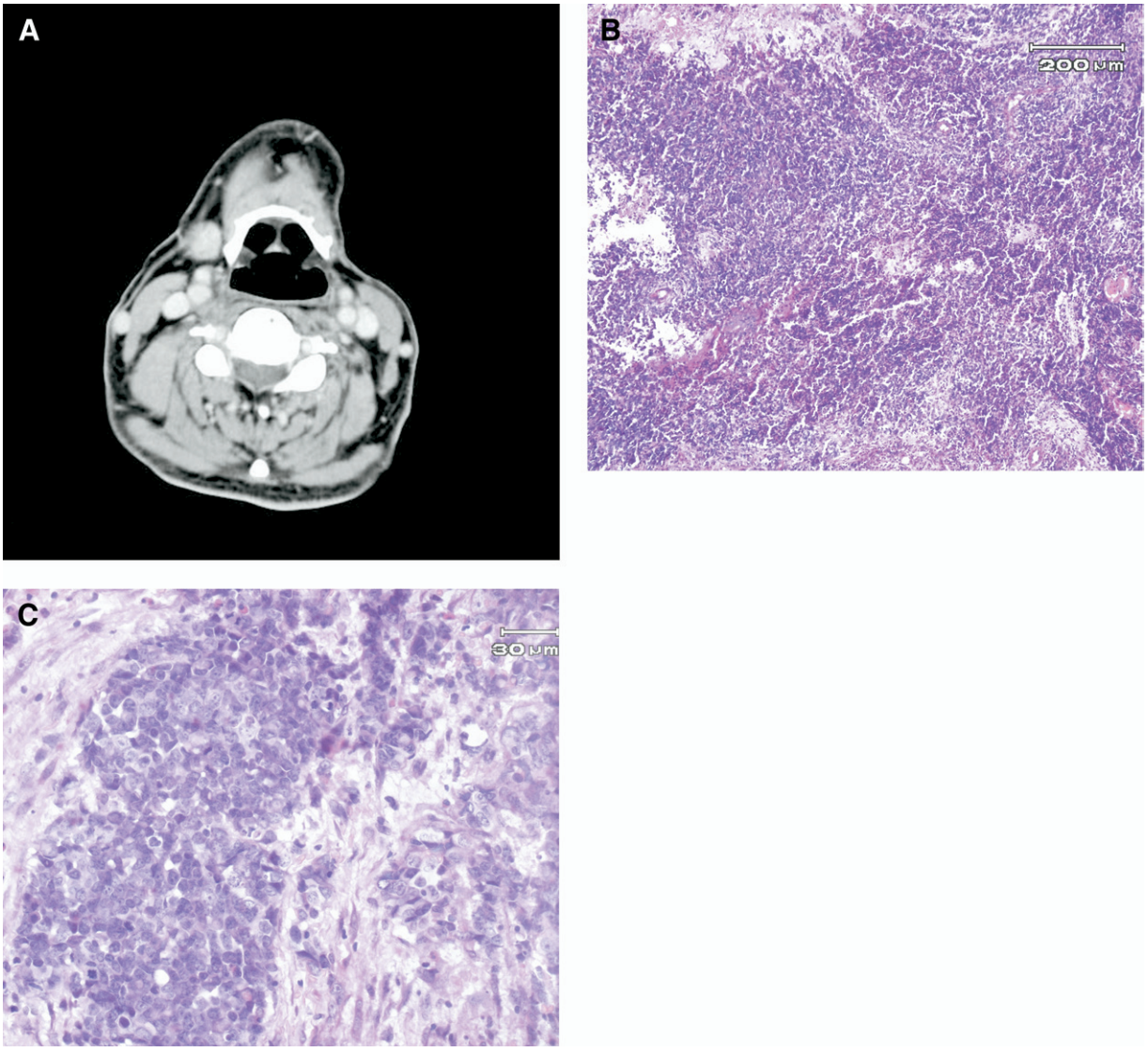

Fig. 4. The clinical and histological findings of the neoplasm in the mandible. **A**, Computed tomography revealed a bony defect with cortical breakthrough in the anterior mandible. **B**, The histology of the incisional biopsy shows a poorly differentiated neoplasm composed of round, hyperchromatic cells with scanty cytoplasm (hematoxylin-eosin stain, original magnification ×5), and **C**, hematoxylin-eosin stain, original magnification ×20.

semblance to the nasal mass, and therefore, we consider it a primary neoplasm in the submandibular gland. The submandibular gland lesion and the tumor in the lymph node show some resemblance in cell morphology and diversity of differentiation, evidenced by histological and IHC studies. Therefore, we think that the tumor in the lymph node may represent a metastatic focus from the submandibular neoplasm. The differential diagnosis of these 2 lesions is discussed below. The lesion in the mandible is essentially a poorly differentiated malignancy evidenced by histology and negative IHC results for cytokeratin, LCA, NSE, synaptophysin, chromogranin, CD56, S-100, SMA, myogenin, and desmin. This lesion proved positive only for vimentin. The relationship of the mandibular tumor to the submandibular gland and lymph node lesion is more difficult to reconcile, but we suggest that it could represent a metastatic focus of an undifferentiated portion of one of the previous lesions.

In our opinion, there are 2 possible, though somewhat related, interpretations for the submandibular lesion: a carcinosarcoma of salivary gland origin with unusual neuroectodermal differentiation or a teratocarcinosarcoma arising in an unusual location. Carcinosar-

coma is a rare salivary gland neoplasm typically associated with benign mixed tumor, although de novo cases have been reported.[19-22] It is characterized by a carcinoma component, usually adenocarcinoma, squamous cell carcinoma, or undifferentiated carcinoma, and a sarcoma component, such as fibrosarcoma, chondrosarcoma, osteosarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, or leiomyosarcoma.[20,21,23-27] Cytokeratin and vimentin stain the malignant epithelial and mesenchymal components of carcinosarcoma, respectively. Depending on the differentiation of the neoplasm, desmin, HHF-35, and markers indicating myoepithelial differentiation such as SMA, S-100, and glial fibrillary acidic protein may or may not stain positive in carcinosarcoma.[20,22-28] Neuroectodermal markers other than glial fibrillary acidic protein (such as neurofilament, chromogranin, and synaptophysin) have never been reported positive in carcinosarcoma.[22] The neoplasm in the submandibular gland in this case demonstrated a malignancy with squamous, glandular, neuroectodermal, and mesenchymal differentiation evidenced by histology and positive IHC staining for CK, vimentin, S-100, CD56, NSE, and SMA. These features seem compatible with carcinosarcoma with 2 exceptions. (1) Prominent neuroectodermal differentiation such as rosette formation and (2) IHC staining for NSE and CD56 are very unusual for a salivary gland neoplasm. To the best of our knowledge, these features have never been reported in carcinosarcoma.

On the other hand, teratocarcinosarcoma is a rare neoplasm that mainly occurs in the nasal cavity and paranasal sinuses.[1-8] There is a marked variation in histology of teratocarcinosarcoma, and the teratoid nature can be reflected in the presence of epithelial, mesenchymal, and neuroectodermal tissues.[17,18] Immunohistochemical studies of teratocarcinosarcoma usually show positive results for CD99, vimentin, and NSE.[7,17] Chromogranin, synaptophysin, S-100, desmin, myogenin, and cytokeratin may or may not show positive staining.[3,7,17] Rosette formation is not an uncommon feature, and CD 56 positivity has been shown in teratocarcinosarcoma.[1,2,4,29,30] Teratocarcinosarcoma seldom occurs outside the nasal and paranasal regions. However, a case has been reported occurring in the floor of mouth; CT, magnetic resonance imaging scans, and intraoperative findings support origin from the oral cavity.[18] In that case, the neoplasm showed histological features of squamous cell carcinoma, intestinal-type epithelia, fibroblastic tissue, cartilage, and small blue tumor cells resembling primitive neuroectodermal tumor, and IHC positive results for pancytokeratin, vimentin, S-100, SMA NSE, synaptophysin, and chromogranin A.[18] Although the neoplasm in the submandibular gland in the presenting case did not show the "organoid structures" of epithelium surrounded by smooth muscle, a more prevalent histological feature for teratocarcinosarcoma in the series reviewed by Heffner and Hyams,[1] it demonstrated features of carcinosarcoma with clear neuroectodermal differentiation. It appears to have fulfilled the diagnostic features of teratocarcinosarcoma with the presence of epithelial, mesenchymal, and neuroectodermal tissues. Therefore, we think a diagnosis of teratocarcinosarcoma is justified. The Armed Forces Institute of Pathology interpretation for both the submandibular and lymph node lesions was "poorly differentiated malignancy with carcinosarcomatous and slight 'teratoid' features," which was essentially compatible with both interpretations.

In this particular case, it seems that the radiotherapy administered for treatment of the first neoplasm in the nasal cavity may have served as a strong insulting agent and contributed to the development of the malignancy in the submandibular gland. It is also worth noting that irradiation has been implicated for inducing carcinosarcoma in 2 cases with previous history of pleomorphic adenoma.[31] On the other hand, it may also seem less likely, since malignant lesions associated with radiation treatment usually arise more than 10 years following such therapy.[32] In this case, the patient did have other risk factors of smoking and alcohol consumption. With a family history of a son who died of nasopharyngeal carcinoma at age 18, it may also indicate a possible genetic vulnerability to tumorigenesis.

In conclusion, this is an interesting and perhaps controversial case, and the diagnoses of these 4 malignant lesions may be subject to individual interpretations. We propose our diagnoses and interpretation for this case as nonkeratinizing undifferentiated carcinoma in the nasal cavity, teratocarcinosarcoma in the submandibular gland, metastatic teratocarcinosarcoma in the lymph node of the neck, and poorly differentiated malignancy in the mandible. We admit that the submandibular gland neoplasm does not seem to have the features cited in the literature as characteristically indicative of teratoid differentiation. In particular, osseous/cartilaginous differentiation and intestinal mucosa were not identified in the lesion, making the diagnosis of teratocarcinosarcoma debatable for those that apply the strict criteria of teratoid differentiation for that diagnosis. We are also aware that our interpretation may expand the spectrum of teratocarcinosarcoma. However, the divergent differentiation and prominent neuroectodermal differentiation in this lesion surpasses the common features reported for carcinosarcoma, and therefore, a diagnosis of teratocarcinosarcoma appears justified.

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