

## Not all Nodules Are Cancer and not all Fungal Infections Are Aspergillus

### Nem todos os Nódulos São Cancro e nem todas as Infecções Fúngicas São Aspergillus

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#### ABSTRACT

*Pithomyces*, a dematiaceous fungus, is a common colonizer of dead leaves and stems of many different plants and is associated with facial eczema in some animals. We report a case of invasive fungal pulmonary disease by *Pithomyces chartarum* in a healthy, non-immunocompromised patient. We aim to demonstrate our diagnostic and therapeutic approach and focus on the major challenges arising from the lack of scientific evidence regarding infection by this fungus in humans.

**Keywords:** Fungi; Humans; Lung Diseases, Fungal; Solitary Pulmonary Nodules

#### RESUMO

*Pithomyces*, um fungo demáceo, é um colonizador comum de folhas e caules de diferentes plantas e está associado a eczema facial em alguns animais. Neste trabalho, descrevemos um caso de infecção fúngica invasiva pelo fungo *Pithomyces chartarum*, numa mulher não imunocomprometida. O nosso objetivo é descrever a abordagem diagnóstica e terapêutica deste caso, realçando os principais desafios que surgem devido à falta de evidência científica relativamente à infecção deste fungo em humanos.

**Palavras-chave:** Fungos; Humanos; Nódulo Pulmonar Solitário; Pneumopatias Fúngicas

#### INTRODUCTION

*Pithomyces chartarum* (*P. chartarum*) is a saprophytic fungus, member of the *Pleosporales* order.<sup>1</sup> Apart from one case of fungal peritonitis caused by a *Pithomyces* species in association with *Curvularia geniculata*,<sup>2</sup> this fungal species has not been reported to be implicated in any human infection. Most reports are limited to those of facial eczema or pithomycotoxicosis in ruminants developing after ingestion of vegetation bearing *P. chartarum* which produces a specific family of mycotoxins named sporidesmins.<sup>3,4</sup> As far as we know, we present the first case of *P. chartarum* pulmonary infection in an immunocompetent patient.

#### CASE REPORT

A 33-year-old woman was admitted to the emergency department with significant haemoptysis lasting a couple of hours. She was a hairdresser, non-smoker, with no recent travels, no animal contact and no humidity or mold at home. Past medical history included conization of the cervix because of cervical dysplasia five years ago. She had no history of respiratory disease or previous similar episodes. On admission, she had no fever, dyspnea or cough. On examination, she was hemodynamically stable, with good peripheral oxygen saturation and no other findings. Blood workup showed no haemoglobin drop and no coagulation test changes. Chest computed tomography (CT) was performed, revealing a single peripheral spiculated nodule with the largest diameter of 3 cm on the left lower lobe, and no

other changes (Fig. 1). Bronchoscopy was also performed, revealing serohematic secretions with no signs of active bleeding. Because of lung cancer suspicion, a transthoracic needle biopsy (TTNB) was performed and a brain magnetic resonance imaging (MRI) and a positron emission tomography - computed tomography (PET-CT) were scheduled for the outpatient setting.

No signs of malignancy were found on bronchoalveolar lavage (LBA) or on TTNB histology, but septate hyphae were identified in the latter (Fig. 2). LBA cultures were negative, even though mycological analysis was not performed, as fungal infection was not suspected at first. MRI showed no lesions and PET-CT revealed fluorodeoxyglucose (FDG) high uptake by the left lower lobe nodule previous known (qSUV max 11.6), with no other findings.

Given these results suggesting a fungal infection, a more exhaustive workup was conducted. HIV serologies were negative, serum lymphocyte populations and immunoglobulin levels were normal. *Aspergillus fumigatus* IgG specific antibody, serum galactomannan *Aspergillus* antigen and fungal DNA detection by PCR on histology were negative.

At this point, an otherwise healthy, young, non-immunocompromised woman, with no lung structural abnormalities, was found to have a suspicious pulmonary nodule. Even though there was evidence of fungal hyphae, there was no other test supporting fungal infection and there were no

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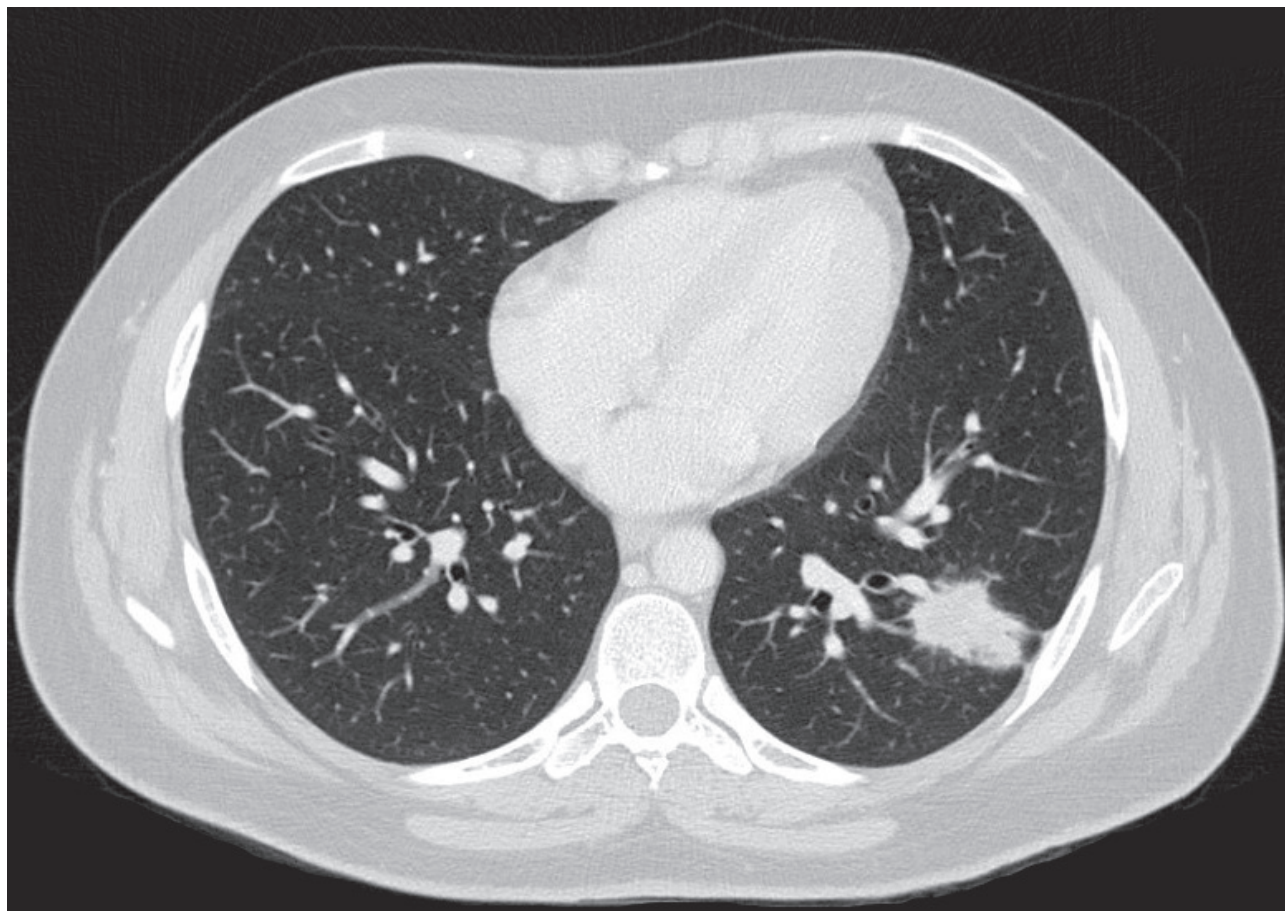


Figure 1 – CT scan revealing a single peripheral spiculated nodule with 3 cm on the left lower lobe

signs of malignancy on cytologic or histologic analyses. In face of a reasonable doubt pending on the differential diagnosis between lung cancer and fungal infection, the thoracic multidisciplinary tumour board decided to propose a left lower lobectomy to the patient.

Left lower lobectomy via uniportal video-assisted thoracic surgery (VATS) was performed and the histological examination of the surgical specimen revealed filamentous septate fungi with tissue damage without vascular invasion, which suggested the diagnosis of chronic necrotising aspergillosis; there were no signs of malignancy. Detection of fungal DNA by PCR on the specimen from surgery revealed *Pithomyces chartarum* with 98% homology and no other fungal DNA detected.

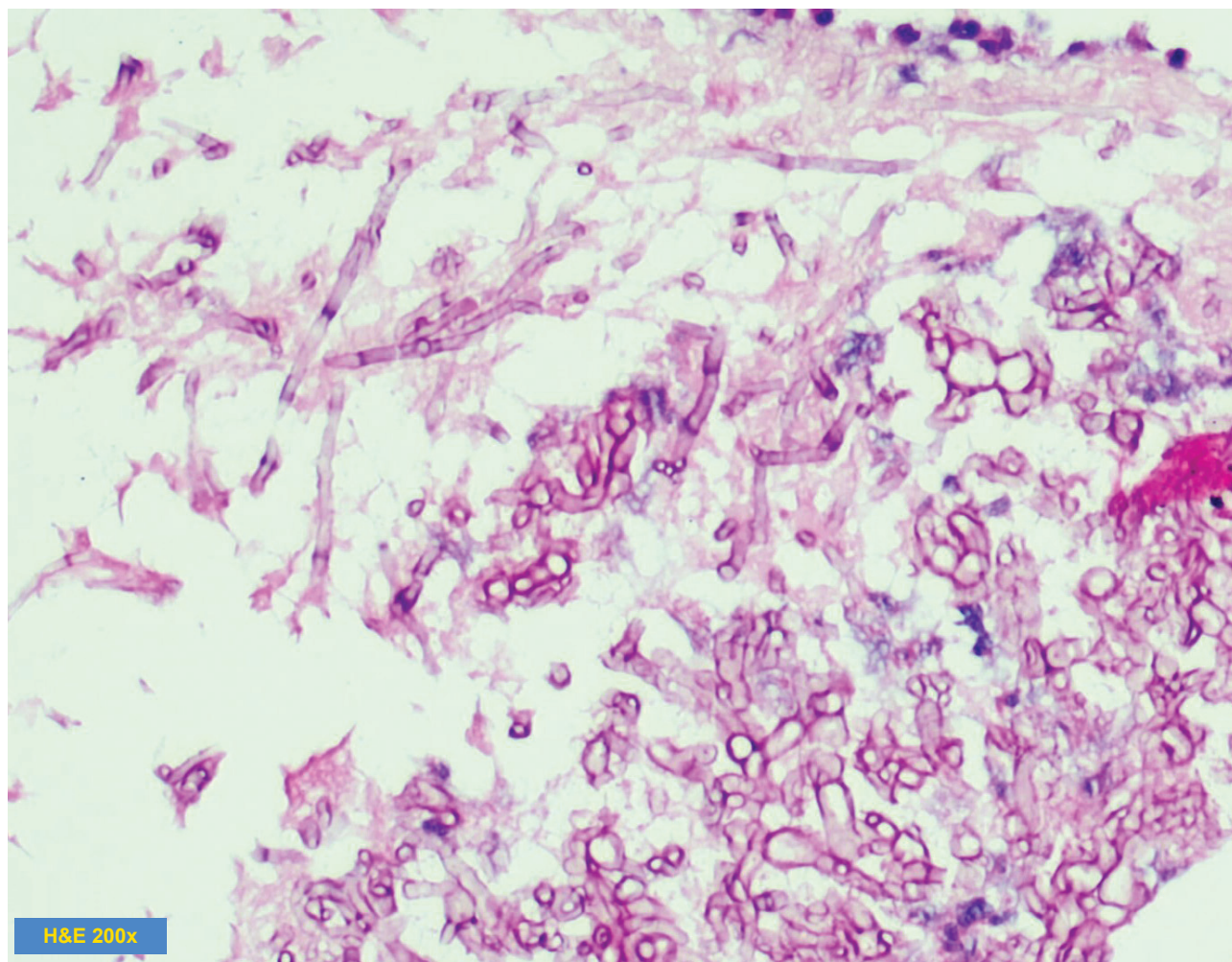
Soon after the surgery, the patient integrated a pulmonary rehabilitation program and resumed her regular personal and professional life. Three months after surgery, the patient was found to be asymptomatic, with no other episodes of haemoptysis and no constitutional symptoms. Follow-up chest x-ray and chest CT scan showed no signs of recurrence (Fig. 3). Regarding the evidence of a localized lesion without signs of systemic infection, it was discussed

and decided between peers not to start antifungal agents as evidence was lacking in regard of this fungal infection in humans and the possibility of antifungal adverse effects. The patient kept close clinical, and imaging follow-up.

## DISCUSSION

In light of a suspicious lung nodule, with no clinical or laboratory signs of infection, the main differential diagnosis is lung cancer. Therefore, our diagnostic approach followed this direction. Once fungal hyphae suggestive of fungal infection were identified on TTNB, our diagnostic approach was broadened. In fact, there are several cases of fungal diseases mimicking lung cancer described in the literature, most frequently by paracoccidioidomycosis, histoplasmosis, cryptococcosis, coccidioidomycosis, aspergillosis, mucormycosis and blastomycosis.<sup>5,6</sup>

Since *Aspergillus* is a filamentous septate ubiquitous fungus that causes a variety of clinical syndromes, we were faced with chronic pulmonary aspergillosis (CPA) as differential diagnosis, more specifically with an *Aspergillus* nodule, an unusual and less severe form of CPA. CPA generally affects immunocompetent patients with a pre-existing



**Figure 2** – Pathological findings of lung biopsy specimen. On 200X hematoxylin and eosin staining, abundant fungal colonies with sparsely septated hyphae and barrel-shaped spores were identified.

pulmonary condition. Our patient was indeed immunocompetent but had no history of previous pulmonary diseases and no structural abnormalities on chest CT scan.

The diagnosis of CPA requires a combination of thoracic imaging and direct evidence of *Aspergillus* infection or an IgG antibody response to *Aspergillus*.<sup>7</sup> In clinical situations like this, in which the criteria of CPA are not fulfilled nor there is evidence of infection by any other fungi, but there is still a suspicious nodule, the best approach is not straightforward. It was decided that a left lower lobectomy via uniportal VATS was the best approach in this patient. With the presence of septate hyphae and tissue damage on two sterile samples and PCR detection of *P. chartarum* in the surgical specimen, two criteria for invasive fungal disease were met, according to the revision and update of the Consensus Definitions of Invasive Fungal Disease.<sup>8</sup>

The *Pithomyces*, order of *Pleosporales*<sup>1</sup> is a dematiaceous fungi (i.e. which have melanin-like pigment in the cell

wall of hyphae or spores) with species commonly colonizing dead leaves and stems of many different plants. Some species have been isolated from mammals with various symptoms. Its fungal spores are part of a significant fraction of the atmospheric bioparticles (bioaerosols) and capable of inducing the production of specific immunoglobulin E, aggravating the clinical symptoms of allergic respiratory diseases in sensitized individuals.<sup>9</sup> *Pithomyces chartarum*, the most widespread species, has been reported to cause facial eczema in some animals (i.e., sheep, cattle, goats, and deer) due to liver damage caused by a mycotoxin (sporidesmin) produced by the fungus.<sup>3,4</sup> There is only one report in humans of an unidentified *Pithomyces* isolate in association with *Curvularia geniculata* as the aetiology of peritonitis in a patient with vulvar cancer.<sup>2</sup>

Due to the lack of evidence on how to manage this kind of infection, we decided to keep our patient under surveillance. Whether antifungals should be started or not, one



Figure 3 – CT scan with signs of lower left lobectomy, no other changes

study showed potent *in vitro* activity of most of the antifungal drugs against *Pithomyces* species, which could offer different therapeutic options for the treatment of infections caused by these fungi.<sup>10</sup>

In conclusion, there are countless species of fungi, and most of them are ubiquitous. This clinical case shows how important it is to have a high suspicion of a pulmonary fungal infection, even in immunocompetent patients and with no lung structural abnormalities. Not all nodules are cancer and not all fungal infections are *Aspergillus*.

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#### AUTHOR CONTRIBUTIONS

AF: First draft and literature review.

DAJ: Data review and image collection.

GA: Literature review.

DC: Critical review of the work.

#### PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association published in 2013.

#### DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

#### PATIENT CONSENT

Obtained.

#### COMPETING INTERESTS

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