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An Atypical Radiological Presentation of Lung Adenocarcinoma[☆]



Presentación radiológica atípica de un adenocarcinoma de pulmón

To the Editor,

Adenocarcinoma of the lung occasionally presents with atypical clinical and radiological manifestations. We report a clinical case with an unusual radiological presentation, and review the diagnostic and therapeutic developments that we believe are of interest to the clinical pulmonologist.

Our patient was a 49-year-old man, originally from Ecuador, non-smoker, with no significant personal history and no known contact with patients with active tuberculosis. He consulted due to a 10-month history of chronic productive cough, mucopurulent, occasionally with bloody sputum, in addition to intense hyporexia and a 3 kg weight loss. Chest X-ray showed bilateral pulmonary infiltrates with some poorly defined, pseudonodular images, predominantly in the upper lobes. He was hospitalized in a respiratory isolation room with an initial suspicion of tuberculosis, but sputum smears were negative. After multiple bilateral

pulmonary nodular opacities, mostly cavitary, were seen on the chest computed tomography (CT) (Fig. 1A and C), a thorough, bilateral bronchoscopy was performed that showed no pathological findings. A cytological study of the bronchoalveolar lavage samples was conducted, yielding a diagnosis of lung adenocarcinoma with micropapillary pattern. The exon 19 deletion was positive, while the rest of the mutations studied were negative (L858R, T790M, G719A/C/S, exon 20, S768I and L861Q, ALK and ROS1). The patient began treatment with gefitinib, with a good clinical and radiological response at 4 months (Fig. 1B and D).

Adenocarcinoma is the most frequent histological type of lung cancer. In 2011, a new, much-needed classification of adenocarcinoma addressing the different patterns and their various prognoses and management was published after a consensus was reached among pulmonologists, thoracic surgeons, oncologists, pathologists, molecular biologists, and radiologists.¹ This classification has been updated over the years to include genetic and molecular biology data. Two groups were differentiated in the latest revision of the lung adenocarcinoma classification in 2015: preinvasive lesions (atypical adenomatous hyperplasia and adenocarcinoma in situ) and invasive lesions (minimally invasive adenocarcinoma and invasive adenocarcinoma).^{2,3}

The spectrum of radiological manifestations of adenocarcinoma of the lung is very variable, ranging from subsolid or solid lesions to consolidations and masses that are usually closely correlated with histology and prognosis, hence the importance of the role of the radiologist. A determining factor in the detection and

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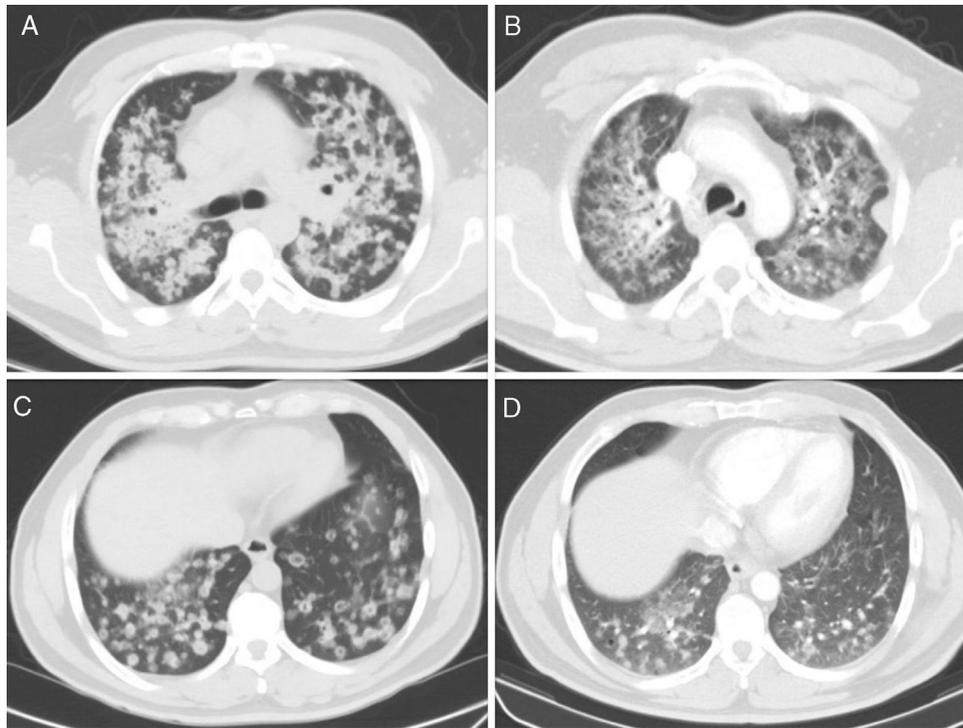


Fig. 1. Computed axial tomography slices before (A and C) and 4 months after starting treatment (B and D).

characterization of lung nodules has been the use of high-resolution multidetector CT instead of the conventional helical CT (with thicker collimation).⁴

Invasive adenocarcinoma represents 70% of resected lung adenocarcinomas and is defined by the presence of an invasive component greater than 5 mm. Histologically, these masses tend to be heterogeneous, with mixed patterns (acinar, papillary, micropapillary, lepidic, and solid), and are given the name of the predominant component. Some subtypes are associated with a specific prognosis. For example, adenocarcinoma with a predominant lepidic component has a better prognosis. In contrast, the presence of a micropapillary component predicts worse survival. For this reason, adenocarcinoma with this pattern has aroused much interest lately, especially due to its high rates of recurrence and metastasis. It is more common in men and non-smokers, and more frequently associated with lymphatic and pleural invasion and lymphadenopathies than other histological subtypes.

Typical radiographic findings in invasive adenocarcinomas are solid or mixed nodular lesions (with part solid component, part ground glass), while purely ground glass nodules are less common. In addition, it is quite important to quantify the size of the solid component, since if it is greater than 9 mm, a diagnosis of invasive adenocarcinoma is 100% specific, while a size of 3–5 mm makes it less likely. This concept seems to be gaining importance, and future classifications will focus more on the size of the solid component than the overall size of the nodule as a criterion for staging the T of the TNM.^{5,6} Another consideration when differentiating pre-invasive lesions from invasive lesions is the cross-sectional diameter of the nodule in the lung window.^{4,6}

With regard to treatment, recent advances are facilitating a more specific approach. These developments have been led by a group of drugs that target the epidermal growth factor receptor

(EGFR), generically known as tyrosine kinase inhibitors. They include erlotinib and gefitinib for first-line treatment, and afatinib in second line when the former fail or after relapse. We now know patients with a mutation in the EGFR gene activator (exon 19 deletion or L858R replacement) are most likely to respond well to these drugs.⁷

Our case is unusual due to the uncommon radiological presentation. Accordingly, we believe that lung adenocarcinoma should be included in the differential diagnosis of this radiological pattern.

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Clinical Deterioration Due to *Exophiala dermatitidis* in a Patient With Cystic Fibrosis[☆]



Deterioro clínico por *Exophiala dermatitidis* en un paciente con fibrosis quística

To the Editor,

An increase in respiratory isolates of *Exophiala dermatitidis* has been described in recent years in patients with cystic fibrosis (CF). We report the case of a CF patient with chronic *E. dermatitidis* bronchial infection.

This was a 21-year-old woman who had been diagnosed with genotype F508del/3849+1G>A CF at the age of 3 months. Chest computed tomography (CT) revealed multiple cylindrical, cystic, and string-of-pearls bronchiectasis in both lungs. Spirometry showed moderate-severe pulmonary obstruction with a forced expiratory volume in 1 second (FEV₁) of 1680 ml (53% predicted). Pancreatic insufficiency and intermittent bronchial infection caused by methicillin-sensitive *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Achromobacter xylosoxidans* were detected. The patient had shown declining lung function, and in recent years only *E. dermatitidis* was isolated from sputum microbiology studies. Given her clinical deterioration and the absence of bacterial growth, we performed a bronchoscopy, obtaining bronchial aspirate (BAS) and bronchoalveolar lavage (BAL) samples. Selective media, Sabouraud agar and blood agar, were seeded quantitatively and incubated for 5 days. MALDI-TOF mass spectrometry was used for the identification of the different pathogens. *E. dermatitidis* grew from both BAL and BAS, and antibiotic sensitivity testing was performed with amphotericin B and voriconazole using the Etest[®] method, obtaining MICs of 0.1 and 0.023, respectively. Treatment with oral voriconazole 300 mg/12 h began, but adverse effects (hallucinations and altered liver profile) led the dose to be reduced to the maximum tolerable level of 100 mg/12 h. During follow-up, the patient has shown important clinical improvement and reduced exacerbations, despite persistent isolation of the fungus.

The prevalence of *E. dermatitidis* in CF patients varies between 2% and 15%.¹ This may be due to the lack of standardized procedures for the detection of this organism in sputum samples. *E. dermatitidis* is a slow-growing opportunistic fungus that is not ubiquitous, and as such is generally an uncommon contaminant in microbiology laboratories. It is mostly detected in patients with CF, so isolation in a non-CF patient should prompt suspicion.²

It was first described in 1990,³ and some cases have been published since then. In 2010, the first case of pigmented sputum

was described, with the black flecks being attributed to fungal hyphae.⁴ In 2017, Grenouillet et al. published 2 cases of patients with bronchiectasis and chronic persistent *E. dermatitidis* colonization which led to the diagnosis of CF.²

For the definitive diagnosis of this fungus, the sample must be cultured in Sabouraud agar, incubated at room temperature or 30 °C, and repeated isolates must be obtained. Cultures must be observed for 3–4 weeks, although colonies are usually detected in less than 7 days.⁵ The colonies are small at first, and over time increase in size and acquire a characteristic intense olive black or dark brown color (Fig. 1). However, *E. dermatitidis* isolation is sometimes complicated, and the use of appropriate media, such as erythritol-chloramphenicol agar (ECA) can increase the recovery rate.⁶ Molecular techniques (LAMP or reverse hybridization) can be powerful alternatives to culture media, increasing the rate of detection in sputum samples.⁶

In patients with CF, chronic or intermittent *E. dermatitidis* isolation usually has no clinical repercussions, although some cases have been reported, such as that of a child with CF who presented symptoms of dyspnea due to *E. dermatitidis* pneumonia.⁷ Two prospective studies in a Swedish cohort of 98 CF patients over 12 years of age found *E. dermatitidis* or elevated serum levels of IgG antibodies to *E. dermatitidis* to be associated with pancreatic insufficiency, more frequent colonization by non-tuberculous mycobacteria, increased inflammatory markers, requirements for more frequent intravenous antibiotic treatment, and lower FEV₁.⁸ Although the clinical impact of this pathogen is still pending investigation, its presence in the respiratory tract must be monitored as it is currently considered to be an emerging opportunistic pathogen in CF.⁹

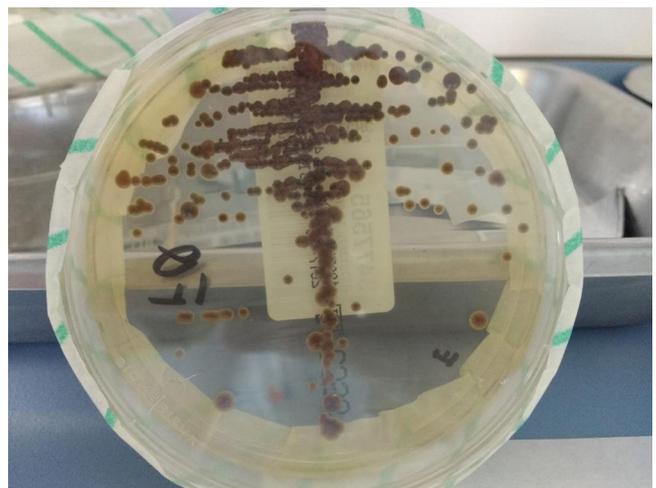


Fig. 1. *Exophiala dermatitidis* colonies in Sabouraud agar with chloramphenicol.

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