Autopsy and Case Reports
E-ISSN: 2236-1960
autopsy.hu@gmail.com
Hospital Universitário da Universidade de São Paulo
Brasil

Depiere Lanzarin, Luciana; Barbosa Mariano, Livia Caroline; Martins de Almeida Macedo, Maria Cristina; Vieira Batista, Marjorie; Nunes Duarte Neto, Amaro

Conidial heads (Fruiting Bodies) as a hallmark for histopathological diagnosis of angioinvasive aspergillosis

Autopsy and Case Reports, vol. 5, núm. 4, octubre-diciembre, 2015, pp. 9-18
Hospital Universitário da Universidade de São Paulo
São Paulo, Brasil

Autopsy Case Reports

Article / Autopsy Case Report
Artigo / Relato de Caso de Autópsia

Conidial heads (Fruiting Bodies) as a hallmark for histopathological diagnosis of angioinvasive aspergillosis

Luciana Depiere Lanzarin[a], Livia Caroline Barbosa Mariano[b], Maria Cristina Martins de Almeida Macedo[b], Marjorie Vieira Batista[c,b], Amaro Nunes Duarte Neto[a,d]

Lanzarin LD, Mariano LCB, Macedo MCMA, Batista MV, Duarte AN No. Conidial heads (Fruiting Bodies) as a hallmark for histopathological diagnosis of angioinvasive aspergillosis. Autopsy Case Rep [Internet]. 2015;5(4):9-18. http://dx.doi.org/10.4322/acr.2015.025

ABSTRACT

Aspergillosis is a mycosis that afflicts immunocompetent and immunocompromised hosts; among the former it exhibits different clinical pictures, and among the latter the infection renders an invasive form of the disease. The histologic diagnosis of invasive aspergillosis is somewhat challenging mostly because of some morphological similarities between other fungi. However, when present, the conidial heads are pathognomonic of aspergillosis. The authors present the case of a 68-year-old woman who was submitted to autologous hematopoietic stem cell transplantation in the pursuit of multiple myeloma treatment. The post-transplantation period was troublesome with the development of severe neutropenia, human respiratory syncytial virus pneumonia, and disseminated aspergillosis, which was suspected because of a positive serum galactomannan antigen determination, and resulted in a fatal outcome. The autopsy findings showed diffuse alveolar damage associated with angioinvasive pulmonary aspergillosis with numerous hyphae and conidial heads in the lung parenchyma histology. The authors call attention to the aid of autopsy in confirming the diagnosis of this deep mycosis, since only the research of the galactomannan antigen may be insufficient and uncertain due to its specificity and of the possibility of false-positive results.

Keywords
Aspergillus; Neutropenia, Hematopoietic Stem Cell Transplantation; Autopsy

CASE REPORT

A 68-year-old female patient with the diagnosis of multiple myeloma with immunoglobulin G lambda pattern secretion (Durie-Salmon stage IIIA) and hypertension, was admitted for hematopoietic stem cell transplantation (HSCT) after six cycles of chemotherapy (cyclophosphamide, thalidomide, and dexamethasone) and sacroiliac region radiotherapy (20 Gy). A melphalan-conditioning regimen was prescribed (200 mg/m^2) and a 3.13 × 10^6/kg total dose of TCD34+ cells was infused intravenously.

[a] Pathology Department - Faculty of Medicine - University of São Paulo, São Paulo/SP – Brazil.
[b] Hematopoietic Stem Cell Transplantation Division - Hospital das Clínicas - Faculty of Medicine - University of São Paulo, São Paulo/SP – Brazil.
[c] Infectious and Parasitic Diseases Department - Hospital das Clínicas - Faculty of Medicine - University of São Paulo, São Paulo/SP – Brazil.
[d] Emergency Department - Hospital das Clínicas - Faculty of Medicine - University of São Paulo, São Paulo/SP – Brazil.

On the second day post-HSCT, she presented post-nasal discharge, cough, mild tachypnea, wheezing and rales without respiratory function impairment. The microbiological investigation was carried out and human respiratory syncytial virus (HRSV) was identified by real time polymerase chain reaction (RT-PCR) on respiratory samples. A chest high-resolution computed tomography (HRCT) was performed showing centrilobular opacities diffusely distributed in the lungs, predominantly in the inferior lobes with a consolidation on the right inferior lobe. Based on these results, HRSV pneumonia was diagnosed and the patient received oral ribavirin and intravenous immunoglobulin.

On the fifth day, the patient presented febrile neutropenia accompanied by mild hypoxemia and delirium. Although the cultures were negative, empiric broad-spectrum antibiotic therapy was prescribed followed by clinical improvement. By the thirteenth day post-HSCT, neutropenia persisted and the patient started presenting fever and respiratory failure, which required mechanical ventilatory support. Liposomal amphotericin B was added empirically to the antimicrobial regimen. A new chest and paranasal sinuses HRCT were performed showing confluence and enhancement of the centrilobular opacities, affecting inferior, posterior, and superior areas of both lungs. The microbiological work-up was positive for the presence of serum galactomannan antigen, which indicated the addition of voriconazole to the prescription. Despite every effort, the clinical outcome was unfavorable and renal dysfunction and circulatory shock ensued. The patient died 29 days after hospitalization. An autopsy was requested, with the agreement of the relatives, to enlighten the nature of the pulmonary lesions.

AUTOPSY FINDINGS

The corpse weighed 65.0 kg and measured 1.58 m. The ectoscopy was unremarkable. At the opening of the cavities, no effusions were drained. The heart weighed 340.0 g (mean reference value [mRV] = 270 g); there was a thrombus in the right atrium; and the right ventricle was dilated especially in the pulmonary artery cone region. At microscopy, interstitial edema and myocardiocyte hypertrophy were found.

The right lung weighed 814.0 g (mRV = 450 g) and the left weighed 880.0 g (mRV = 375 g). They were markedly congested in the posterior areas. The pleural surfaces exhibited bilateral scattered "target lesions", which were characterized by a whitish central area surrounded by hemorrhage; they measured up to 1.5 cm in diameter in the right lung and 3.0 cm in the left. The cut surface of the lungs showed marked congestion of the central and upper pulmonary parenchyma, which drained foamy pinkish liquid when compressed. The parenchyma was firm, hepatized, and purplish on the basal and posterior regions, with thrombotic vessels surrounded by hemorrhagic infarct (in a wedge-shape), corresponding to those "target" lesions observed on the pulmonary surface. Yellowish mucous secretion was present in the airways. At microscopy, the lung parenchyma had diffuse alveolar damage, with edema, hemorrhages, and hyaline membranes associated with multiple focal areas of thrombosis with hemorrhagic necrosis corresponding to the "target lesions" observed on gross examination (Figure 1).

The vascular thrombi were composed by fibrin and hyaline hyphae invading the vessel wall (with vascular necrosis) and extending to the adjacent parenchyma, producing necrosis of the alveolar septa (Figure 2).

The visceral pleura was also involved by the infection (Figure 3A). Of note, the inflammatory reaction was minimal or absent in most of the represented tissue. Some medium- and large-sized vessels showed hyphae and numerous conidial heads compatible with *Aspergillus* spp. within their lumens (Figure 3B and 3C).

Grocott's methenamine silver stain showed morphological details of the hyphae, namely: parallels walls, regular septa, and acute angled and dichotomous branches (Figure 4).

The trachea mucosa was covered by thick mucus. A darkened/purplish elastic plug filled up to 90% of the lumen of the left main bronchus extending to its distal branches. At microscopy, the mucosa had squamous metaplasia and the left bronchi plug was composed of fibrin, mucus, and hemorrhage with amphophilic, bluish, and round *Aspergillus* conidia (Figure 5D and Figure 3D).

The liver weighed 1746 g (mRV = 1530 g) and the parenchyma seemed congested, showing a "nutmeg"

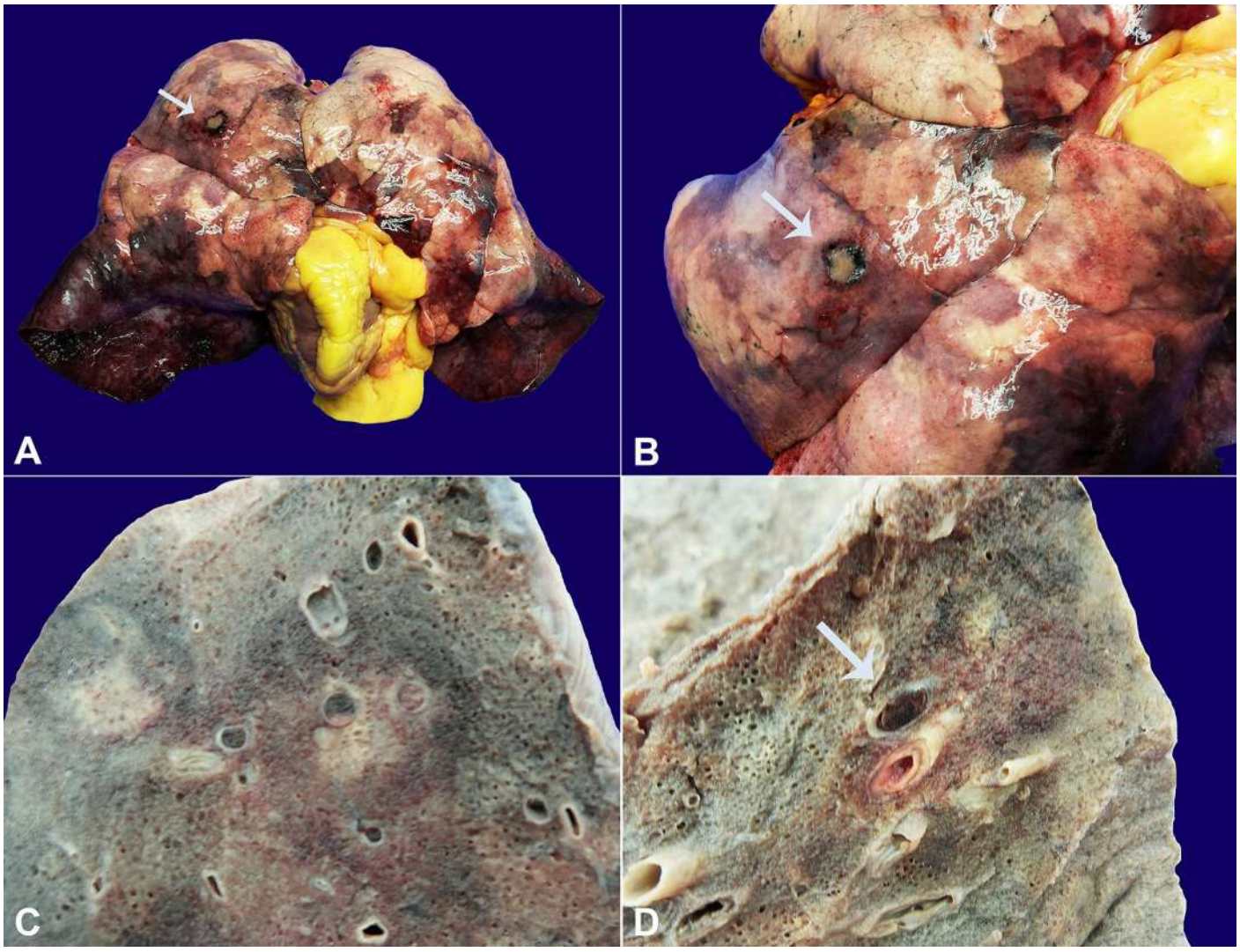

Figure 1. Gross view of the lungs. **A** - Anterior view of the thoracic organs showing marked congestion in the basal regions and "target lesions" (arrow) and petechial hemorrhages in the upper lobes; **B** - The "target lesion" in detail (arrow) in the right upper lobe: a pale and necrotic center surrounded by hemorrhage and petechiae; **C** and **D** - Arterial thrombi in the center of the ischemic and hemorrhagic area. Lung hepatization is observed.

pattern. At microscopy, sinusoidal congestion, loss of hepatocytes trabeculation and apoptotic bodies – especially in the centrilobular region ("shock liver" or ischemic hepatitis) – was evident.

The right kidney weighed 144 g and the left kidney 194 g (mRV of both = 295 g). Both organs exhibited a brownish, finely granular surface, with some cysts measuring up to 0.3 cm in diameter, after the removal of the capsule. The corticomedullary limit was well-defined, with slightly softened and pale cortex, and congested medullary. At microscopy, the kidneys showed interstitial edema, acute tubular necrosis, and some hyalinized glomeruli.

The spleen was friable and weighed 138 g (mRV = 112 g). Microscopically, the red pulp was markedly congested and the white pulp was depleted. The lymph nodes exhibited lymphoid depletion. The bone marrow showed marked hypoplasia of all hematopoietic series with less than 10% of cellularity represented by scattered or grouped foamy macrophages, hemosiderin-containing macrophages, and few plasma cells.

The uterus had a piriform shape, with a calcified intramyometrial nodule that measured 1.5 × 1.5 cm, which was localized in the right portion of the uterus. At microscopy, the nodule corresponded to a leiomyoma with hyaline degeneration and calcification. At microscopy, the pituitary gland had a microadenoma, which measured 0.5 cm in diameter. The remaining organs did not show significant alterations.

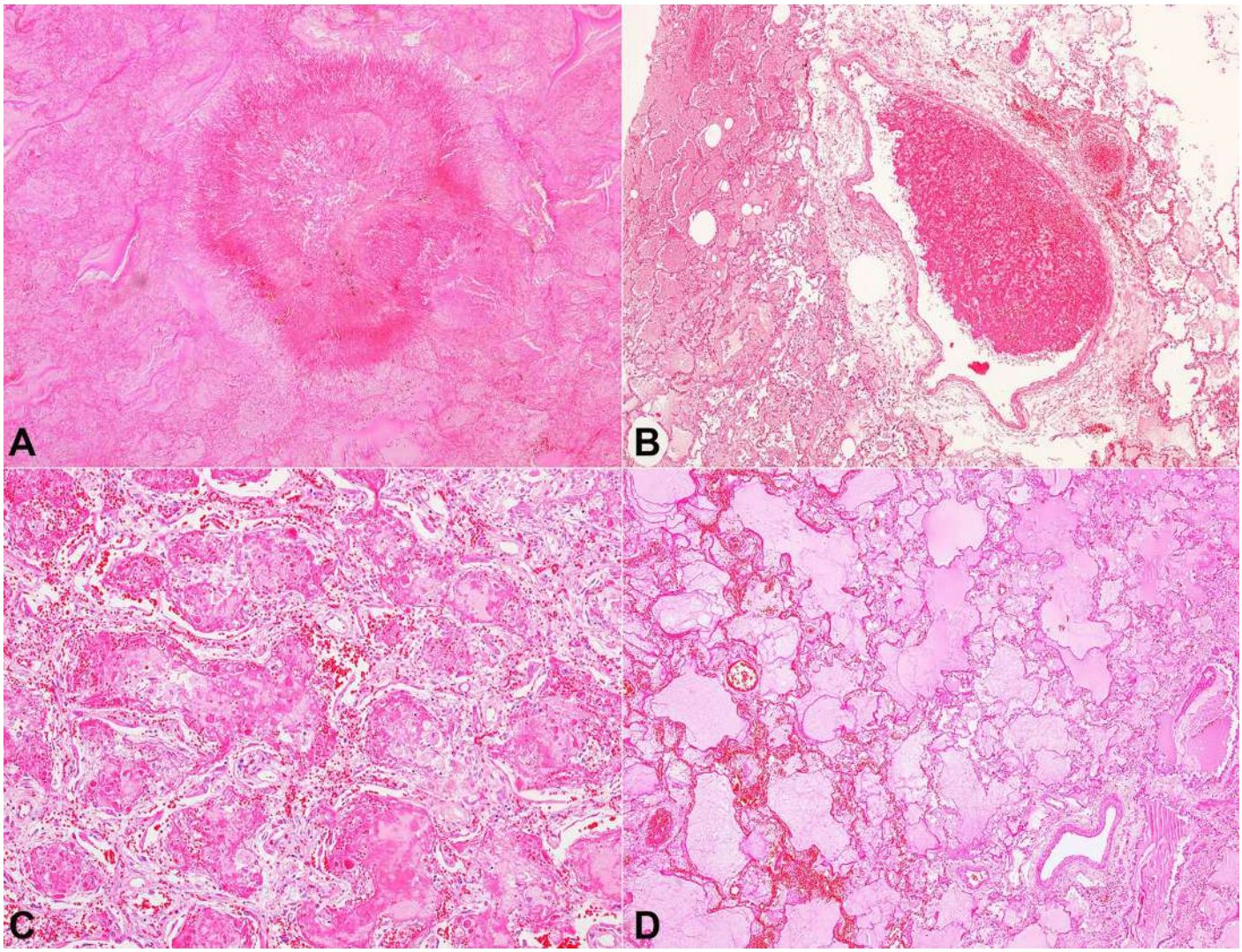

Figure 2. Photomicrography of the lungs. **A** - Angioinvasion of a pulmonary artery due to hyaline hyphae (starburst pattern), surrounded by alveolar edema and septal necrosis (H&E, 40X); **B** - Vascular thrombus with hyaline hyphae (H&E, 40X); **C** - Areas of organizing diffuse alveolar damage (H&E, 100X); **D** - Areas of septal congestion, necrosis, and alveolar edema (H&E, 40X).

DISCUSSION

Aspergillus is a hyalohyphomycete from the Eurotiales order, first identified by the Italian biologist Pier Antonio Micheli in 1729, who named the fungus because of its similarity with the *aspergillum*, a liturgical object used to sprinkle holy water.[1,2] *Aspergillus* spp. are ubiquitous in nature, are distributed worldwide, and are found in soil, plants, decaying matter, air, and water systems. It is a common respiratory fungal agent that causes a wide range of clinical syndromes. The most common pathway of infection is the inhalation of infective conidia.[3]

In the immunocompetent host, *Aspergillus* colonizes or causes superficial infection in the nasal cavity, sinuses, and bronchi, producing allergic reactions, such as sinusitis and allergic bronchopulmonary aspergillosis. *Aspergillus* is also a common cause of fungus ball in cavitary lung lesions or in paranasal sinuses. Chronic pulmonary aspergillosis occurs in patients with pulmonary cavities due to tuberculosis, sarcoidosis, bronchiectasis, and others. Cutaneous wounds (trauma, surgical, burns, etc.) can be infected by *Aspergillus* spp.[3] Similar to prolonged neutropenia or impaired T-cell function, in the immunocompromised host, *Aspergillus* is the major agent of invasive infection, such as pulmonary aspergillosis, necrotizing sinusitis, soft tissue infections, and others. The infection can spread systemically from the respiratory tract to other organs, causing necrotizing lesions and abscesses.[4] Clinical features of these cases are characterized by fever, cough, pleuritic chest pain (due to lung

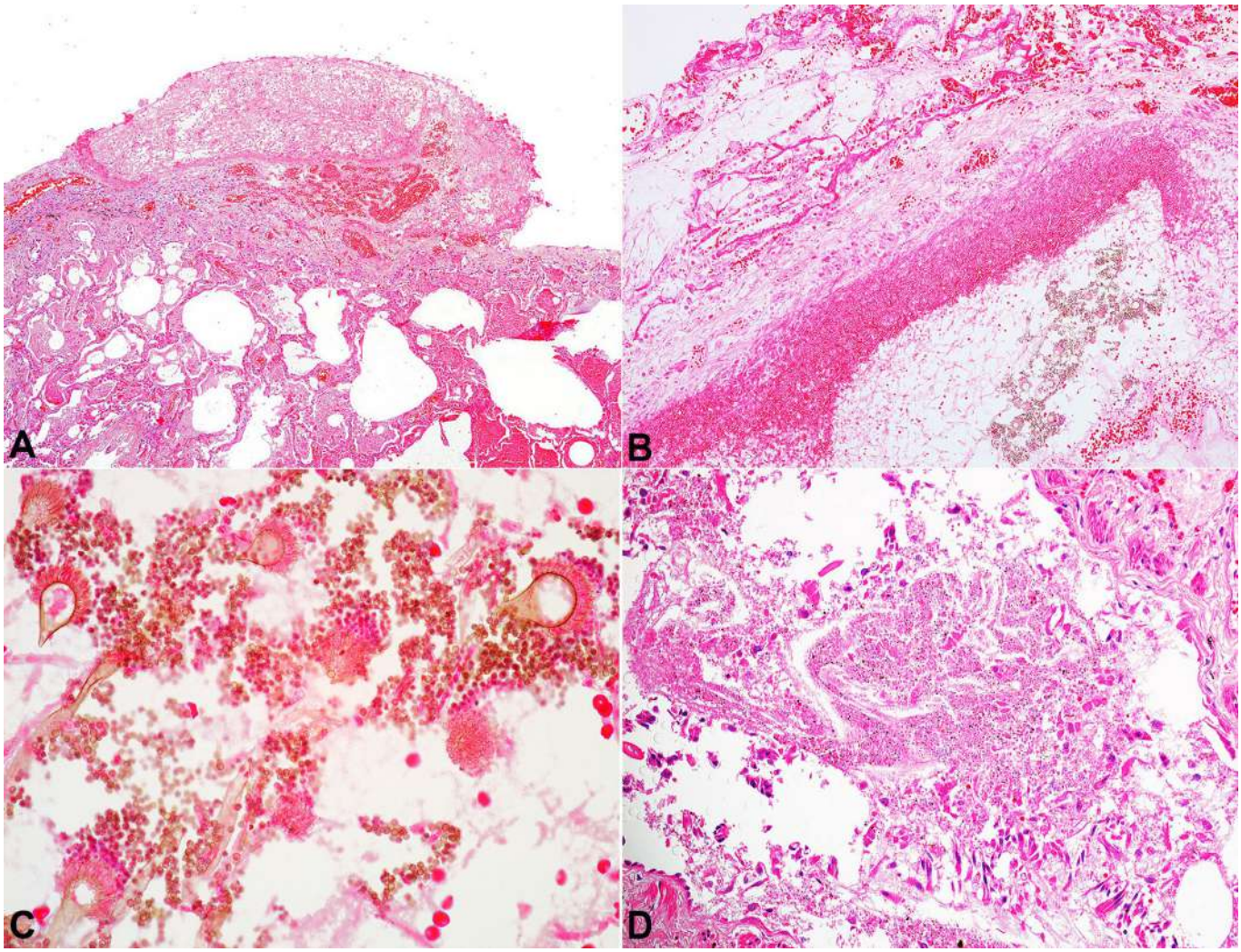

Figure 3. Photomicrography of the lungs. **A** - Pleural surface exhibiting fibrinous exudate associated with hyaline hyphae (H&E, 40X); **B** - Angioinvasion of a large pulmonary artery by hyaline hyphae with numerous conidial heads within the vessel lumen (arrow), surrounded by septal necrosis, congestion, and edema (H&E, 100X); **C** - Conidial heads within a vessel, with a hyaline aspect, discreetly ocher; **D** - A bronchus exhibiting slaughtered epithelium and conidia within the lumen mixed with mucus.

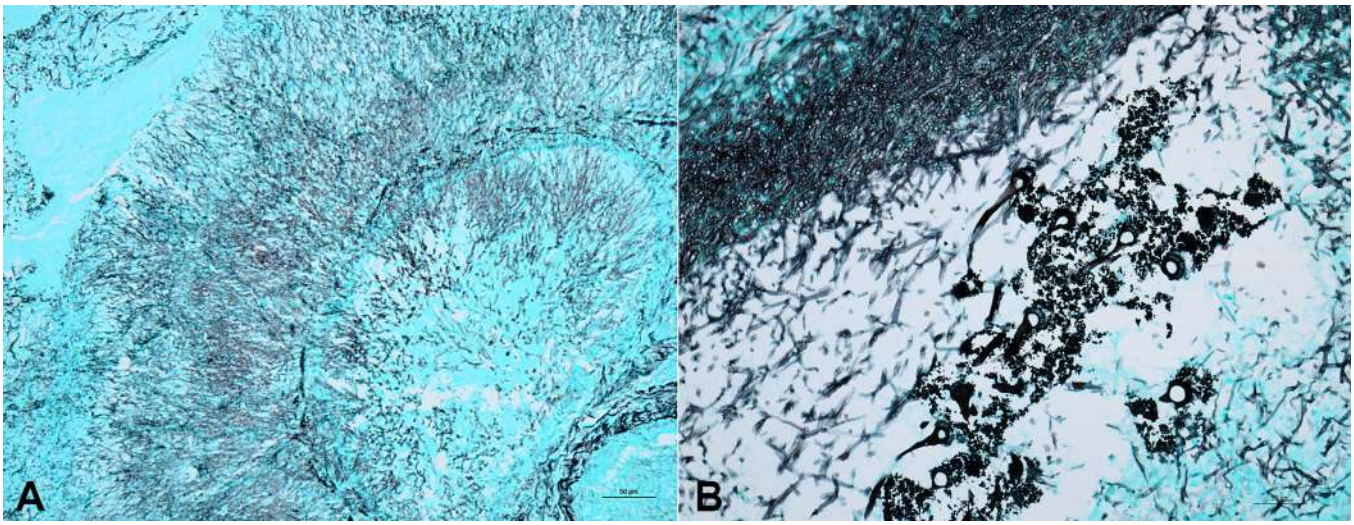

Figure 4. Photomicrography of the lung: Grocott's methenamine silver stain revealing details of the angioinvasive pulmonary aspergillosis. **A -** Hyphae invading the arterial wall into the adjacent parenchyma (100X); **B** - Conidial heads within the arterial lumen and hyphae trespassing the arterial wall (200X).

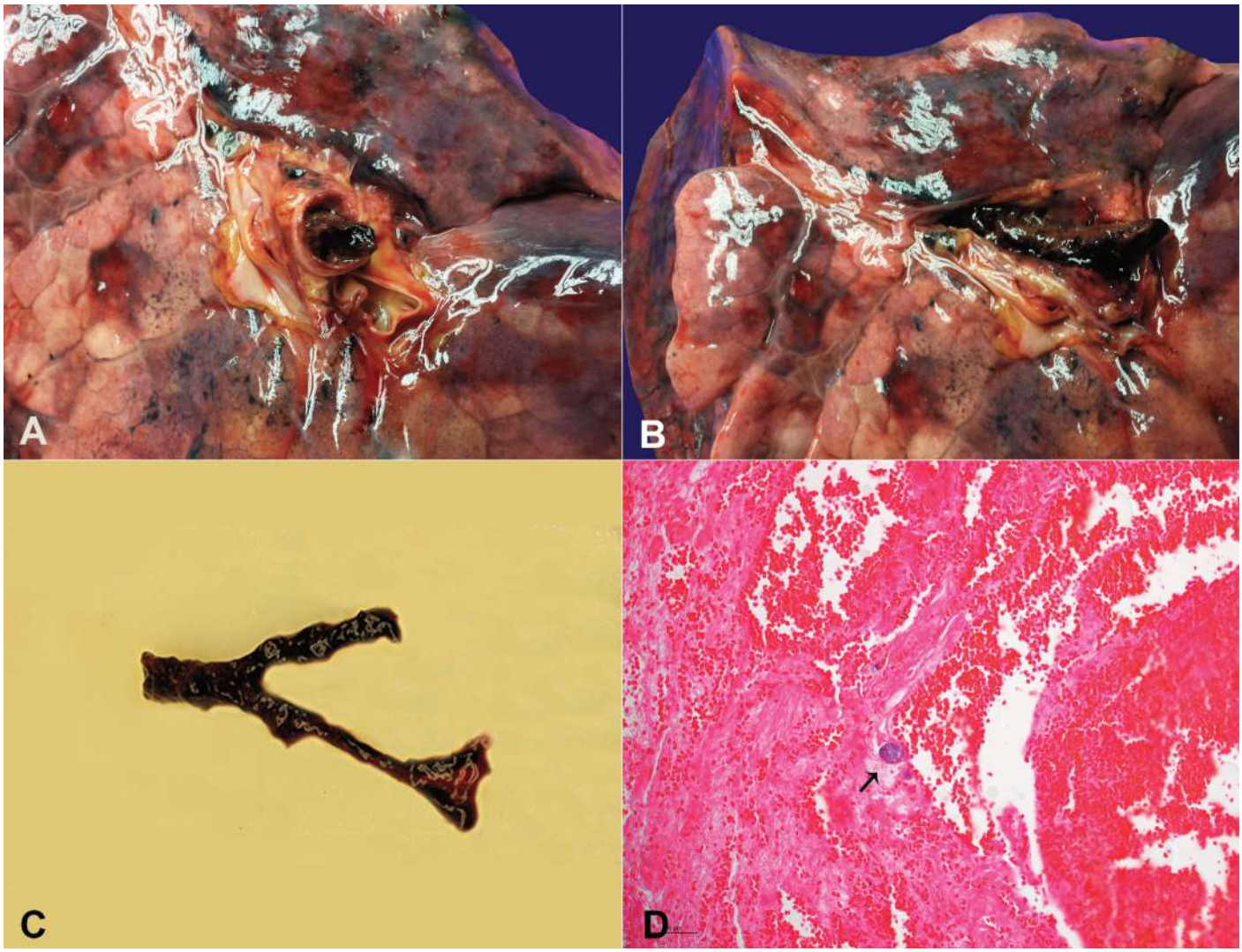

Figure 5. Gross view of the mediastinal surface of the left lung. **A -** Hemorrhagic and elastic plug filling the left bronchial lumen; **B -** Plug extension to the proximal branches; **C -** Detail of the bronchial plug after removal; **D –** Photomicrography of the plug, which was composed of fibrin, hemorrhage, and a group of bluish *Aspergillus* conidia, reflecting the transmission of the agent through inhalation (H&E, 400X).

infarction), pulmonary rales, necrotic lesions in the nasal cavity (darkened mucosa and skin), pulmonary infiltrates at chest roentgenograms, and computed tomography.[4,5] The population under greater risk are patients with hematological malignancy, post-HSCT, solid organ transplantation, an advanced stage of AIDS, granulomatous disease, extensive burns, premature newborns, and others. Mortality rates are over 70%.[3,4]

The definitive diagnosis of invasive aspergillosis is made with the histological demonstration of invasive hyphae accompanied by tissue-positive culture, which is generally obtained through a biopsy or fine-needle aspiration, while the probable and possible diagnosis (in immunocompromised patients) is defined on clinical grounds, imaging and serology compatible with the infection, but do not require a positive cultures.[5] Cultures have a low diagnostic yield in invasive aspergillosis, since its positivity is up to 50% in bronchoalveolar lavage (BAL) and 5% in blood cultures. The galactomannan antigen (1, 3-β, D-Glucan) has high sensitivity (82%) and specificity (86%) in post-HSCT patients, which is measured by an enzyme immunoassay commercial test in serum or BAL fluid (Platelia Aspergillus test, Bio-Rad, Hercules, CA, USA). However, false-positive results may occur with the concomitance of antibiotics administration (piperacillin, ticarcillin, and amoxicillin), plasmalyte (*A. niger* fermented product), and other fungal infections (*Paecilomyces*, *Penicillium*, *Alternaria*, and *Histoplasma*).[6] Imaging may suggest the diagnosis when at HRCT a halo sign (a nodule surrounded by ground glass opacities, corresponding to angioinvasion)

and a crescent sign (a nodule with air, corresponding to ischemic necrosis) are present.[3,7]

Aspergillus colonies in culture media may show a varied appearance (different colors), depending on the species. The microscopic exam is mandatory to identify the mycelial structure and the conidiophore with conidial head (fruiting bodies). The conidial head is composed of a vesicle, which is crowned by one or two layers of phialides (or sterigmata), ending in chains of conidias at the extremity. The conidias are propagules – the infective forms of *Aspergillus* – which are present in the environment and, under suitable conditions, develop the mycelial structures (hyphae). The morphology of the conidial head can be auxiliary in distinguishing the species of *Aspergillus*. *A. fumigatus* has one-third of the vesicle topped by one layer of phialides. *A. terreus* has two-thirds of the small vesicle covered by two layers of phialides and has aleurioconidia along the hyphae. *A. flavus* and *A. niger* have vesicles completely capped by one layer of phialides. In addition, *A. niger* has a colored ocher conidial head at microscopy and produces black colonies on culture media.[3]

In histopathologic sections, *Aspergillus* is the prototype of the hyalohyphomycetes fungus.[7] The *Aspergillus* hyphae measures 3-6 µm in width, has parallel walls, regular septations, and dichotomous branching at 45 degrees. At low magnification microscopy, the hyphae are an ensemble, going through the tissue in the same direction resembling a shoal of fish. Angioinvasion is typical of invasive infections, causing vascular necrosis and thrombosis with consequent hemorrhagic ischemic tissue necrosis. The hyphae can be seen within the vessel lumens as a thrombi, trespassing their walls, and invading the adjacent parenchyma. The angioinvasion caused by *Aspergillus* sp. produces the "target" lesions observed on the gross examination of the affected organs. With the H&E stain, *Aspergillus* spp. structures have amphophilic, bluish, pinky hyaline aspects. However, Periodic acid-Schiff and silver stains (Gomori's methenamine silver and Gridley's fungus) will precisely detail the fungus. Although rare, the presence of the conidial heads, commonly found in areas with high oxygen tension, such as cavitary lesions (paranasal sinuses, bronchi, lungs) or in lesions with a high fungal burden, is pathognomonic of the diagnosis of aspergillosis.[7,8] In the medical literature, the description of the histological finding of conidial heads is scant. Searching the keywords Aspergillus, conidial heads, and fruiting bodies at PubMed during the period 1920-2015, we found only seven cases reported where hyphae and conidial heads were found in histological specimens. Panke et al.[9] described the case of a young man with an extensive wound burn infected by multiple fungi, including *Aspergillus* spp. with hyphae and conidial heads. Falsey et al.[10] reported a fatal case of refractory invasive *Aspergillus fumigatus* skin infection in a woman with diabetes, who acquired a perineal and abdominal necrotizing fasciitis. The samples collected from surgical debridement had hyphae and conidial heads in the subcutaneous and muscular tissues. Shinohara et al.[11] reported the case of a man who had *Aspergillus* infection in a post-surgical periorbital wound, after basal cell carcinoma excision. The histopathologic study showed necrosis, pigmented hyphae, and conidial heads with the isolation of *Aspergillus niger* in the tissue cultures. Khurana et al.[12] reported a case of a man with ocular, periorbital, and paranasal cellulitis caused by *Aspergillus flavus*, identified in tissue cultures and histopathology, with hyphae and conidial heads. Anila et al.[8] described a biopsied lung with small-cell carcinoma, associated with *Aspergillus* infection with conidial heads and extensive necrosis. Chandra et al.[13] and Hoda et al.[14] described pap cervical smears from two healthy women, which were contaminated with *Aspergillus* spp., exhibiting hyphae and conidial heads.

When the conidial heads are not present and the other diagnostic methods, such as culture and galactomannan antigen detection, are negative or unavailable, pitfalls can happen in the diagnosis of aspergillosis, based only on the histopathology. Firstly, *Fusarium* spp., *Scedosporium* spp., *Trichophyton* spp., *Pseudallescheria* spp., *Paecilomyces* spp., and *Trichoderma* spp. can mimic *Aspergillus*. Zygomycetes, especially *Mucorales* genera can occasionally resemble *Aspergillus*. Secondly, Aspergillus can exhibit degenerated hyphae with varicosity, dilatation and constrictions in necrotic areas, with atypical morphology, resembling other hyalohyphomycetes, which challenges the diagnosis. The rate of discordance among pathologists can reach 20% when the morphological diagnosis, concerning the acute angled branching and septate hyphae are seen in tissue sectioning.[15] Thirdly, dual fungal infection is also

possible in an immunocompromised host, making the precise histopathologic diagnosis a tough task. Table 1 shows the morphological aspects of the most common filamentous microorganisms found in tissue samples. Although of limited availability, current molecular techniques can be useful in aiding the pathologic diagnosis, such as a PCR (fresh or paraffin embedded tissues) and in situ hybridization.[16] The specific and definitive diagnosis must be pursued, as the sensitivity of different genera of hyalohyphomycetes to antifungals (amphotericin, imidazole, and chandin) is quite variable.[7] Moreover, the antifungal drugs have several side-effects; however, unnecessary reactions can be prevented in a critically ill patient when the correct diagnosis is performed.[3,7]

Autopsy researchers have shown aspergillosis as the main cause of death in different immunocompromised populations. Boon et al.[17] identified 32 cases of invasive aspergillosis among 2,315 autopsies (1.4%) performed in a general hospital in Birmingham (UK), between 1980 and 1989. Most cases were associated with hematological malignancies (50%) or post-liver transplantation (37%), with dissemination beyond the lungs in 20 cases (most commonly to the brain) and 8 cases (25%) with a proven-culture diagnosis. In a university hospital in the city of Milan, Italy,

Table 1. Filamentous microorganisms and morphologic diagnostic aspects in tissues

Agents	Histopathology	Tissue response
Candida* spp.	3-6 µmD. Yeast Pseudo-hyphae with constrictions True septate hyphae in invasive infections Angio and tissue invasion	Acute neutrophilic inflammatory response. Absence in neutropenic necrosis
Phaeohyphomycetes	2-6 µmW. Pigmented hyphae (ocher to brown) at H&E; frequent and irregular septations with constrictions; branched randomly or unbranched; conidial-like structures (dilated hyphae) Fontana-Masson stain is helpful	Mixed inflammatory response (suppurative center surrounded by granuloma with giant cells)
Aspergillus	3-6 µmW. Hyphae with thin and parallels walls, uniform aspect, regular septations, dichotomous branching (45°). Conidial heads in aerated lesions (cavities) or rarely, in tissue with high burden. Varicose hyphae in necrotic areas. Angio and tissue invasion.	Acute neutrophilic inflammatory response. Absence of inflammatory response in neutropenic patient. Ischemic and suppurative necrosis. Granulomatous response in case of recovering neutropenia
***Geotrichum* spp.**	3-6 µmW. Septated hyphae with few branches. Round yeast-like cells; arthroconidia 4-10 µmW with round or squared ends. Angio and tissue invasion	Minimal inflammatory reaction to acute neutrophilic inflammatory response. Necrosis
***Fusarium* spp.**	3-8 µmW. Septated hyphae, parallel walls, uniform aspect, branching at 45° or 90°. Angio and tissue invasion	Acute neutrophilic inflammatory response. Absence of inflammatory response in neutropenic patient. Ischemic and suppurative necrosis. Granulomatous response in case of recovering neutropenia
Zygomycetes	3-30µmW. Irregular, broad, varicose, ribbon-like hyphae. Rare septations with constrictions. Walls are not parallel. Random branching (45° or 90°). Angio and tissue invasion	Acute neutrophilic inflammatory response. Absence of inflammatory response in neutropenic patient. Ischemic and suppurative necrosis. Granulomatous response in case of recovering neutropenia
Nocardia* spp.*	≤1 µmD. Filamentous and delicate bacteria, septations, branching at 45°, scattered in the lesions. Gram-positive (beaded appearance), acid-fast-positive (modified stain)	Acute neutrophilic inflammatory response. Abscesses. Necrosis
Actinomyces* spp.*	≤1 µmD. Filamentous and delicate bacteria, septations, branching at 45°, organized in granules (30-3000 µmD). Gram-positive, Grocott-positive	Acute neutrophilic inflammatory response. Splendori-Hoeppli phenomenon. Abscesses, sinus tracts. Fibrosis surrounding granules

**Candida* spp.: excluding *C. glabrata*, which does not produce pseudo-hyphae or hyphae. ***Nocardia* and *Actynomyces* are bacterial agents. µmD = µm in diameter; µmW = µm in width.

Antinori et al.[18] found 297 invasive fungal infections (IFI) among 1,630 autopsied cases of AIDS between 1984 and 2002. Aspergillosis was the second most common IFI (83 cases [27.9%]), after pneumocystosis, and was followed by cryptococcosis, candidiasis, histoplasmosis, and zygomycosis. Of note, the authors found a steady occurrence of aspergillosis during the study period, showing the disease confined to the lung in 61 cases (73%); disseminated in 19 cases (23%) affecting lungs, central nervous system, kidneys, and heart; a low rate of ante-mortem diagnosis (only 10 out of 83 cases [12%]). *Aspergillus* infection contributed directly to death in 18 cases (21.7%), which had a high rate of misdiagnosis during life (16 cases [89%]).[18] Lewis et al.[19] reported *Aspergillus* infection as the most common hyphal agent of IFI in 196 out of 234 (83%) autopsies performed in a large US hospital (Houston/Texas) that specialized in the treatment of hematological malignancies

CONCLUSION

We reported the case of a woman submitted to an unsuccessful HSCT, who developed HRSV pneumonia and pulmonary angioinvasive aspergillosis with diffuse alveolar damage, and a fatal outcome. The autopsy was performed and showed the rare and definitive histopathological feature of aspergillosis – the conidial heads associated with dichotomous branching hyphae in the lungs. The post-mortem diagnosis was concordant with the ante-mortem suspicion/diagnosis, as the serum galactomannan antigen was positive. Conidial heads are a rare histological finding. When they are absent, the definitive diagnosis of aspergillosis becomes difficult and requires clinical and microbiological correlation. Autopsies are still necessary, especially in the field of infectious diseases of the immunocompromised hosts, where the literature points to a high discrepancy between the ante- and post-mortem diagnoses.

ACKNOWLEDGEMENTS

The authors wish to thank Mrs. Deryn Pompeia and Mr. Reginaldo Silva do Nascimento for their technical assistance in the preparation of this manuscript.

REFERENCES

1. Centers for Disease Control and Prevention – CDC. Etymologia: *Aspergillus.* Emerg Infect Dis. 2006;12(3). http://dx.doi.org/10.3201/eid1203.ET1203.
2. Micheli PA. *Nova plantarvm genera ivxta Tovrnefortii methodvm disposita*. 1729. Typis Bernardi Paperinii. Firenze; Plate 91.
3. Sherif R, Segal BH. Pulmonary aspergillosis: clinical presentation, diagnostic tests, management and complications. Curr Opin Pulm Med. 2010;16(3):242-50. PMid:20375786.
4. Camargo JF, Husain S. Immune correlates of protection in human invasive aspergillosis. Clin Infect Dis. 2014;59(4):569-77. http://dx.doi.org/10.1093/cid/ciu337. PMid:24803380.
5. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46(12):1813-21. http://dx.doi.org/10.1086/588660. PMid:18462102.
6. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis. 2006;42(10):1417-27. http://dx.doi.org/10.1086/503427. PMid:16619154.
7. Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. Clin Microbiol Rev. 2011;24(2):247-80. http://dx.doi.org/10.1128/CMR.00053-10. PMid:21482725.
8. Anila KR, Somanathan T, Mathews A, Jayasree K. Fruiting bodies of Aspergillus: An unusual finding in histopathology. Lung India. 2013;30(4):357-9. http://dx.doi.org/10.4103/0970-2113.120623. PMid:24339500.
9. Panke TW, McManus AT Jr, McLeod CG Jr. "Fruiting bodies" of *Aspergillus* on the skin of a burned patient. Am J Clin Pathol. 1978;69(2):188-9. PMid:343572.
10. Falsey AR, Goldsticker RD, Ahern MJ. Fatal subcutaneous aspergillosis following necrotizing fasciitis: a case report. Yale J Biol Med. 1990;63(1):9-13. PMid:2356626.
11. Shinohara MM, Miller CJ, Seykora JT. Pigmented fruiting bodies and birefringent crystals in a surgical wound: A clue to *Aspergillus niger* infection. J Cutan Pathol. 2011;38(8):603-6. http://dx.doi.org/10.1111/j.1600-0560.2011.01748_1.x. PMid:21762198.
12. Khurana U, Raghubanshi G, Handa U, Chander J. "Fruitingbodies" of *Aspergillus flavus*: A rare finding in histopathology. Int J Surg Pathol. 2012;20(1):60-

1. http://dx.doi.org/10.1177/1066896911425486. PMid:22084428.

13. Chandra S, Gaur D, Harsh M, Chaturvedi J, Kishore S. An unusual presentation of Aspergillus species in a routine cervicovaginal pap smear: A case report. Acta Cytol. 2009;53(2):229-31. http://dx.doi.org/10.1159/000325131. PMid:19365982.

14. Hoda RS, Colello C, Roddy M, Houser PM. "Fruiting body" of Aspergillus species in a routine cervico-vaginal smear (Pap test). Diagn Cytopathol. 2005;33(4):244-5. http://dx.doi.org/10.1002/dc.20267. PMid:16138367.

15. Lee S, Yun NR, Kim KH, et al. Discrepancy between histology and culture in filamentous fungal infections. Med Mycol. 2010;48(6):886-8. http://dx.doi.org/10.3109/13693780903512835. PMid:20092421.

16. Montone KT, Guarner J. In situ hybridization for rRNA sequences in anatomic pathology specimens,applications for fungal pathogen detection: a review. Adv Anat Pathol. 2013;20(3):168-74. http://dx.doi.org/10.1097/PAP.0b013e31828d187d. PMid:23574773.

17. Boon A, O'Brien D, Adams DH. 10 year review of invasive aspergillosis detected at necropsy. J Clin Pathol. 1991;44(6):452-4. http://dx.doi.org/10.1136/jcp.44.6.452. PMid:2066421.

18. Antinori S, Nebuloni M, Magni C, et al. Trends in the postmortem diagnosis of opportunistic invasive fungal infections in patients with AIDS: a retrospective study of 1,630 autopsies performed between 1984 and 2002. Am J Clin Pathol. 2009;132(2):221-7. http://dx.doi.org/10.1309/AJCPRAAE8LZ7DTNE. PMid:19605816.

19. Lewis RE, Cahyame-Zuniga L, Leventakos K, et al. Epidemiology and sites of involvement of invasive fungal infections in patients with haematological malignancies: a 20-year autopsy study. Mycoses. 2013;56(6):638-45. http://dx.doi.org/10.1111/myc.12081. PMid:23551865.

Conflict of interest: None

Submitted on: October 15th, 2015
Accepted on: November 5th, 2015

Correspondence
Amaro Nunes Duarte Neto
Pathology Department - Faculty of Medicine - University of São Paulo
Av. Dr. Arnaldo, 455 – Cerqueira Cesar – São Paulo/SP – Brazil
CEP: 01246-903
Phone: +55 (11) 98546-4225
E-mail: amaro.ndneto@hc.fm.usp.br