Quiz Case

Non-cellular morphologic markers in pleomorphic adenoma: A rare observation

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A 43-year-old male presented with complaint of swelling in the left parotid region for the past 7–8 years. The swelling was painless, insidious in onset, and progressively increased in size. Local examination revealed a single, well-defined, non-tender, and firm swelling measuring 3.5 × 3 cm in the left preauricular region. Fine-needle aspiration cytology (FNAC) stained smears show the following findings [Figure 1a-d].

Figure 1: (a) Abundant fibrillary chondromyxoid material, numerous basophilic refractile structures (Giemsa, ×400), (b) Myoepithelial cell admixed with clusters of orangeophilic, refractile structures (Papanicolaou stain, ×1000), (c) Radially arranged, glossy, petal-like structures (Thin red Arrow) with blunt ends of refractile structures. (Papanicolaou stain, ×1000), (d) Few epithelial cells have intranuclear cytoplasmic inclusion (Thick Red Arrow) (Papanicolaou stain, ×1000).

Q1. What is your interpretation?
A. Tyrosine-rich crystalloid
B. Collagenous crystalloid
C. Amylase crystalloid
D. Calcium oxalate crystalloid

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Answer: Q1-A. Tyrosine-rich crystalloid

Tyrosine-rich crystalloids (TRCs) are round to oval, refractile, floret-shaped orangeophilic (Papanicolaou stain) structures with symmetrical lobulated contour, central rounded core, and peripheral “rosette like” arrangement.[1] TRCs appear reddish-brown with Millon’s stain and turn deep purplish-red with the diazotisation coupling method, confirming the presence of tyrosine.[1] Other histochemical reactions such as tryptophan, arginine, and sulfhydryl groups are also positive in TRC.[2] Collagenous crystalloids (CCs) are non-refractile, eosinophilic, rounded structures composed of radially arranged needle-shaped fibers with central clear space, occupied by a fibroblast or a small blood vessel.[3] Histochemically, CC stains bright blue with trichrome, black with methenamine silver, and gray to black on reticulin staining; while it is negative for Millon’s stain or diazotization coupling reaction.[4] Alpha-amylase crystalloids (ACs) are non-birefringent having various shape such as rod like, rhomboid, cuboidal, square, polyhedral, or needle like, appear bright orange with Papanicolaou stains, deep blue by Giemsa stains, and pink by hematoxylin-eosin stains.[4] Millon’s reagent or diazotization coupling reactions are negative.[4] Calcium oxalate crystals (COCs) are birefringent, irregular or polygonal, transparent to pinkish structure.[5] Millon’s reagent or diazotization coupling reactions are negative.[5]

Q2. What is your most probable diagnosis?
A. Mucoepidermoid carcinoma
B. Basal cell adenoma
C. Warthin tumor
D. Pleomorphic adenoma (PA)

Answer: Q2-D

PA is characterized by a variable admixture of ductal epithelial cells, myoepithelial cells, and mesenchymal matrix. The mesenchymal matrix may be either chondromyxoid matrix as in most of the cases or less commonly reveal amyloid, collagenous substance, and/or elastic fibers.[6] Rare cytomorphological variations include presence of crystalloids such as TRC, CC, calcium oxalate crystalloid, and amylase crystalloids along with the presence of nuclear changes in epithelial component such as inclusions/grooves are also identified in PA.[6,7]

Q3. Which of the following statement is incorrect?
A. TRCs are refractile structures seen in both neoplastic and non-neoplastic lesions of parotid glands
B. Histochemical reactions (Millon’s stain and diazotization coupling reaction) help to confirm the presence of tyrosine.
C. Intranuclear cytoplasmic inclusions are the most commonly observed features in pleomorphic adenoma.
D. All of the above

Answer: Q3-C

TRCs are found in both neoplastic and non-neoplastic salivary gland lesions such as PA, myoepithelioma, carcinoma ex pleomorphic adenoma, adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma, terminal duct adenocarcinoma, and parotid cysts.[8-12] Intranuclear cytoplasmic inclusions in the epithelial component of PA are rare findings described in a few case reports.[13]

BRIEF REVIEW OF THE TOPIC

In 1953, Bullock first described the “innumerable crystalline aggregate” present in histologic section of PA as tyrosine crystals because its structure resembles that of tyrosine.[14] Nochomovitz and Kahn (1974) described the physical and histochemical properties as refractile, rosette-like structure exhibiting a positive reaction with Millon’s reagent.[15] On electron microscopy, TRCs are non-birefringent, electron dense, granular without internal structure thus designated as crystalloid.[16] Based on the histochemical reaction and ultrastructural findings, the correct nomenclature is tyrosine-rich crystalloids rather than tyrosine crystal.[8] The incidence of TRC in PA varies from 1.8 to 5%; however, Lemos et al. reported an incidence of up to 33% in African patients.[2,9,15,16] The pathogenesis of TRC remains ambiguous. Thomas et al. proposed that as tyrosine plays an important role in pigment metabolism, therefore, there is high prevalence of TRC in parotid tumors in Black races.[9] This hypothesis was refuted as tyrosine crystals do not get deposited in the tissues of patients suffering from tyrosinosis.[9,17] Many authors hypothesized that TRC deposition is either a manifestation of disturbed protein synthesis or by precipitation onto stromal collagen secreted by myoepithelial cells.[2,9,17] Morphology and histochemical stains may help to differentiate TRC from other crystalloids. Nuclear changes such as nuclear inclusion/grooves are rare cytomorphological variations seen in PA.[13] In the present case, we emphasize on the presence of two rare cytomorphological features seen in PA.

SUMMARY

Since TRCs are the most common crystalloids found in PA, some authors suggest that TRC can serve as a non-cellular morphologic marker of salivary gland neoplasia which might be helpful in paucicellular smears. This case report also aims to emphasize the importance of this novel observation to the novice budding cytopathologists.

COMPETING INTERESTS STATEMENT BY ALL AUTHORS

The authors declare that they have no competing interests.

AUTHORSHIP STATEMENT BY ALL AUTHORS

Each author has participated sufficiently in the work and takes public responsibility for appropriate portions of the
content of this article. All authors read and approved the final manuscript. Each author acknowledges that the final version was read and approved.

ETHICS STATEMENT BY ALL AUTHORS
As this is case without identifiers, our institution does not require approval from the Institutional Review Board (IRB) (or its equivalent).

LIST OF ABBREVIATIONS (In alphabetic order)
FNAC – Fine-needle aspiration cytology
TRCs – Tyrosine-rich crystalloids
CCs – Collagenous crystalloids
ACs – Alpha-amylase crystalloids
COCs – Calcium oxalate crystals
PA – Pleomorphic adenoma

EDITORIAL/PEER-REVIEW STATEMENT
To ensure the integrity and highest quality of CytoJournal publications, the review process of this manuscript was conducted under a double-blind model (authors are blinded for reviewers and vice versa) through automatic online system.

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