Cytological Diagnosis Of Collegenous Spherulosis: A Rare Incidental Finding In Proliferative Breast Lesions

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Abstract: Collagenous spherulosis is a rare incidental finding characterized by collagen rich spherules made up of basement membrane material and is frequently associated with other benign lesions of the breast like fibroadenoma, papilloma, sclerosing adenosis, radial sclerosing lesion, adenomyoepithelioma and florid ductal hyperplasia. The estimated incidence of this innocuous condition is only about 0.2% in cytological material. It is of utmost importance to differentiate collagenous spherulosis from atypical proliferations and malignant mimics especially adenoid cystic carcinoma to avoid unnecessary treatment. Here we discuss the cytological findings of a case of collagenous spherulosis associated with benign proliferative breast disease, along with brief review of literature.

Key Words: Collagenous spherulosis, Mucinous spherulosis, adenoid cystic hyperplasia

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Introduction: Collagenous spherulosis of the breast was first described as an entity by Clement et al in 1987.[1] It is frequently associated with other proliferative benign lesions of the breast. Carcinoma may be coincidentally present within the same specimen, but they are neither associated with malignancy nor they are precancerous. Collagenous spherulosis presents almost always as incidental finding in women in third to fifth decade of life, and is rarely associated with palpable or mammographically detected mass or density. There have been very few reports in the english literature describing cytological features of collagenous spherulosis.[2-4] Here, we report a case of collagenous spherulosis in a 35 year old female detected by fine-needle aspiration cytology (FNAC) and discuss the cytomorphological findings.

Case presentation: A 35 year old woman presented with a history of painless lump in the left breast for 1-year. On examination, a firm well-defined, non tender, mobile nodule measuring 1x0.8 cm was palpable in the left infraareolar region with excoriated nipple. It was not attached to overlying skin and underlying tissues. Menstrual and obstetric history was not significant. Ultrasonography, revealed a hypoechoic lesion of size 1.2x0.7 cm in left breast. On mammography no calcification was noted. Clinically, diagnosis of fibroadenoma was made.

FNAC was done using a 22-gauge needle and 20 mL syringe. Air-dried smears were stained with May-Grünwald-Giemsa (MGG) stain and the ethanol fixed smears with Papanicolaou stain. On microscopic examination, smears yielded moderate cellularity, comprising of tight cohesive groups, papillaroid fragments and monolayered sheets of benign ductal epithelial cells intimately mixed with many spherical, acellular homogeneous, eosinophilic hyaline globules. Cells revealed occasional nuclear overlapping, bland nuclear chromatin, inconspicuous nucleoli and scanty cytoplasm. Bare bipolar nuclei, stromal fragments, few macrophages and hyaline globules surrounded by cells were noted in the background (Figure 1,2). Periodic acid Schiff (PAS) stain showed strong positivity for these globules (Figure 3). No strongly birefringent material was seen on viewing the foci with polarized light, suggesting that calcium oxalate was not present. Cytological findings were suggestive of benign proliferative breast disease with collagenous spherulosis. The case has not yet been biopsied, but no signs of progression have been observed on close clinical follow-up.

Discussion: Collagenous spherulosis (CS) of the breast is a rare benign lesion with reported incidence of <1% in excisional specimens and about 0.2% in cytology material.[2,5] The number of reported cases are few because of the lack of awareness of this entity among the cytopathologists and the limited volume of diagnostic cells and spherules in the aspirated material.[5] Most of the time it is found incidentally, but may rarely present as palpable breast mass.[6] In our case it presented as a palpable lump.

It is associated 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.[1,5] Carcinoma may be present coincidently, but this usually are incidental processes

and there is no evidence to indicate that it is a precancerous lesion. It is seen more commonly in ducts than in lobules.[1,7] In view of the structural similarities to breast, CS has been seen in salivary gland and cutaneous myo-epithelial tumors like chondroid syringoma.

Figure 1,2: Moderately cellular smear, comprising of tight cohesive groups, papillaroid fragments and monolayered sheets of benign ductal epithelial cells intimately mixed with many spherical, acellular homogeneous, eosinophilic hyaline globules (MGG 100x,200x).

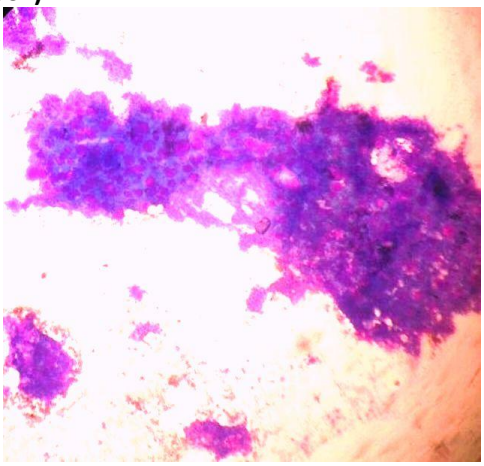


Figure 1

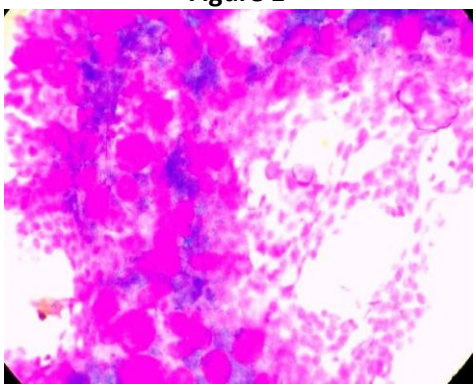
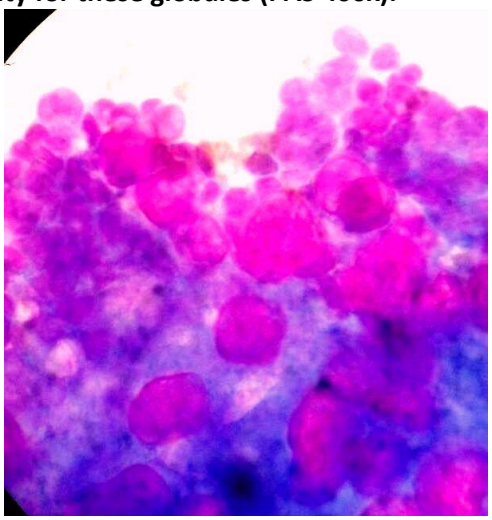


Figure: 2

On cytology, spherules measures 20 – 200 micrometer in diameter and appears magenta in MGG stain, light pink in H & E, while light green in PAP stain. They are surrounded by cresentic myoepithelial cells or clusters of epithelial cells. Fibrillary quality may be detected in spherules with Diff-quick stain, either arranged in star shaped configuration or a laminar concentric appearance.[1] Some of the spherules may eventually calcify and are encountered as microcalcifications on mammography.[2] Degenerative changes may occur in spherules creating myxoid appearance. On histologic examination, intraluminal clusters of eosinophilic or rarely basophilic ("mucinous spherulosis") collagen rich spherules within spaces, surrounded by flattened myoepithelial cells are present.

Figure 3: Periodic acid Schiff stain showed strong positivity for these globules (PAS 400x).



Actually collagen spherules are stromal reaction composed of abundant basement membrane material like proteoglycans such as heparan sulfate, laminin, and fibronectin. As a result they stain blue with trichrome, pinkish red with Van Gieson, black with reticulin and are variably positive with PAS and alcian blue stains. Immunohistochemical (IHC) and ultrastructural studies confirm that they are produced as a result of proliferation of myoepithelial cells and are positive for cytokeratin, S-100 protein, actin, calponin, p63 and smooth muscle myosin.[8,9]

It should be distinguished from malignant lesions including adenoid cystic carcinoma (ACC) of the breast and so-called adenoid cystic hyperplasia or intraductal signet-ring carcinoma. Adenoid cystic carcinoma is seen in older women, shows more obvious stromal invasion and forms mass. Cytologically, smears shows syncytial, multilayered, branching clusters of cells having high nuclear/cytoplasmic ratio, nuclear over-crowding, overlapping, anisonucleosis, slightly hyperchromatic nuclei and small nucleoli. Bipolar bare nuclei are absent and the spherules surrounded by several layers of cells.[10] These features were not seen in our case, hence favoring collagenous spherulosis.
In difficult cases, it is advisable to recommend an open biopsy to make an accurate diagnosis. ACC shows PAS positive material within duct like spaces and alcian blue positive material within pseudocyst. While in CS, there is variable positivity for both stains. IHC is also useful in differentiating these entities as smooth

muscle myosin heavy chain and calponin are uniformly and strongly positive in CS and negative in ACC. C-kit (CD117) is a sensitive marker of adenoid cystic carcinoma, which is not expressed in collagenous spherulosis.[11] Another less common pitfall is cribriform DCIS, which forms multiple secondary lumens with round, regular spaces having sharp borders that appear to be made from "cookie-cutters" but no amorphous pink material is present within these lumens.

Upon re-review of referral material, CS may go unrecognized in about 48% of cases; however, it could also be misdiagnosed as atypical in 17% of cases, or in situ and/or invasive carcinoma in an additional 11% of cases.[12] Pathologists must remain vigilant to this form of mimicry, because classification of in situ/invasive carcinoma carries important clinical implications for patient management. Collagenous spherulosis in its simple form requires no treatment, but treatment may be necessary if it is associated with malignancy.

Conclusion: Although, collagenous spherulosis is rarely reported in cytological smears yet the real incidence may be much more. It is necessary for cytopathologists to be aware of this innocuous lesion as failure to recognize it as a benign lesion may result in overestimation of subsequent risk of invasive cancer, or at worst may cause inappropriate treatment on the basis of this diagnosis. A proper correlation with imaging modalities and clinical features is recommended with close follow-up.

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