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Next-generation sequencing reveals rare genomic alterations in aggressive digital papillary adenocarcinoma☆,☆☆

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ABSTRACT

Aggressive digital papillary adenocarcinoma (ADPA) is a rare cutaneous adnexal neoplasm that occurs on the fingers, toes, palms, and soles. It is characterized by aggressive biological behavior, with a relatively high potential for local recurrence (30%-40% of cases) and distant metastasis (up to 14%). This retrospective study assessed the mutation status of ADPA lesions to identify possible therapeutic targets. We performed comprehensive genomic profiling of 9 ADPA cases that had been identified in our database. We identified a BRAF-V600E (BRAF c.1799T>A p.V600E) mutation in 1 patient (11%). Complete surgical excision is the treatment of choice for ADPA; however, there are no uniform diagnostic guidelines or recognized effective treatments for metastasis, and no therapeutic targets have been identified. Targeted therapy may be a treatment option for patients with metastatic ADPA if a relevant oncogene mutation is identified. Further studies with a larger sample size are required to confirm our findings and identify more molecular mechanisms.

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1. Introduction

Aggressive digital papillary adenocarcinoma (ADPA) is a rare cutaneous sweat gland malignancy with high potential for aggressive local invasion, resulting in a high recurrence rate. It was first described by Helwig [1] as "eccrine acrospiroma" in 1984. The term *aggressive digital papillary adenocarcinoma* was coined by Duke et al in 2000 [2].

Most ADPA patients are middle aged (mean age, 43 years), with a wide age range of 14 to 67 years; there is a strong male preponderance (approximate male to female ratio of 15:1) [1,2]. Aggressive digital papillary adenocarcinoma usually presents as a slow-growing (a few weeks to years) painless solitary mass of 10 to 40 mm (mean, 20 mm). The predominant site of involvement is the distal portions of the digits, followed by the webspaces of the hand (more commonly than the feet). The diagnosis is often missed or delayed because the disease is clinically inconspicuous.

Three large histopathologic studies have been performed of ADPA, including 1 by our research group [3-5]. The pathologic study by Kao et al in 1987 [4] described 57 patients with both ADPA and carcinoma. The lesions were classified as benign or malignant based on histologic findings, such as poor glandular differentiation; cellular atypia; necrosis; pleomorphism; lymphovascular invasion; and infiltration into the adjacent structures, such as the bone and soft tissue. Later, the same group retrospectively analyzed the same data with a longer follow-up period and concluded that all lesions should be regarded as adenocarcinomas because none of the histologic or clinical parameters studied were predictive of recurrence or metastasis.

Histologically, ADPA is usually a poorly circumscribed multilobular lesion with a focally infiltrative border involving the dermis alone or the dermis and subcutis. It is composed of solid and cystic components in variable proportions. The solid portion consists of tubuloalveolar and ductal structures, with areas of papillary projections protruding into the cystic lumina. The solid structures are lined by cuboidal or columnar epithelium and surrounded by an outer myoepithelial layer. The glandular lumina may contain eosinophilic secretory material. There are usually mild to moderate (with focally severe) cytologic atypia and scattered mitotic figures. The background stroma may vary from thin fibrous to dense hyalinized collagen. In some cases, there is poor glandular differentiation, focal necrosis, lymphovascular invasion, or invasion of the underlying soft tissues and bone.

Immunohistochemically, ADPA tumor cells are positive for pancytokeratin, and luminal cells express carcinoembryonic antigen, epithelial membrane antigen, and S-100 protein. The myoepithelial layers are highlighted by calponin, smooth muscle actin, or p63.

There is no standard treatment for ADPA, especially for metastatic disease. To our knowledge, no specific molecular findings, such as translocations or mutations, have been identified that would be helpful in the differential diagnosis or be a therapeutic target in cases of widespread disease.

Advances in DNA sequencing, such as next-generation sequencing, provide massive parallel throughput and data volumes that eclipse the nucleic acid information content possible with other technologies, making it feasible to perform extensive genome analyses of groups of individuals, including analyses of sequence differences, polymorphisms, mutations, copy number variations, epigenetic variations, and transcript

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Table
Demographic, clinicopathologic, and molecular characteristics of 9 patients with ADPA

Case	Age (y)/sex	Location	SLN status	Follow-up (mo)	Sequenom
1	52/F	Third finger	Negative	NED, 36	No mutations
2	48/F	Ankle	Negative	NED, 48	No mutations
3	41/M	Index finger	Positive (2/5)	NED, 54 mo	No mutations
4	58/M	Fifth finger	Negative	NED, 6	No mutations
5	39/F	Heel	Positive (1/4)	NED, 18	No mutations
6	58/F	Fifth finger	Positive	NED, 6	No mutations
7	57/M	Third finger	N/A	NED, 36	No mutations
8	40/M	Third finger	N/A	DOD, lung metastasis	No mutations
9	31/F	Ankle	Negative	NED, 12	BRAF c.1799T>A p.V600E

Abbreviations: SLN, sentinel lymph node; NED, no evidence of disease; DOD, died of disease.

abundance. Biomarker discovery is an attractive potential application of this new technology.

In this retrospective study, we used a platform that probes 190 common, potentially targetable oncogenic mutations to identify possible therapeutic targets in the molecular profiles of tumor tissues in a small ADPA cohort; our studies were focused mainly on targets in metastatic disease, for which there is no effective treatment.

2. Materials and methods

2.1. Tissue specimens

After obtaining institutional review board approval, we retrieved primary formalin-fixed, paraffin-embedded ADPA specimens, along with patients' demographic information, histologic findings, and clinical outcomes, from the files of the Department of Dermatopathology at The University of Texas MD Anderson Cancer Center (Houston, TX).

2.2. Mutation analysis

Genomic DNA was isolated from 5-μm-thick paraffin sections that had undergone de-paraffinization and proteinase K treatment using the Epicentre Master pure DNA and RNA isolation kit (Illumina Biotechnologies, Santa Clara, CA) according to the manufacturer's protocol. The Sequenom MALDI TOF mass array platform was used to profile 190 common oncogenic point mutations in 50 genes. One microgram of genomic DNA per sample was submitted to the Sequencing and Microarray Facility at our institution. Each specimen was tested in duplicate for every mutation in the Sequenom panel.

2.3. Immunohistochemistry

Slides were loaded on the Ventana BenchMark ULTRA (Ventana, Tucson, AZ) and tested with diaminobenzidine IHC detection kit from the mutation-specific anti-BRAF V600E mouse monoclonal antibody (Ventana, Tucson, AZ) according to the manufacturer's protocols.

3. Results

3.1. Clinical and histologic data

We identified 9 ADPA cases. The patients' clinicopathologic characteristics are given in the Table. Mostpatients were middle aged (mean age, 37 years; range, 31-58 years), and there was a slight female

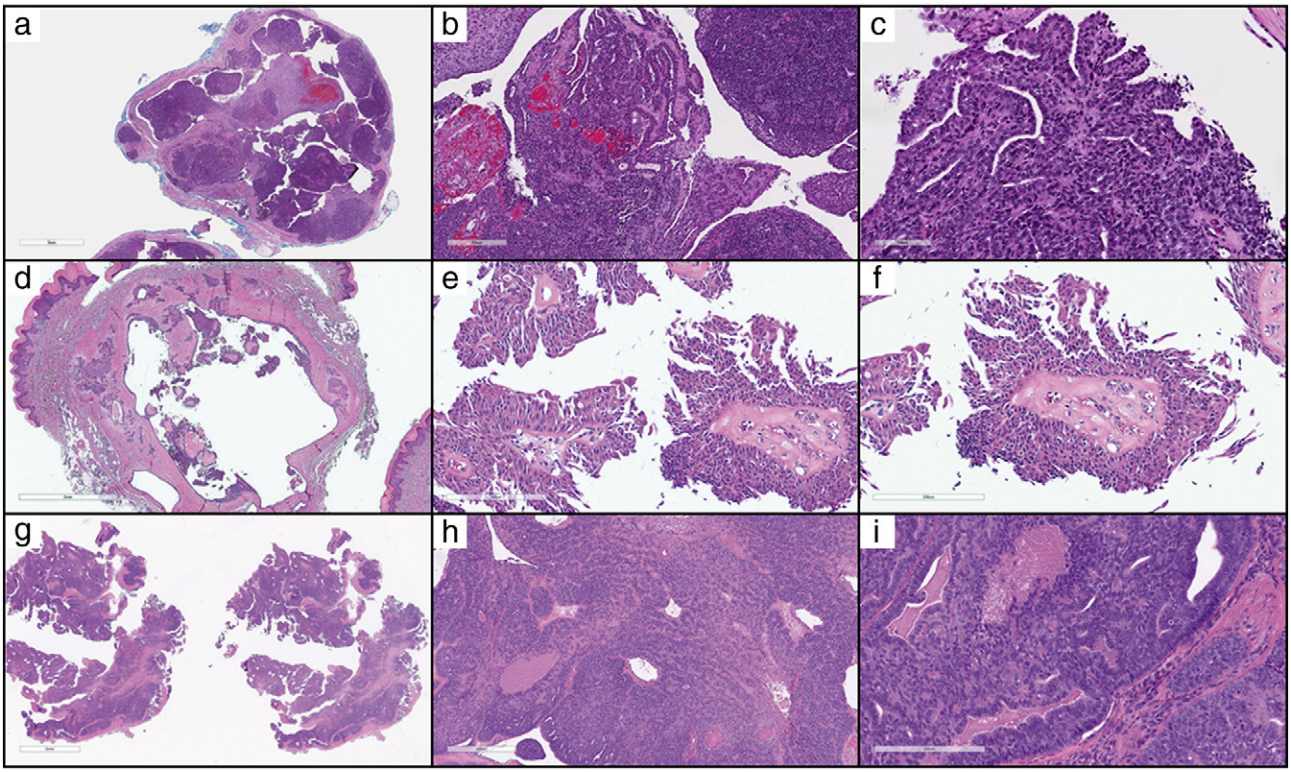

Fig. 1. Hematoxylin and eosin–stained sections of several lesions show a dermal multilobular tumor that is predominantly papillary (A-C), papillary structures within a cystic component (D-F), and solid structures with cystic changes (G-I). Minimal cytologic atypia and stromal hyalinization are visible.