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Aggressive Digital Papillary Adenocarcinoma With Multiple Organ Metastases: A Case Report and Review of the Literature

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Abstract: Aggressive digital papillary adenocarcinoma (ADPA) is a rare sweat gland neoplasm with a high recurrence rate and metastatic potential. In this study, the authors describe a case that originally appeared to benign spiradenoma, but took an ominous course eventually resulting in the diagnosis of ADPA. A 73-year-old woman developed a gradually growing nodule on the second toe of her left foot, which she had first noticed 4 years previously. An excisional biopsy was performed followed by histological examination. The authors initially considered the tumor to be a benign spiradenoma and did not perform reexcision. However, she experienced local recurrence 24 months later, and multiple pulmonary metastasis 31 months later. On histological examination, both the primary and locally recurrent tumors were found to be composed of discrete and well-circumscribed solid nodules, lacking cystic space. All tumors (the primary tumor, locally recurrent tumor, and lung metastases) presented with a pattern of fused back-to-back tubular structures and myoepithelial differentiation confirmed by immunohistochemical examination. On the basis of these findings, the authors finally diagnosed ADPA with multiple pulmonary metastases. The patient underwent chemotherapy, but died of disease 49 months later. This case highlights the importance of high clinical suspicion of ADPA when digital lesions present.

Key Words: aggressive digital papillary adenocarcinoma, digital papillary carcinoma, metastasis

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INTRODUCTION

First described by Helwig[1] in 1979 as a rare sweat gland neoplasm, aggressive digital papillary adenocarcinoma (ADPA) has a high recurrence rate and significant metastatic potential.[2] ADPA is often misdiagnosed,[3,4] which can delay the standard treatment of excision or amputation. In this study, we report a patient with ADPA that was initially considered to be a benign spiradenoma and was subsequently locally recurrent and progressed to metastatic disease. In addition, we present detailed histological findings of the primary tumor, locally recurrent tumor, and metastatic lesion.

CASE REPORT

A 73-year-old woman developed a gradually growing nodule on the second toe of her left foot, which she had first noticed 4 years previously. She denied any preexisting lesions at the site and her medical and family histories were unremarkable. On physical examination, the tumor was found to be a 3 mm red-brown nodule with tenderness, which presented on the second toe of the patient's left foot (Fig. 1A). An excisional biopsy was performed followed by histological examination. Hematoxylin and eosin (H&E) staining revealed a well-circumscribed solid tumor in the dermis containing tubular structures and hemorrhages (Fig. 1B). Higher magnification revealed that the tumor presented with closely aggregated back-to-back tubular structures lined by cuboidal or columnar epithelium (Fig. 1C). Some tubules showed evidence of decapitation secretion, and the neoplastic cells presented with nuclear atypicality and numerous mitoses (45 mitoses per 10 high power fields) (Fig. 1D). The tumor also had papillary structures formed by heaped-up epithelium with fibrovascular cores, and necrosis surrounding hemorrhages (Fig. 1E). There was no microscopic finding of invasion into the surrounding tissue. We initially considered the tumor to be a benign spiradenoma as the overall features resembled spiradenoma with apparent tubules and hemorrhages. Moreover, because histological examination did not reveal an apparent positive margin, we did not perform reexcision.

Two years later, the small nodule had regrown and physical examination revealed a 4.5 mm red-purple fluid-filled nodule located adjacent to the previous postoperative scar (Fig. 2A). There was no lymphadenopathy or organomegaly. Histological evaluation with H&E staining revealed a multilobular, solid tumor that contained fewer tubular structures than in the previous specimen (Fig. 2B). Tubular structures were mainly found at margins of the tumor and the central region consisted of sheets of neoplastic cell proliferation. Within the overlying epidermis was a blister containing red blood cells. As was the case with the previous specimen, the tumor contained hemorrhages. Higher magnification revealed that neoplastic cells presented with nuclear atypicality and increased mitoses (62 mitoses per 10 high power fields) (Fig. 2C). Necrosis and stromal hyalinization were presented focally. In addition, the tumor

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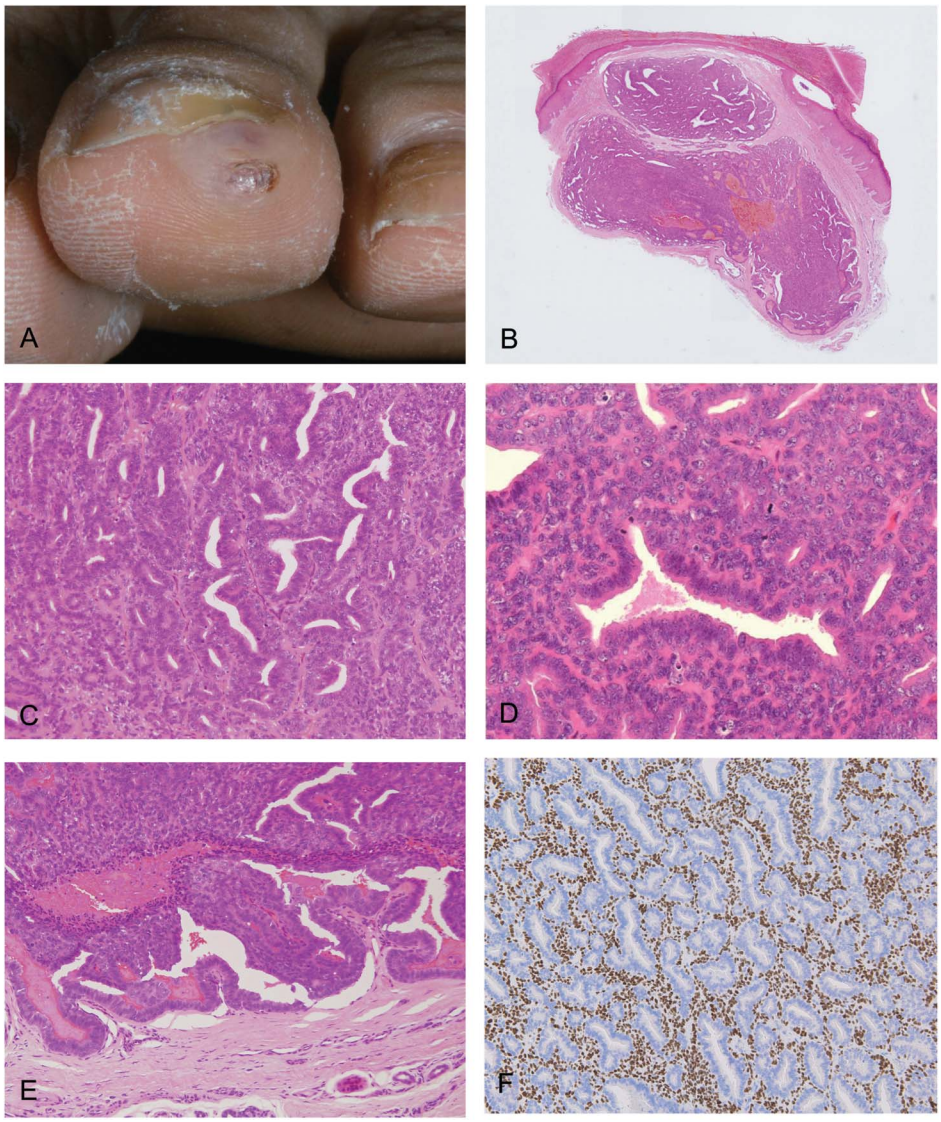

FIGURE 1. A, Clinical appearance of the red-brown nodule on the second toe of the patient's left foot. B, Well-circumscribed tumor nodule in the dermis containing tubular structures and hemorrhage (hematoxylin and eosin ×20). C, Closely aggregated back-to-back tubular structures lined by cuboidal or columnar epithelium (hematoxylin and eosin ×100). D, Some tubules displayed evidence of decapitation secretion. Neoplastic cells presented with atypical nuclei and mitoses (hematoxylin and eosin ×400). E, Papillary structures formed by heaped-up epithelium with fibrovascular cores and necrosis surrounding hemorrhages (hematoxylin and eosin ×100). F, Tumor cells, with the exception of those lining the tubular structures, were positive for p63 expression (×100).

showed foci of squamous differentiation (Fig. 2D). There was no microscopic finding of invasion into the surrounding tissue. Although we considered the tumor to be a malignant sweat gland neoplasm based on the above findings, we took a wait-and-see approach because of the free margin in the histological preparation and the lack of perineural or vascular invasion.

Seven months later, multiple nodular shadows were identified on the patient's chest x-ray during a routine examination; however, the patient did not report any symptoms. A whole-body computed tomography (CT) showed multiple pulmonary nodules without evidence of other sites of involvement (Fig. 3A). A subsequent CT-guided lung biopsy and H&E staining of the lung biopsy specimen revealed a solid lesion with a fibrous partition (Fig. 3B) and numerous tubules with features of decapitation secretion (Fig. 3C). The neoplastic cells presented a moderate number of mitoses (9 mitoses per 10 high power fields).

In the immunohistochemical examination of the primary specimen, the secondary specimen, and lung biopsy specimen, all tumor cells were found to be negative for thyroid transcription factor-1, suggesting that the nodules on the toe and in the lung were not metastatic lesions of lung cancer. In contrast, the tumor cells stained positive with antibodies against cytokeratin 7 and p53. Furthermore, the luminal borders of the tubular structures were positive for epithelial membrane antigen and carcinoembryonic antigen. These findings were common between the primary specimen, the secondary specimen, and the lung biopsy specimen. In addition, the tumor cells of the primary and secondary specimens were partially positive for S-100 protein, whereas the lung biopsy specimen exhibited less intense staining. In regard to hormone receptors, only the tumor cells lining the tubular structures in the primary specimen were weakly estrogen receptor–positive and all tumor cells were negative for the progesterone and androgen receptors. In addition, all tumor cells, except those lining the tubular structures, were positive for p63 (Figs. 1F, 2E and 3D) and α-smooth muscle actin staining. Considering that these cells were also positive for cytokeratin 7 and S-100 protein, these findings suggest that the tumor cells, with the exception of those lining the tubular structures, underwent myoepithelial differentiation. The Ki-67 labeling indices of the primary specimen, the secondary specimen, and the lung biopsy specimen were 22%, 39%, and 36%, respectively.

On the basis of these findings, we finally diagnosed an ADPA with multiple pulmonary metastases. Because the patient agreed to

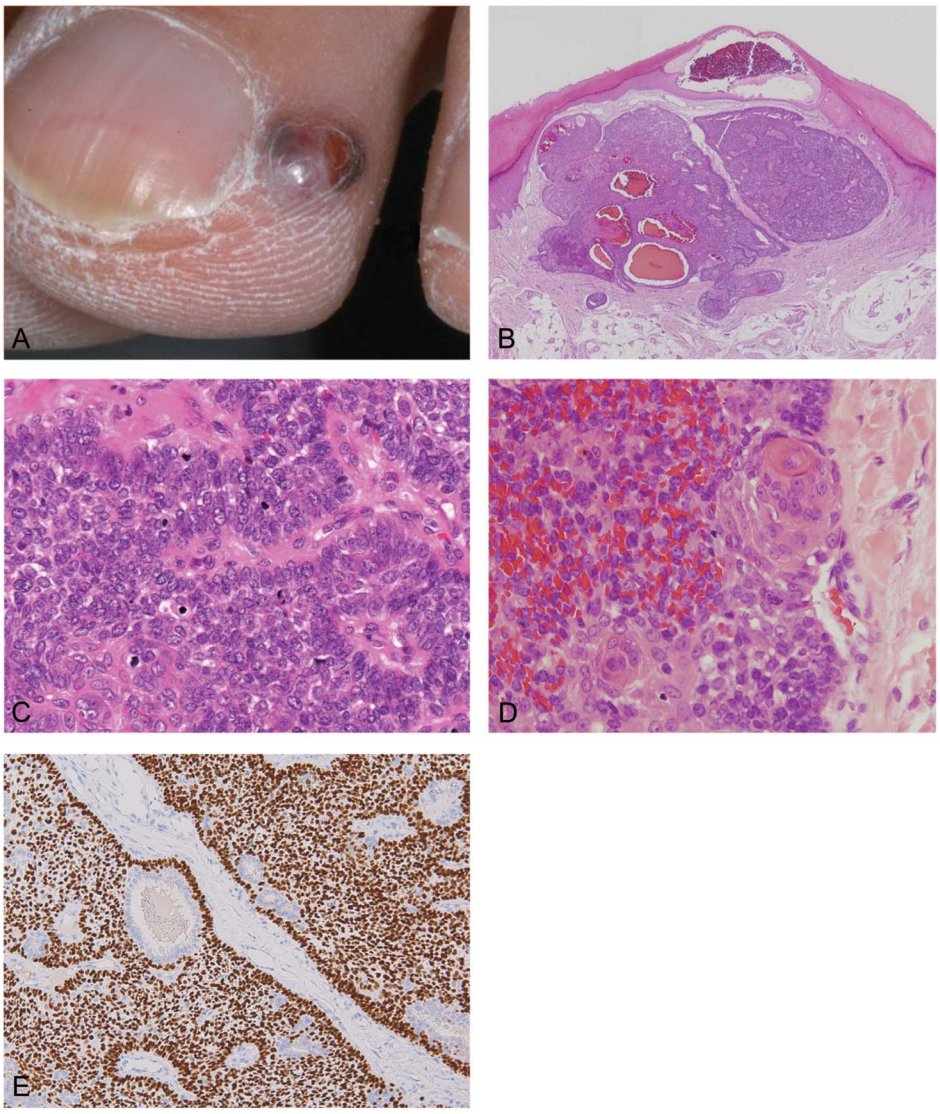

FIGURE 2. A, Clinical appearance of the red-purple fluid-filled nodule that appeared adjacent to the operative scar tissue resulting from the removal of the previous tumor. B, The tumor consisted of discrete nodules that were well circumscribed and, as was the case with the previous specimen, the tumor contained hemorrhages, although there were fewer tubular structures than in the previous specimen (hematoxylin and eosin ×20). C, Neoplastic cells exhibit nuclear atypicality and an increased number of mitoses compared with the previous specimen (hematoxylin and eosin ×400). D, Distinctive squamous foci were present (hematoxylin and eosin ×400). E, p63 staining showing that tumor cells, with the exception of those lining the tubular structures, were positive for p63 expression (×100).

a trial of chemotherapy, she was started on a regimen of weekly docetaxel (25 mg/m^2). After 16 months, the number and size of multiple pulmonary metastases increased and pleural effusions appeared. After much consultation with the patient, we stopped the chemotherapy and provided only symptomatic therapy. Twenty months later, multiple skin metastases, multiple small intestinal metastases, and multiple brain metastases appeared. Fourty-nine months after the first episode of multiple pulmonary metastases, the patient died of disease.

DISCUSSION

Kao et al[5] reported a series of 57 cases of ADPA and divided the cases into adenoma and adenocarcinoma, the latter being differentiated by poor glandular differentiation, necrosis, cellular atypia, and invasion of surrounding tissue. However, a subsequent study from the same institution that included the same cases found that none of the clinical or histologic findings previously described were predictive of recurrence or metastasis.[2] In their follow-up study, Duke and others described 67 cases, of which 50 were originally diagnosed as adenoma and 17 as adenocarcinoma. Metastasis occurred in 6 cases with 3 deaths. Remarkably, 3 of these metastatic cases had met the earlier criteria for adenoma. These findings indicate that all of these neoplasms could be designated as ADPA, without a benign counterpart.

Previous reviews summarized the clinical features of ADPA.[2,5] These features include a broad patient age range (19–83 years), the most common tumor site being the hand (85%) (with 79% on the fingers) and the other 15% located on the foot (with 9% on the toes) and an average tumor size of 1.7 cm (range, 0.4–4.3 cm). Moreover, ADPA is located in the dermis or subcutis and is multinodular.[2] Grossly, these tumors are generally flat to slightly elevated, although some protrude above the surface, and are occasionally ulcerated or show thickened skin at the involved site. In addition, most lesions are freely movable.

ADPA can be easily forgotten in the differential diagnosis and treatment is often delayed because of misdiagnosis,[3,4] as

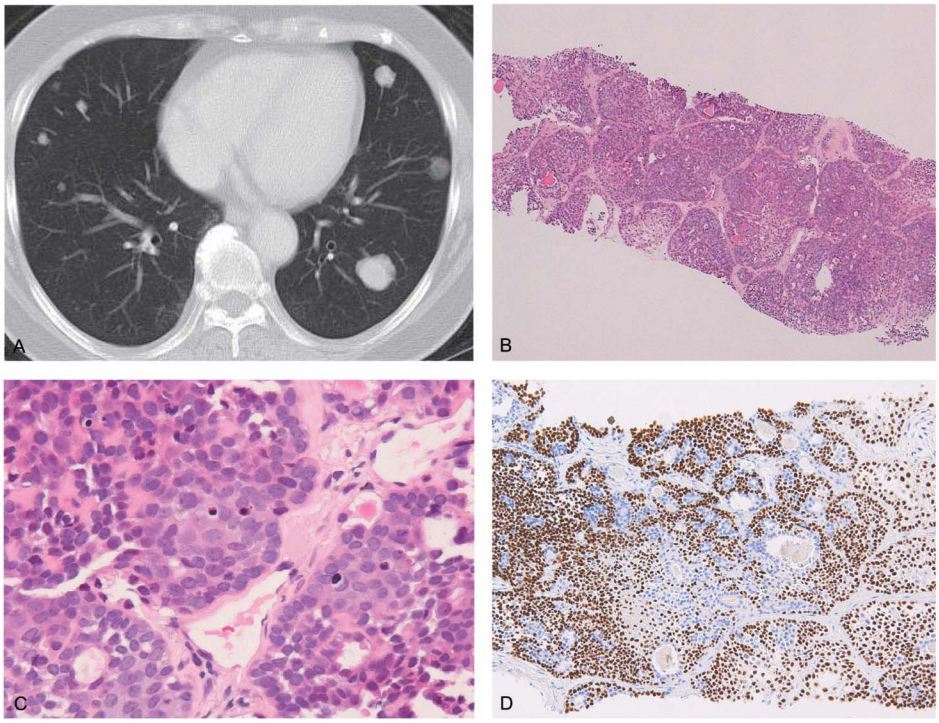

FIGURE 3. A, CT showing multiple nodular shadows in the bilateral lung field. B, Hematoxylin and eosin staining of the lung biopsy specimen revealing a solid lesion with a fibrous partition and numerous tubules (×40). C, Tubules within the solid lesions showed evidence of decapitation secretion (hematoxylin and eosin ×400). D, Tumor cells, with the exception of those lining the tubular structures, were positive for p63 expression (×100).

with our case. In light of previous reports, it is important to have a high clinical suspicion of ADPA when digital lesions such as soft tissue infections, cysts (ganglion, inclusion, mucous), calluses, pyogenic or foreign body granulomas, hemangiomas, osteomyelitis, gout, and cutaneous or subcutaneous tumors (adnexal tumors, squamous cell carcinomas, giant-cell tumors, or metastases of papillary adenocarcinoma originating in the colon, thyroid, or breast) present.

The local recurrence rate in patients with subsequent reexcision or digital amputation was only 5% versus 50% in patients without subsequent reexcision or amputation.[2] Therefore, these data indicate that complete excision of the neoplasm should be performed. In our case, we did not perform reexcision after initial resection, which might have resulted in the local recurrence.

Because lymph node metastases have been reported to occur in 9%–12% of cases,[2,6] the use of sentinel lymph node biopsy for ADPA has been recommended[7–11]; however, for such rare tumors the effectiveness is not yet clear and additional study is needed.

Distant metastases have been reported to occur in 14%–22% of cases.[2,6] Duke and others reported that 10% of patients treated by reexcision or amputation and 9% of patients not treated by reexcision or amputation developed subsequent metastases. Thus, this suggests that having a reexcision or amputation does not absolutely protect against metastatic disease. The most frequent site of distant metastasis is the lung parenchyma. Some cases (2%–17%) had distant metastases in the absence of lymph node metastases, as with our case. Thus, taking into consideration the potential not only for lymphatic metastasis but also hematogenous metastasis, imaging tests such as chest x-rays should be performed on patients after surgery. Aggressive surgical therapy for limited metastatic disease seems warranted for the limited number of cases studied, although no standard effective treatment of extensive metastatic disease is yet apparent.[2]

The typical histologic features of ADPA include a multinodular, solid, and cystic growth pattern with papillae formation, whereas some tumors are essentially only solid, lacking cystic space.[2] Characteristic of all lesions is a pattern of fused back-to-back tubules lined by cuboidal to low columnar epithelial cells, surrounded by an outer myoepithelial layer. The tumors are just as likely to be well circumscribed as not. Recurrent and metastatic tumors vary from cystic to solid, but all cases focally retain a pattern of fused back-to-back tubules. In our case, the primary and recurrent tumors were well circumscribed and solid, lacking cystic space. All tumors (the primary tumor, locally recurrent tumor, and lung metastases) presented with a pattern of fused back-to-back tubular structures and myoepithelial differentiation was confirmed by immunohistochemical examination. Suchak et al[6] suggested that the presence of tumor-associated myoepithelial cells should not be construed as an indication of benignity, but rather another indication for a primary adnexal tumor should metastasis be a clinical or diagnostic consideration.

With regard to differential diagnosis, we considered that this case shares morphological common points with spiradenocarcinoma. These include that both tumors consist of neoplastic cells with atypical nuclei arranged in multinodular epithelial aggregates including tubular structures, and that both tumors present with dilated vascular spaces containing erythrocytes, hemorrhage into the lesions of tumors,[12] foci of squamous differentiation, and small hyalinized globules in the stroma.[13] However, these findings are also seen in ADPA.[2,6]

Because spiradenocarcinoma generally arises from a long-standing spiradenoma, the histopathologic features of spiradenocarcinoma include transitional zones that feature benign areas merging into malignant areas.[13] However, the tumors in our case lacked the transitional zone and apparent benign area, but presented with back-to-back tubular structures surrounded by an outer myoepithelial layer and papillary structures, which are findings characteristic of ADPA. In regard to clinical features, ADPA exclusively occurs on digits,[2,5,6] whereas spiradenocarcinoma is extremely rare at this site.[14,15] Taken together, we conclusively considered these findings to indicate that our case is ADPA rather than spiradenocarcinoma.

In summary, we described a rare case of ADPA that had an ominous course. In histological findings, the primary and recurrent tumors were well circumscribed and solid, lacking cystic space. All specimens presented with a pattern of back-to-back tubules and myoepithelial differentiation. Because clinical suspicion ultimately leads to a histologic diagnosis, it is important to have a high clinical suspicion of ADPA when digital lesions present.

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