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Endobronchial masses encountered on fine-needle aspiration biopsy: a focus on unusual entities

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Abstract

Fine-needle aspiration biopsy (FNAB) is a useful technique in the evaluation of central lung tumors which is commonly encountered in clinical cytology practice. Some of these tumors may show endobronchial, polypoid growth which is readily apparent to the endoscopist. Pulmonary salivary gland-type tumors and carcinoid tumors are overall uncommon in the lung, but these tumors tend to occur centrally and show endobronchial involvement. The prognosis of these tumors is generally better than that of small cell or non-small cell carcinomas of the lung and more conservative surgical resection is often indicated. The identification of salient cytological features and a high index of suspicion when considering the differential diagnosis of a central lung tumor is essential to accurate diagnosis. This review focuses on cytological clues as well as ancillary techniques that may be useful to the practicing cytopathologist.

KEYWORDS

carcinoid tumor, endobronchial mass, fine-needle aspiration biopsy (FNAB), salivary gland-type tumors

1 | INTRODUCTION

Fine-needle aspiration biopsy (FNAB) is one of the most commonly used biopsy techniques in the diagnosis of lung cancer.[1,2] Examination of the radiology (particularly CT scan) is useful to narrow the differential diagnosis prior to evaluation of the cytological smears. The location of the tumor (central vs peripheral) is particularly useful. When faced with a central tumor demonstrating endobronchial involvement, awareness of unusual entities which have a predilection for this site is important in establishing the correct diagnosis.

In this review article, we will highlight the more commonly encountered pulmonary salivary gland-type tumors that occur centrally as well as central carcinoid tumors (Table 1).

2 | DISCUSSION

Pulmonary salivary gland-type tumors are uncommon, comprising less than 0.2% of all primary lung tumors.[3] Mucoepidermoid carcinoma (MEC) and adenoid cystic carcinoma (ACC) are the most commonly encountered malignant tumors (Table 2). Despite their rarity, it is important to correctly identify these tumors since the prognosis of these patients is generally better than for those with non-small cell carcinomas.[1] Surgical management can also be more conservative for these low-grade neoplasms. The full spectrum of morphological features seen on cytology in salivary gland tumors is not always evident in aspirates from their pulmonary counterparts. Additionally, there are some differences in the frequency of their occurrence, clinical behavior and molecular genetic features. The use of the Milan system for reporting salivary gland cytopathology has not been validated for pulmonary salivary gland-type tumors.

Carcinoid tumors are the other major differential diagnostic consideration for central endobronchial tumors, and similarly need to be separated from non-small cell carcinoma for optimal patient management.

2.1 | Mucoepidermoid carcinoma

Pulmonary MEC occurs in patients with a wide age range (3-78 years), but most cases are reported in the pediatric and young adult

TABLE 1 The differential diagnosis of endobronchial tumors highlighting useful features

	Cytomorphology	Immunocytochemistry
Mucoepidermoid carcinoma	Tissue fragments with squamoid, intermediate and mucinous cells; mucinous background	*Positive*: p63, p40, CK7, CK5/6 *Negative*: CK20, TTF1, Napsin A
Adenoid cystic carcinoma	Tissue fragments; homogeneous small cells; matrix balls	*Positive*: CK, EMA, CD117, focal S-100
Epithelial-myoepithelial carcinoma	Tissue fragments; dual cell population; background hyalinized basement membrane material	*Positive*: CK, S-100 (myoepithelial cells) *Negative*: CD117
Carcinoid tumor	Tissue fragments with tumor cells clinging to capillaries and single-lying cells; homogeneous cells; stippled chromatin	CK, CD56, synaptophysin, chromogranin A, INSM1
Adenocarcinoma	Tissue fragments and individually dispersed cells; translucent or vacuolated cytoplasm; peripheral round nucleus; prominent nucleolus	TTF1, Napsin A
Squamous-cell carcinoma	Tissue fragments and single-lying cells; at least moderate cytonuclear atypia; orangeophilic dense cytoplasm; "tadpole" cells; central hyperchromatic nucleus	p63, p40
Small cell carcinoma	Solitary tumor cells or loose aggregates; high nuclear-to-cytoplasmic ratio; nuclear molding; necrosis; "blue bodies"; chromatin smearing	Cytokeratins, CD56, synaptophysin, chromogranin A, INSM1

TABLE 2 The proportion and age range of salivary gland-type tumors of the lung

	Proportion[a]	Age range (years)
Mucoepidermoid carcinoma	43%	3–78
Adenoid cystic carcinoma	24%	18–79
Epithelial-myoepithelial carcinoma	2%	33–71
Other salivary gland-type tumors	31%	

[a]Data from study by Fonseca et al.[5]

population.[4] Fonseca et al examined 493 cases of pulmonary salivary gland-type tumors in Southern Brazil, and found MEC to be the most common malignant salivary gland-type tumor, representing 43% of cases.[5] Classically these tumors arise as well-circumscribed exophytic endobronchial masses, but they can also involve the segmental bronchi or peripheral lung.[6] Low-grade and high-grade forms, similar to their salivary gland counterparts, occur in the lung.

Most reported cases are of low-grade MEC and the distinction between low and high-grade forms of MEC is best made on the excision specimen. The low-power cytology pattern is that of epithelial tissue fragments with or without glandular differentiation (Figure 1A), with a variable number of dispersed cells, with or without background necrosis.[2] There is often a mucinous background, and an important clue is to identify goblet/mucinous cells; particularly lying in strips (Figure 1B). Stromal tissue fragments, relatively bland intermediate cells and nonkeratinizing squamoid cells are seen in variable proportions.[7-9] The presence of intimately admixed glandular and intermediate cell elements and/or squamous cells allows for accurate recognition of MEC (Figure 1C).[9,10] The glandular cells are cuboidal to columnar in shape and contain basally orientated round nuclei with moderate mucin-positive cytoplasm. Nucleoli in these cells are not prominent. Intermediate cells are characterized by round contours, dense cytoplasm and bland nuclei. The squamoid cells are large and polygonal with abundant eosinophilic cytoplasm and central round bland nuclei (Figure 1D).

Immunocytochemistry for p63, p40, and cytokeratin (CK) 5/6 is positive in the squamoid cells. CK7 highlights the glandular component. Thyroid transcription factor 1 (TTF1), Napsin A and CK20 are generally negative. Pulmonary MEC demonstrates the characteristic translocation, t(11;19)(q21;p13), resulting in CREB regulated transcription coactivator 1 (CRTC1) and mastermind-like 2 (*MAML2*) gene rearrangement. Fluorescent in situ hybridization (FISH) for *MAML2* rearrangement is a useful ancillary test.[11]

The major differential diagnostic considerations include well-differentiated squamous cell carcinoma (SCC) and adenocarcinoma. Bronchogenic SCC typically demonstrates a greater degree of cytonuclear atypia than MEC. SCC may also show cytoplasmic

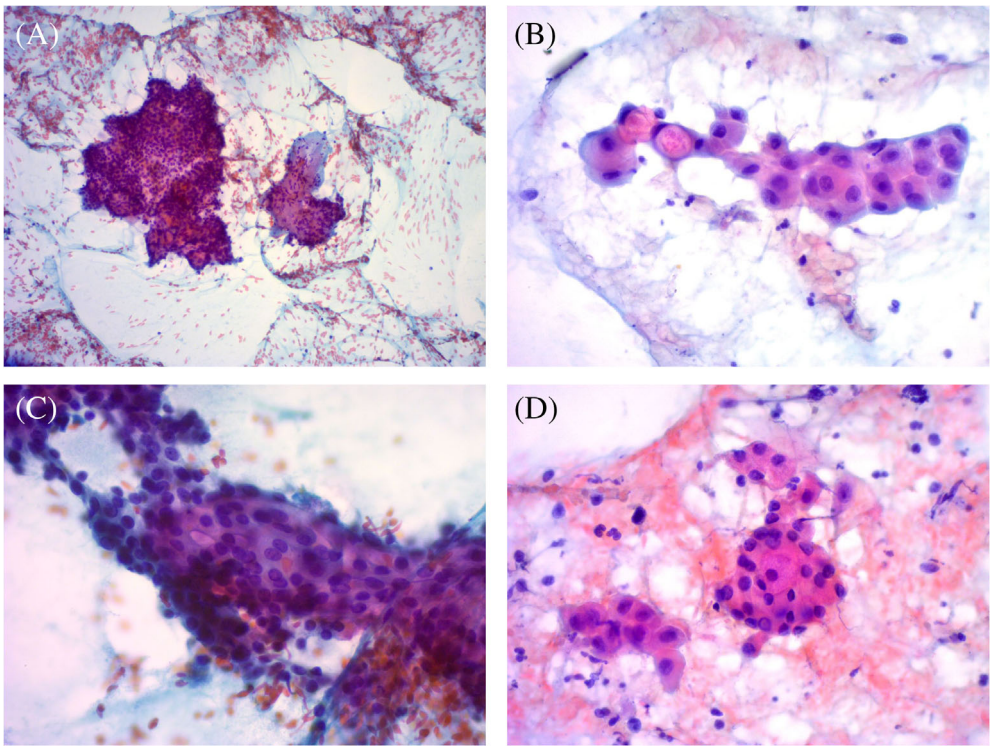

FIGURE 1 Mucoepidermoid carcinoma. A, Epithelial and stromal tissue fragments in a mucinous background (Papanicolaou, ×100). B, Strip of epithelium with admixed squamoid and goblet cells (Papanicolaou, ×400). C, Epithelial tissue fragment composed of admixed intermediate and mucinous cells (Papanicolaou, ×400). D, Squamoid cells are large and polygonal with abundant eosinophilic cytoplasm and central round bland nuclei (Papanicolaou, ×400) [Color figure can be viewed at wileyonlinelibrary.com]

orangeophilia (keratinization). MEC lacks the myoepithelial component which is present in the other salivary gland-type tumors, aiding in this distinction. Although the mucinous cells may prompt consideration of adenocarcinoma, the presence of intermediate cells in MEC and the negative immunolabeling for TTF1 and Napsin A allow for correct identification. Adenosquamous carcinoma is another differential diagnostic consideration which can be difficult to distinguish from MEC. However, adenosquamous carcinoma typically presents as a peripheral lesion, lacks an intermediate cell component, and the glandular component usually shows a greater degree of cytological atypia. The glandular component also labels with TTF1 and Napsin A, unlike the glandular cells in MEC.

2.2 | Adenoid cystic carcinoma

ACC typically occurs in the lower trachea and main bronchi.[3,12] There is a wide age range 18 to 79 years. These tumors present commonly as endobronchial masses, usually in a central location. There is often widespread extension within the bronchial wall.

Cytological aspirates show an epithelial neoplasm demonstrating small relatively uniform cells, arranged as either small, irregular tissue fragments, tubular structures or loose lying (Figure 2A,B).[2,9,13] The cells contain a scant rim of cytoplasm, ovoid nuclei with smooth nuclear membranes, delicate chromatin and inconspicuous nucleoli (Figure 2C). The presence of three-dimensional spheres of homogeneous basement membrane-like material is highly characteristic. This material is pale and translucent on the Papanicolaou stain but stains metachromatically on Romanowsky preparations which aids recognition (Figure 2D). However, these matrix balls can be scant to absent particularly if the ACC demonstrates a solid growth pattern.

Immunocytochemistry performed on a cell block will highlight the dual cell population. Epithelial cells are positive for cytokeratins and epithelial membrane antigen (EMA). The myoepithelial cells express cytokeratins, smooth muscle actin (SMA), SOX10 and show focal S-100 protein labeling. CD117 (c-Kit) is frequently expressed in pulmonary ACC, but *KIT*-activating mutations are not found.[14] There is little molecular data on pulmonary ACC, and *MYB-NFIB* fusions which occur frequently in head and neck ACC do not seem to occur. Recently, comparative genomic hybridization (CGH) has shown losses at 3p, 4p, and 15q, with gains at 12q15 (*MDM2* locus).[15]

In the absence of the characteristic matrix spheres, the differential diagnosis includes carcinoid tumor, small cell carcinoma and basaloid SCC. Carcinoid tumors are more likely to present as a discohesive cell population, and contain cells with more voluminous cytoplasm and nuclei with granular chromatin and small nucleoli. Therefore, the nuclei are not as dark-appearing as those seen in ACC. Small cell carcinoma comprises cells which are "larger" than those seen in ACC, and there is more nuclear membrane irregularity and hyperchromasia, though the chromatin is finer and less dark than seen in ACC. Nuclear molding, chromatin smearing, necrotic and karyorrhectic debris, and prominent mitosis are also evident in small cell carcinoma. Basaloid SCC also shows a relatively uniform population of cells, but these cells are significantly larger than those seen in ACC. Basaloid SCC may also show background necrosis and focal keratinization.

2.3 | Epithelial-myoepithelial carcinoma

Epithelial-myoepithelial carcinoma (EMC) is extremely rare in the lung. Pulmonary EMC occurs in adults with an age range of 33 to

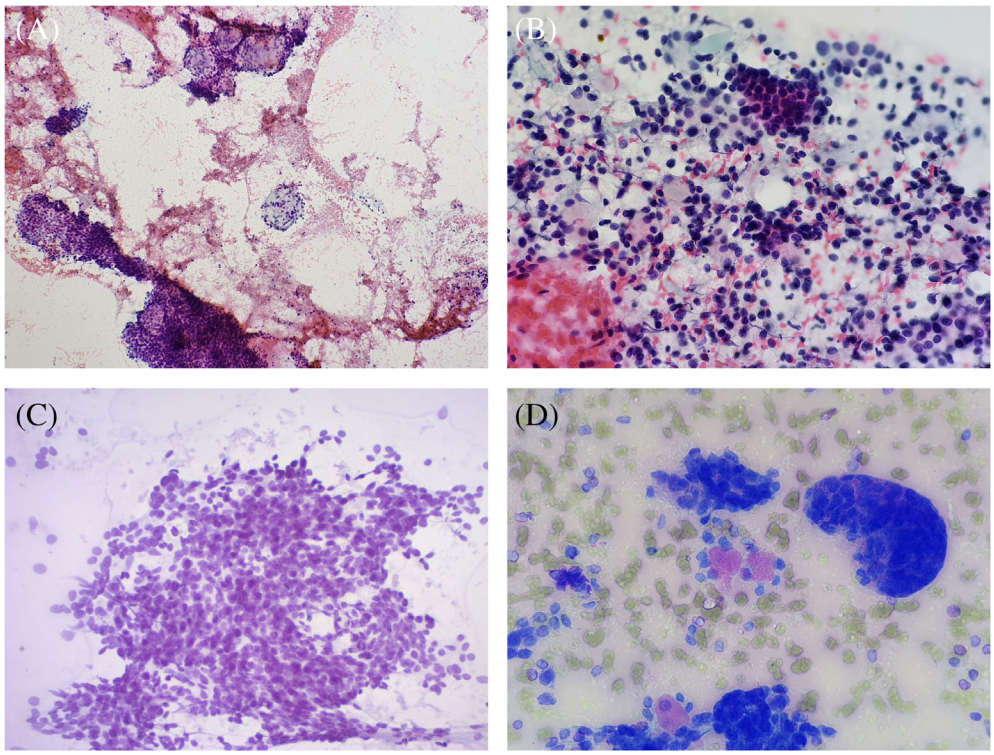

FIGURE 2 Adenoid cystic carcinoma. A, Cellular epithelial tissue fragments in a clean background (Papanicolaou, ×100). B, Predominantly discohesive cellular pattern with small epithelial fragments and scattered pale matrix balls (Papanicolaou, ×400). C, Cellular epithelial fragment with features of a basaloid neoplasm (Papanicolaou, ×400). D, Metachromatic matrix balls surrounded by myoepithelial cells (Giemsa, ×400) [Color figure can be viewed at wileyonlinelibrary.com]

71 years.[16,17] These tumors are endobronchial and may show intraluminal polypoid growth. One case of a peripheral lesion has been reported.[18]

There are no descriptions of the cytological features of pulmonary EMC in the literature. In the salivary gland, this tumor falls into the pattern of a biphasic tumor with acellular basement membrane material (Figure 3A,B).[2,19,20] Tissue fragments may contain tubular or sphere-like structures, or cribriform areas (representing the epithelial component). The epithelial cells are small, basaloid (high nuclear-to-cytoplasmic ratio) and contain hyperchromatic nuclei (Figure 3C). The myoepithelial cell population is often present as discohesive cells with bare naked nuclei. These cells are larger than the epithelial cells and may contain moderate clear glycogenated cytoplasm, round vesicular nuclei and small distinct nucleoli. Appreciation of a dual cell population is often difficult, and the classic histological description of ductal structures surrounded by myoepithelial cells with clear cytoplasm is difficult to appreciate. The relative proportions of these cellular constituents are variable and often misleading. Acellular homogeneous hyalinized basement membrane material is often present. Some cases show clusters of cells surrounding metachromatic proteinaceous matrix spheres, somewhat resembling those seen in ACC.

Immunocytochemistry reveals a dual cell population comprising epithelial cells which label with cytokeratins and EMA, and myoepithelial cells which stain with SMA, SOX10 (Figure 3D) and S-100 protein. CD117 is negative which is helpful in distinguishing EMC from ACC.

The differential diagnosis includes other biphasic salivary gland-type tumors and SCC. Bronchogenic SCC typically demonstrates more cytonuclear atypia than salivary gland-type tumors and the presence of cytoplasmic orangeophilia is also a useful clue. The presence of a biphasic population of cells and negative CD117 immunocytochemistry help to separate EMC from ACC, however this distinction may best be deferred to the excision specimen.

2.4 | Carcinoid tumor

Carcinoid tumors are malignant well differentiated neuroendocrine neoplasms which in the lung are divided into typical and atypical subtypes. The mean age of patients reported in the literature is 45 to 55 years (range from childhood to 82 years).[21] Bronchial carcinoids are the most common lung tumor in children.[22] Approximately one third of carcinoid tumors occur centrally, and these typically have an intraluminal component.[23]

The low power pattern is that of small, loosely cohesive epithelial tissue fragments, dispersed cells and scattered thin papillary meshworks (Figure 4A).[2] The proportion of these components is variable. The cellular aggregates are arranged as flat sheets, acini, trabecular and vascularized fragments. The latter arrangement, with one to a few layers of uniform tumor cells tightly adherent to straight and branched capillaries, is highly characteristic of carcinoid tumors. The tumoral cells are uniform with moderate amounts of basophilic variably granular cytoplasm, and contain a round to ovoid nucleus with finely stippled "salt and pepper" chromatin (Figure 4B). If present, nucleoli are generally small and inconspicuous. The single-lying neoplastic cells tend to have an eccentric nucleus which imparts a plasmacytoid appearance. Spindle cell and oncocytic carcinoid variants are recognized.

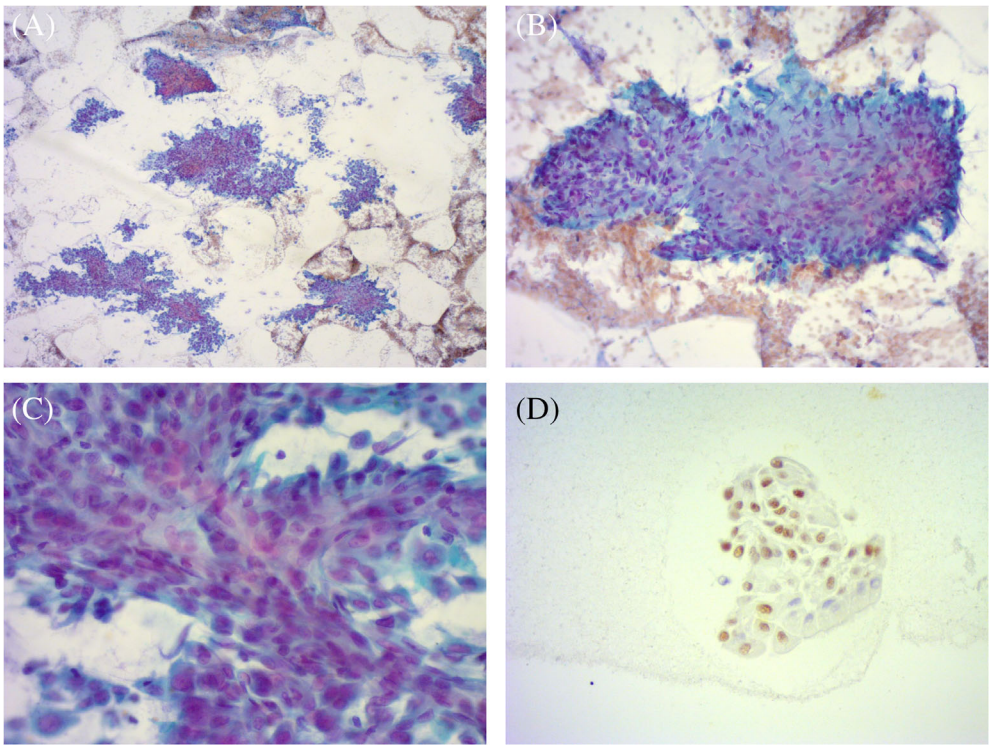

FIGURE 3 Epithelial-myoepithelial carcinoma. A, Cellular tissue fragments with clinging basement membrane material and dispersed cells (Papanicolaou, ×100). B, Myoepithelial cells with spindled morphology in hyaline basement membrane material (Papanicolaou, ×200). C, Epithelial cells with high nuclear-to-cytoplasmic ratios and dark nuclei with 1-2 nucleoli (Papanicolaou, ×400). D, SOX10 immunohistochemistry highlighting myoepithelial cell component (×400) [Color figure can be viewed at wileyonlinelibrary.com]

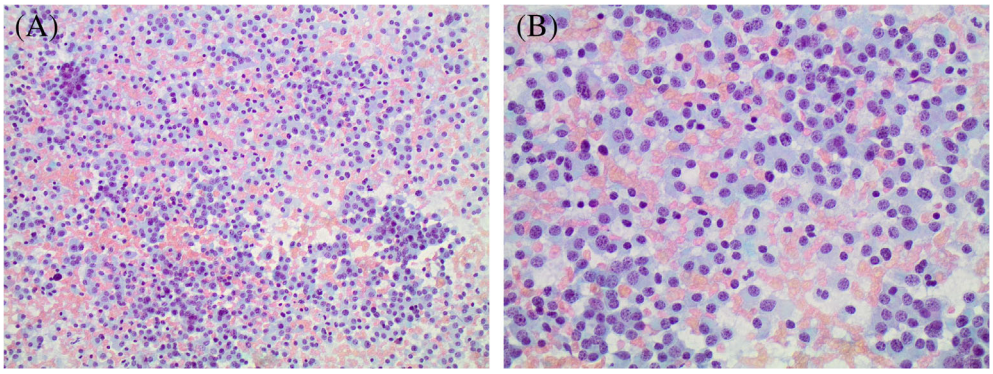

FIGURE 4 Carcinoid tumor. A, Monotonous loosely cohesive and dispersed cells (Papanicolaou, ×200). B, Uniform cells with moderate basophilic variably granular cytoplasm, round to oval nuclei and finely stippled "salt and pepper" chromatin (Papanicolaou, ×400) [Color figure can be viewed at wileyonlinelibrary.com]

Carcinoid tumors generally show immunocytochemical labeling with cytokeratins (20-25% can however be negative), and show diffuse strong expression with chromogranin A, synaptophysin and CD56. Recently, the neuroendocrine transcription factor Insulinoma-associated protein 1 (INSM1) has been shown to be a useful neuroendocrine marker in pulmonary neoplasia.[24]

The distinction between typical and atypical carcinoid tumors is best made on the excision specimen, as it is difficult to accurately assess the mitotic rate and presence of necrosis on cytological preparations. Separating carcinoid tumors from metastatic adenocarcinoma (especially breast and prostate) on cytology can be challenging. Neuroendocrine immunocytochemical stains may occasionally be positive in these tumors. NKX3.1 is the most specific marker for prostate carcinoma and GATA3 positivity will identify breast carcinoma.

2.5 | Other uncommon salivary gland-type tumors

Other salivary gland-type tumors have very rarely been reported in the lung. These include acinic cell carcinoma, hyalinizing clear cell carcinoma, salivary duct-like carcinoma, pleomorphic adenoma, myoepithelial carcinoma, and oncocytoma.

3 | CONCLUSION

Pulmonary salivary gland-type tumors and carcinoid tumors are not frequently encountered in routine cytology practice. These tumors have a better prognosis than non-small cell carcinoma. Predilection for a central location with endobronchial growth should prompt the attending cytopathologist to consider these entities in the differential

diagnosis. Identification of salient cytological features, together with a high index of suspicion, will prompt the correct diagnosis. Ancillary tests such as a cell block with immunocytochemistry and FISH can be employed to confirm the diagnosis.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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