ENIGMATIC MORPHO INSIGHT

Collagenous spherulosis

The term "Collagenous spherulosis" (CS) was first introduced by Clement and colleagues in 1987 to describe a peculiar change of the breast.[1] It is an uncommon benign change (occurs in less than 1-2% of all biopsies) and is an incidental microscopic finding involving lobular acini and ductules. It consists of intra-luminal clusters of eosinophilic spherules.[1]

ALTERNATE/HISTORICAL NAMES

- Mucinous spherulosis
- Spherulosis
- Adenoid cystic hyperplasia

The spherules that appear basophilic are called as mucinous spherulosis. According to Mooney *et al*., collagenous and mucinous spherulosis are related lesions. CS is considered as an end-stage lesion resulting from transformation of its predecessor, mucinous spherulosis of the early stages.[2]

On histologic examination, CS is characterized by presence of eosinophilic intra-luminal collagen rich spherules measuring 20-100 microns in diameter, surrounded by flattened myoepithelial cells.[3] Most frequently, it shows a central floccular aggregate with radiating spikes that merge with the scalloped projections at the periphery. The material may also be finely granular and more evenly distributed. The periphery of the sphere may be marked by an eosinophilic cuticle of variable thickness and staining intensity. Sometimes the cuticle is associated with a myoepithelial cell nucleus[2] [Figure 1a-c]. A hand-drawn illustration of the same has been presented in Figure 1b. As many as 50 spherules can be seen per section of the lesion and are usually discrete but may coalesce. It was shown that the hyaline material present within the intraluminal space was rich in collagen by conventional histochemistry, and was subsequently proved by immunocytochemistry that it was one of the component of the basement membrane.

CS has been described in association with various benign and malignant lesions, including sclerosing adenosis, radial scar, intraductal papilloma, fibroadenoma, atypical ductal hyperplasia, ductal carcinoma *in situ* and lobular carcinoma *in situ* of the breast.

CS has been seen in salivary gland tumors like sclerosing polycystic adenosis, epithelial-myoepithelial carcinoma, polymorphous low grade adenocarcinoma and cutaneous myoepithelial tumors.[3]

The most accepted theory on the mechanism of spherule formation is the secretion of extracellular material by the proliferative myoepithelium.[3] Based on the observations of a circumscribed spherule with frequent identification of a compressed myoepithelial cell nucleus surrounding collagenous spherulosis, the spherules can be interpreted to be formed by extracellular material deposition. The finding of laminin and type IV collagen in the spherules within "collagenous spherulosis" suggests that the spherules contain basement membrane material. In some instances, the contents of the spherule can undergo calcification (25% of cases of collagenous spherulosis have associated calcifications).[4]

Collagenous spherulosis seems to be heterogeneous in that some cases show a mature collagen core in the spherules, whereas in most cases the spherules contain reduplicated basal lamina only, without mature collagen. The electron microscopical results suggest that the degree of collagen formation within the spherule is related to the degree of myoepithelial differentiation of the cells surrounding the spherule and further suggest that this change occurs due to production of basement membrane material, and in some cases, due to mature collagen by the myoepithelial component.

The presence of the multiple intraluminal spherules, surrounded by an epithelial and myoepithelial proliferation, gives the involved ducts a cribriform appearance. This can lead to a misdiagnosis of atypical ductal hyperplasia (ADH), cribriform ductal carcinoma *in situ* (DCIS), cribriform carcinoma or adenoid cystic carcinoma.

Intraductal hyperplasia

Compared with intraductal hyperplasia or atypical intraductal hyperplasia, the basophilic material in CS is arranged in a more structured pattern and the radial spokes reach to the periphery on a more regular basis. It is coarser, more irregular in distribution both within and between spaces, and tends to retract to the center without a uniform radial spike pattern peripherally.

Adenoid cystic carcinoma

The main differential diagnosis and pitfall in recognizing CS is adenoid cystic carcinoma.[5] Some distinguishing characteristics features are as follows:

- In CS, the ductal epithelium is present as cellular lobules and forms variable-sized ductal lumina. Whereas, it is rare or forms only small-sized ductal lumina in ACC.[1] The features of dysplasia are evident.
- Myoepithelial cells surrounding collagenous spherules stains for smooth muscle actin, smooth muscle myosin heavy chain, p63 and calponin but no immunoreactivity is noted with c-kit/CD117, which is typically positive in the cells of adenoid cystic carcinoma.

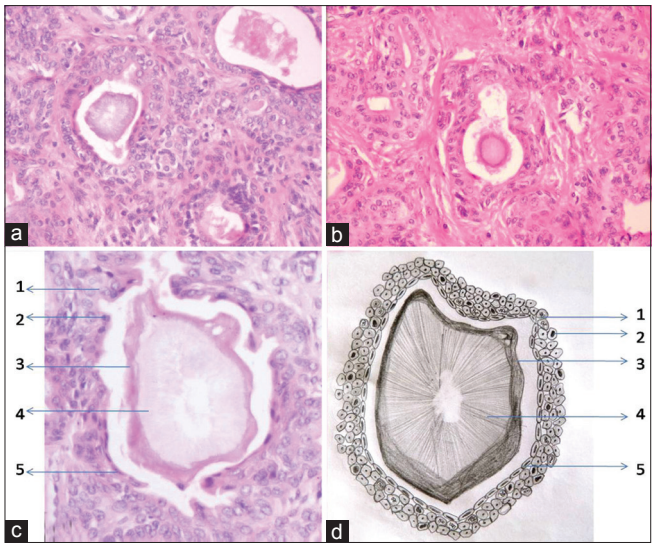

Figure 1: (a) Photomicrograph of a Collagenous spherule (H&E stain), (a) ×100, (b) ×100, (c) ×400, (d) Hand- drawn illustration of a Collagenous spherule. 1- Ductal cells with open face nuclei, 2- Ductal cells with close face nuclei, 3- Outer cuticle of the spherule, 4 - Central floccular aggregate showing radiating spikes from center towards the periphery, 5- Flattened myoepithelial cells

Ductal carcinoma *in situ*

Presence of thin cuticle that is variably present in cases of spherulosis[1] can be used to distinguish collagenous spherulosis from ductal carcinoma in situ (DCIS).

Failure to recognize CS as a benign lesion may result in overestimation of a patient's subsequent risk of invasive cancer, or at worst may cause inappropriate treatment based on this diagnosis. Collagenous spherulosis in its simple form requires no treatment, but treatment may be necessary if it is associated with malignancy.[6]

Access this article online	
Quick Response Code:	Website: www.jomfp.in
	DOI: 10.4103/0973-029X.125174

ACKNOWLEDGEMENT

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How to cite this article: Bavle RM. Collagenous spherulosis. J Oral Maxillofac Pathol 2013;17:322-3.
Source of Support: Nil. **Conflict of Interest:** None declared.