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Chronic Cavitary Pulmonary Aspergillosis: A Case Report and Review of the Literature

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Patient: Female, 69
Final Diagnosis: Chronic cavitation pulmonary aspergillosis
Symptoms: Shortness of breath • weight loss
Medication: —
Clinical Procedure: —
Specialty: Pulmonology

Objective: Challenging differential diagnosis

Background: *Aspergillus* spores have the ability to affect patients with or without intact immune systems; because of this disease's wide patient involvement it deserves a place on the differential diagnosis list, with endocarditis and tuberculosis, for those presenting with new pulmonary nodules or cavitation.

Case Report: This case report involves the presentation, diagnosis, and treatment of a 69-year-old female who presented with new rapidly progressing cavitary lung lesions in the setting of copious administration of systemic steroid use. Given the patient's past history of alcoholism and environmental exposure, her case was not straight forward in regard to a diagnosis. Ultimately, she was diagnosed with chronic cavity pulmonary aspergillosis in the setting of chronic immunosuppression secondary to systemic steroid administration. Due to her convoluted medical history and the poor differential diagnosis list, there was a delay in final diagnosis.

Conclusions: This case report and clinical review aims to prevent anchoring when the patient's presentation is not straight forward and aims to remind the clinician of the importance of a differential diagnosis.

MeSH Keywords: Aspergillosis, Allergic Bronchopulmonary • Invasive Pulmonary Aspergillosis • Pulmonary Disease, Chronic Obstructive

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Background

Aspergillus species are a significant cause of morbidity in both immunocompetent and immunocompromised patients. Disease involvement ranges from a spectrum of allergic bronchopulmonary aspergillosis to chronic (saprophytic) forms and can have an invasive component to its disease process.

The chronic form of pulmonary aspergillosis favors those individuals with none or minimally suppressed immune systems or those with minimal alterations of pulmonary parenchyma due to underlying disease. Diagnosis ideally consists of tissue and fluid samples, though because these samples are not always obtainable (1–>3) beta-D-glucan and galactomannan antigen assays continue to play a pivotal role achieving this diagnosis.

Despite Aspergillus spores being pervasive in nature and inhalation common, the clinical suspicion for this disease remains low as tissue invasion is uncommon. Because of this, the disease is often overlooked as holding a strong place on a differential diagnosis for cavitary lung lesions, which can delay diagnosis and treatment. Once diagnosed, chronic pulmonary Aspergillus treatment is straight forward; outside of monitoring liver function tests, long term treatment with a triazole is recommended as first-line treatment.

Case Report

A 69-year-old Caucasian female with intermittent medical follow-up was treated for an acute exacerbation of chronic obstructive pulmonary disease (COPD) and discharged to a rehabilitation bed on the other side of town.

The patient's past medical history was significant for chronic systemic steroid administration due to undiagnosed COPD, hypothyroidism, and anxiety/depression. Her social history was remarkable for exposure to tetrachloroethylene while working in the dry-cleaning business, a history of alcohol abuse (a box of wine every other day) as well as tobacco abuse (100 pack years). She had been institutionalized since her index admission. Her family history was unremarkable for pulmonary disease. Review of systems was negative for a history of rashes or family history of connective tissue diseases.

Her hospitalization was uneventful. There was a concern of sepsis, but with a qSOFA (Modified Sequential Organ Failure Analysis) score of 1 on admission and negative blood cultures and improving vital signs, sepsis was quickly ruled out. Computed tomography (CT) scan (Figure 1) of the chest performed on admission indicated disseminated tree in bud opacities with bilateral bronchial wall thickening, which were initially thought to signify acute on chronic bronchitis and left atypical

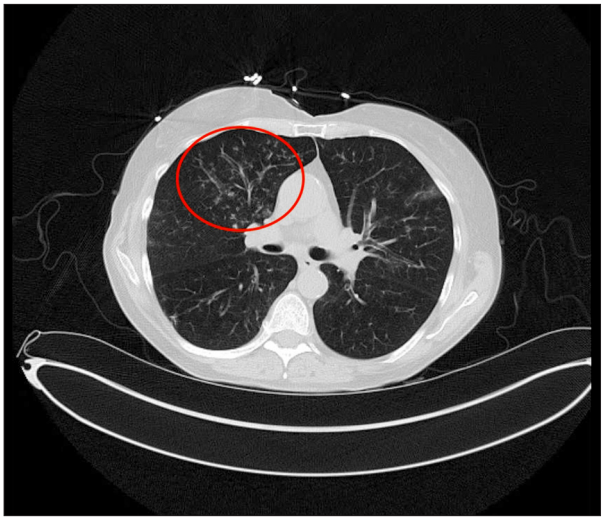

Figure 1. Computed tomography chest: lung windows at the level just below the carina showing small tree in bud abnormalities.

bronchopneumonia. The patient did not have prior pulmonary function tests, yet appeared to be treated for multiple acute exacerbations of COPD with systemic steroids prior to hospital admission. Prior to discharge, a bedside spirometry was performed and was notable for a forced expiratory volume 1 (FEV1) of 34% (0.54 L). Ultimately, the patient was treated for acute exacerbation of COPD and a left lobar bronchopneumonia with 5 days of azithromycin and 7 days of ceftriaxone. Once her antibiotic courses were completed, she was discharged to a skilled nursing facility (SNF) for restorative rehabilitation.

She returned to the index hospital from rehabilitation due to complaints of 6 days of worsening dyspnea and increasing supplemental oxygen needs from a baseline of 3 L. Her vital signs were 36.4°C, 100 beats per minute, 99/59 mm Hg, 93% oxygen on 2 L nasal cannula, 36.7 kg weight. Primary physical examination was notable for a frail, chronically ill appearing female who was able to speak in full sentences. The chest wall anterior-posterior (AP) diameter was enlarged in a barrel shape. Cardiac examination revealed tachycardia without murmurs or gallops. The patient's lungs were clear to auscultation bilaterally, though breath sounds severely diminished at the bases. Janeway lesions and Osler's nodes were notably absent, though bilateral upper extremity digits were positive for significant clubbing. Her nails were without evidence of splinter hemorrhages. A small left forearm ecchymotic area was circled marking a prior purified protein derivative (PPD) test. The official radiological read from a CT chest (Figure 2) that was performed just prior to hospital arrival remarked on "interval development of multiple necrotic-appearing pulmonary nodules consistent with septic emboli and micro-nodularity to all lung zones with consolidation anterior and posterior right lung base and inferior segment of the lingula."

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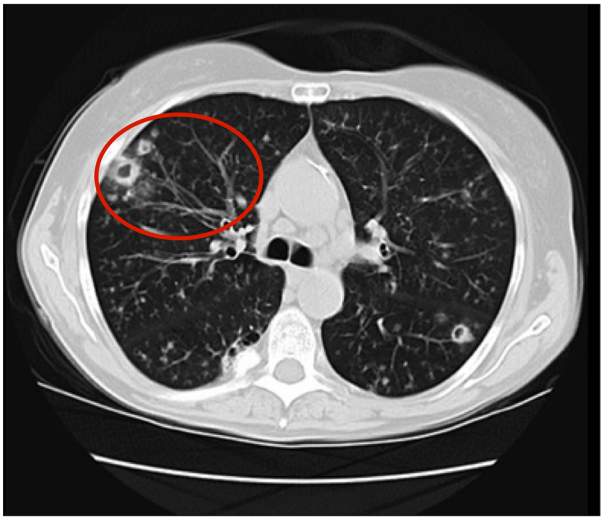

Figure 2. Computed tomography chest; lung window at the level of the carina depicting large pulmonary cavitation at the end of terminal bronchi.

The patient was admitted to a negative pressure room with plans for 3 acid- fast bacilli (AFB) smears to be collected due to a concern for tuberculosis. Empiric treatment consisted of ampicillin, gentamicin, and vancomycin for a high suspicion of infective endocarditis. A transesophageal echocardiogram (Figures 3, 4) was scheduled to rule out endocarditis; this study was negative for a patent foramen ovale (PFO) or valvular vegetations. Broad spectrum antibiotics were tapered down to piperacillin/tazobactam and vancomycin on the second hospital day after echocardiography was negative for vegetations.

Laboratory studies performed on admission consisted of an erythrocyte sedimentation rate (ESR) that was 115 mm/hour, and antinuclear antibody (ANA) and antineutrophil cytoplasmic antibodies (ANCA), both of which were negative; a complete metabolic profile and complete blood count were unremarkable. The patient's PPD was read as negative after 48 hours.

Further laboratory evaluation revealed a negative DNA double stranded antibody and rheumatoid factor. Blood cultures remained negative twice. A sputum culture grew an unspecified fungus-like organism. The serum assays (1–>3) beta-D-glucan (Fungitell) and galactomannan were ordered.

The infectious disease service was consulted, and additional tests were run on the patient's sputum culture, which was ultimately identified as *Aspergillous fumigatus*. The galactomannan test returned negative, but the (1–>3) beta-D-glucan (Fungitell) was positive. An aspergillus IgG was positive as well. The constellation of findings in the setting of an immunocompetent host with structural lung disease confirmed the diagnosis of chronic cavitary aspergillus. A bronchoscopy was foregone due to the diagnosis being made from serology and sputum cultures.

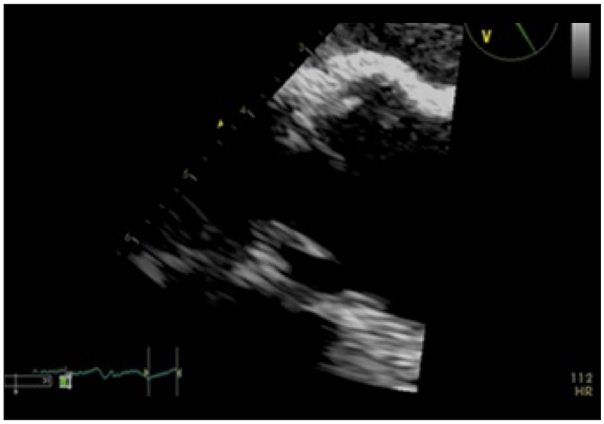

Figure 3. Transesophageal echocardiogram, long axis view of the aortic valve without vegetations.

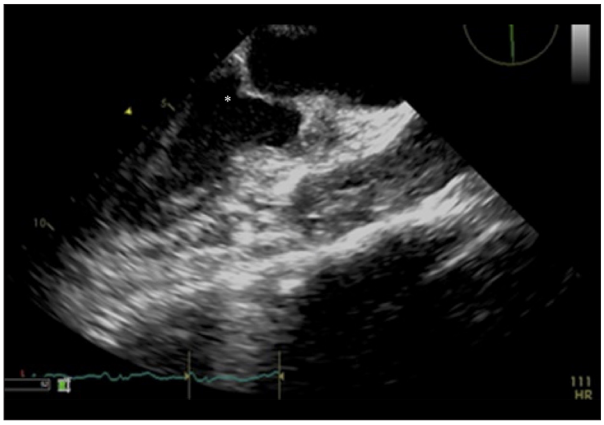

Figure 4. Transesophageal echocardiogram, long axis view of the mitral valve without vegetations (mitral valve is marked by an asterisk).

Outcome and follow-up

Once the patient's sputum culture identified aspergillus, voriconazole was started, with a baseline level being obtained prior to hospital discharge. Liver function tests were measured as well, as the patient will require antifungal therapy for at least 6 months.

Unfortunately, the patient was lost to outpatient pulmonary clinic follow-up; it is unknown what her follow-up scans indicated or whether she successfully cleared her disease burden.

Discussion

Pulmonary cavities are gas filled pockets whose nidus for formation is an inflammatory consolidation within the pulmonary parenchyma [1]. Most cavities can be visualized with plain films and because of their broad etiology, it is often difficult to predict which pathology will result in a cavitation. Infections,

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malignancy, rheumatologic disorders, aspiration, pulmonary infarction, and displacement of pulmonary parenchyma within the thorax are just some of the pathology on the differential diagnosis list when a cavitation is discovered. One cause that is often forgot is aspergillus, a ubiquitous spore that is often indolent in the general population.

Bronchopulmonary aspergillosis, while an infrequent condition in the immunocompetent population, is spread by the inhalation of mycotic spores from the *Aspergillus* species. The exact extent of involvement in the United States is currently unknown as this is not a reportable disease, though *A. fumigatus* appears to be the most virulent [1,2]. The spores are inherent in the environment and most often are indolent in those individuals lacking structural lung disease or individuals who are immunocompromised [2]. For those patients with structural lung disease and/or an immunocompromised status, such as the case presented in this report, the *Aspergillus* spores can lead to a spectrum of pulmonary involvement, which are classified into 4 different forms.

The acute forms of this disease comprise allergic broncho-pulmonary aspergillosis and invasive aspergillosis. Allergic broncho-pulmonary aspergillosis has a predilection for those with asthma or cystic fibrosis, while invasive aspergillosis (angioinvasive or broncho-invasive forms) tends to occur in severely immuno-compromised patients. The chronic forms of *Aspergillus* infection are composed of 2 syndromes (aspergilloma and chronic cavitary pulmonary aspergillosis [CCPA]) that can be crippling to those with established pulmonary parenchymal damage [3–6]. The incidence of the acute and chronic manifestations outlined aforementioned is dependent on the immunologic status of the host and the existence of an underlying lung disease.

Specific to this case is CCPA; CCPA most often favors middle-aged patients with abnormal lung structure (chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis or chronic lung cavities) [5] versus those patients who are immunocompromised. The disease process consists of a slowly progressive course that has the ability to last for years. The frequent, though vague, constitutional symptoms of fever, malaise, fatigue, and weight loss can accompany CCPA, which make it difficult to place at the top of a differential diagnosis list and makes the diagnosis one of high suspicion. Non-specific pulmonary symptoms can range in severity from a chronic productive cough to hemoptysis [5]. Further difficulty in a diagnosis is hindered by non-specific parenchymal structural changes that can be seen on imaging, these changes can range from pleural thickening to an empyema and anything in between [7]. Mycobacterium infection and obstructive lung diseases (sans asthma) are the most frequent pulmonary diseases that are associated with CCPA. The patient presentation in this case report was not different: vague constitutional symptoms coupled with non-specific radiographic findings, made it difficult to have a high index of suspicion.

The diagnosis of CCPA was formulated by Godet et al. [3] in 2014: the constellation of immunosuppression, constitutional symptoms, the formation of a single/multiple lung cavitation, a positive serum *Aspergillus* percipitins test, increased biological inflammatory markers and the absence of other pathology that could mimic the aforementioned symptoms (malignancy, tuberculosis, atypical mycobacterium) help comprise the diagnostic criteria. Unfortunately, none of the aforementioned criteria in singularity is able to diagnose CCPA, though the combination of the criteria with patient specific factors often strongly argues for the diagnosis. This combination of clinical and diagnostic manifestations was chosen to help aid in the diagnosis of this disease by the updated 2016 IDSA guidelines for *Aspergillus* [8].

Confirmative diagnosis can be aided by the combination of histopathologic/cytologic and culture specimens. The "gold standard" procedure for obtaining a tissue sample and bronchioalveolar lavage is via bronchoscopy [6,8]. Complicating matters is the fact that the yield from obtaining an adequate specimen via bronchioalveolar lavage is low for lesions in the periphery of the pulmonary parenchyma; because of this, a lung biopsy, achieved either percutaneous or via navigational bronchial technique, should be considered in this population [9].

In the case that histopathologic specimens are unable to be obtained, such as this case, a serum assay for (1–>3) beta-D-glucan (Fungitell) should be ordered. A Fungitell assay helps in diagnosis of a fungal organism, but is not specific for *Aspergillus* as it is present in all fungi cell walls. Obtaining a serum and bronchioalveolar lavage galactomannan can help aid in the diagnosis as this assay is a more accurate marker for *Aspergillus* in both the pediatric and adult patient populations [8]. The primary laboratory test for making a diagnosis of chronic pulmonary aspergillosis is a positive serum *Aspergillus* immunoglobulin (Ig)G antibody level [10].

First-line treatment encompasses oral medications from the triazoles anti-fungal group. When triazoles cannot be administered, amphotericin B (AmB) deoxycholate and echinocandins serve as useful second-line therapy options for *Aspergillus* infections. Six months of treatment is the desired duration for patients with CCPA and radiographic progression of disease, or for patients who experience either pulmonary or general symptoms. Six months is also an acceptable treatment duration for those patients who are unfortunate to experience a progressive loss of lung function. Obtaining trough drug levels for those patients who are on prolonged azole therapy is recommended [10,11].

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After 2 weeks of treatment, a non-contrast CT scan of the chest to evaluate the patient's response to treatment is recommended for those that are diagnosed with CCPA.

Conclusions

In an immunocompromised patient with rapidly progressing radiologic findings concerning of pulmonary cavitation, *Aspergillus* should not be forgotten when formulating a differential diagnosis list. Diagnosis by the combination of serum and tissue specimens is easily made and the treatment consists of a prolonged duration of triazole administration.

Acknowledgements

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Conflict of interests

None.

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