



СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО
SERBIAN ARCHIVES
OF MEDICINE

Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia

+381 11 4092 776, Fax: +381 11 3348 653

E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted*

ISSN Online 2406-0895

Case report / Приказ болесника

Dejan Moskovljević¹, Nikola Čolić², Anđela Dimkić-Milenković³, Jelena Marković⁴,
Vladimir Milenković^{1,*}

**Incidental finding of pulmonary tumorlet in a case of surgically treated
bronchiectatic cavity superimposed by aspergilloma**

Узгредни налаз плућних туморлета у случају хируршки лечене бронхиектатичне
шупљине насељене аспергиломом

¹University Clinical Center of Serbia, Clinic for Thoracic Surgery, Belgrade, Serbia;

²University Clinical Center of Serbia, Center for Radiology and Magnetic Resonance Imaging, Belgrade, Serbia;

³University Clinical Center of Serbia, Clinic for Burns, Plastic and Reconstructive Surgery, Belgrade, Serbia;

⁴University Clinical Center of Serbia, Department of Thoracopulmonary Pathology, Pathohistology Service,
Belgrade, Serbia

Received: June 9, 2022

Revised: July 29, 2022

Accepted: September 1, 2022

Online First: September 5, 2022

DOI: <https://doi.org/10.2298/SARH220609092M>

***Accepted papers** are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.

When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

***Correspondence to:**

Vladimir MILENKOVIĆ

University Clinical Center of Serbia, Clinic for Thoracic Surgery

Dr Koste Todorovića 26, 11000 Belgrade, Serbia

Email: vlada1309@gmail.com

Incidental finding of pulmonary tumorlet in a case of surgically treated bronchiectatic cavity superimposed by aspergilloma

Узгредни налаз плућних туморлета у случају хируршки лечене
bronhiektatичне шупљине насељене аспергиломом

SUMMARY

Introduction Intracavitary aspergilloma is the consequence of a saprophytic infection of the lung with cavitary disease. Pulmonary tumorlet are nodular proliferations of the neuroendocrine cells less than 5 mm in diameter. Both aspergilloma in the bronchiectatic cavity of the lung and pulmonary tumorlet has rare been seen.

Case Outline We present a 71-year-old woman with a medical history of recurrent pneumonia complicated with cough and hemoptysis. Computed tomography (CT) scan of the chest showed pulmonary soft tissue mass in the right lower lobe of the lung 42×50 mm in diameter. Direct microscopy of the specimens of bronchioalveolar lavage showed spores of *Aspergillus*. Galactoman Ag test was also positive. Right lower lobectomy and mediastinal lymph node sampling was performed via thoracotomy. Pathohistological findings showed aspergilloma with the presence of pulmonary tumorlet and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) in the lymphovascular spaces. Five years follow up showed no abnormalities on the CT scan, and the patient remained alive without medical problems.

Conclusion The concomitant occurrence of bronchiectasis, aspergilloma as well as precancerous lesions such as pulmonary tumorlet and DIPNECH is rare and further increases the risk of developing malignant tumors as well as recurrent infections. Therefore, surgical treatment can prevent the development of premalignant lesions and the occurrence of recurrent infections accompanied by dyspnea and hemoptysis as the main symptoms. The question of the connection between pulmonary tumorlet and chronic inflammatory lung diseases is raised. We hope that future researches will provide answers to this question.

Key words: bronchiectasis; aspergilloma; pulmonary tumorlet; DIPNECH

САЖЕТАК

Увод Интракавитарни аспергилом је последица сапрофитне инфекције плућа са кавитарном болешћу. Плућни туморлети су нодуларне пролиферације неуроендокриних ћелија пречника мањег од 5 мм. Ретки су случајеви истовременог откривања аспергилома у бронхиектатичној шупљини плућа и плућних туморлета.

Приказ болесника У раду је приказан случај пацијенткиње старосне доби 71 годину, са понављаним упалама плућа које су праћене кашљем и хемоптизијама. Компјутеризована томографија грудног коша показала је мекоткивну масу у доњем десном плућном режњу пречника 42×50 мм. Узорци бронхиоалвеоларна лаважа су показали споре *Аспергилуса* (директна микроскопија).

Galactoman Ag тест је такође био позитиван.

Учињена је десна доња лобектомија и узorkовање медијастиналних лимфних чворова приступом кроз торакотомију. Патохистолошки налаз је показао бронхиектатичну шупљину у плућима са аспергилом и присуством плућних туморлета у лимфоваскуларним просторима. Након пет година праћења пацијенткиња је била без тегоба и абнормалности на *CT* грудног коша.

Закључак Истовремена појава бронхиектазија, аспергилома као и преканцерозних лезија као што су плућни туморлети и дифузна идиопатска хиперплазија неуроендокриних ћелија плућа (*DIPNECH*) је ретка и додатно повећава ризик од развоја малигнух тумора као и рекурентних инфекција. Хируршким лечењем може се спречити развој малигнух тумора и појава рекурентних инфекција праћених диспнејом и хемоптизијама као главним симптомима. Поставља се питање повезаности прекарцинозних лезија плућа и хроничних инфламаторних болести. Надамо се да ће будућа истраживања дати одговоре на ово питање.

Кључне речи: бронхиектазије; аспергилом; плућни туморлети; *DIPNECH*

INTRODUCTION

Aspergillus is a genus of mold which includes about 200 species, including *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus terreus* and *Aspergillus nidulans*,

which are most common human pathogens [1]. Spreading of the disease depends of the patients immunological and respiratory systems. *Aspergillus* causes infectious as well as allergic diseases [2]. Chronic pulmonary aspergillosis (CPA) is often seen in patients with lung diseases that cause structural damage to lung parenchyma, and have the whole spectrum of progressive disease manifestations caused by *Aspergillus* species [3]. Chronic cavitary pulmonary aspergillosis (CCPA) is a slow destructive type of chronic pulmonary aspergillosis [4]. Aspergillosis is most often seen in patients with common chronic lung disease or in immunocompromised patients. *Aspergillus* species, a saprophytic fungus, can colonize pulmonary cavities caused by tuberculosis, sarcoidosis, echinococcosis and bronchiectasis [5]. Also, it is well known to complicate malignant diseases [6]. Fungus ball, intracavitary mycetoma, aspergilloma, is the consequence of a saprophytic infection of the lung with cavitary disease. Cough and haemoptysis are the most common symptom [7]. Furthermore, pulmonary tumourlet, defined as nodular proliferations of neuroendocrine cells less than 5 mm in diameter, are a rare pathology [8]. In most cases they are detected incidentally, the most common in bronchiectatic cavity or in areas of lung destruction that are removed surgically. The coexistence of a pulmonary neuroendocrine tumourlet and aspergilloma has rarely been seen [9].

The aim of this case report was to present a rare case of surgically treated pulmonary bronchiectatic cavity superimposed with aspergilloma and an incidental finding of pulmonary tumourlet.

CASE REPORT

A 71-year-old woman with a medical history of recurrent episodes of pneumonia followed by hemoptysis and cough, with expectoration of brown-yellow sputum, was admitted to our department. The patient had a medical history of smoking, chronic obstructive

pulmonary disease, arterial hypertension and mastectomy due to breast cancer. The results of spirometry, diffusion of CO (carbon monoxide) and laboratory were normal. Chest CT scan is the golden standard for diagnosing of the lung diseases. It showed pulmonary soft tissue mass in the right lower lobe of the lung, oval cavitation approximately 42x50 mm in diameter, presence of "air in the form of a crescent sign", and the communication with subsegmental branches of the apicobasal segmental bronchus. Chronic pneumonitis and traction bronchiectasis, with no pathologic enlargement of the lymph nodes was also seen (Figure 1). Direct microscopy of the specimens of BAL identified spores of *Aspergillus*. Galactoman Ag test was positive. The patient was initially treated with antimicrobial therapy for two weeks before surgery. Right lower lobectomy and mediastinal lymph node sampling was performed via thoracotomy.

Pathological examination of the specimen showed intrapulmonary cavity in the right lower lobe, 45 mm in diameter. Intracavitary material was brown, necrotic, compatible with aspergilloma. Aspergilloma composed of numerous hyphae of *Aspergillus* was seen on the sections of the lung parenchyma along the bronchial wall. Hyphae were visualized by immunohistochemical methods PAS and Grocott. Signs of vascular invasion by tumour cells, round, bright cytoplasm, in predominantly organoid arrangement, were observed in the vascular spaces. Group of uniform tumor cells were detected in a microscopic focus and measured less than 5 mm. Immunohistochemical staining for CD56, TTF-1, Synaptophysin, Cytokeratin were positive, Napsin A, CD34, p40, LCA were negative. Ki67 level was 2-3% in these cells. Lymph nodes specimens showed no metastatic tumor cells. The specimen contained a several areas of pulmonary tumorlet and DIPHECH. Final pathohistological findings corresponded to aspergilloma with the presence of pulmonary tumorlet and DIPNECH in the lymphovascular spaces (Figure 2).

Five years follow up showed no abnormalities on the chest CT scan, and the patient was without medical problems.

We confirm that we have read the journal's position on issues involving ethical publication and affirm that this work is consistent with those guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

DISCUSSION

Aspergilloma occurs as a consequence of saprophytic infection of the previously formed cavity of the lung parenchyma. Cough and hemoptysis are the most common symptoms. After the formation of aspergilloma, the effect of antimicrobial drugs is drastically reduced. In such situations, surgical treatment may be the only choice [7]. Pulmonary tumorlet, which represents nodular proliferations of neuroendocrine cells, are rare and do not exceed 5 mm in diameter [8]. These proliferations occur most often as a consequence of Kulchitsky cells hyperplasia in various lung diseases. They often occur in several places. Hyperplastic foci of these cells larger than 5 mm in diameter represents Carcinoid tumors [8,10-12]. They are most often detected on surgical material after lung resections due to diseases that cause destruction of the lung parenchyma. There are several subgroups of neuroendocrine tumors with common characteristics: pulmonary tumorlet, DIPNECH, carcinoid tumors [10]. Concomitant occurrence of neuroendocrine tumors and aspergilloma is rare [9]. They are most often asymptomatic and occur in other lung diseases characterized by destruction of the lung parenchyma and the presence of a chronic inflammatory process. Cellular atypia and cell necrosis are rare, while mitotic activity is usually absent [11]. Recently published studies consider pulmonary tumorlet and DIPNECH precancerous lesions. However, proliferation to

Carcinoid tumors is rare [12,13]. Nodal metastases are very rare and usually occurs in hilar lymph nodes [14].

They most often appear between the ages of 60 and 70, four times more in men than in woman (1:4). Dyspnoea is the most common symptom. Small nodules up to 5 mm in diameter on a chest CT scan in patients with dyspnea without clear causes may raise the suspicion of the presence of pulmonary tumorlet and DIPNECH. PET/CT (positron emission tomography/computed tomography) in those cases is not the best diagnostic choice due to their size [8]. There are still no clear guidelines for monitoring and selecting the treatment for pulmonary tumorlet and DIPNECH. Also, prevention measures for their occurrence have not been determined yet. However, risk groups should be advised to quit smoking, practice physical activity, avoid exposure to certain physical and chemical substances such as asbestos, arsenic, tar, chromium, nickel, etc. Avoiding alcohol consumption is also advised [9]. Octreotide, 18F-DOPA amino acid analogs, inhaled corticosteroids, and beta agonists were part of the studies examining their effect in the treatment of neuroendocrine tumors and precancerous lesions such as pulmonary tumorlet and DIPNECH [8,13]. Chronic inflammatory lung diseases, granulomatous lung diseases and bronchiectasis are the most common lung diseases in which pulmonary tumorlet occurs [10]. In our case, the presence of pulmonary tumorlet and aspergilloma in the bronchiectatic cavity were identified at the same time.

The question of the connection between pulmonary tumorlet and chronic inflammatory lung diseases is raised. The presence of bronchiectasis, aspergilloma and precancerous lesions such as pulmonary tumorlet and DIPNECH further increase the risk of developing malignant tumors as well as recurrent infections. So far, no consensus has been reached on the timing and type of surgery in patients with aspergilloma. Despite no comparative studies of antifungal therapy in patients preparing for surgery, Voriconazole remains the first option, as it has been related to reduced mortality [15-19]. The presence of chronic inflammation and the negative

effect of the infection on the remaining part of the lung parenchyma further complicate recovery after surgery. Therefore, surgical treatment can prevent the development of premalignant lesions and the occurrence of recurrent infections accompanied by dyspnea and hemoptysis as the main symptoms. We hope that the future researches will provide answers to those questions.

Conflict of interest: None declared.

Paper accepted

REFERENCES

1. Nilsson JR, Restrepo CS, Jagirdar J. Two cases of endobronchial carcinoid masked by superimposed aspergillosis: A review of the literature of primary lung cancers associated with *Aspergillus*. *Ann Diagn Pathol*. 2013 Feb;17(1): 131-6. Doi:10.1016/j.anndiagpath.2011.06.005. Epub 2011 Nov 10. PMID: 22079170.
2. Rasheed A, McCloskey A, Foroutan S, Waheed A, Rodgers A, Seraj SM, et al. Pulmonary Aspergilloma in a Young Immunocompetent Female: A Rare Clinical Dilemma. *Cureus*. 2022 Feb 28;14(2):e22724. Doi:10.7759/cureus.22724. PMID: 35371658; PMCID: PMC8971099.
3. Bongomin F, Asio LG, Baluku JB, Kwizera R, Denning DW. Chronic Pulmonary Aspergillosis: Notes for a Clinician in a Resource-Limited Setting Where There Is No Mycologist. *J Fungi (Basel)*. 2020 Jun 2;6(2):75. Doi:10.3390/jof6020075. PMID: 32498415; PMCID: PMC7345130.
4. S Kumar S, Ray A, Vikram NK, Vyas S. Unusual case of chronic cavitary pulmonary aspergillosis presenting as spontaneous pneumothorax in an immunocompromised man. *BMJ Case Rep*. 2021 Aug 2;14(8):e241655. Doi:10.1136/bcr-2021-241655. PMID: 34340987; PMCID: PMC8330574.
5. Goyal RC, Tyagi R, Garg B, Mishra A, Sood N. Pulmonary Hydatid Disease with Aspergillosis - An Unusual Association in an Immunocompetent Host. *Turk Patoloji Derg*. 2019;35(2):166-169. Doi: 10.5146/tjpath.2017.01396. PMID: 29630082.
6. Nivoix Y, Velten M, Letscher-Bru V, Moghaddam A, Natarajan-Amé S, Fohrer C, et al. Factors associated with overall and attributable mortality in invasive aspergillosis. *Clin Infect Dis*. 2008 Nov 1;47(9):1176-84. Doi:10.1086/592255. PMID: 18808352.
7. Harmouchi H, Sani R, Issoufou I, Lakranbi M, Ouadnoui Y, Smahi M. Pulmonary aspergilloma: from classification to management. *Asian Cardiovascular and Thoracic Ann*. 2020 Jan;28(1):33-38. Doi:10.1177/0218492319895113. Epub 2019 Dec 4. PMID: 31799858.
8. Kallianos A, Velentza L, Zarogoulidis P, Baka S, Kosmidis C, Labaki S, et al. Progressive dyspnea due to pulmonary carcinoid tumorlets. *Respir Med Case Rep*. 2017;21:84-5. Doi:10.1016/j.rmcr.2017.03.024. PMID: 28417065; PMCID: PMC5389108.
9. Yazgan S, Gursay S, Turk F, Dinc ZA. Conjunction of a Fungus Ball and a Pulmonary Tumorlet in a Bronchiectatic Cavity. *Korean J Thorac Cardiovasc Surg*. 2018 Apr;51:138-141. Doi:10.5090/kjtc.2018.51.2.138. Epub 2018 Apr 5. PMID: 29662813; PMCID: PMC5894579.
10. He P, Gu X, Wu Q, Lin Y, Gu Y, He J. Pulmonary carcinoid tumorlet without underlying lung disease: analysis of its relationship to fibrosis. *J Thorac Dis*. 2012 Dec;4:655-8. Doi:10.3978/j.jssn.2072-1439.2012.06.11. PMID: 23205296; PMCID: PMC3506797.
11. Churg A, Warnock ML. Pulmonary tumorlet. A form of peripheral carcinoid. *Cancer*. 1976;37:1469-77. Doi:10.1002/1097-0142(197603)37:3<1469::aid-cnrcr2820370332>3.0.co;2-h. PMID: 177168.
12. Hendifar AE, Marchevsky AM, Tuli R. Neuroendocrine Tumors of the Lung: Current Challenges and Advances in the Diagnosis and Management of Well-Differentiated Disease. *J Thorac Oncol*. 2017 Mar;12:425-36. Doi:10.1016/j.jtho.2016.11.2222. Epub 2016 Nov 24. PMID: 27890494.
13. Wirtschafter E, Walts AE, Liu ST, Marchevsky AM. Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia of the Lung (DIPNECH): Current Best Evidence. *Lung*. 2015 Oct;193:659-67. Doi:10.1007/s00408-015-9755-1. Epub 2015 Jun 24. PMID: 26104490.
14. D'Agati VD, Perzin KH. Carcinoid tumorlets of the lung with metastasis to a peribronchial lymph node: report of a case and review of the literature. *Cancer*. 1985 May 15;55(10):2472-6. Doi:10.1002/1097-0142(19850515)55:10<2472::aid-cnrcr2820551027>3.0.co;2-y. PMID: 3986742.
15. Akram W, Ejaz MB, Mallhi TH, Syed Sulaiman SAB, Khan AH. Clinical manifestations, associated risk factors and treatment outcomes of Chronic Pulmonary Aspergillosis (CPA): Experiences from a tertiary care hospital in Lahore, Pakistan. *PLoS ONE*. 2021 Nov 12;16(11): e0259766. Doi.org/10.1371/journal.pone.0259766. PMID: 34767589; PMCID: PMC8589179.
16. Bongomin F, Asio LG, Baluku JB, Kwizera R, Denning DW. Chronic Pulmonary Aspergillosis: Notes for a Clinician in a Resource-Limited Setting Where There Is No Mycologist. *J Fungi (Basel)*. 2020 Jun 2;6(2):75. Doi: 10.3390/jof6020075. PMID: 32498415; PMCID: PMC7345130.
17. Mir T, Uddin M, Khalil A, Lohia P, Porter L, Regmi N, et al. Mortality outcomes associated with invasive aspergillosis among acute exacerbation of chronic obstructive pulmonary disease patient population. *Respir Med*. 2022 Jan;191:106720. Doi: 10.1016/j.rmed.2021.106720. Epub 2021 Dec 21. PMID: 34959147.
18. Molinos-Castro S, Pesqueira-Fontán PM, Rodríguez-Fernández S, Rodríguez-Framil M, Barbeito-Castiñeiras G, Gayol-Fernández MC, et al. Clinical factors associated with pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. *Enferm Infecc Microbiol Clin (Engl Ed)*. 2020 Jan;38(1):4-10. Doi:10.1016/j.eimc.2019.06.007. Epub 2019 Aug 9. PMID: 31405617.
19. Guziejko K, Klukowska K, Budzińska U, Mróz RM. Case Report: Chronic Pulmonary Aspergillosis-An Unusual Long-Term Complication of Lung Cancer Treatment. *Front Med (Lausanne)*. 2022 Jan 12;8:777457. Doi: 10.3389/fmed.2021.777457. PMID: 35096873; PMCID: PMC8789659.

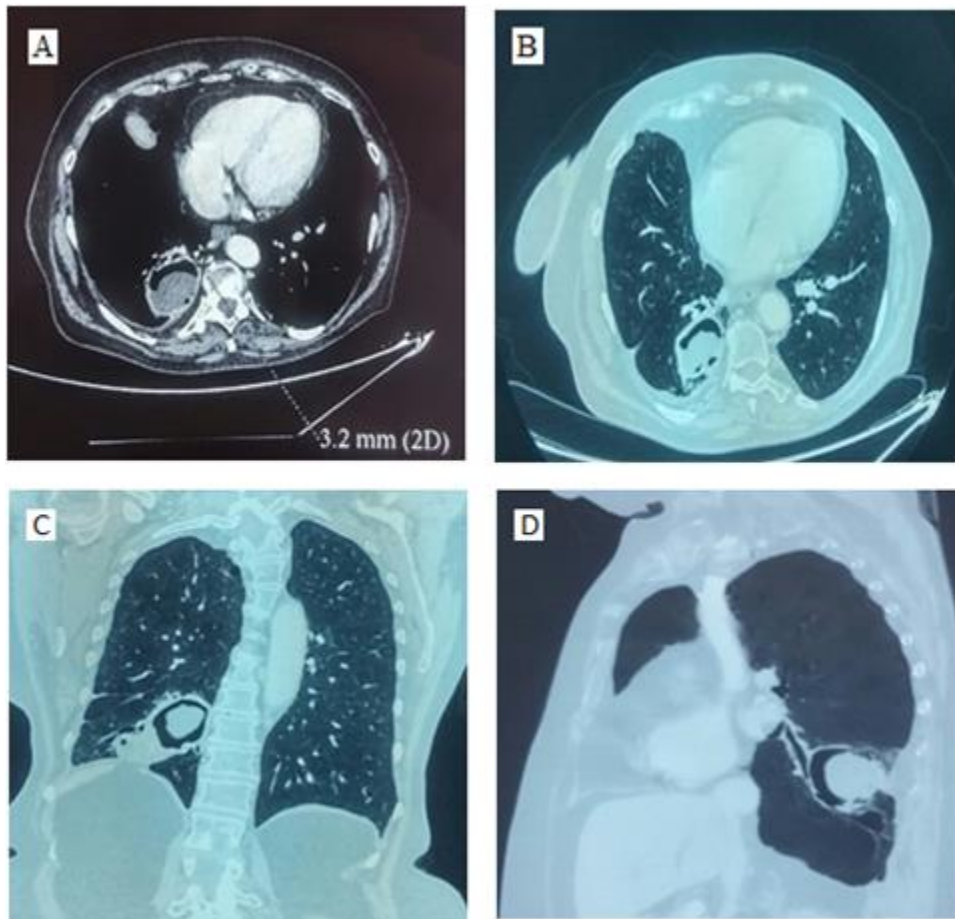


Figure 1 The Aspergilloma in the intrapulmonary cavity; A – soft tissue window, axial section; B – lung parenchymal window, axial section; C – lung parenchyma window, coronal section; D – lung parenchyma window, sagittal section

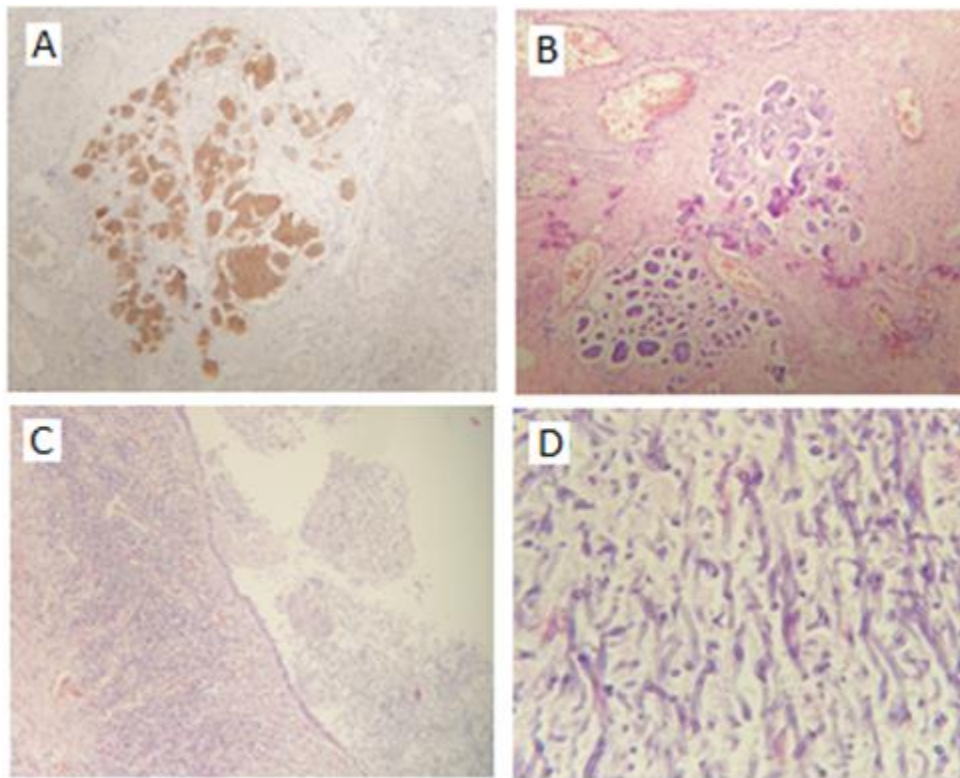


Figure 2 A – hematoxylin-eosin staining of bronchiectatic wall filled with fungus ball, mass consisted of fungal hyphae and necrotic fragments; bronchial wall is infiltrated by inflammatory cells, consisted mainly from lymphocytes, plasma cells and eosinophil leukocytes, lined by metaplastic squamous epithelial cells; magnification $\times 100$; B – branching elongated hyphae of *Aspergillus*; periodic-acid-Schiff stain; magnification $\times 400$; C – diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; magnification $\times 200$; D – neuroendocrine marker CD 56 expression in neuroendocrine cell hyperplasia; magnification $\times 200$