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Editorial

Low-Grade Adenosquamous Carcinoma [LGASC] of the Breast and Syringomatous Adenoma of the Nipple [SAN]: A Single Entity with Two Homes?

Kanthan R* and Senger JL

Department of pathology, University of Saskatchewan, Canada

***Corresponding author**

Kanthan Rani SktnHR, Department of pathology, University of Saskatchewan, Canada, Email: Rani.Kanthan@saskatoonhealthregion.ca

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EDITORIAL

Metaplastic breast cancer characterized by the presence of non-epithelial cellular elements is rare: representing less than 1% of breast carcinomas of typically highly aggressive, heterogeneous, chemo-resistant malignant tumors [1]. Low grade adenosquamous carcinoma [LGASC] is a rare variant of metaplastic carcinoma that is also characterized as a subgroup of triple negative breast cancers. Initially identified by Rosen and Ernsberger in 1987, LGASC continues to be reported sporadically as case reports or case series in the published English literature [2,3]. Clinically, LGASC occur in patients of any age (20-85 years) and more commonly presents as a palpable mass rather than an incidental finding on mammography [2]. LGASC is locally invasive, yet, despite a 'triple-negative' immunoprofile, these lesions are characterized by an indolent behavior with axillary nodal and /or systemic metastases being extremely uncommon and patients usually have an overall favorable prognosis [1].

Accurate diagnosis of LGASC preoperatively is often impossible at fine-needle aspiration cytology (FNAC) due to the paucity of classical cytological features of malignancy [4]. Certain features potentially suggestive of LGASC on FNAC include the presence of glandular/ductal epithelial cells and 'squamoid' elements admixed with fibroblast like nondescript spindle-cells. The presence of moderate nuclear atypia and mild cellular pleomorphism differentiates this lesion from fibroadenoma and carcinosarcoma [5]. Diagnosis by core biopsy is also challenging as the overall architectural histological features are usually not appreciable. Similarly, the utility of intraoperative frozen section is low often due to possible fragmentation and limited sampling [4,6]. Histologic findings suggestive of LGASC include the presence of epithelial -glandular/ductal cells with squamous differentiation embedded in a dense collagenized stroma with a stellate/infiltrating configuration and poorly defined margins. Small tubular glands with low-grade cytologic atypia and rare mitoses with a lack of necrosis may be recognized; though, precise identification is often challenging [7]. The adeno-carcinomatous components can be seen extending between intact ducts and lobules, reflecting the infiltrative nature of this tumor. The stroma appears to emerge from the epithelial elements, with contents ranging from collagenous/paucicellular to mildly cellular, thereby suggesting spindle cell metaplasia [4]. The use of immunohistochemistry as a diagnostic tool for LGASC is limited, with a paucity of specific and sensitive antibodies.

Accurate identification of LGASC from 'mimickers' is often challenging; such lesions include benign fibrosclerosing lesions (sclerosing adenosis, radial scar), tubular carcinoma, and syringomatous adenoma of the nipple (SAN) [4]. Differentiation of LGASC from fibrosclerosing lesions can be made by the absence of lobular configuration in LGASC on the excision biopsy specimen [4]. Histologically, LGASC differs from tubular carcinoma by the presence of squamous differentiation. Distinguishing between LGASC and SAN, however, remains less well understood.

Traditionally, LGASC and SAN have been regarded as separate entities, yet accurate distinction between the two continues to present a considerable challenge. Whereas LGASC is classified as a metaplastic carcinoma, SAN is regarded as a benign, invasive tumor arising from the sweat duct [8]. The histological diagnostic criteria of SAN include a) the location-dermis and subcutis of the nipple or areola, b) presence of irregular, compressed tubules that infiltrate smooth muscle bundles and/or nerves, c) presence of myoepithelial cells surrounding the tubules, d) presence of cysts lined by stratified squamous epithelium and filled with keratinous material and e) lack of necrosis and mitoses [9].

An emerging school of thought, however, proposes that LGASC and SAN are of a common origin, representing identical lesions arising in different anatomical locations [8]. This close association explains why many of these lesions have been 'incorrectly' labeled as the other throughout the literature [4], while other authors continue to use the terms 'LGASC' and 'infiltrating syringomatous adenoma' synonymously [1,6,9]. It has been suggested that accurate differentiation between LGASC and SAN may be impossible, particularly if the former involves

the nipple areolar complex [10]. The predominant difference between the two lesions is the location: LGASC arises within the breast parenchyma whereas SAN involves the epidermal layer of the skin/nipple [4]. Despite a different anatomical location, the two lesions are clinically similar, as SAN too arises over a wide range of ages (11-76 years) and most commonly presents as a mass which, given its location, may cause nipple inversion, discharge, or itching [10]. On imaging, neither LGASC nor SAN have individual specific radiological features that are characteristic.

At a microscopic level, LGASC and SAN have been deemed "essentially histologically identical" [4] as both are composed of well-differentiated angulated or 'comma-shaped'infiltrative glands [10]. No histologic feature that specifically differentiates LGASC from SAN has been reported in the literature. A recent study comparing the immunohistochemistry of these two lesions found that both LGASC and SAN share a common morphology with an identical immunoprofile of being positive for CK5/6, CD10 and p63, with no expression of ER, PR, and HER2 [11]. Additionally, Boecker et al's recent data provides evidence that LGASC and 'syringomatous tumors of the nipple' are identical or *nearly identical* lesions. Both lesions have squamous differentiation in the solid epithelial proliferations as well as the double-layered tubular structures, as detected by a switch from basal keratins (K5, K14) to squamous keratin (K10). These authors additionally concluded that in the glandular differentiation, p63 is downregulated in the K5/14+ glandular progenitors from which K8/18+ tumor cells emerge. They conclude that LGASC and SAN are a single entity arising from immunophenotypically identical progenitors; wherein p63+/K5/14+ cells play a key role in the neoplastic development of both entities with the preservation of certain differentiation features in the respective tumor types. [8]. Thus, the debate regarding the exact histogenesis of these two lesions remains unresolved. In conclusion, the jury is still out between the 'splitters' and the 'lumpers' for LGASC and SAN lesions of the breast.

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