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Mediastinal cryptococcosis simulating thyroid neoplasia in immunocompetent patient with prior diagnosis and treatment for COPD

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ABSTRACT

We report a case of mediastinal cryptococcosis with thyroid invasion in a patient who presented dry cough and persistent dyspnea. This patient has been treated for COPD, presenting no clinical responses. Spirometry showed fixed flattening of inspiratory and expiratory loops, suggesting extrinsic tracheal compression. A freezing biopsy revealed a mass consisting of lymph nodes and yeasts with characteristics of *Cryptococcus* spp. After surgical resection of the lesion, the patient was treated with fluconazole, showing total remission of the disease and symptomatology.

1. Introduction

Cryptococcosis is a systemic infection, most often opportunistic, caused by fungi of the genus *Cryptococcus* [1], mainly related to patients with immunosuppression. C. *neoformans* is the most frequent species and it is usually associated with immunosuppression [2], while C. *gattii* is capable of also affecting immunocompetent individuals. Cryptococcosis as a primary infection is often asymptomatic [3], usually beginning in the lung and usually presenting spontaneous resolution. In symptomatic forms, the most common manifestation is meningoencephalitis [4,5]. Less commonly, cryptococcosis can affect other sites, such as skin, bones, liver, lymph nodes, peritoneum, urinary tract, adrenal glands, among others.

Annually, one million new cases are diagnosed worldwide, with a mortality rate of approximately 600,000 per year [6,7]. In Brazil, cryptococcosis is the third invasive fungal infection, with the highest incidence is in individuals between 30 and 59 years old and the mortality rate due to this infection is high [8]. Patients with no history of immunosuppression, with mediastinal manifestations due to cryptococcosis are rarest. Therefore, the objective of this study is to report a case of mediastinal cryptococcosis in an immunocompetent patient with thyroid invasion, simulating neoplasia. Besides, it is intended to provide a differential diagnosis for persistent dyspnea in smokers, with previous treatment for chronic obstructive pulmonary disease (COPD) without clinical response. Spirometry was the tool that guided the initial diagnostic hypothesis of thyroid neoplasm by compressing the trachea, but the freezing biopsy performed later, confirmed that it was cryptococcosis.

2. Case

In September of the year of 2014, we received in the pneumology clinic in Maringá, Paraná, Brazil (day 0), a female patient, a 73 years-old retired teacher with a 30 pack-year smoking history who had been facing dyspnea on moderate exertion and dry cough for three months. The patient was using bronchodilators in a daily basis as treatment for a suspected Chronic Obstructive Pulmonary Disease (COPD) and had no previous history of diabetes, rheumatic diseases or other immunosuppressive diseases. She reported that three weeks earlier she had been diagnosed with a bronchial infection and remained hospitalized for 7 days, receiving ceftriaxone, hydrocortisone and bronchodilators, however without improvement of dyspnea. At day 0, the physical examination presented 95% oxygen saturation in ambient air and auscultation without adventitious sounds. Spirometry showed moderate obstructive ventilatory disorder and fixed flattening of inspiratory and expiratory loops, without bronchodilator response (Fig. 1A and B).

Chest x-ray with mediastinal enlargement and chest tomography showed a right anterior mediastinal mass compressing the trachea and diverting it contralaterally (Fig. 1C and D). On day +14, during a surgical procedure, a freezing biopsy was performed, which discarded neoplasia. It was opted to use a mass resection combined with right partial thyroidectomy since the lesion was invading the thyroid and

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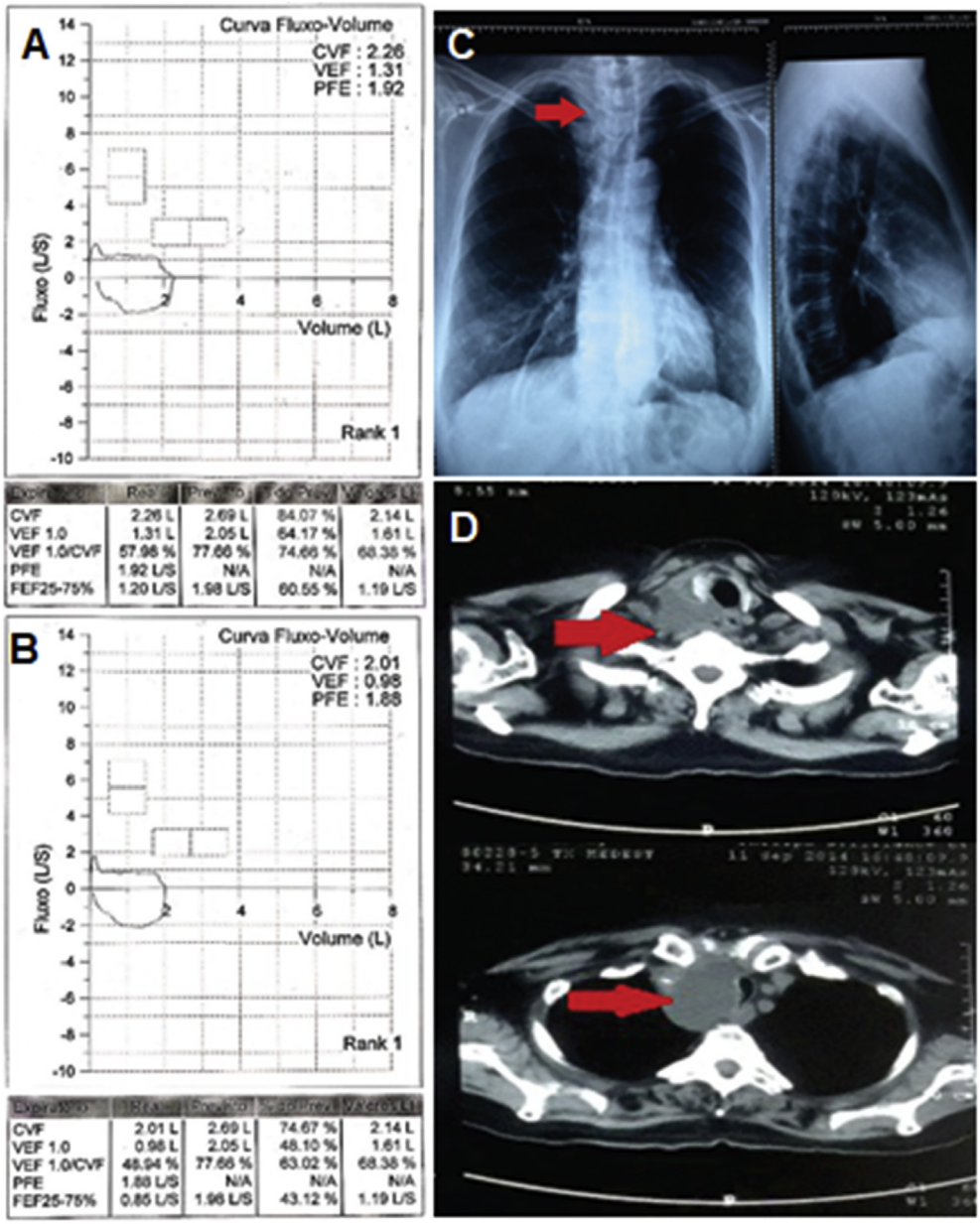


Fig. 1. A - Preoperative Spirometry; B - post-bronchodilator preoperative spirometry. A and B- Moderate obstructive pulmonary ventilation disorder without bronchodilator response; C - Radiography of preoperative thorax demonstrating tracheal deviation to the left and increased mediastinum (arrow); D - Preoperative thorax tomography with mediastinal mass compressing and diverting the trachea.

there was no cleavage plan. Histology showed a mass consisting of lymph nodes and mediastinal fat, with structures stained by Meyer's Mucicarmin compatible with *Cryptococcus* spp (Fig. 2).

There was a good evolution in the postoperative period and on day +21, fluconazole 150 mg/day was introduced orally for 6 months. 30 days after surgery (day + 44) the patient had no dyspnea and presented only persistent hoarseness due to right vocal fold paralysis. At that time, normalization of spirometry also occurred. Chest radiographs and posterior tomography showed no more mediastinal lesion or tracheal compression (Fig. 3A, B, C). Since the end of the drug treatment, after almost four years of outpatient follow-up, the patient has been asymptomatic and presenting normal spirometry.

3. Discussion

Cryptococcosis is a systemic infection caused by the inhaling of fungi of the genus *Cryptococcus* (*C. neoformans* or *C. gatti*), mainly related to patients with immunosuppressive conditions such as AIDS, prolonged treatment with corticosteroids, organ transplants, neoplasms, liver diseases and sarcoidosis [2]. In these cases, the most common manifestation is meningoencephalitis [6,7], followed by pulmonary conditions and reaching specific anatomical sites at a lower frequency, such as skin, soft tissues and bones. There may still be the dissemination of the fungus to the liver, lymph nodes, peritoneum, urinary tract, adrenal glands and eyes [9]. In people without immunocompromising factors, most times, the inhalation of the basidiospore occurs, but there is no development of symptoms or signs of infection and there is also a total absence of fungi in the tissues [10,11]. The patient of this case did not present any immunosuppressive disease, however, the age of 73 may have been a decisive factor for the evolution of the case in a slightly unusual way. It is important to highlight that the most common chest X-ray pattern in immunocompetent patients is composed of large nodular lesions or alveolar infiltrates, whereas in immunocompromised patients, interstitial infiltrates and

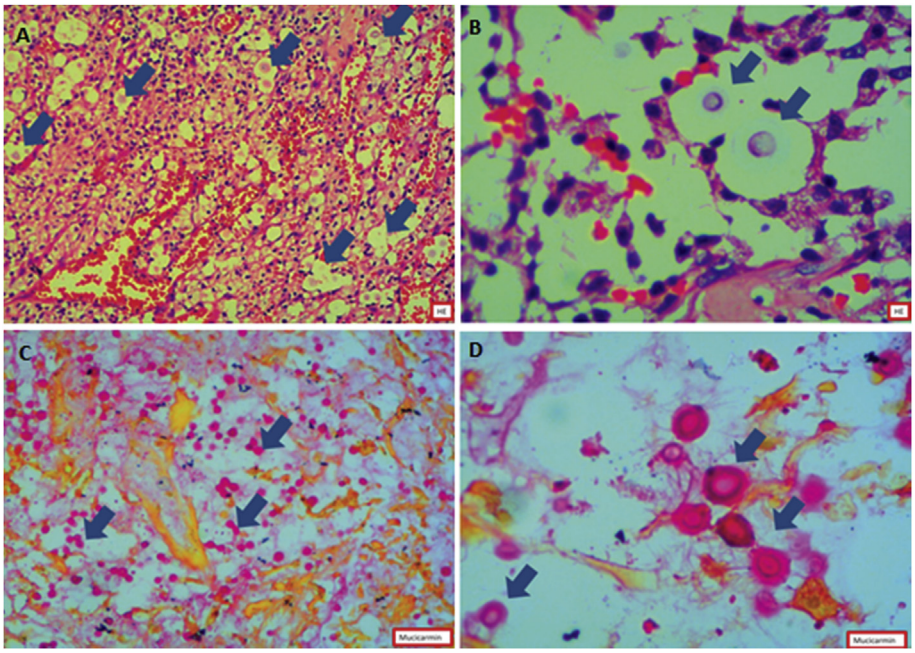
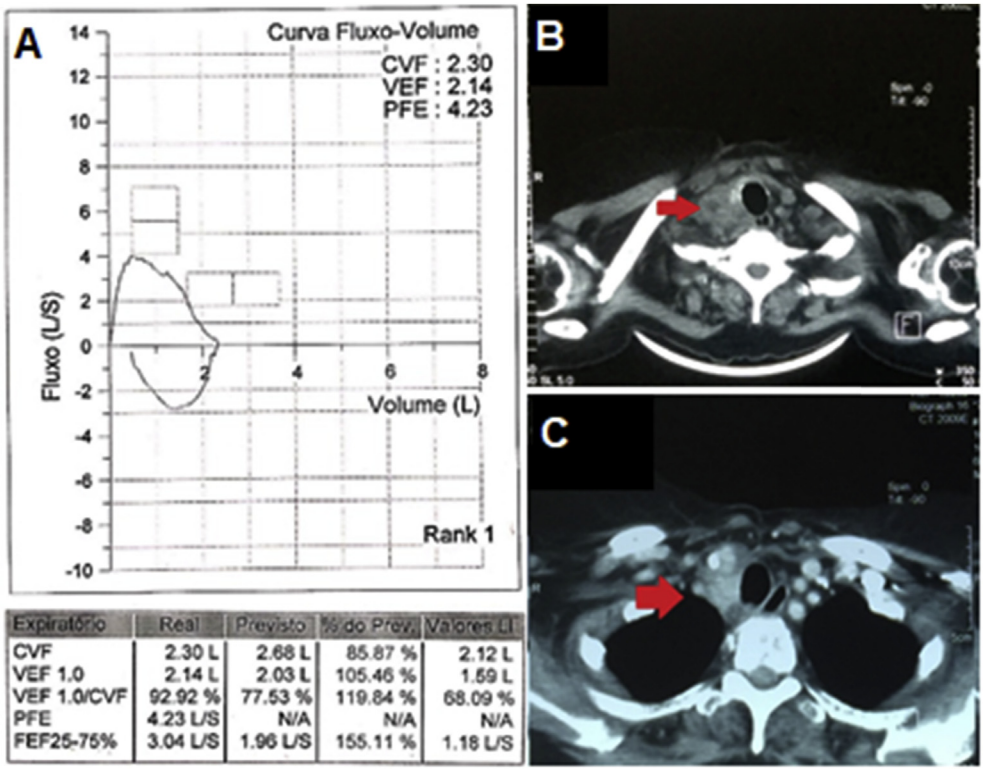


Fig. 2. A - HE showing numerous spherical and/or oval microorganisms, measuring 2–20 μm of diameter, surrounded by a light halo and arranged extracellularly. Minimal inflammatory process in the parenchyma. B-HE in increasing magnification (400X) showing the same structures. C- Numerous spherical microorganisms exhibiting mucopolysaccharide capsule structure evidenced by Meyer's Mucicarmin Stain. D- At higher magnification (400X) confirming these structures.

lymph node diseases are the most common findings. Additionally, in lymph node infection with *Cryptococcus* sp. the lesions are generally smaller than 1.5 cm and are accompanied by pulmonary parenchymal changes [12]. This patient, however, was affected in an uncommon pattern, that is, presenting lymph node disease in the mediastinum under absence of immunocompromising.

Therefore, this study presents a case of atypical evolution of cryptococcosis, with lymph nodes compromising in the anterior mediastinal region, invasion of the right lobe of the thyroid, and extrinsic compression of the trachea. With this, there was a perpetuation of nonspecific symptoms such as cough and dyspnea, which are also the most common clinical findings of neoplasia in this region, such as lymphomas, thyroid cancer or mediastinal lymph node metastasis [13]. In addition, the fact of being a smoker led to the prior evaluation of an alleged COPD, which had been treated empirically for three months, without showing clinical improvement. This fact was a confounding factor for the differential diagnosis.

During the diagnostic investigation, spirometry was initially performed, which showed moderate obstructive ventilatory disorder and fixed flattening of inspiratory and expiratory loops, without response to the bronchodilator. This result was fundamental for the suspicion of a disease causing extrinsic compression of the trachea instead of COPD



Expiratório	Real	Previsto	% do Prev.	Valores LI
CVF	2.30 L	2.68 L	85.87 %	2.12 L
VEF 1.0	2.14 L	2.03 L	105.46 %	1.59 L
VEF 1.0/CVF	92.92 %	77.53 %	119.84 %	68.09 %
PFE	4.23 L/S	N/A	N/A	N/A
FEF25-75%	3.04 L/S	1.96 L/S	155.11 %	1.18 L/S

Fig. 3. A - postoperative spirometry (80 days) revealing normal aspect; B - Chest tomography performed 30 days after surgery demonstrating the reduction of mediastinal mass - patient undergoing treatment with fluconazole; C - Chest tomography performed 90 days after surgery demonstrating the reduction of mediastinal mass - patient under treatment for 3 months with fluconazole.

[14]. From this examination, a radiological investigation of the thoracic and cervical region was initiated, identifying a mediastinal mass responsible for the symptoms. After a surgical procedure, histological analysis of this mass provided the correct diagnosis of the disease and subsidized the appropriate and definitive treatment. Unfortunately, the diagnosis was solely based on histopathology since the surgical sample was fixed in formalin. Currently, the most used method for the diagnosis of mediastinal and hilar lymph node diseases is EBUS-TBNA [7], with lower morbidity compared to the surgical approach. However, its high cost makes it restricted to a few centers in Brazil, justifying the option, in this case, for surgery for simultaneous diagnosis and treatment.

According to the Infectious Diseases Society of America (IDSA) for central nervous system infections and severe pulmonary cryptococcosis, the drug of choice is amphotericin-B associated with intravenous flucytosine, followed by oral fluconazole. For mild pulmonary conditions in immunocompetent patients, the use of fluconazole 400mg or 6mg/kg for 6–12 months is recommended [15]. In this case, after the removal of the mass, the patient was treated with fluconazole 150mg/day for 6 months. This choice was made seeking to reduce hepatotoxicity and the risk of interaction with other drugs, taking into consideration that is was a patient aged over than 70 years-old. Fortunately, the treatment proved to be effective as there was complete resolution of the condition.

Conflict of interest

The authors have no conflicts of interest to state and confirm that each one has made substantial contributions to information and materials submitted for publication.

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