Metastatic adenoid cystic carcinoma with high-grade transformation (“dedifferentiation”) in pleural effusion and neck lymph node: A diagnostic challenge on cytology?

Marc P. Pusztaszeri | Victor Brochu

Department of Pathology, McGill University, Montreal, Quebec, Canada

Correspondence
Marc P. Pusztaszeri, Department of Pathology, Jewish General Hospital, McGill University, 3755, Chemin de la Côte Ste Catherine, H3T 1E 2, Montréal, Québec, Canada.
Email: marc.pusztaszeri@mcgill.ca

Abstract
High-grade transformation (HGT) or "dedifferentiation" is an uncommon phenomenon among salivary gland carcinomas including adenoid cystic carcinoma (ACC), which is important to recognize because it is associated with increased tumor aggressiveness, with a high propensity for lymph node and distant metastases. ACC with HGT is histologically characterized by a distinct population of poorly differentiated cells with loss of the typical biphasic ductal and myoepithelial differentiation seen in conventional ACC, associated with pleomorphism, necrosis and increased mitotic activity. We report the cytologic features of a case of metastatic ACC-HGT in cervical lymph node and effusion, which, to the best of our knowledge, have not been described previously. When ACC presents both in atypical locations and with HGT, the danger of misdiagnosis is increased if the clinical history is lacking, incomplete or inaccurate. Since ACC-HGT are rare (and possibly underdiagnosed) and do not have a specific set of cytological and/or immunohistochemical features, it is important for practicing cytopathologists to be aware of the possibility of encountering them, especially in specimens from patients with a history of ACC, in order to render the correct diagnosis.

KEYWORDS
adenoid cystic carcinoma, cytology, dedifferentiation, high-grade transformation

1 | INTRODUCTION

Adenoid cystic carcinoma (ACC) is a malignant neoplasm most commonly originating in salivary glands of the head and neck (H&N) area.1 A protracted course of many years with multiple local recurrences and late appearance of metastatic disease, mainly in the lungs and bone, is the characteristic clinical course for these slow-growing tumors.2 Rarely, patients may initially present with metastatic disease of unknown origin. In such patients, further evaluation may reveal an unexpected synchronous primary ACC or the patient may have a remote history of ACC.2 A definitive cytologic diagnosis of ACC, especially the cribriform type, in salivary gland FNA specimens is feasible in a subset of cases.4,5 Typical ACC has characteristic cytologic features with small, often angulated, hyperchromatic nuclei with uniformly dispersed chromatin and scant cytoplasm imparting a basaloid appearance.5 Mitoses, necrosis and significant pleomorphism are uncommon in the absence of high-grade transformation (see below). The most important cytologic feature of ACC is its characteristic matrix that forms variably sized spheres (aka hyaline globules), cylinders, and branching tubules with sharp edges ("cookie cutter").4,7 Diagnostic difficulties can be caused particularly by the absence of matrix, especially in the solid variant of ACC, which can mimic other basoloid neoplasms such as cellular pleomorphic adenoma or basal cell adenoma/adenocarcinoma.4,7 Therefore, without supporting ancillary studies, a subset of ACC are diagnosed as “Salivary Gland Neoplasm of Uncertain Malignant Potential” (SUMP) or
as “Suspicious for Malignancy” according to the recent Milan System for Reporting Salivary Gland Cytopathology.\(^5\)

High-grade transformation (HGT) or “dedifferentiation” is an uncommon phenomenon among salivary gland carcinomas including ACC, which is important to recognize because it is associated with increased tumor aggressiveness, with a high propensity for lymph node and distant metastases.\(^8-10\) HGT is defined as the transformation of a well-differentiated tumor into a high-grade malignancy that lacks the distinct histologic characteristics of the original neoplasm and usually corresponds to undifferentiated or poorly differentiated carcinoma.\(^9,10\) HGT in ACC (ACC-HGT) was first described in 1999 by Cheuk et al. as “dedifferentiated ACC”,\(^8\) and since then >50 cases have been reported in the literature, most of them involving sinonasal and palatal minor glands and the submandibular glands.\(^9-11\) ACC-HGT is histologically characterized by a distinct population of poorly differentiated cells with loss of the typical biphasic ductal and myoepithelial differentiation seen in conventional ACC, associated with pleomorphism, necrosis and increased mitotic activity.\(^9,10\) HGT in ACC may be apparent at the time of primary excision of the tumor or may develop in a recurrence, especially in patients who underwent radiotherapy.\(^9-12\) Most common reported metastatic sites of ACC-HGT include lungs, cervical lymph nodes, bones, liver, and brain.\(^9-11\) Metastatic ACC involving an effusion has been exceptionally reported with only three cases, including a primary cutaneous ACC metastatic in pericardial fluid.\(^2,3,13\) In these three cases, hyaline globules admixed with small cohesive round basoid epithelial cells were observed, corresponding to conventional ACC. To the best of our knowledge, however, the cytologic features of metastatic ACC-HGT in an effusion have not been described previously.

### 2 | CASE PRESENTATION

A 72-year-old man complaining of shortness of breath was admitted for the investigation of cervical lymphadenopathy and a large left pleural effusion which were suspicious for metastatic disease. The patient was a smoker and had a history of base of tongue ACC initially staged T4 N2C in 2013. He was treated with neoadjuvant chemotherapy and neutron beam therapy in 2014, because he refused surgery. A local recurrence at the base of tongue was treated by radical surgery and bilateral neck dissection in 2017. Current cervical and thoracic CT scans showed a large left pleural effusion with complete whiteout/collapse of the left lung, associated with multiple bilateral pulmonary parenchymal and pleural nodular densities consistent with metastatic disease. There were also a left level IV 3 cm supraclavicular necrotic lymphadenopathy and a mass-like area at the right floor of mouth suspicious of local recurrence. FNAB of the cervical lymphadenopathy and thoracentesis were performed. The material was received in the cytology laboratory the same day and was processed into Cytospin and Cell block preparations which were stained with Papanicolaou and H&E stains, respectively.

### 3 | CYTOLOGY RESULTS

Cytospin and Cell block preparations from the pleural effusion demonstrated many clusters of large cohesive round epithelial cells with abundant, sometimes vacuolated, cytoplasm, and pleomorphic nuclei on Cytospin (Papanicolaou stain) and B, cell block preparations (H&E stain, \(\times 400\)). By immunohistochemistry, C, the tumor cells are diffusely positive for CK5/6 and D, CK8/18, and E, show focal positivity with CK7. F, The lymph node aspirate also demonstrated similar cytological details, but a minor population of small basoid cells, highlighted by p63 positive immunostain and G, admixed with larger pleomorphic cells, was also present in the latter (Cell block H&E stain) (A-G: \(\times 400\)) [Color figure can be viewed at wileyonlinelibrary.com]
positive staining for Ber-EP4, CK5/6, and CK8/18; focal positivity for CK7, p40, and p63 (rare tumor cells); and were negative for CEA, CD117, TTF-1, Napsin-A, and S100 (Figure 1C-E). The tumor in the pleural fluid was similar to what was aspirated from the neck lymph node. A minor population of small basaloid cells, highlighted by p63 positive immunostaining (Figure 1F), admixed with larger pleomorphic cells was also present in the latter (Figure 1G). The tumor was then compared to the previous resection specimen from 2017 (see below); in the latter, the ACC contained high-grade areas which were initially overlooked. These foci of ACC-HGT were comparable to the current specimens. Therefore, the lymph node FNAB and pleural effusion specimens were both diagnosed as metastatic carcinoma, high grade, consistent with a HGT (dedifferentiation) of the known ACC.

4  |  PATHOLOGY RESULTS

A retrospective review of the surgical resection from 2017, consisting of a total glossectomy, total laryngectomy, and bilateral neck dissection, was performed. The tumor was located at the tongue base, bilateral, measuring 6.4 × 4.9 × 3.1 cm. On microscopic examination, the tumor was primarily composed of conventional ACC (grade II) (Figure 2A,B). Extensive perineural and intraneural invasion by tumor cells was seen. Focally, sheets and nests of larger cells with pleomorphic nuclei, prominent nucleoli, abundant eosinophilic cytoplasm, frequent mitosis (20/10 hpf), and small foci of necrosis were present, corresponding to areas of ACC-HGT (Figure 2C-E). These tumor nests were lacking myoepithelial cells, and focal squamous areas and micropapillary growth, which are unique features of ACC-HGT as compared to conventional ACC, were also present.9,11 There was one metastatic lymph node out of 46 in the lymph node dissection, showing mostly conventional ACC, with extranodal extension. The submandibular glands showed post radiation atrophy. By immunohistochemistry, the primary tumor was negative for p16, androgen receptor and HER2, ruling out an HPV-associated carcinoma and a salivary duct carcinoma.

5  |  DISCUSSION

In ACC-HGT, the high-grade carcinoma is usually either poorly differentiated adenocarcinoma or less commonly “undifferentiated” carcinoma.9-12 Because of its rarity and the lack of specific features, cytologic specimens from metastatic ACC-HGT may be easily confused with a variety of poorly differentiated primary or secondary carcinomas that may be more commonly encountered at the site of distant metastasis. Therefore, the differential diagnosis of metastatic ACC-HGT can be broad. In our case, the main differential diagnosis given the clinico-radiological findings, included metastatic lung carcinoma. The diagnosis was greatly facilitated in our case because of the patient’s known history of ACC with a current imaging suggestive of recurrent and widespread disease and a concomitant cervical lymph

---

**FIGURE 2**  High-grade transformation of adenoid cystic carcinoma on histology. A, Low-power view showing two distinct carcinomatous components: conventional adenoid cystic carcinoma (left portion) and high-grade carcinoma with a predominantly solid growth pattern, forming irregular and confluent tumor nests (right portion) (H&E stain, ×100). B, Conventional adenoid cystic carcinoma exhibiting cribriform pattern with excessive extracellular basal lamina material and two cell-layered tubular structures (H&E stain, ×200). The tumor cell nuclei have a bland, uniform appearance. C-E, High-grade carcinoma component. Solid and micropapillary growth (D, H&E stain, ×200) patterns of carcinoma cells exhibiting large pleomorphic nuclei with a moderate amount of cytoplasm (E, H&E stain, ×600). Comedonecrosis is also present (C, H&E stain, ×200) [Color figure can be viewed at wileyonlinelibrary.com]
node FNAB that yielded similar findings. Gathering complete and accurate clinical history and radiological data, obtaining adequate diagnostic material for ancillary studies (Cell block), and comparing the morphology of the tumor with that of the patient’s known primary are essential for the diagnosis of metastatic ACC, with or without HGT, in effusion or in other unusual locations. Since ACC-HGT has far more propensity than conventional ACC to metastasize to lymph node (43%-57% vs 5%-25%) and distant metastatic sites including effusion, the non-specific features of a high-grade carcinoma would be more likely at metastatic sites than in the primary tumor, and the classification may be limited to “high-grade carcinoma.” In contrast, an adequately sampled tumor from the primary site may show features of both the conventional and the higher grade component facilitating the diagnosis.14 Especially, recognition of occasional clusters of basaloid cells and/or hyaline globules, when present, in association with larger poorly differentiated malignant cell population in aspiration smears can be a helpful clue in cytological diagnosis.14

In our case, a minor population of basaloid cells, positive for p63, admixed with larger poorly differentiated malignant cells was present in the metastatic lymph node (Figure 1F,G) but not in the pleural effusion.

Immunohistochemistry results may be misleading since there is an altered immunoprofile in ACC-HGT as compared to conventional ACC.7-11 The expression of myoepithelial markers is typically lost in ACC-HGT, along with CD117 and S-100.9-11 Immunohistochemistry is essentially helpful to rule out other common sources of metastatic carcinomas with a panel of “organ specific” markers such as TTF-1, Napsin A, CDX-2, Gata-3, and PAX-8, depending on the clinico-radiological features. Detection of the specific MYB-NFIB gene translocation by FISH or molecular testing, which is present in ~60% of ACCs, could also be helpful for diagnostic purposes.12,15 However, to the authors’ knowledge, the specificity and sensitivity of MYB immunohistochemistry in the setting of a high-grade metastatic carcinoma are unknown. One should be very cautious before concluding that MYB overexpression can be useful to suggest the origin or type of neoplasm in a metastatic high-grade carcinoma. While overexpression of MYB protein is present in about 80% in ACC with or without MYB gene rearrangement, other mechanisms of MYB activation may have a role in MYB protein overexpression, as has been demonstrated in colon and breast cancers where MYB oncogene is activated, thereby reducing its specificity, especially at metastatic sites.16 MYB protein expression is also not helpful when trying to distinguish ACC from the uncommon HPV-related Mutphenotypic Sinonasal Carcinoma (formerly known as HPV-related Carcinoma With Adenoid Cystic Carcinoma-like Features).17 Finally, in ACC, the presence of MYB rearrangement and/or MYB overexpression between conventional areas and areas with HGT, based on limited data, appears to be inconsistent, and the MYB-NFIB translocation is not necessarily an early event or fundamental for the progression to ACC with HGT.18

A meticulous review of the previous pathology, if available, is essential since HGT in ACC may be very focal11 and easily overlooked or under-diagnosed as a “solid” component in the resection specimens, even by a H&N pathologist, as in our case. Importantly, a morphologic spectrum with significant overlap between solid ACC and ACC-HGT is recognized, but the latter should have larger cells with more pleomorphism than solid ACC and a complete or partial loss of the myoepithelial component.9,10,12

In conclusion, since ACC-HGT are rare (and possibly under-diagnosed) and do not have a specific set of cytological and/or immunohistochemical features, it is important for practicing cytopathologists to be aware of the possibility of encountering them, especially in specimens from patients with a history of ACC, in order to render the correct diagnosis. Indeed, when ACC presents both in atypical locations and as a HGT, the danger of making an erroneous diagnosis is increased if the clinical history is lacking, incomplete or inaccurate.

ORCID
Marc P. Pusztaszeri https://orcid.org/0000-0001-6490-4189

REFERENCES

How to cite this article: Pusztaszeri MP, Brochu V. Metastatic adenoid cystic carcinoma with high-grade transformation ("dedifferentiation") in pleural effusion and neck lymph node: A diagnostic challenge on cytology? Diagnostic Cytopathology. 2020;48:679–683. https://doi.org/10.1002/dc.24431