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CASE REPORT

CHRONIC NECROTIZING PULMONARY ASPERGILLOSIS AFTER SARS-COV-2 INFECTION – A CASE REPORT

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Abstract: *Aspergillosis is a fungal infection, caused by the mould Aspergillus, most commonly Aspergillus fumigatus species. Chronic pulmonary aspergillosis after SARS Cov-2 infection is a rare presentation that is commonly misdiagnosed. The prolonged corticosteroid and antibiotic application and the pro-inflammatory state in COVID-19 patients predisposes to Aspergillus infection and its chronification. Surgery plays a pivotal role in cases with unclear diagnosis, ineffective medical therapy or when complications develop. We present a case of a 73-year-old woman with chronic pulmonary aspergillosis, developed after COVID-19 pneumonia. A right lateral muscle-sparing thoracotomy, right upper lobectomy and atypical resection of the 9th and 10th segments were performed.*

Key words: *chronic pulmonary aspergillosis, COVID-19, surgery*

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INTRODUCTION

Aspergillosis is a fungal infection, caused by the mould Aspergillus, most commonly Aspergillus fumigatus species. Lung is the most common site of infection. The disease is clinically presented as: 1) allergic bronchopulmonary aspergillosis; 2) acute invasive pulmonary aspergillosis; 3) chronic pulmonary aspergillosis (CPA) [1]. Aspergillosis is a major cause of morbidity and mortality in immunocompromised patients. Successful treatment depends on early diagnosis and adequate therapy. Indications for surgery are aspergilloma complication, pleural aspergillosis and lung biopsy for diagnosis of invasive aspergillosis.

CASE PRESENTATION

A 73-year-old female patient was admitted to the Thoracic Surgery Department with complaints of intermittent scant hemoptysis that persisted for 5 months. She was in the hospital 9 months ago because of SARS-CoV-2 pneumonia. A computed tomography (CT) scan during that time revealed bilateral ground glass opacities. Three months later a new CT scan was performed. Two newly formed lesions in the right lung and a small pleural effusion were depicted. Antibiotic treatment was initiated under the assumption of abscess formation. Despite that, the CT three months after therapy visualized the same formations. They were both reduced, but a third lesion in the right

lower lobe appeared. By that time scant hemoptysis occurred and persisted despite treatment. The fiber-optic bronchoscopy (FBS) image revealed atrophic mucosa and distended orifices of the segmental bronchi. The histological result showed subepithelial epithelioid cell granuloma without calcification. The T-SPOT-TB and the sputum culture for tuberculosis were negative.

The patient reported of arterial hypertension, non-insulin dependent diabetes mellitus, bronchiectasis and operative treatment of a pilonidal cyst some years ago. The physical examination was normal. The paraclinical tests showed elevated erythrocyte sedimentation rate (40 mm/h), elevated blood glucose level (10,3 mmol/l). The pulmonary function test and blood-gas analysis were both normal.

The patient remained undiagnosed. A consecutive CT scan, performed 6 months after the antibiotic treatment (Fig. 1) revealed the presence of three peripheral oval lesions with liquid content and thin, contrasting walls. Their image was consistent with pulmonary abscesses. The adjacent pleura was slightly pulled up and thickened. The ipsilateral mediastinal and hilar lymph nodes were enlarged and persisted without dynamics. Bilateral peripheral pulmonary fibrosis was visible. There was no dynamic in the image, compared to the previous CT examination three months ago. A new FBS was performed. Scant sanguinization from B2 on the right lung was found. The cytologic analysis of the lavage fluid showed ciliated bronchial epithelium, macrophages, lymphocytes, segmented nuclear neutrophils and eosinophils. The specific staining for fungi, however, was negative. The patient was referred for surgical treatment due to persistent cavitary lesions and hemoptysis.

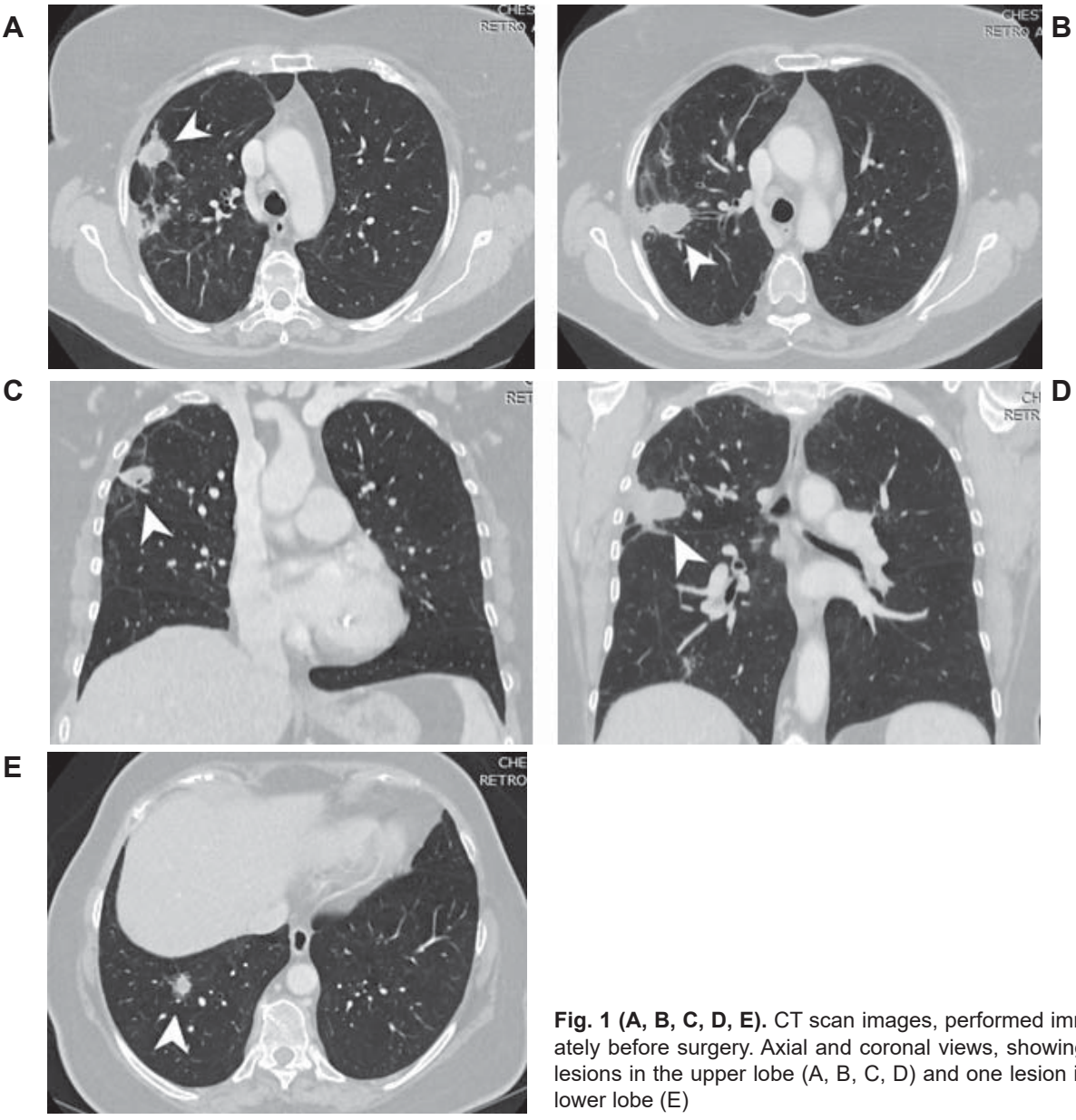

Fig. 1 (A, B, C, D, E). CT scan images, performed immediately before surgery. Axial and coronal views, showing two lesions in the upper lobe (A, B, C, D) and one lesion in the lower lobe (E)

A right lateral muscle-sparing thoracotomy was performed (Fig. 2). Pleural cavity was partially obliterated; adhesions were found between the upper lobe and the lateral chest wall. Extrapleural dissection was performed in this region. Two dense, elastic formations were found in the upper lobe, with a diameter of about 30/3 mm and 30/40 mm. A small part of the wall of one of the lesions was excised and sent for fresh frozen section analysis. The result was aspergillosis and right upper lobectomy was carried out (Fig. 3). Dissection of several visibly anthracotic hilar lymph nodes was performed. During the exploration of the lower lobe, a third formation with a diameter of 20/20 mm was palpated, and an atypical resection of the 9th and 10th segments was carried out.

The histological results showed bronchocentric necrotizing granulomas containing aspergillus hyphae; adjacent hemorrhagic fields and birefringent crystals of calcium oxalate, mixed with hyphal elements (Fig. 4). Purulent bronchitis was also present; as hyphal elements were observed in the bronchial lumen. Peribronchiolar lymphocytic inflammatory infiltrate, reactive pneumocyte hyperplasia and areas with squamous metaplasia and pneumosclerosis were also visible. The morphological picture corresponded to chronic necrotizing aspergillosis (broncho- and bronchiolocentric type). The dissected lymph nodes were all with chronic sinus lymphadenitis and pronounced anthracosis.

The patient was discharged on the 9th postoperative day and sent to the Pulmonology Clinic. Antifungal treatment with voriconazole – 200 mg once daily for 2 months was undertaken. The liver enzymes (ALAT and ASAT) were elevated, resulting in treatment suspension. Up to now, five months after surgery, the patient is in excellent general condition, with no paraclinical and imaging data for active or recurrent disease.

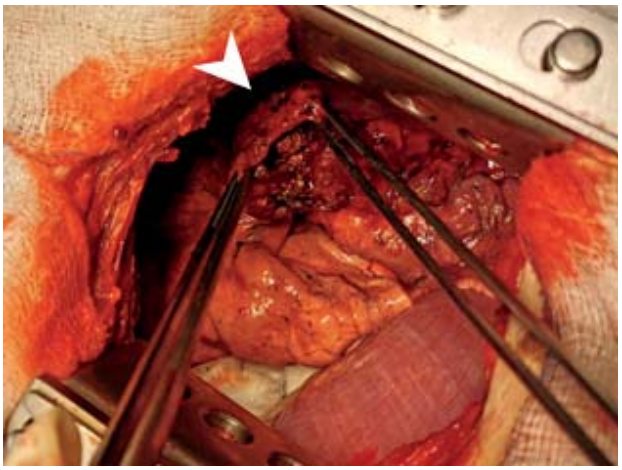

Fig. 2. Intraoperative view of an upper lobe aspergilloma with an open cavity

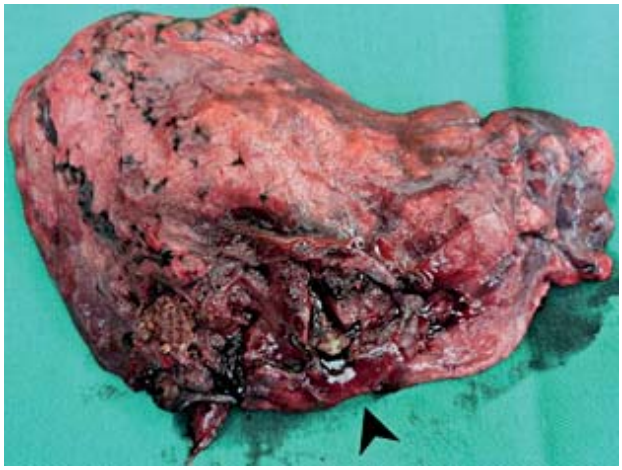

Fig. 3. Postoperative specimen of right upper lobe, showing a sectioned aspergilloma formation

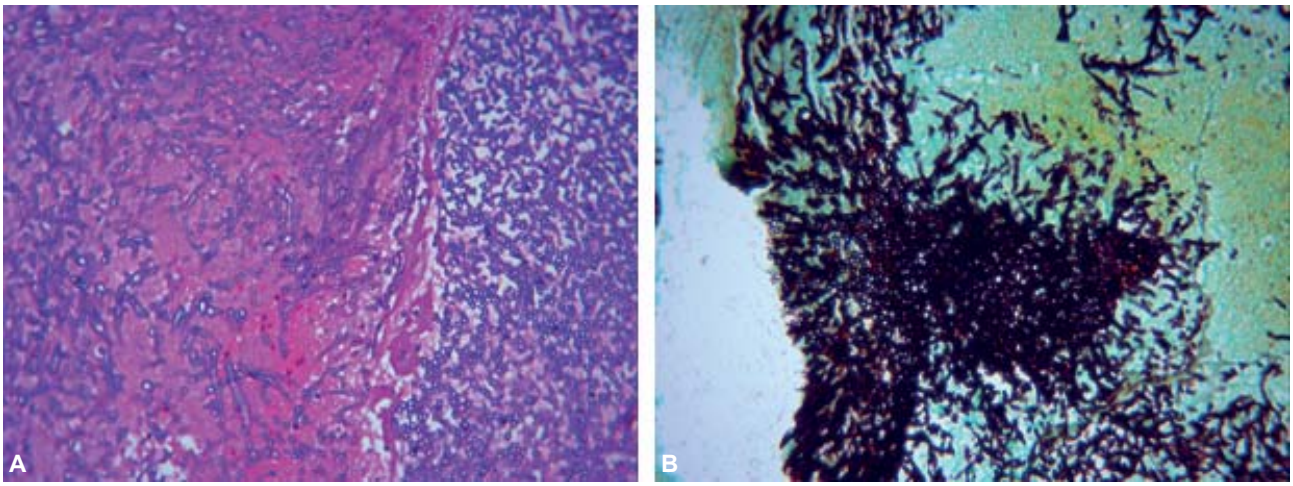

Fig. 4 (A, B). Histopathological images of aspergillosis. Hematoxylin-eosin staining x20 (A). Grocott staining x20 (B)

DISCUSSION

Chronic cavitary pulmonary aspergillosis (CCPA), chronic fibrosing pulmonary aspergillosis (CFPA), subacute invasive aspergillosis (SAIA), aspergilloma and Aspergillus nodules are staying under the umbrella of CPA [2]. SAIA was formerly known with the terms chronic necrotizing aspergillosis or semi-invasive aspergillosis [3]. Simple aspergilloma was the most common type of CPA – 56%, followed by CCPA – 31.2% [4].

The diagnosis of CPA requires the following criteria for at least 3 months: 1) thoracic imaging data for a cavity with or without a fungal ball or nodules; 2) microscopic, cultural or immunological response to Aspergillus; 3) rejection of alternative diagnosis [1]. Aspergillus IgG is a sensitive confirmatory assay that facilitates the monitoring of treatment and the relapse of the disease. It is, however, unspecific, as it may be positive in patients with Aspergillus bronchitis, sinusitis or allergic bronchopulmonary aspergillosis [5]. In addition, sputum PCR is more sensitive than cultural testing [6]. The histopathological examination may also confirm the diagnosis, as it was in our case.

As opposed to invasive aspergillosis, CPA affects individuals with ostensibly normal immune system and underlying lung disease [2]. Only 5% of patients do not have any underlying pulmonary or systemic disease [5]. The most prevailing primary lung diseases in patients with CPA are lung tuberculosis and non-tuberculous mycobacterial infections [1]. Tuberculosis, asthma and COPD were found in respectively – 20%, 26% and 50% of the cases [7]. The prevalence of CPA along the treatment course of tuberculosis is considered to vary between 6-17% at baseline, and 8-17% at the end of therapy [8]. Common underlying disorders predicting a poor outcome are diabetes mellitus, hematological malignancies and chronic kidney disease [4]. In our case bronchiectasis and a previous COVID-19 infection were predisposing factors. Most probably prolonged corticosteroid and antibiotic application, as well as the pro-inflammatory state in COVID-19 patients are important preconditions for Aspergillus growth and chronification. The prevalence of COVID-19-associated pulmonary aspergillosis varies between 3-28% in critically ill patients [9]. Direct injury of respiratory epithelium, immune dysregulation, and immunosuppressants may promote Aspergillus respiratory tract colonization and invasion and are all associated with COVID-19 disease [9].

Patients are usually 45.75 ± 6.26 year-old, males (73.4%) with diabetes (29.8%) [4]. In our case we presented a 73-year-old woman with diabetes. The most common symptoms are hemoptysis, mild but persistent chest pain, discomfort, or tightness, weight loss and fatigue, cough (usually productive), dyspnea, night or day sweats [10]. Our patient reported only intermittent scant hemoptysis, that was incurable conservatively.

Imaging plays an important role in the diagnostic process. Cavitation, fibrosis, and thickened pleura are the hallmarks of this rare, but slowly destructive pulmonary syndrome, called CPA [11]. Alteration over time is the most characteristic CT distinction of CPA [5]. The disease has upper lobe predominance, and commonly visualized are pericavitary infiltrates [8], consolidations and fungal balls. Aspergillus nodules are usually less than 3 cm in size, non-cavitating, solid lesions [2]. Pleural thickening on CT images comprises of pleural fibrosis overlying a cavity or consolidation and indrawing of extrapleural fat [10]. Differential diagnosis of a cavity is inflamed bulla, cavitary carcinoma, tuberculosis, abscess, etc. In the reported case, CT scan revealed three peripheral oval lesions in the right upper and lower lobes. They were with liquid content, thin, contrasting walls, which made us think of abscesses. There was also pleural thickening, bilateral peripheral pulmonary fibrosis, mediastinal and hilar lymph node enlargement. There was no dynamics in the image compared to the previous CT examination 3 months ago, but the picture differed essentially from the baseline CT scan, performed 9 months ago.

The aim of CPA treatment is to alleviate symptom burden, decrease haemoptysis, prevent pulmonary fibrosis, and preserve lung function [2]. In case of hemoptysis, treatment consists of oral tranexamic acid, antifungal therapy, embolization of the bronchial artery, and if these are ineffective – surgical resection [6]. In the case, we described, haemoptysis was irresponsible to medication and therefore surgery was performed.

Lung resection is reasonable in case of localized disease, ineffective medical therapy, presence of panazole-resistant Aspergillus fumigatus or persistent hemoptysis [6]. Surgery ensures good outcomes with an acceptable morbidity, but high recurrence rate [7]. Patients with pulmonary aspergillosis treated with surgery had a lower inpatient mortality compared to medical treatment; mortality rate was lower in video assisted thoracoscopic surgery, compared to open surgery [12]. In our case open surgery was recommended because the preoperative diagnosis was unclear. Open surgery gave us the opportunity to palpate the right lung, as well as, to detect the preceding post-inflammatory adhesions. Indeed, pleural adhesions and three dense-elastic formations were found

in the region of the upper and lower lobes. Fresh frozen section analysis diagnosed correctly the disease.

The established risk factors for postoperative complications were chronic fibrosing pulmonary aspergillosis, longer operative time, and the volume of intraoperative blood loss [13]. The major complications after surgery are: prolonged air leak (23%); empyema (20%); respiratory failure, requiring tracheostomy/reintubation (13%); recurrence of CCPA (26%) [7]. Relapses usually occur 15 months after surgery [13]. In our case no complications in the early or late postoperative period emerged, no recurrence of the disease has been detected up to now. Conservative treatment of chronic aspergillosis consists of antifungal drugs; oral application of itraconazole 200–400 mg/day or voriconazole 150–200 mg twice daily, for at least 3–6 months [1]. Voriconazole is the medication of choice, especially in patients with higher disease burden – with elevated Aspergillus serology or multiple aspergillomas [11]. We used voriconazole 200mg/daily. Posaconazole is third line therapy. In case of resistance, therapeutic failure or adverse events caspofungin, amphothericin B or micafungin may also serve as alternative treatment options [6, 14]. It was confirmed, that antifungal therapy improves patients' health status and prevents progression of CPA [15]. Overall mortality rate is 27.1%, and it depends on the duration of hospital stay, presence of hematological malignancies, consolidation and intensive care unit admission [4].

CONCLUSION

Chronic pulmonary aspergillosis after SARS Cov-2 infection is a rare presentation with commonly mistaken preoperative diagnosis. Most probably prolonged corticosteroid and antibiotic application, as well as the pro-inflammatory state in COVID-19 patients predispose to Aspergillus growth and chronification. Surgery is of importance if the diagnosis remains unclear, the medical therapy is ineffective or if complications develop. Further studies are needed to illustrate the pathophysiological connection between COVID-19 and chronic pulmonary aspergillosis, as well as to address the need of a more effective medical therapy with less adverse effects for this destructive lung disease.

Disclosure Summary: *The authors have nothing to disclose.*

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