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Case Report

Adenoid Cystic Carcinoma of the Submandibular Gland with Symptomatic Ovarian Metastases

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Summary: We report the clinical and pathologic features of an adenoid cystic carcinoma of the submandibular gland that metastasized to the ovaries 10 years after initial presentation. A 30-year-old woman underwent excision of a right submandibular adenoid cystic carcinoma followed by regional external beam radiation therapy. Three years later, she underwent extended hepatic resection and localized radiotherapy to the hepatic region for metastatic disease. The patient was without evidence of disease for 7 years when she developed pelvic pain and a pelvic mass was found. A solid and cystic 10-cm left ovarian mass and a single metastatic tumor nodule involving the right ovary were excised via the laparoscope. Histologically, the tumor was identical to the patient's initial salivary gland neoplasm. The neoplastic cells were CAM 5.2 positive, S100 positive, muscle-specific actin positive, and smooth muscle actin positive. Ultrastructurally, characteristic pseudocysts (pseudolumina) with abundant basal lamina and true glandular lumina lined by short microvilli were present. Other than a single anecdotal account of a parotid gland adenoid cystic carcinoma, this case represents the first documented report of an adenoid cystic carcinoma of salivary gland origin that was associated with symptomatic ovarian metastases. This case demonstrates that the ovary is a potential site for metastatic disease many years following the diagnosis and treatment for a primary neoplasm however uncommon or remote the site of origin. Since metastatic adenoid cystic carcinoma can rarely present as an ovarian mass, a clinical history of this neoplasm should be heavily weighed in the differential diagnosis of any unusual ovarian tumor with a predominant cribriform, trabecular, or tubular pattern. **Key Words:** Adenoid cystic carcinoma—Ovary—Ovarian metastases—Ovarian neoplasms—Salivary gland—Immunohistochemistry.

Adenoid cystic carcinoma is a histologically distinctive malignant neoplasm occurring in the salivary glands (1,2), larynx and tracheobronchial tree (3), breast (4–6), Bartholin gland (7,8), skin (9,10), and uterine cervix (11–18). Rare examples of primary ovarian tumors resembling adenoid cystic carcinoma have been reported (19,20). However, with the exception of occasional anecdotal references to ovarian metastases from salivary gland tumors (21–23), we are not aware of any published articles describing symptomatic ovarian metastases from adenoid cystic carcinoma. We report an adenoid cystic carcinoma of the submandibular gland that was associated with bilateral symptomatic ovarian metastases 10 years after presentation and 7 years after successful treatment of a hepatic recurrence and review the reported examples of primary adenoid cystic carcinoma of the ovary. The differential diagnosis of ovarian tumors with a predominant cribriform pattern is discussed.

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CASE REPORT

A 30-year-old, gravida 1, para 1 woman presented with a 2-cm mass in the right submandibular gland. Excisional biopsy showed an adenoid cystic carcinoma with prominent perineural invasion. The patient was staged T1N0M0 and treated with external beam radiation (5,000 rads) to the region of the right neck and supraclavicular fossa. The patient had another child and was without evidence of disease for 2 years. In the following year, an 11-cm mass was found in the right lobe of the liver. Fine needle aspiration biopsy showed metastatic adenoid cystic carcinoma. The patient was treated with two courses of cis-platinum and 5-fluorouracil with little reduction in mass size. She was started on tamoxifen (10 mg twice daily) and underwent extended right lobe hepatectomy followed by 4,500-rad external beam radiation to the right upper quadrant and 2,800 rads via intrabiliary iridium beads. The patient subsequently developed biliary strictures with secondary biliary cirrhosis within the radiation field, requiring stint drainage. Multiple imaging studies, common duct brushings, and liver biopsies failed to disclose any evidence of residual or recurrent disease. Seven years later, the patient developed pelvic pain. A left pelvic mass was detected and sonogram showed a large, 10-cm, mixed solid and cystic mass anterior to the fundus of the uterus and superior to the bladder. Chest x-ray, abdominal computed tomography scan, and mammogram showed no evidence of malignancy. At laparoscopy, a large, 10-cm-diameter, multicystic mass replaced the entire left ovary. A left salpingo-oophorectomy was performed, and frozen section of the left ovarian mass showed adenoid cystic carcinoma, consistent with the patient's primary submandibular neoplasm. The right ovary contained a single, 8-mm, solid, pale yellow nodule that was biopsied. There were extensive adhesions between the omentum and liver as well as to the midline incision, but no other evidence of pelvic or intraabdominal tumor spread was identified. The patient subsequently underwent a complete right salpingo-oophorectomy and hysterectomy. Eleven months postoperatively, she is without evidence of disease.

PATHOLOGY

The right submandibular gland contained a 2-cm-diameter adenoid cystic carcinoma with a predominant cribriform pattern. A focal solid component was present, but it constituted <20% of the neoplasm. Mitotic figures were scattered throughout the neoplasm, but they were not numerous (≤1/10 high-power fields). There was no significant cytologic atypia. Perineural invasion was prominent. A single lymph node within the adjacent soft tissue showed no evidence of metastatic carcinoma.

The right hepatectomy specimen contained two masses consisting of metastatic adenoid cystic carcinoma with histologic features similar to the primary tumor. Mitotic figures were more prominent than in the primary tumor, but there was no significant difference in cytologic atypia. The surrounding liver showed parenchymal fibrosis.

The left ovary was replaced by a 10-cm, multiloculated, cystic neoplasm with multiple, solid, pale yellow and tan, mural nodules. The cyst walls contained multiple foci of adherent blood clot. The neoplasm in the right ovary consisted of a single solid nodule that was similar in appearance to the polypoid mural nodules in the left ovarian mass. The microscopic appearance of the neoplasm was similar in all sections and resembled the patient's primary submandibular gland tumor as well as the hepatic metastasis (Fig. 1A). The tumor was composed of small, uniform, basaloid cells with scanty cytoplasm and uniform, darkly staining nuclei. There was minimal nuclear pleomorphism. Nucleoli either were not evident or were small and inconspicuous. Mitotic figures ranged from 1 to 3/10 high-power fields. The cells were arranged in large clusters of variably sized cribriform nests, trabeculae, and irregular, anastomosing cords. The larger cell nests were punctuated by numerous clear or faintly basophilic spaces or amorphous deposits of eosinophilic hyaline material. The hyaline material was periodic acid-Schiff positive, whereas the intraluminal material was mucicarmine positive. Rare glandular structures were also identified within the cell nests. A focal ductal or tubular pattern (more prominent in the right ovary) was also present (Fig. 1B). No significant solid pattern was identified. There was no associated inflammatory cell response or necrosis. The surrounding stroma was fibrous with minimal reaction.

The ovarian tumor cells showed heterogeneous but strong (3+) cytoplasmic staining for cytokeratin (clone CAM 5.2; Becton Dickinson, Mountain View, CA, U.S.A.) (Fig. 2A). Monoclonal carcinoembryonic antigen (mCEA; clone 0062, Boehringer Mannheim Biochemicals, Indianapolis, IN, U.S.A.)

1A,B

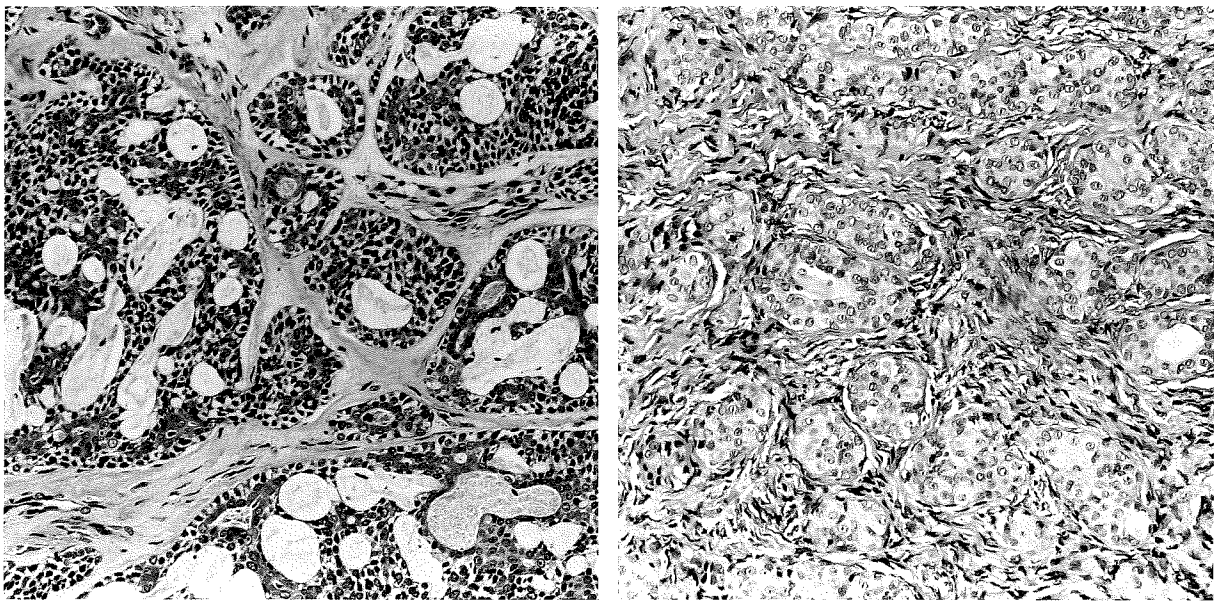


FIG. 1. A: Metastatic adenoid cystic carcinoma in ovary with prominent cribriform pattern and myxoid or hyaline material in the gland-like spaces and stroma. B: Metastatic adenoid cystic carcinoma in ovary with small ductal or tubular pattern. Nests of tumor cells with pale-staining nuclei replace ovarian stroma.

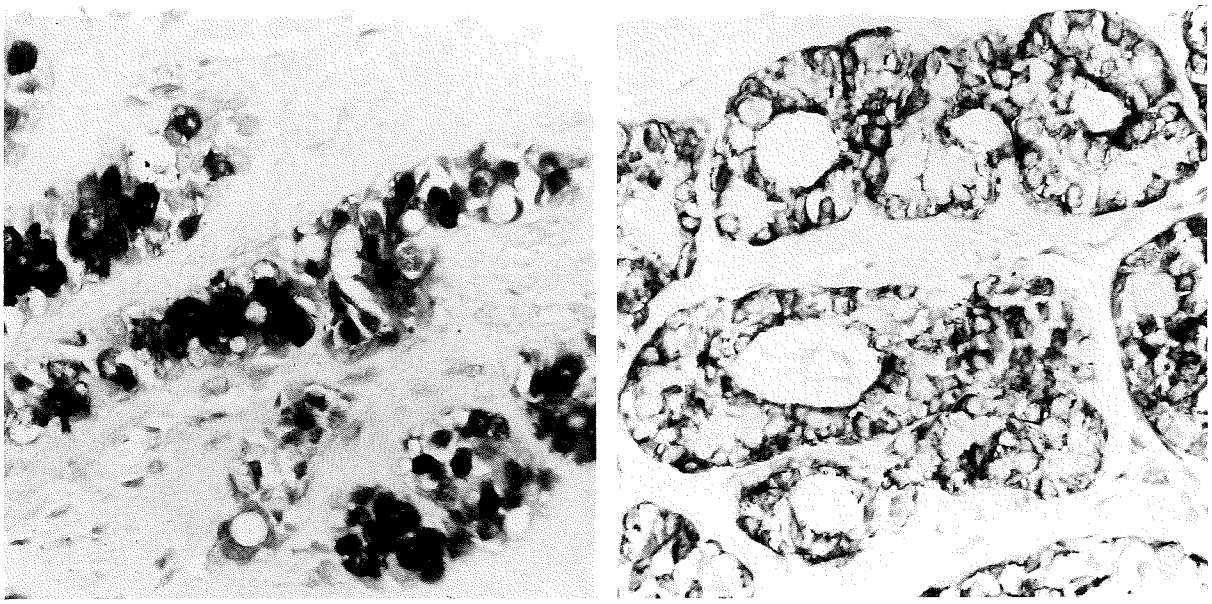
was present only focally (2+) along the luminal cell membranes and within the true gland lumina; cytoplasmic staining for mCEA was not present. The cells along the periphery of the trabeculae and cribriform structures were positive for anti–muscle-specific actin (clone HHF35; Dako, Carpinteria, CA, U.S.A.) and anti–smooth muscle actin (clone 1A4; Sigma Diagnostics, St. Louis, MO, U.S.A.); both markers stained the cytoplasm of the tumor cells (3+) and some of the pseudoluminal cells (3+), but not true luminal cells (Fig. 2B). Cytoplasmic and nuclear staining with polyclonal rabbit anti-S100 (Dako) was also noted in the tumor cells and pseudoluminal cells (3+) (Fig. 2C).

Ultrastructurally, the ovarian neoplasm contained numerous characteristic pseudocysts (pseudolumina) with abundant basal lamina and occasional true glandular lumina lined by short microvilli (Fig. 3). Bundles of parallel microfilamentous processes were also present in the cells along the periphery of the tumor nests.

DISCUSSION

Adenoid cystic carcinoma occurs most commonly in the salivary glands, where it accounts for ~10% of all carcinomas in these areas. In the female genital tract, adenoid cystic carcinoma occurs mainly in the Bartholin gland and cervix (7,8,11–18). Primary adenoid cystic carcinoma of the ovary is extraordinarily rare. A primary unilateral ovarian adenoid cystic carcinoma has been recently reported by Feczko et al. (19). Eichhorn and Scully (20) described six ovarian neoplasms resembling adenoid cystic carcinoma, five of which were of mixed histology (i.e., areas of serous, mixed clear cell and endometrioid, or endometrioid type were also present). All but one of these neoplasms were stage IIIc and three of five patients with follow-up died 1–11 years after initial presentation (20,24). Myoepithelial cells were not identified by standard light microscopy or immunohistochemistry, and it is likely that, despite the light microscopic resemblance to adenoid cystic carcinoma, these neoplasms constitute examples of "carcinoma with adenoid cystic carcinoma-like pattern" as opposed to adenoid cystic carcinoma of the classic salivary gland type (20). Metastatic adenoid cystic carcinoma to the ovary is also extremely uncommon. In their chapter concerning metastatic tumors of the ovary, Young and Scully (25) refer to a single patient who had an adenoid cystic carcinoma of the parotid gland excised at the age of 12 years followed by local recurrence and pulmonary metastases with bilateral symptomatic ovarian metastases 11 years after presentation. Variakojis et al. (23) reported a 36-year-old patient with adenoid cystic carcinoma

2A,B



2C

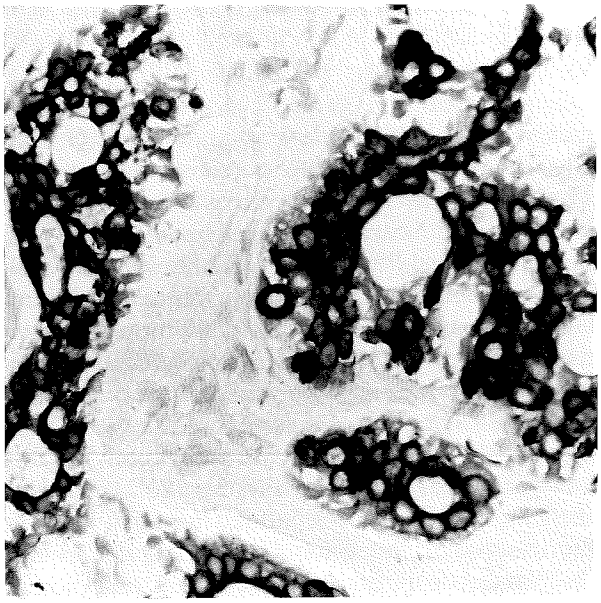


FIG. 2. A: CAM 5.2 staining of metastatic adenoid cystic carcinoma does not differentially stain tumor cell types. B: In contrast, the pseudoluminal and basal cells preferentially stain for actin. C: The true luminal cells stain strongly for S100.

of the submandibular gland who developed local recurrence 1.5 years following excision of the primary tumor, followed by pulmonary and intracranial metastases. The patient subsequently developed pelvic and bone metastases and died 2.5 years after the initial excision. At autopsy, there was widespread disease involving thyroid, pancreas, liver, adrenals, and bone with large metastases to both ovaries. Histologically, the primary neoplasm was unusual, in that most of the neoplasm was poorly differentiated (23). With the exception of one other reference to the existence of ovarian metastases in a patient with widespread metastases from a salivary gland carcinoma at autopsy (no further details were provided), we are not aware of any other documented examples of adenoid cystic carcinoma of salivary gland origin with symptomatic ovarian spread (21). Our patient presented with a T1N0M0 adenoid cystic carcinoma of the submandibular gland that was complicated by hepatic metastases, but she was without evidence of disease for 7 years until she developed symptomatic ovarian disease. She has had no local recurrences or pulmonary metastases.

Adenoid cystic carcinoma of the salivary gland is a clinically and pathologically well defined entity (2). The clinical behavior of this neoplasm is often

3A,B

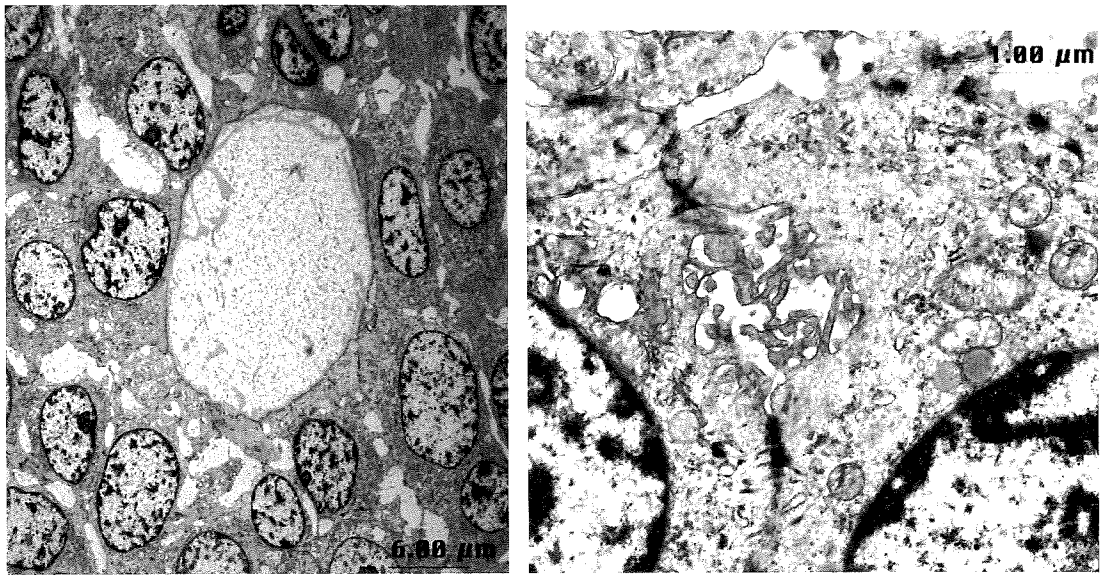


FIG. 3. Low-power electron micrographs demonstrate basal lamina material within pseudolumen (A) and microvilli within true lumen (B).

initially indolent with distant metastases occurring late in the course of the disease. Perineural invasion is a hallmark of adenoid cystic carcinoma. Despite the favorable 5-year survival for this neoplasm, the 20-year survival is significantly decreased, depending on the initial stage of disease and the occurrence of distant metastases (26). Complete excision, if possible, at the first surgical procedure offers the best chance for long-term survival. The neoplasm features three major histologic patterns: cribriform, in which the architectural configurations resemble small cylinders; tubular, in which the epithelial cells form ductules and small cords; and solid. Most tumors contain a mixture of architectural patterns. Numerous studies have demonstrated the presence of duct cells and myoepithelial cells with fewer numbers of acinar and undifferentiated cells (1,27–29). The ductal cells express keratin and S100, whereas the myoepithelial cells express actin with or without keratin and S100 (29). Characteristic ultrastructural features include the presence of pseudocysts or pseudolumina, highly replicated basal lamina, intracellular microfilaments resembling myofilaments, and occasional true gland lumina with microvilli (1,27,28). The pseudolumen is considered to be one of the most distinctive ultrastructural features and consists of a round extracellular space resembling a gland lumen that is filled with replicated basal lamina (27,30).

In contrast to adenoid cystic carcinoma of salivary gland origin, those occurring in the female genital tract consist of a clinically and pathologically heterogeneous group of neoplasms (8,12,14,15,18–20,31,32). Many of the reported cases of primary cervical adenoid cystic carcinoma are clinically very aggressive, and this is reflected histologically by the more frequent presence of necrosis, cytologic atypia, and increased mitotic figures (12,14,15, 18). Also, not all cases that have been reported under this label have uniformly demonstrated the standard light microscopic, ultrastructural, or immunohistochemical characteristics of this tumor type, as defined in the salivary glands (14). Because the light microscopic impression may be deceptive, most authors advocate the inclusion of additional ultrastructural, immunohistochemical, or histochemical diagnostic criteria before establishing a diagnosis of adenoid cystic carcinoma outside the salivary gland or tracheobronchial tree (6,17,30). In one of the largest series of adenoid cystic carcinomas of the cervix, Ferry and Scully (14) suggest the use of quotation marks to draw attention to this incomplete identity. The adenoid cystic carcinomas of Bartholin's gland have not been as well studied, but these neoplasms appear to represent a more homogeneous group, with significantly more uniform histologic and clinical similarity to their salivary gland counterparts (7,8).

The major differential diagnostic problem posed by a metastatic adenoid cystic carcinoma of the ovary is, in the absence of a clinical history of prior neoplasia, the exclusion of a primary ovarian neo-

plasm. A benign, borderline, or well differentiated endometrioid neoplasm composed of small cells and containing tubules and acinar structures with prominent "cribriform" intraglandular bridging can simulate the standard light microscopic features of an adenoid cystic carcinoma (31,32). However, endometrioid neoplasms typically contain foci of squamous differentiation and possess more cellular heterogeneity. Microcystic serous carcinoma may also demonstrate an adenoid cystic-like pattern, but distinct ductal-type cells and myoepithelial cells with large spaces filled with basal lamina are absent. A microfollicular granulosa cell tumor may enter the differential diagnosis, especially since these neoplasms possess immunohistologic features similar to adenoid cystic carcinoma, but granulosa cells characteristically contain pale, oval or angulated nuclei with nuclear grooves. Another potential mimic is a primary (or metastatic) carcinoid tumor. Carcinoid tumors can induce extensive stromal fibroplasia, occasionally with hyalinization. These neoplasms typically possess microacinar structures with luminal eosinophilic material, but the acini are uniform with little variation in size and do not characteristically contain basal lamina material. Primary carcinoids are usually associated with a mature teratoma and are usually unilateral. The small tubular or ductal pattern of adenoid cystic carcinoma can closely simulate metastatic breast carcinoma (Fig. 1B). Although there are a variety of immunohistochemical studies that can be performed to differentiate between these two possibilities, the importance of obtaining a complete clinical history in the evaluation of an ovarian neoplasm, especially one that does not match a specific diagnostic category, is obvious.

The probability that an ovarian cancer found on exploration of a pelvic or abdominal mass is a metastasis is ~6–7% (33). Most metastases are of gastrointestinal (gastric, intestinal, or appendiceal) origin, followed by breast, uterus, and pancreas (25). However, clinically significant metastases from sites as diverse as kidney, biliary tract, liver, urinary tract, lung, and mediastinum have been reported (25). Symptomatic ovarian involvement by malignant melanoma as well as a variety of sarcomas has also been well documented (25). A constellation of features that can be useful in identifying an ovarian neoplasm as a metastasis have been elaborated by Young and Scully (22). Briefly, these features include bilaterality, extraovarian disease at unusual sites, multiple discrete surface nodules, blood vessel or lymphatic space involvement, and unusual morphologic features. Perhaps the single most important piece of information is a clinical history of prior neoplasia. The occurrence of symptomatic ovarian metastases in a patient 10 years following presentation for an adenoid cystic carcinoma of the salivary gland demonstrates that the ovary is a potential site for metastatic disease many years following the diagnosis of an extraovarian neoplasm however uncommon or remote the site of origin. Since metastatic adenoid cystic carcinoma can rarely present as an ovarian mass, a clinical history of this neoplasm should be heavily weighed in the differential diagnosis of any unusual ovarian tumor with a predominant cribriform, trabecular, or tubular pattern.

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