Cystadenoma of Minor Salivary Gland With Cervical Metastasis: Benign or Malignant?

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A cystadenoma originating in the salivary gland is a rare neoplasm that can originate from the major or minor salivary glands. Although this tumor has the potential to recur if it is incompletely excised, it has been regarded as a benign tumor because it has not been determined to be associated with local tissue destruction or metastasis. This report serves as an update to the current understanding of cystadenoma. The patient in this case study presented with a recurrent painless mass in her left retromolar and submandibular regions that had persisted for more than 2 years. Histologic analysis showed that this lesion was a recurrent cystadenoma of the minor salivary gland, with cervical lymph nodes testing positive for tumor cells. After more than 3 years of clinical follow-up, no signs of recurrence were observed. A case of cystadenoma with cervical metastasis is presented; further attention should be paid to patients with recurrent cystadenoma that also might contain lymph node metastasis.

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Cystadenoma, one type of cystic adenoma originating in the salivary gland, is an extremely rare neoplasm that constitutes 2 to 4.7% of all minor salivary gland neoplasms.[1,2] Cystadenoma can be subdivided into papillary and mucinous types and is primarily distributed among the major and minor salivary glands, larynx, nasopharynx, and lachrymal gland.[1] Most reports describe the origination of these tumors in the minor salivary glands, although other common sites include the lip, palate, and buccal mucosa. Tumors in the tongue also have been described.[3]

Surgery is the mainstay treatment for cystadenoma; radiotherapy and chemotherapy, as adjuvant modalities, are not recommended. Although this tumor has the potential to recur if it is incompletely excised, it has been regarded as a benign tumor because it has not been observed to be associated with local tissue destruction or metastasis. Because of the rarity of recurrent cystadenomas, they have been infrequently reported in the English-language literature.[2]

This report describes a case of recurrent cystadenoma of the minor salivary gland with cervical metastasis. This report serves as an update to the current understanding of cystadenomas and as a reminder for oncologists to consider the possibility of lymph node metastasis in recurrent cases.

Report of Case

A 45-year-old woman was admitted to the hospital complaining of a recurrent painless mass in her left retromolar and submandibular regions. The patient stated that she underwent an operation for a neoplasm of the retromolar region 5 years previously; histologic examination showed that the neoplasm was a cystadenoma of the minor salivary gland (Fig 1). At the time of

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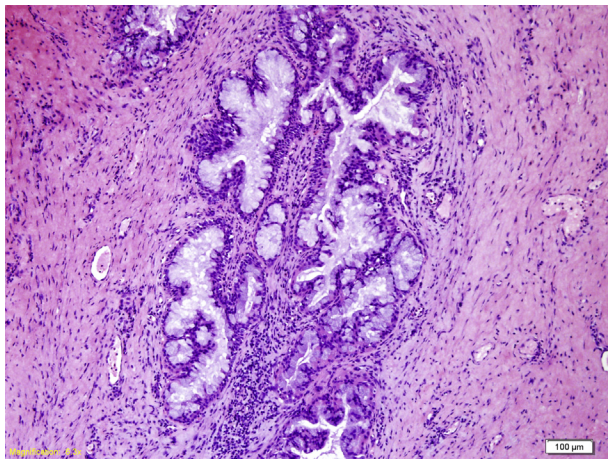

FIGURE 1. Tumor displays cystic spaces of variable size exhibiting intraluminal papillary projections (hematoxylin and eosin stain; × 80).

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this presentation, the mass had been present for more than 2 years without pain or numbness. Her medical history and family history were unremarkable.

Physical examination showed a smooth, nontender 4- × 5-cm mass in the patient's left submandibular region. The patient's mouth opening was not limited. Oral examination showed a mass in the left retromolar region that protruded into the oral cavity and parapharyngeal covering with normal mucosa. The lesion was solid to the touch. Contrast-enhanced computed tomographic (CT) scan showed multiple well-circumscribed masses in the left parapharyngeal and submandibular regions, bone compression, and enlargement of multiple cervical lymph nodes. Notably, the CT scan showed only slight enhancement of the lesion and an obvious enhanced rim of the lymph nodes (Fig 2).

Histologic analysis of an intraoral biopsy specimen of the retromolar region disclosed the cystadenoma. After discussion, radical surgery for the recurrent tumor and simultaneous resection of the enlarged lymph nodes were recommended. Neck dissection or adjunctive therapy was controversial based on current evidence. The tumor was subsequently resected with wide (3- to 4-mm) surgical margins, and the enlarged lymph nodes were resected together under general anesthesia. Bone compression and absorption of the mandible were confirmed during the operation. Therefore, the lingual compressed region of the mandible was ground and stripped.

At gross examination, the specimen appeared to be cystic with a gelatinous interior. After routine processing and embedding in paraffin, 6-µm sections were cut and stained with hematoxylin and eosin. Histology showed that the tumor was well circumscribed and predominantly cystic; it was composed of variably sized cystic spaces lined mostly by a single layer of rather cytologically bland mucous epithelium. A papillary architecture was observed in certain regions. No cellular atypia or mitotic figures were observed, indicating the benign character of the tumor (Fig 3).

Several lymph nodes with intact capsules were positive for metastatic tumor cells. The numbers of positive lymph nodes classified as levels I, II, and III were 2, 5, and 1, respectively. Large cysts containing mucus were observed in the cystic cavity. In capsules of other regions, microcysts were enveloped by lymph cells. Several well-formed papillae projected into the cystic cavity. The cystic epithelial stratum consisted of cells containing small amounts of mucus that are characteristic of mucous cells (Fig 4).

Because of the lack of cellular atypia, mitotic figures, and the spread of neoplastic cells beyond the capsule in the tumor and the nodes, the tumor was diagnosed as a recurrent cystadenoma of the minor salivary gland with cervical metastasis of levels I, II, and III. Neck dissection or external beam radiotherapy was recommended because of the presence of multiple lymph node metastases, but the patient was willing to be carefully followed, rather than undergoing adjunctive treatment. After more than 3 years of clinical follow-up, no sign of recurrence was observed.

Discussion

Cystadenoma of the salivary gland is a rare tumor that has been histologically characterized by prominent cysts and frequent papillary growth and has been defined as a benign, well-circumscribed or encapsulated, multicystic neoplasm with intracystic papillations.[1,2] Cystadenoma can originate from the major or minor salivary glands. Although several groups have stated that cystadenomas are distributed among major and minor salivary glands at rates of 65 and 35%, respectively, data from many case reports have suggested that cystadenoma more commonly originates from the minor salivary glands.[1,3,4]

In this report, because the biopsy result was cystadenoma and cystadenomas are typically regarded as benign tumors, multiple cervical lymph nodes could have been misdiagnosed as originating from ectopic salivary glands in the neck.[5] However, by considering the medical history and the presence of multiple neoplasms and enlarged lymph nodes on the CT scan, a diagnosis of a heterotopic salivary gland tumor could be excluded. Postoperative histologic results confirmed that the cervical neoplasms were indeed lymph nodes with metastasis.

Two other important entities in the differential diagnosis of cystadenoma are cystadenocarcinoma and mucoepidermoid carcinoma.[4,6] However, distinguishing between the 2 can be difficult, and differentiation of

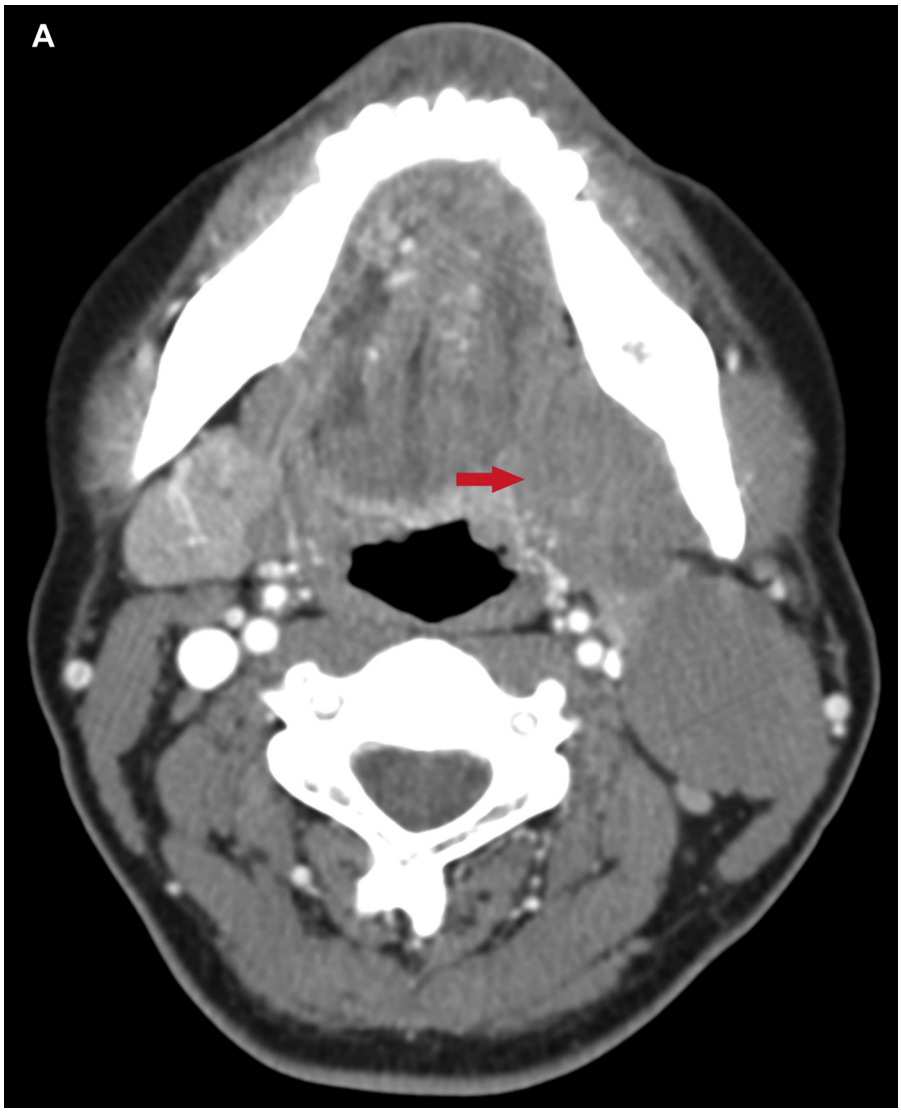

FIGURE 2. Computed tomograms before the operation. *A*, Well-circumscribed masses (*arrow*) in the left parapharyngeal region. **(Fig 2 continued on next page.)**

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the tumor types depends largely on the identification of actual infiltration of the salivary gland parenchyma or the surrounding connective tissue by cystic or solid epithelium in cystadenocarcinoma and mucoepidermoid carcinomas.[4] Cervical metastasis rates for cystadenocarcinoma and mucoepidermoid carcinomas are 10% and 20 to 75%, respectively.[7,8] Step sections of a borderline tumor can yield unequivocal evidence of invasion.[7] For more than 3 years of clinical follow-up, no sign of recurrence was observed, indicating a benign cystadenoma.

In this case, cellular atypia and mitotic figures were absent in serial sections that were taken for histologic examination, and no tendency for invagination of the cyst or local infiltration of cell nests into the surrounding stroma was observed. However, multiple regional lymph node metastases were observed. Using a comprehensive approach and considering the clinical, radiographic, and histologic features, the final diagnosis was recurrent cystadenoma of the minor salivary gland with cervical metastasis. To the best of the authors' knowledge, no case of cystadenoma with cervical metastasis or distant metastasis has been reported to date.

That a tumor with a benign histologic appearance can present with metastasis and behave in a clinically malignant manner is highly unusual but not unique. In the literature, pleomorphic adenoma of salivary glands also can behave in this way,[9,10] although the mechanism underlying this behavior is not clear to date.[9] Metastasizing pleomorphic adenoma (MPA) of the salivary glands usually presents with local recurrence; therefore, it has been hypothesized that incomplete surgery, enucleation, or surgical manipulation

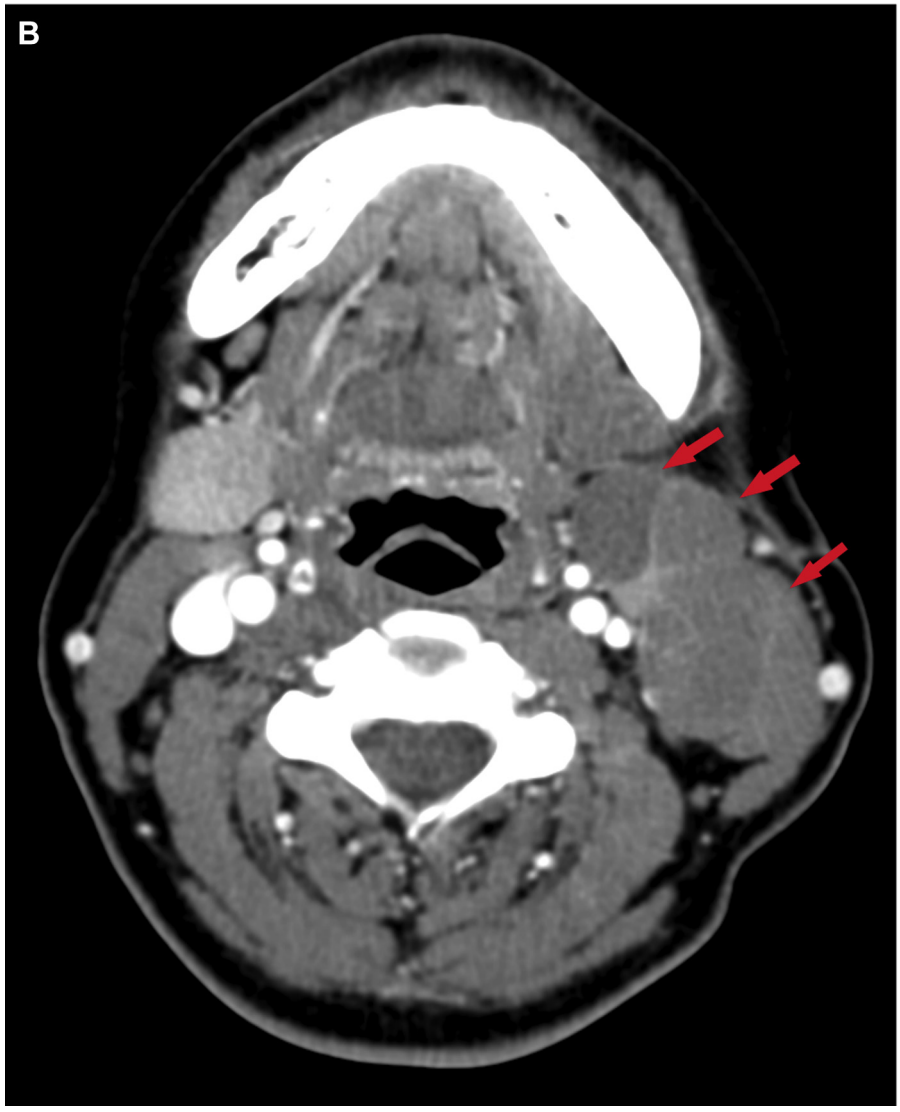

FIGURE 2 (cont'd). *B*, Multiple swollen lymph nodes (*arrow*) in the submandibular regions.

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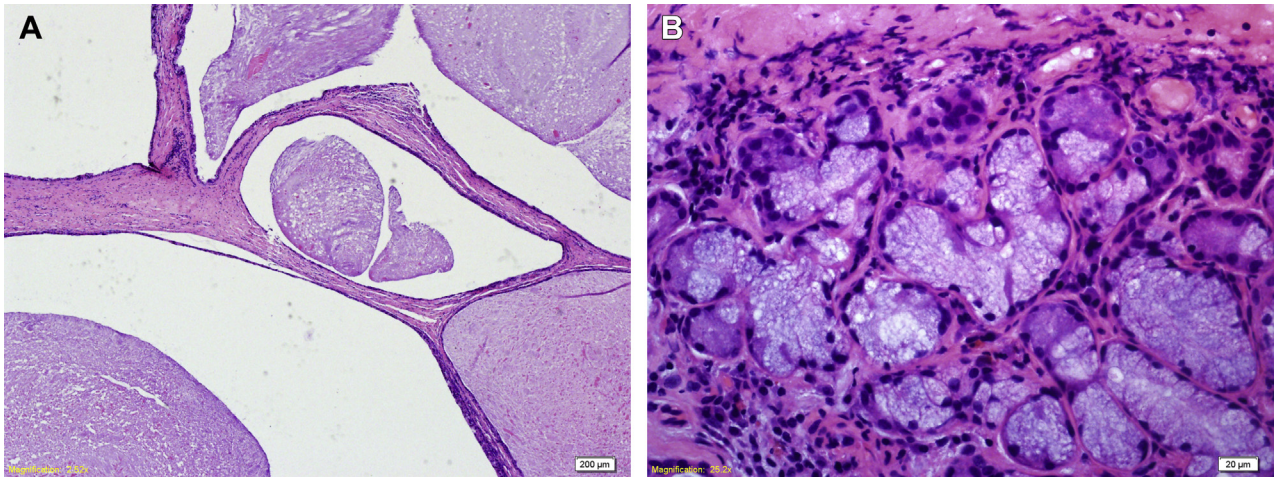

FIGURE 3. *A*, Tumor is well circumscribed and predominantly cystic (hematoxylin and eosin stain; × 40). *B*, Tumor is composed of variably sized cystic spaces lined mostly by a single layer of rather cytologically bland mucous epithelium; no cellular atypia or mitotic figures are observed (hematoxylin and eosin stain; × 400).

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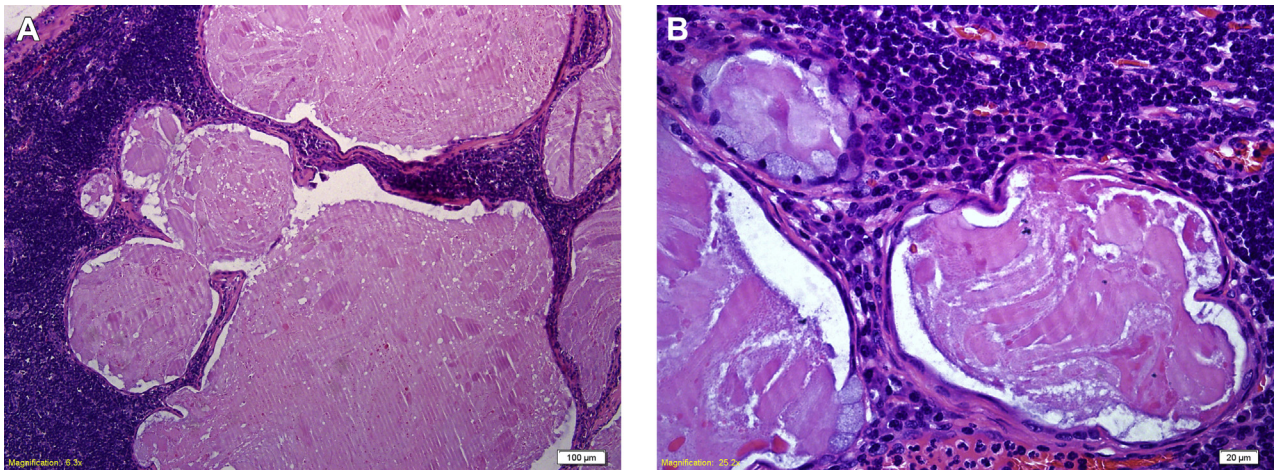

FIGURE 4. *A*, Lymph nodes exhibit large cysts containing mucus in the cystic cavity (hematoxylin and eosin stain; × 80). *B*, The cystic epithelial stratum consists of cells containing small amounts of mucus that are characteristic of mucous cells, whereas microcysts are enveloped by lymph cells in some regions (hematoxylin and eosin stain; ×400).

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can cause tumor cell dislodgement and vascular penetration with subsequent hematogenous spread.[9,10] According to a comprehensive literature review by Nouraei et al,[10] bone is the most common site for metastasis of MPA (45% of examined cases with metastasis), and metastasis to regional lymph nodes is fairly frequent (17%). Compared with salivary pleomorphic adenoma, cystadenoma of salivary glands has certain similar characteristics, such as being benign, slow growing, and usually well circumscribed.[3,4] Furthermore, in this case, cervical metastasis occurred simultaneously with an episode of recurrent cystadenoma 5 years after the initial surgery in the retromolar region.[9,10] Therefore, the association of cervical metastasis of the cystadenoma in this case with a prior incomplete operation was inferred.

Because of its rarity, the characteristics of salivary cystadenoma are unclear. Considering the potential for recurrence after surgery and lymph node metastasis, a hypothesis on the features of salivary cystadenoma can be formulated. Certain types of cystadenoma can have low-grade malignancy, similar to MPA. Although current methods of histologic diagnosis cannot differentiate a metastasizing cystadenoma from a benign cystadenoma, its natural history might be that of an aggressive malignant entity. In addition, a rare case of cystadenoma invading a lymph node and adipose tissue has been reported in the pancreas.[11]

Surgery is the mainstay treatment for salivary cystadenoma, and most reported cases have been treated by simple excision without recurrence. However, recurrence at the surgical site has been reported on occasion, albeit usually years after the surgical procedure. In the authors' opinion, similar to other carcinomas of the salivary gland, for patients with clinically detectable enlargement of the lymph nodes, neck dissection or postoperative radiotherapy is recommended.[12] However, careful follow-up might be indicated in certain cases.

In conclusion, a case of cystadenoma with cervical metastasis was presented, and further attention should be paid to patients with recurrent cystadenoma that might contain lymph node metastasis. Considering information from the current literature and the present report, regular follow-up of patients with cystadenoma is recommended. For this reason, the present patient will continue to be seen at regular follow-up intervals, and the authors recommend a similar management plan for all patients with tumors diagnosed as recurrent cystadenoma of the minor salivary gland.

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