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An "alternative" clinical course of COPD exacerbation and pulmonary embolism

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Abstract. – Patients with chronic diseases, such as Chronic Obstructive Pulmonary Disease (COPD) and diabetes mellitus, are exposed to particular complications that require a careful diagnostic algorithm. Pulmonary Embolism (PE) in COPD patients often demands an accurate differential diagnosis and a prompt therapeutic intervention.

***Aspergillus spp.* infection comprises a large spectrum of pathological manifestations, depending on immune status and the presence of underlying lung disease. These manifestations may range from invasive pulmonary aspergillosis (IPA) in gravely immunocompromised patients, to chronic necrotizing aspergillosis (CNA) in patients with chronic lung diseases and moderately compromised immune systems. Aspergilloma is generally observed in patients with cavitary lung diseases, and allergic bronchopulmonary aspergillosis (ABPA) is reported in patients with hypersensitivity to Aspergillus antigens.**

We report a case with pulmonary aspergillosis arisen on a pulmonary infarction after PE in a patient with COPD and diabetes mellitus. To date, report with this clinical evolution was not reported in literature.

This report is intended to describe an accurate diagnostic path in a complex overlap of different pathological conditions, highlighting the great importance of differential diagnosis and an appropriate diagnostic algorithm. In addition, open issues on the real diagnostic value of clinical, radiological, and laboratory features for COPD exacerbation, PE and aspergillosis have been discussed.

Key Words:
Chronic obstructive pulmonary disease, Pulmonary embolism, Chronic necrotizing aspergillosis, Voriconazole.

Case Report

An 81 year-old man, ex-locksmith, with COPD, was admitted to our Respiratory Disease Unit because of cough with increase in production of purulent sputum, exertional dyspnea, hemoptysis and chest pain arisen seven days before.

Past medical history included arterial hypertension, diabetes mellitus, atrial fibrillation, glaucoma and prior peptic ulcer, and a chronic pharmacological therapy with oral hypoglycaemic agents, ticlopidine, nebivolol, digoxin and ramipril.

The patient was a current smoker since he was 11 years old (71 pack-years).

At arrival, his vital signs were: body temperature 36.8°C, blood pressure 130/70 mmHg, heart rhythm about 85 beats/min (arrhythmic) and respiratory rate 14 breaths/min.

Examination revealed inspiratory crackles and wheezing after forced expiration.

Investigations showed a neutrophil leukocytosis (total white cells count $13.13*10^3/\mu l$, with neutrophil $9.97*10^3/\mu l$), increased erythrocyte sedimentation rate (ESR) (86 mm/h) and serum C-reactive protein (CRP) levels (16.37 mg/dl), normal D-dimer with semiquantitative latex agglutination D-dimer assay (204 ng/ml), high levels of functional fibrinogen (712 mg/dl). The arterial blood gas analysis revealed normal gas exchange at rest on room air (pH 7.43; pO_2 77 mmHg; pCO_2 38 mmHg).

Chest X-ray showed vague COPD signs, with hyperinflated lungs, flattened diaphragm, and central pulmonary artery enlargement, and the pulmonary function test revealed a Stage III COPD, with a severe airflow obstruction (forced expiratory volume in one second (FEV_1): 1.33 L, 46.7% of predicted; forced vital capacity (FVC): 2.60L, 67% of predicted; FEV_1/FVC: 51%).

Electrocardiography showed atrial fibrillation with normal ventricular response, left axis deviation, aspecific alterations of ventricular ripolarization.

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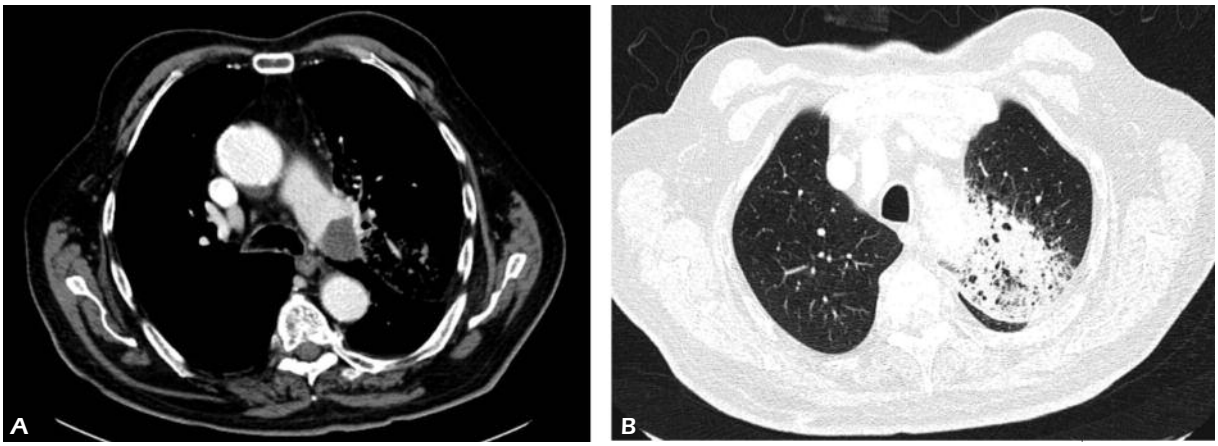

Figure 1. Chest CT. ***A,*** contrast-enhanced CT scans show a clot in the left pulmonary artery extending into the lower lobar branches. ***B,*** lung window setting shows a large consolidation in the upper left lobe resting typically and largely upon scissural, mediastinal, and apical pleura. In addition, several bronchiectasis by retraction are observable in its context.

Two-dimensional echocardiography revealed global left ventricular hypokinesis, increased left and right atrial size, left ventricular ejection fraction 40%; mild mitral and aortic regurgitation.

As the initial clinical suspicion was a COPD exacerbation, the patient started a standard treatment with steroids given intravenously (iv CS, methylprednisolone 20 mg twice a day), antibiotics (piperacillin-tazobactam 4.5 g twice a day), inhaled bronchodilators and theofilline at standard dosage. We decided to administer Enoxaparin at a prophylactic dosage (20 mg, 2000 U.I.). After 48 hours of treatment, despite the improvement in total white cells count ($10.05*10^3/\mu l$), neutrophils ($7.65*10^3/\mu l$), serum CRP (9.12 mg/dl) and ESR (42 mm/h), the patient reported a persistence of the hemoptysis and chest pain.

The sputum culture (sample collected at admission) was positive for *Escherichia coli* sensitive to piperacillin-tazobactam.

Together with COPD exacerbation we suspected a lung cancer or an acute pulmonary embolism. Three other sputum samples were collected for the detection of neoplastic cells (negative). Additionally, it seemed to us reasonably to recommend a chest Computed Tomography (CT), which revealed a clot in the left pulmonary artery extending into the lower lobar branches, and an adjacent consolidation in the left upper lobe (Figures 1 and 2).

The radiological features of the consolidation did not allow us to reach a certain diagnosis, as they can be seen in different conditions such as lung cancer, pneumonia, hemorrhagic lung infarct.

The patient underwent a duplex ultrasonography of extremity veins, which revealed a deep vein thrombosis of the popliteal vein.

Immediately we started a treatment with subcutaneous low-molecular-weight heparin (LMWH, Enoxaparin 1 mg/kg every 12 hours); the therapy with iv CS was then suspended.

The patient has been discharged a week later with adequate long-term anticoagulant therapy (Acenocoumarol, with doses adjusted in order to maintain the INR at a target of 2.5, range 2.0-3.0).

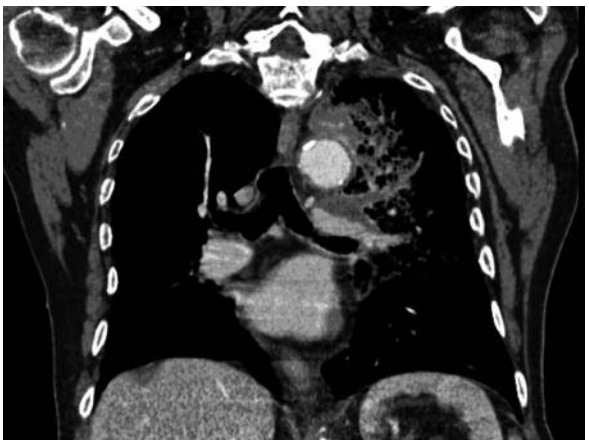

Figure 2. Chest CT, coronal plane. Pulmonary infiltrate with pleural evolvement. Infarctioned area shows an advanced fibrotic retraction in which a rich vascularization and consequent cystic bronchiectasis are evident.

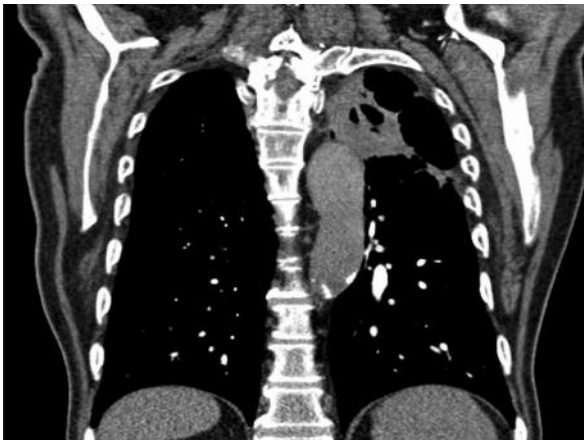

Figure 3. Chest CT control after 1 month, coronal plane. In the context of pulmonary infarction (upper left lobe) are observable retraction and pseudo-cavity images.

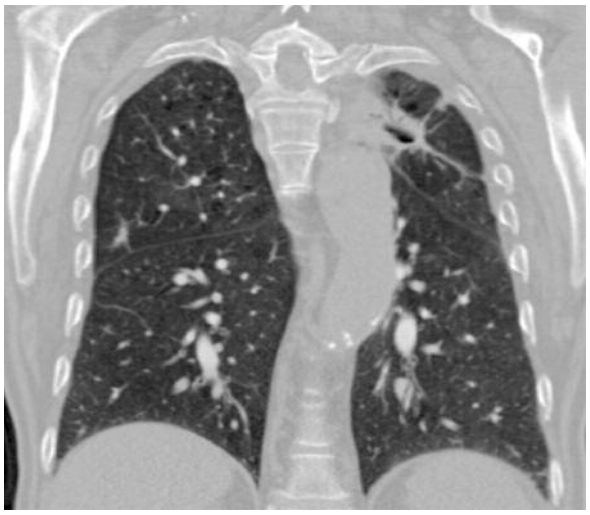

Figure 4. Chest CT control after 4 months, coronal plane. Lung window setting shows a marked cicatricial retraction in the upper left lobe with associated an empty cavity. Evident diffuse signs of COPD (phenotype B: emphysema and chronic bronchitis) coexist in both lungs.

One month later a new chest CT control showed a reduction in size of the thrombus visible in the left pulmonary artery; the focal consolidated area appeared lowered in size, with some small pseudocavities inside (Figure 3).

The response to the treatment with LMWH and then Acenocoumarol allowed us to make a clear diagnosis of PE with hemorrhagic lung infarction.

A new chest CT was performed four months after the discharge: it revealed the complete resolution of the PE and a striking cicatricial retraction in the upper left lobe with associated an empty thin-walled cavity (Figure 4).

We collected a sputum sample and performed a culture for fungal species, resulting positive for Aspergillus Sp.

As in routine clinical practice most Aspergillus isolates from non-sterile body sites do not represent disease, the patient underwent fiberoptic bronchoscopy to perform a brochoalveolar lavage culture, which confirmed a positive result for Aspergillus Sp.

What is your Diagnosis?

Diagnosis: Chronic Necrotizing Aspergillosis (CNA) in an elderly, previously hospitalized patient, with underlying pulmonary disease (COPD), diabetes mellitus, previous low-dose corticosteroid use, and a pulmonary infarction with ischemic necrosis of the lung parenchyma.

Clinical course: An anti-fungal therapy with intravenous Voriconazole (400 mg every 12 hours in the first 24 hours, and then 200 mg every 12 hours) was immediately established. Sputum culture turned out negative for Aspergillus after 28 days of antifungal therapy.

The clinical course is represented in Figure 5.

Discussion

This report is intended to describe an accurate diagnostic path in a complex overlap of different pathological conditions, highlighting the importance of differential diagnosis and of an appropriate diagnostic algorithm, to discriminate proven and probable pulmonary aspergillosis from Aspergillus colonization, as previously described[1].

This case clearly describes the difficulty that clinicians encounter in clinical practice when predisposing diseases coexist in a single patient.

We observed in a patient with COPD and diabetes mellitus, diseases with high prevalence, a clinically underhand event of PE. The application of an accurate diagnostic algorithm, using CT scan, as well as BAL, with semiquantitative culture and cytological examination, made us able to carry out appropriate diagnostic exams, indentify the onset of pulmonary infarction and consequent superimposition of Aspergillus infection and chronic necrotizing aspergillosis[1-3], and establish a prompt therapy in a complex process of differential diagnosis (Figure 5).

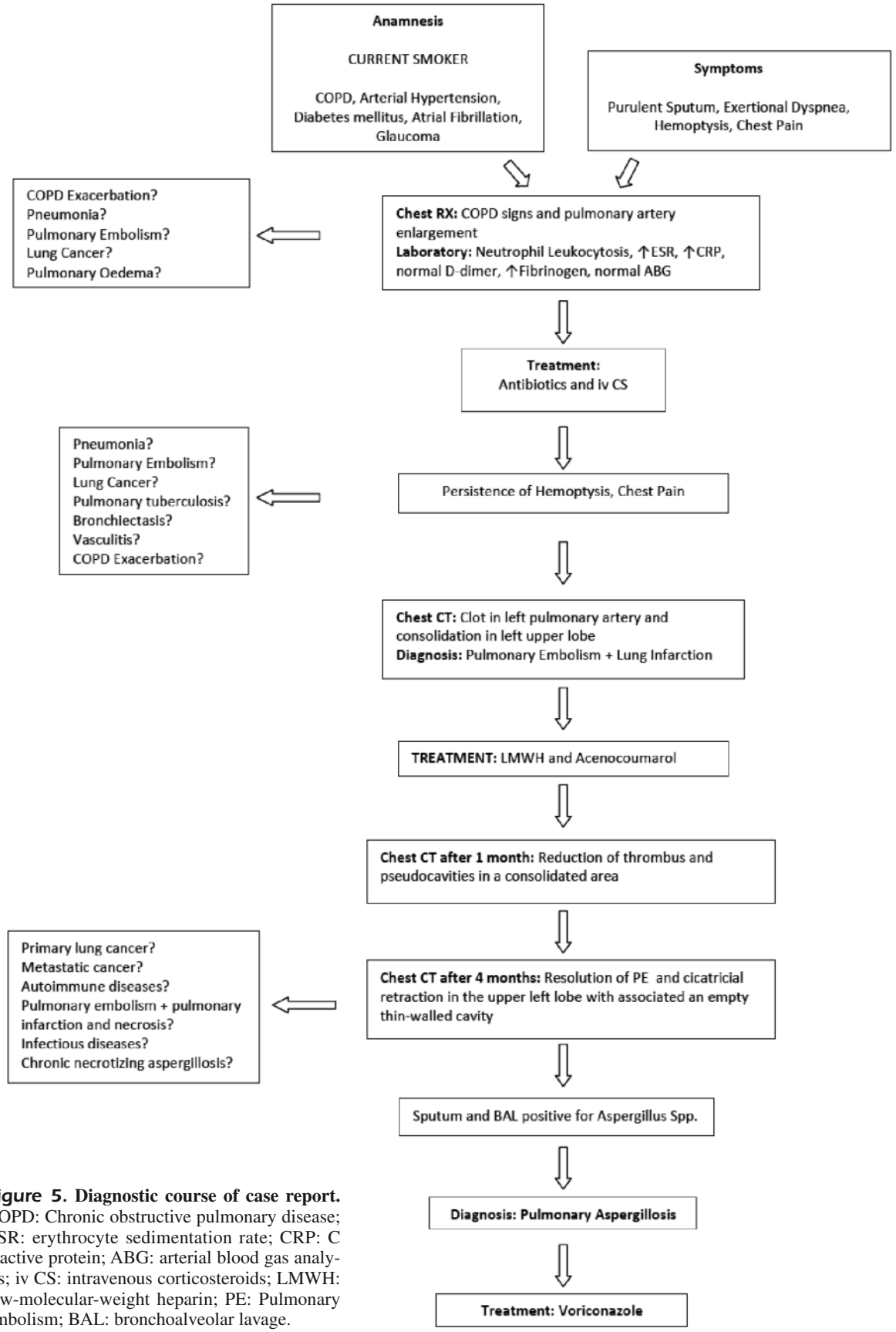

Figure 5. Diagnostic course of case report. COPD: Chronic obstructive pulmonary disease; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; ABG: arterial blood gas analysis; iv CS: intravenous corticosteroids; LMWH: low-molecular-weight heparin; PE: Pulmonary embolism; BAL: bronchoalveolar lavage.

Table I. Diagnostic criteria for chronic pulmonary aspergillosis (CNA).

	Denning's Criteria[9]	Kohno's Criteria[10]
Clinical	Chronic (41 month) pulmonary or systemic symptoms, including at least one of: weight loss; productive cough; haemoptysis No overt immunocompromising conditions (e.g. haematological malignancy, neutropenia, organ transplantation) No dissemination	Chronic symptoms with fever, cough, hemoptysis, and body weight loss
Radiological	Cavitary pulmonary lesion with evidence of paracavitary infiltrates New cavity formation, or expansion of cavity size over time	Chest X-ray and CT scan abnormalities showing infiltrates and cavities in the upper lobes
Laboratory	Elevated levels of inflammatory markers (C-reactive protein, plasma viscosity, or erythrocyte sedimentation rate) Isolation of Aspergillus spp from pulmonary or pleural cavity, or Positive serum Aspergillus precipitin test exclusion of other pulmonary pathogens, by results of appropriate cultures and serological tests, that are associated with similar disease presentation, including mycobacteria and endemic fungi	Positive levels of serum precipitation antibody for *Aspergillus* and β-Dglucan Isolation of Aspergillus spp. from lung specimens, and e) failure to detect other bacterial, fungal, or mycobacterial pathogens

Today, the use of modern diagnostic techniques let us assess the possible alternative diagnosis up to reach the certain diagnosis.

Pulmonary aspergillosis may be under-recognized in patients with COPD; the factors contributing to its development in these patients have not been yet entirely defined. In addition, clinicians should consider PE in a diagnostic workup of COPD exacerbations, especially in patients where the underlying aetiology is not apparent and in whom there is a history of additional risk factors that may increase the clinical likelihood of PE[4-6].

Aspergillus spp are ubiquitous fungi acquired by inhalation of airborne spores and may cause lifethreatening infections, especially in immunocompromised hosts. The spores are commonly isolated from the soil, plant debris, and the indoor environment, including hospitals.

Aspergillus spp. infection comprises a large spectrum of pathological manifestations, depending on immune status and the presence of underlying lung disease[7]. These manifestations may range from invasive pulmonary aspergillosis (IPA) in gravely immunocompromised patients, to chronic necrotizing aspergillosis (CNA) in patients with chronic lung diseases and moderately compromised immune systems. Aspergilloma is generally observed in patients with cavitary lung diseases, and allergic bronchopulmonary aspergillosis (ABPA) is reported in patients with hypersensitivity to *Aspergillus* antigens[8].

Tables I and II describe diagnostic criteria for CNA and differential diagnosis of pulmonary aspergillosis.

Table II. Differential diagnosis of pulmonary aspergillosis (aspergilloma and necrotizing pneumonia).

Infectious pulmonary diseases
Anaerobic bacterial infections
Gram negative bacterial infection
Influenza pneumonia
Staphylococcus aureus infection
Streptococcus pyogenes pneumonia
Tuberculosis
Mycobacterium avium
Mycobacterium Kansasii
Atypical mycobacteria
Legionaires disease
Pseudomonas infection
Amebiasis
Hydatid cyst
Actinomycosis
Blastomycosis
Coccidioidomycosis
Histoplasmosis
Nocardiosis
Abscesses
Septic Pulmonary Embolism
Granulomatous inflammatory diseases
Sarcoidosis
Wegeners granulomatosis
Neoplastic diseases
Carcinoma lung squamous cell/large cell
Metastatic lung disease
Pulmonary lymphoma
Vascular diseases
Pulmonary infarction
Pulmonary infarction with cavitation
Trauma
Pulmonary contusion
Pneumoconiosis and poisoning
Silicosis
Talc dust mining exposure
Silico-tuberculosis
Chemical pneumonitis
Chemical fumes inhalation

In a hospitalized COPD patient with severe nosocomial pneumonia, we ought to exclude aspergillosis, so corticosteroid therapy should be revaluated and systemic antifungal therapy considered. Outcomes can be improved by rapid diagnosis and prompt therapy with voriconazole.

Conclusions

To our best knowledge cases with aspergillosis as complication of pulmonary infarction from PE were not yet reported in literature. Instead cases of pulmonary aspergillosis causing infarction with pulmonary necrosis and PE were relatively frequent.

This case report is interesting as well as exclusive for its clinical evolution and, thus, may be a typical example of clinical practice.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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