Sclerosing Polycystic Adenosis of the Parotid Gland: Report of a Bifocal, Paucicystic Variant with Ductal Carcinoma in situ and Pronounced Stromal Distortion Mimicking Invasive Carcinoma

Fredrik Petersson · Puay Hoon Tan ·
Jacqueline Siok-Gek Hwang

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Abstract We present a case (female patient, age 45 years) with a bifocal, paucicystic variant of sclerosing polycystic adenosis of the parotid gland with cribriform ductal carcinoma in situ (DCIS) and pronounced stromal distortion affecting the in situ component to such an extent that it gave a distinct impression of intralesional invasive adenocarcinoma. P63—and calponin-positive myoepithelial cells were present in the periphery of the acini and ducts in the benign component, somewhat discontinuously in the DCIS-component, and even in the periphery of the small irregular atypical cell nests that appeared infiltrative on the haematoxylin and eosin stained sections. Strong cytoplasmic immunoreactivity for GCDFP-15 was detected in the benign component with a variable, patchy and mostly weak positivity in the DCIS. More than 90% of the cells in the DCIS component displayed strong nuclear immunoreactivity for androgen receptors and 10% of the benign ducts showed positivity. Weak to moderate nuclear immunoreactivity for estrogen receptors was seen in 30% of cells in the benign ductal component whereas the DCIS was negative. Occasional cells in the adenosis-component were weakly positive for PR. The proliferative activity (Mib-1/Ki-67) was low (1–2%) in the benign component whereas increased proliferation was seen in the DCIS and in the areas with pseudoinfiltration which also featured atypical mitoses.

Keywords Sclerosing polycystic adenosis · Salivary gland · Carcinoma

Introduction

Sclerosing polycystic adenosis (SPA) is a rare tumorous condition of the salivary glands with characteristic histological features reminiscent of mammary fibrocystic disease/apocrine adenosis. SPA was first described by Smith et al. in 1996 in a series of 9 cases [1]. Since then just over 50 cases in a few larger series and several case reports have been published [2–14]. The most common site is the parotid gland with less frequent occurrence in the submandibular gland and intraoral minor salivary glands. SPA is most frequently seen in women and occurs in a wide age spectrum including infants and the elderly. Reportedly, the mean age at presentation is around 40 years. SPA is most commonly seen as an isolated pathologic finding in the salivary gland, but cases associated with recurrent pleomorphic adenoma, oncocytoma and a combined sebaceous lymphadenoma-Warthin's tumor are on record [5]. Similarly, SPA is most often seen as a single lesion, but rare cases with multifocality have been published [5]. The reported size range of SPA is between 1 and 12 cm. The nature of this lesion was initially believed to be reactive/inflammatory in nature [1]. However, using HUMARA-analysis, later investigators have shown that SPA is a clonal process [12] and not infrequently harbors intraductal dysplastic epithelial proliferations including cases where the degree of atypia and structural changes reached that of ductal carcinoma in situ (DCIS) [2, 4, 5, 8, 12, 13]. To date no case of invasive carcinoma arising in SPA has been reported. In this paper we present the clinicopathological features of one case of bifocal SPA with DCIS and a prominent stromal distortion

F. Petersson (✉)
Department of Pathology, National University Health System,
5 Lower Kent Ridge Road, Singapore 119074, Singapore
e-mail: fredrikpetersson@live.se

P. H. Tan · J. S.-G. Hwang
Department of Pathology, Singapore General Hospital,
Singapore, Singapore

of the in situ component to such an extent that the features on hematoxylin and eosin-stained sections were highly suspicious for intralesional invasive adenocarcinoma.

Case Report

A previously healthy 45 year old female presented with an asymptomatic nodule in the right parotid gland. A fine needle aspiration cytology (FNAC) biopsy was done and subsequently, a superficial parotidectomy was performed. The case was recently diagnosed and thus, no meaningful follow-up is available.

Materials and Methods

The whole specimen was fixed in neutral formalin, embedded in paraffin, 4 µm thick sections were cut and stained with hematoxylin and eosin (H&E). An immunohistochemical study with commercial antibodies using protocols according to the manufacturers' recommendation was employed. Antibodies to the following antigens were included: estrogen- (ER) (Neomarker ThermoScientific; SP1, 1:100, Biomed Diagnostics, Singapore), androgen- (AR) (Novocastra; AR27, 1:30, Chemoscience, Singapore), progesterone- (PR) (Neomarker ThermoScientific; SP2, 1:300, Biomed Diagnostics, Singapore) receptors, p63 (DAKO; 4A4, 1:50, Biomed SPD, Singapore), calponin (DAKO; CALP, 1:100, Biomed SPD, Singapore), Ki-67 (DAKO; Mib-1, 1:100, Biomed SPD, Singapore) and gross cystic disease fluid protein (GCDFF-) 15 (Neomarker ThermoScientific; 23A3, 1:150, Biomed Diagnostics, Singapore). Periodic-acid Schiff (PAS)-stains with and without diastase digestion were performed.

Results

FNAC

The smears showed epithelial cells in acinar or trabecular arrangements. Some cells exhibited mild nuclear atypia and had ample granular to microvacuolated cytoplasm. Cells in ductal arrangements were also observed. A small number of lymphoid cells and naked nuclei were present in the background. No high-grade malignant cells were identified. An excision to exclude an acinic cell carcinoma was suggested.

Gross Features

On gross inspection, two well-circumscribed, firm, whitish nodules measuring 15 and 7 mm were identified. The

non-lesional salivary gland tissue appeared unremarkable and surgical margins were not involved by the nodules (confirmed on microscopical evaluation).

Routine Histology

Histologic examination revealed two sharply demarcated, unencapsulated nodules surrounded by unremarkable salivary gland parenchyma (Fig. 1a). The nodules contained dense sclerotic collagenous connective tissue with some scattered mature adipocytes. A predominantly lobular proliferation of small acini, some small caliber ducts and a few dilated larger ducts (in the larger nodule) were present (Fig. 1b). Dispersed and small aggregates of lymphocytes and plasma cells were seen in the stroma. The acinar proliferation was composed of small lesional cells with monomorphic nuclei having inconspicuous nucleoli. The cytoplasm of the cells frequently contained numerous slightly basophilic to deeply eosinophilic (PAS-positive, diastase resistant) globules of varying sizes (from barely discernible to large irregular with a coarse quality) (Fig. 1c). Intermixed with these cells were lesional cells with the same nuclear features, but with a different character of the cytoplasm, displaying a microvacuolated structure which, when pronounced, imparted a clear character (Fig. 1d). No nuclear indentations were identified. Frequently, cells with intermediate (granulated and microvacuolated) cytoplasm were identified. Hence, there was a gradual transition of acinar cells with the above mentioned cytoplasmic features. The histological features of these acinar cells were reminiscent of the “sebocrine”-type metaplasia in the breast, as described by Tavassoli. [15] The smaller ductular component was histologically uncharacteristic and the few slightly cystically dilated ducts (only seen in the larger nodule) were focally rimmed by foam cells. In the center of the larger nodule, there was a 3 mm sized area composed of dilated ducts with a radically different character. These expanded ducts were surrounded by a paucicellular fibromyxoid stroma and contained an atypical epithelial proliferation with scattered mitotic figures in cribriform arrangements conforming to DCIS (Figs. 1e, 2d). The atypical cells had enlarged irregular hyperchromatic nuclei with focal prominent nucleoli, abundant slightly eosinophilic cytoplasm and displayed scattered mitotic figures (including atypical forms). Focally, the DCIS displayed small areas of necrosis. Immediately adjacent to the DCIS, irregular, distorted nests and small tubules composed of atypical epithelial cells with enlarged nuclei and similar cytoplasmic features as present in the DCIS-component were identified (Fig. 1f).

Fig. 1 **a–e** Low-power examination shows two sharply demarcated, unencapsulated nodules surrounded by unremarkable salivary gland parenchyma (**a**). The nodules are composed of a predominantly lobular proliferation of small acini, some small caliber and a few dilated larger ducts embedded in a dense sclerotic connective tissue (**b**). The acinar cells feature cytoplasmic eosinophilic globules (**c**) intermixed with cells with microvacuolation which, when pronounced, impart a clear character (**d**). In the larger nodule,

expanded ducts with enlarged irregular and hyperchromatic nuclei and abundant slightly eosinophilic to vacuolated cytoplasm in cribriform arrangements (DCIS) are seen (**e**). Immediately adjacent to the DCIS, irregular, distorted nests and small tubules composed of atypical epithelial cells with similar cytomorphological features as present in the DCIS are seen. Note one atypical mitotic figure to the right (**f**)

Immunohistochemistry

The immunohistochemical study showed strong cytoplasmic immunoreactivity for GCDPF-15 in the benign small caliber and slightly dilated (larger) ducts as well as the adenosis component with a distinct diminution of reactivity in the cells that featured vacuolated to clear cytoplasm. The DCIS component displayed a variable, patchy and mostly weak positivity with occasional atypical cells showing up to moderate staining intensity (Fig. 2a). Weak to moderate nuclear immunoreactivity for ER was seen in 30% of the cells in the benign component. The DCIS was negative. Occasional cells in the adenosis component were weakly positive for PR, but no immunoreactivity was seen in the ductal or DCIS-components. 10% of the benign ducts displayed moderate and strong immunoreactivity for AR. Scattered acinar cells were weakly positive whereas >90% of the cells in the DCIS showed strong nuclear immunoreactivity (Fig. 2b). P63-positive (myoepithelial) nuclei were present in the periphery of the acini and ducts in the benign component and somewhat discontinuously in the DCIS-component. These p63-positive myoepithelial nuclei were also present in the periphery of the small irregular nests composed of atypical cells in close association to the DCIS. In fact, even when atypical single cells were seen in the stroma, small oval, p63-positive nuclei were discerned decorating the peripheral aspect of these cells (Fig. 2c). The staining pattern for calponin was virtually identical to

that of p63 (data not shown). The proliferative activity (Mib-1/Ki-67) was low (1–2%) in the benign (both ductular and adenosis-) components whereas a significantly increased proliferation was seen in the DCIS and in the small groups of atypical cells (Fig. 2d).

Discussion

Sclerosing polycystic adenosis is a very rare tumorous lesion of salivary glands featuring a characteristic set of histomorphological changes including acinar and ductal components with variable cytomorphological characteristics, including foamy, clear, microvacuolated, apocrine, mucous and squamous cells, embedded in a sharply delineated, dense, mildly chronically inflamed sclerotic collagenous stroma. Initially SPA was felt to be a reactive, “pseudoneoplastic” inflammatory process [1, 16]. The case presented herein showed bifocal involvement of a parotid gland with light microscopical features conforming to SPA. Based on the verbal descriptions and presented photomicrographs of previous cases of SPA, our case displayed unusual (paucicystic) features with only a few mildly dilated ducts exclusively confined to the larger nodule. With time, cases of SPA with superimposed dysplastic epithelial changes including cases with DCIS were reported [4, 5, 13, 14] and in 2006, using the HUMARA methodology, Skalova et al. could establish clonality

Fig. 2 Photomicrographs from the immunohistochemical study showing (a) the DCIS component with a variable, patchy and mostly weak positivity for GCDFP-15. Occasional cells show up to moderate staining intensity (*upper left*). The benign acinar component is strongly positive (*lower right*). Most of the cells in the DCIS component are strongly positive for androgen receptor (b). In addition to being present around the DCIS component, p63-positive

(myoepithelial) nuclei are also present in the periphery of the small irregular nests composed of distinctly atypical cells. Note the positive oval nuclei decorating the peripheral aspect of a highly atypical cell (c). The proliferative activity (Mib-1/Ki-67) is increased in the DCIS component and in the small groups of atypical cells. Note the atypical (hexapolar) mitotic figure slightly to the left (d)

(non-random pattern of inactivation of X-chromosomes) in six out of six successfully analyzed (female) cases. All these cases displayed areas with epithelial atypia (“nuclear pleomorphism, ranging in severity from mild up to severe”) [12]. Hence it is still an open question whether cases of SPA without atypical epithelial proliferations are also clonal. In our case, the larger nodule exhibited a central 3 mm large area with dilated ducts featuring a distinctly atypical cribriform proliferation including both mitotic activity and focal necrosis, which to our eyes clearly reached the threshold for DCIS. Both in the adenosis- and in the small ductal components as well as in areas with atypical epithelial (ductal) proliferation, a “pseudoinfiltrative” pattern related to stromal distortion of the epithelial structures has been reported previously and immunohistochemical studies have demonstrated the presence of myoepithelial cells in these instances [5, 12]. So far no invasive carcinoma arising in SPA has been described. Also in our case was there significant stromal distortion, with small irregular nests of atypical cells, at times composed of only a few cells, present immediately adjacent to the DCIS component. These small aggregates of cells gave us the impression of invasive carcinoma, but

benign appearing, ovoid nuclei with distinct positivity for p63 were detected, thus establishing the presence of myoepithelial cells associated with these irregular atypical cells nests which thereby strongly suggested a pseudoinfiltrative pattern rather than progression to invasive carcinoma. Moreover, in support of a non-invasive interpretation of this phenomenon, the light microscopical character of these small irregular cell nests were virtually identical to the atypical cells present in the clear cut DCIS-component on the routine stained sections.

Regarding the presence of ER in both the benign and atypical components and the presence of GCDFP-15 in the acinar component in our case, our findings are in accordance with previously published data [12, 13]. But in contrast to previous authors, we could not demonstrate any significant positivity for PR. We could not find any previous data on positivity for GCDFP-15 in the dysplastic or DCIS components. In the case presented herein, there was a variable but still clearly focal discernible immunoreactivity for GCDFP-15 in the DCIS. In keeping with the apocrine character of the DCIS in our case, we could demonstrate strong nuclear immunoreactivity for AR in the majority of cells.

The differential diagnostic considerations for SPA has been discussed and commented on by previous authors [1, 5, 13, 16] and include acinic cell carcinoma (ACC), polycystic (dysgenetic) disease, sclerotic sialadenitis, salivary duct carcinoma including the low-grade variant (low-grade cribriform cystadenocarcinoma) and adenocarcinoma NOS. Given the yield of cells with predominantly acinar differentiation, mild nuclear abnormalities and the absence of cytologic cyst-material, the differential diagnosis of an ACC on FNAC is problematic. The difficulties pertaining to the cytological differential diagnoses of SPA have been discussed and commented on by other investigators [3, 4, 6, 8, 11]. However, in contrast to the cytological findings, the histological features of SPA are in our opinion highly characteristic. Awareness of these allows for a diagnosis of this lesion based on hematoxylin and eosin stained sections with the caveat that an immunohistochemical study focusing of myoepithelial cells may be necessary to reveal the pseudoinfiltrative nature of atypical epithelial nests, as highlighted by the case presented herein and in other similar reported cases. Also, a metastasis should be excluded when confronted with SPA harbouring cells with a carcinomatous appearance. However, once the pseudoinfiltrative nature of such carcinomatous cells is established on immunohistochemistry, this becomes less imperative.

Our case is recently diagnosed with no meaningful follow-up. Recurrences, sometimes multiple, have been reported quite frequently (29% as summarized by Gnepp et al.) [16]. The proposed mechanism behind this is either incomplete surgical resection and/or multifocal disease [5]. Since our patient had bifocal disease and was subjected to a superficial parotidectomy (with the possibility of residual foci present in the deep lobe), our patient is undergoing close follow-up.

In summary, we present a rare case of a bifocal, paucicystic variant of sclerosing polycystic adenosis of the parotid gland with DCIS and pronounced stromal distortion of the in situ component mimicking intralesional invasive adenocarcinoma. This case highlights the value/indispensability of immunohistochemistry focusing on myoepithelial cells in establishing an unequivocal diagnosis of invasive carcinoma in lesions with DCIS and pronounced stromal fibrosis.

References

1. Smith BC, Ellis GL, Slater LJ, Foss RD. Sclerosing polycystic adenosis of major salivary glands. A clinicopathologic analysis of nine cases. *Am J Surg Pathol*. 1996;20:161–70.
2. Bharadwaj G, Nawroz I, O'regan B. Sclerosing polycystic adenosis of the parotid gland. *Br J Oral Maxillofac Surg*. 2007; 45:74–6.
3. Etit D, Pilch BZ, Osgood R, Faquin WC. Fine-needle aspiration biopsy findings in sclerosing polycystic adenosis of the parotid gland. *Diagn Cytopathol*. 2007;35:444–7.
4. Fulciniti F, Losito NS, Ionna F, Longo F, Aversa C, Botti G, Foschini MP. Sclerosing polycystic adenosis of the parotid gland: report of one case diagnosed by fine-needle cytology with in situ malignant transformation. *Diagn Cytopathol*. 2010;38:368–73.
5. Gnepp DR, Wang LJ, Brandwein-Gensler M, Slootweg P, Gill M, Hille J. Sclerosing polycystic adenosis of the salivary gland: a report of 16 cases. *Am J Surg Pathol*. 2006;30:154–64.
6. Gupta R, Jain R, Singh S, Gupta K, Kudesia M. Sclerosing polycystic adenosis of parotid gland: a cytological diagnostic dilemma. *Cytopathology*. 2009;20:130–2.
7. Gurgel CA, Freitas VS, Ramos EA, Santos JN. Sclerosing polycystic adenosis of the minor salivary gland: case report. *Braz J Otorhinolaryngol*. 2010;76:272.
8. Imamura Y, Morishita T, Kawakami M, Tsuda G, Fukuda M. Sclerosing polycystic adenosis of the left parotid gland: report of a case with fine needle aspiration cytology. *Acta Cytol*. 2004;48: 569–73.
9. Meer S, Altini M. Sclerosing polycystic adenosis of the buccal mucosa. *Head Neck Pathol*. 2008;2:31–5.
10. Noonan VL, Kalmar JR, Allen CM, Gallagher GT, Kabani S. Sclerosing polycystic adenosis of minor salivary glands: report of three cases and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2007;104:516–20.
11. Perottino F, Barnoud R, Ambrun A, Poupart M, Pignat JC, Merrot O. Sclerosing polycystic adenosis of the parotid gland: diagnosis and management. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2010; 127:20–2.
12. Skalova A, Gnepp DR, Simpson RH, Lewis JE, Janssen D, Sima R, Vanecek T, Di Palma S, Michal M. Clonal nature of sclerosing polycystic adenosis of salivary glands demonstrated by using the polymorphism of the human androgen receptor (HUMARA) locus as a marker. *Am J Surg Pathol*. 2006;30:939–44.
13. Skalova A, Michal M, Simpson RH, Starek I, Pradna J, Pfaltz M. Sclerosing polycystic adenosis of parotid gland with dysplasia and ductal carcinoma in situ. Report of three cases with immunohistochemical and ultrastructural examination. *Virchows Arch*. 2002;440:29–35.
14. Mackle T, Mulligan AM, Dervan PA, O'dwyer T. Sclerosing polycystic sialadenopathy: a rare cause of recurrent tumor of the parotid gland. *Arch Otolaryngol Head Neck Surg*. 2004;130: 357–60.
15. Tavassoli F. Pathology of the breast. Second edition. 1992. p. 121.
16. Gnepp DR. Sclerosing polycystic adenosis of the salivary gland: a lesion that may be associated with dysplasia and carcinoma in situ. *Adv Anat Pathol*. 2003;10:218–22.