

Sclerosing Polycystic Adenoma of Salivary Glands: A Novel Neoplasm Characterized by PI3K-AKT Pathway Alterations-New Insights Into a Challenging Entity

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The American Journal of Surgical Pathology

46(2):p 268-280, February 2022. | DOI: 10.1097/PAS.0000000000001807

PMID: 34510113

Abstract

Sclerosing polycystic adenoma (SPA) is a rare salivary gland neoplasm originally thought to represent a non-neoplastic lesion. Recently we have encountered an index case of apocrine intraductal carcinoma of parotid gland of 62-year-old man with invasive salivary duct carcinoma component arising from SPA, a combination of tumor entities that has never been published so far. Here, we further explore the nature of SPA by evaluating 36 cases that were identified from the authors' consultation files. The patients were 25 females and 11 males aged 11 to 79 years (mean, 47.8 y). All tumors originated from the parotid gland. Their size ranged from 11 to 70 mm (mean, 28 mm). Histologically, all cases revealed characteristic features of SPA, such as lobulated well-circumscribed growth, focal hyalinized sclerosis, presence of large acinar cells with abundant brightly eosinophilic intracytoplasmic granules, and ductal components with variable cytomorphologic characteristics, including foamy, vacuolated, apocrine, mucous, clear/ballooned, squamous, columnar and oncocyte-like cells. In all cases, there were foci of intraluminal solid and cribriform intercalated duct-like epithelial proliferations with variable dysplasia which were positive for S100 protein and SOX10, and fully enveloped by an intact layer of myoepithelial cells. In addition, 14/36 cases (39%) had focal intraductal cribriform and micropapillary apocrine-type dysplastic epithelial structures composed of cells positive for androgen receptors and negative for S100/SOX10. The intraductal proliferations of both types showed focal mild to severe dysplasia in 17 cases (17/36; 47%). Two cases showed overt malignant morphology ranging from high-grade intraductal carcinoma to invasive carcinoma with an apocrine ductal phenotype. Next generation sequencing using ArcherDX panel targeting RNA of 36 pan-cancer-related genes and/or a TruSight Oncology 170/500 Kit targeting a selection of DNA from 523 genes and RNA

from 55 genes was performed. Tumor tissue was available for molecular analysis in 11 cases, and 9 (9/11; 82%) of them harbored genetic alterations in the PI3K pathway. Targeted sequencing revealed *HRAS* mutations c.37G>C, p.(Gly13Arg) (2 cases) and c.182A>G, p.(Gln61Arg) (2 cases), and *PIK3CA* mutations c.3140A>G, p.(His1047Arg) (3 cases), c.1633G>A, p.(Glu545Lys) (1 case), and c.1624G>A, p.(Glu542Lys) (1 case). Moreover, mutations in *AKT1* c.49G>A, p.(Glu17Lys) and c.51dup, p.(Tyr18ValfsTer15); c.49_50delinsAG, p.(Glu17Arg) (as a double hit) were found (2 cases). In addition, germinal and somatic mutation of *PTEN* c.1003C>T, p.(Arg335Ter); c.445C>T, p.(Gln149Ter), respectively, were detected. Gene fusions were absent in all cases. These prevalent molecular alterations converging on one major cancer-related pathway support the notion that SPA is a true neoplasm with a significant potential to develop intraluminal epithelial proliferation with apocrine and/or intercalated duct-like phenotype. The name SPA more correctly reflects the true neoplastic nature of this enigmatic lesion.