

Pseudofungi Associated with a Granulomatous Response in a Lymph Node – A Case Report –

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We present herein a case of pseudofungi incidentally found in the mediastinal lymph nodes of a 31-year-old woman who had a left pneumonectomy for a pulmonary blastoma. The pseudofungi were located in the subcapsular sinuses of the lymph nodes with an associated granulomatous reaction. They revealed yellowish-brown hyphae-like structures with pseudosepta and irregular branching at various angles intermingled with round yeast-like forms. These structures stained positively with periodic acid-Schiff and Gomori methenamine silver, but also stained strongly positive for Prussian blue suggesting that they contain iron. The characteristic morphological features of pseudofungi are discussed with emphasis on the features that distinguish them from true fungal organisms.

Key Words : Hyphae-Lymph nodes-Granuloma

Fungal infections are often diagnosed pathologically by microscopic examination of tissue sections, further aided by special stains such as periodic acid-Schiff (PAS) or Gomori methenamine silver (GMS). As fungal infections often require either topical or systemic antifungal treatment, it is important to carefully examine tissue specimens, especially in immunocompromised patients who may be unaware of the infection. Structures remarkably similar in morphology to fungal hyphae or yeasts have been reported on in the literature, referred to as yellow-brown or Hamazaki-Wesenberg bodies¹ and pseudofungi.^{2,3} We encountered a similar case recently at our institution and herein describe the morphological features of these structures, which may help to distinguish them from true fungal organisms.

CASE REPORT

A 31-year-old woman presented at our institution after 2 months of dyspnea. She had been previously healthy without any remarkable medico-surgical illnesses until 4 years ago,

when a 1.5 cm-sized solitary nodule was incidentally discovered in the left upper lobe of her lung on routine health examination. The patient subsequently received medication under a provisional diagnosis of tuberculosis. She was lost to follow-up thereafter, and appeared at our hospital this time complaining of dyspnea. Computed tomography revealed a pleura-based 13 cm-sized mass in the left upper lobe with heterogeneous enhancement, and obstructive pneumonia in the left lower lobe, with multiple enlarged lymph nodes at the left hilar area and left supraclavicular fossa. A left pneumonectomy with mediastinal lymph node dissection was performed.

The pneumonectomy specimen showed severe adhesion on the pleural surface, and cut section of the lung revealed a huge cavitory mass filled with hemorrhage, measuring 12 × 7 × 4 cm, and occupying almost the entire left upper lobe. Multiple enlarged lymph nodes were noted on the hilar surface, measuring up to 2 × 1.7 cm in maximum size. Histological examination revealed the pulmonary lesion to be a biphasic pulmonary blastoma associated with massive tumor necrosis and hemorrhage.

The dissected lymph nodes did not show any evidence of

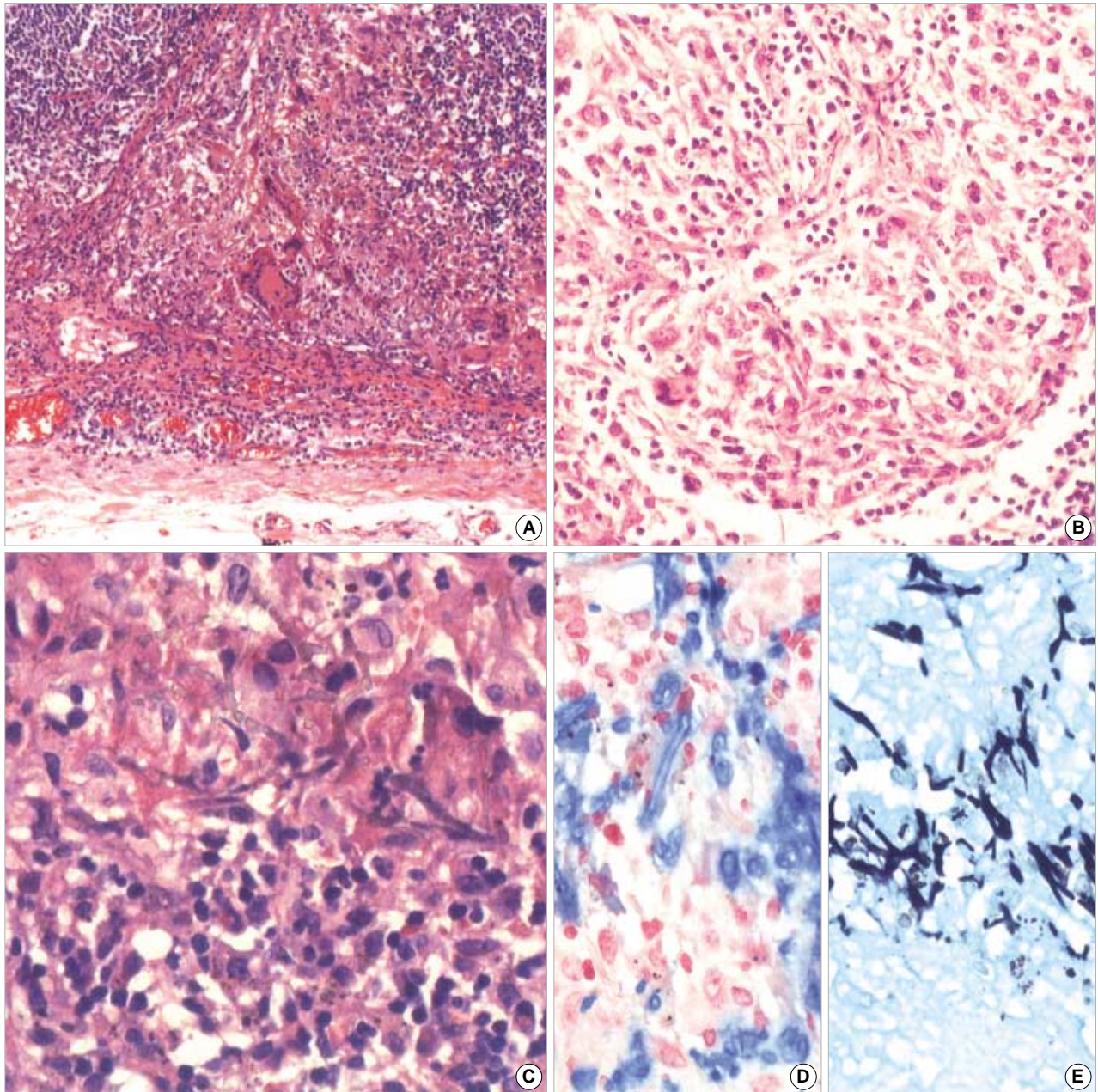


Fig. 1. (A, B) Microscopic examination of the mediastinal lymph nodes reveals ill-defined granulomas in the subcapsular sinuses with scattered multinucleated giant cells. (C) Yellowish-brown branched structures resembling fungal hyphae with intermingled round yeast-like structures are noted within the granulomas. The pseudofungi show positive staining with Prussian blue (D) and Gomori methenamine silver (E).

tumor metastasis. However, on careful inspection, ill-defined granulomas were noted in the subcapsular sinuses of several lymph nodes (Fig. 1A, B). A few multinucleated foreign-body type giant cells were scattered amongst the granulomas. Examination at high-power magnification revealed multiple slender slightly refractile structures ranging from 30-50 μm in length and about 4 μm in thickness with a yellowish-brown hue, remarkably similar to fungal hyphae (Fig. 1C). They were

found within the subcapsular sinus, some within the granulomas, and some being engulfed by the multinucleated giant cells. Septa-like structures were irregularly placed within the hyphae. They showed variable branching at 45 to 90 degree angles. Occasional round yellowish-brown yeast-like structures were dispersed within the granulomas, measuring 3-4 μm in diameter. These structures were strongly positive on PAS, GMS, and Prussian blue stains (Fig. 1D, E), stained blue on

Masson's trichrome stain, but were negative on Fontana-Masson stain. The remaining areas of the lymph nodes did not show any remarkable findings apart from the flecks of black dust irregularly dispersed within the nodal parenchyma and the sinuses.

DISCUSSION

There are three reports so far in the literature, mentioning structures morphologically resembling true fungi,¹⁻³ and these structures have been classified into two groups on the basis of their morphological features.² The first group comprises those displaying features similar to those of yeast, including Hamazaki-Wesenberg bodies and myospherules, and the other group demonstrates structures resembling fungal hyphae and include Gamna-Gandy bodies, small branching blood vessels, and pseudofungi as encountered in the present case. It is essential not to misinterpret these structures as true fungi as it may call for unnecessary and potentially toxic antifungal treatment. The pseudofungi seen in our case could be differentiated from true fungi, especially species such as *Aspergillus* and *Fusarium*, by the characteristic morphological findings and special stain results. Typically, *Aspergillus* and *Fusarium* species are septated, have acute branching angles, and are often colorless on routinely processed tissue sections, whereas pseudofungi are yellowish-to-golden brown in color and have diverse branching angles. Although these pseudofungi may appear to demonstrate 'septa', these may represent fractures created by the microtome blade during tissue sections. As for the location, pseudofungi have been found to be limited to the subcapsular sinus of lymph nodes with a perpendicular arrangement in relation to the lymph node capsule,^{2,3} whereas true fungal hyphae are arranged haphazardly and can exist either inside or outside the capsule. Moreover, special stains reveal that pseudofungi, including those of our case, show positive staining for iron, a finding that is unexpected in true fungi.

Aside from true fungi, pseudofungi may also be similar in structure to Gamna-Gandy bodies. Gamna-Gandy bodies are often seen in the congested spleen, representing calcium and iron encrusted in areas of fibrosis, and are elongated hypha-like structures occasionally branching at acute angles. Sometimes, the basement membranes of small branching blood vessels may be accentuated by PAS and GMS stains and therefore closely resemble pseudofungi or even true fungi. However, the presence of red blood cells in the lumina serves to distinguish these

blood vessels from the latter.

The pseudofungi in our case were intermingled with occasional round yellowish-brown structures resembling yeasts, which may indeed mislead the pathologist into believing that they are true fungal organisms before an iron stain is performed. As previously mentioned, Hamazaki-Wesenberg (yellow-brown) bodies and myospherules are known to mimic yeasts in tissue sections. However, myospherules are negative on PAS stain⁴ and Hamazaki-Wesenberg bodies have been reported to be negative on iron stain and are thought to be lipofuscin pigments.¹

The exact nature of these pseudofungi remains obscure. An energy-dispersive x-ray elemental analysis study of pseudofungi demonstrated that these structures were composed of iron, calcium and phosphorus.² An interesting point that deserves mention in this case is the positive staining with GMS, conflicting with the findings of previous case reports. Although GMS is a helpful staining procedure in the identification of fungal organisms, it is known to rarely stain fibrin.⁵ Fibrin is easily identified in damaged tissues, and is thought to originate from the extravascular conversion of plasma fibrinogen, triggered by the transudation of fluid and plasma proteins. It is interesting to postulate that degraded hemoglobin from extravasated red blood cells may subsequently become deposited on the fibrin material, possibly accounting for the yellowish-brown hue of the structures and the positive staining on Prussian blue. This partly agrees with the previous suggestions that pseudofungi may originate from collagen fibers heavily encrusted from iron, probably related to extravasation of blood due to previous surgery or trauma.³ Although the patient in our case had no history of previous surgery or trauma, the pulmonary blastoma in her left upper lobe demonstrated massive hemorrhage, which may account for the extravasation of red blood cells and subsequent drainage to the regional lymph nodes. Moreover, it is interesting to note that the pseudofungi in the present case appeared blue on Masson's trichrome stain, similar to collagen fibers and old fibrin.

In addition, the anthracotic pigmentation around the pseudofungi in this patient suggests another possibility that these structures may be related to the black dusts scattered within the lymph nodes, similar to the formation of ferruginous bodies, further eliciting a granulomatous response. It is noteworthy that a granulomatous response with multinucleated giant cells around the pseudofungi as seen in our case has not been described in the literature although the case of Connelly *et al.* showed that some pseudofungi were engulfed by multinucle-

ated histiocytes without evidence of acute inflammation or granulomas.² Taken together with the fact that pseudofungi may stain positive for GMS, we suggest that the presence of granulomas in association with such structures and their positivity for GMS should not directly mislead one into drawing the conclusion of a true fungal infection.

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