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Antonio Moreno-Flores, Carmen Potel-Alvarellos, Maximiliano Álvarez-Fernández *

Servicio de Microbiología, Complejo Hospitalario Universitario de Vigo (Hospitales Álvaro Cunqueiro y Meixoeiro), Instituto de Investigación Sanitaria Galicia Sur (IISGS), Vigo, Pontevedra, Spain

* Corresponding author.
E-mail address: mxalvfer@gmail.com (M. Álvarez-Fernández).

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Pleural effusion as a manifestation of a Cryptococcal infection in an HIV patient

Derrame pleural como manifestación de una infección criptocócica en un paciente con VIH

A 37-year-old male HIV+ individual (CD4 cell nadir of 153 cells/mm^3 and HIV-1 RNA viral load zenit of 9832 copies/mL), treated with emtricitabine/tenofovir disoproxil fumarate/efavirenz with poor therapeutic adherence and without medical follow up for the last 4 years was admitted to the emergency department with history of 3 days of left sided pleuritic chest pain, mild dyspnea and a temperature of 37.5 °C. He was a daily consumer of amphetamines for 5 years and previously had received treatment for intestinal giardiasis and syphilis. Vital signs at arrival showed BP 110/70 mmHg, temperature 37.5 °C, heart rate 85 bpm, respiratory rate 22, SpO_2 96%. Physical examination revealed decreased breathing sounds over the left lung base. Rest was unremarkable.

The laboratory findings showed a normocytic, normochromic anemia (Hemoglobin 11.7 g/dl) with normal white blood count (WBC) and platelets, a normal renal and liver function and mild increase of C-reactive protein to 1.7 mg/dl. HIV-1 RNA viral load was 122,000 copies/mL and CD4+ T cell count 13 cells/mm^3. Chest X-ray showed a left costophrenic recess blunting and a left perihilar cavitary nodule. A computed tomography (CT) scan was performed revealing moderate left pleural effusion with atelectasis, a thick-walled cavitary nodule in the left superior lobule, and left hilar calcified lymph nodes (Fig. 1A and B).

A thoracentesis was made, with positive lights criteria suggesting exudative effusion [proteins 52 g/L, LDH 173 U/L; serum values: proteins: 63 g/L, LDH 166 U/L, WBC: 3710 cells/mm^3 (49% neutrophils, 37% lymphocytes and 12% mesothelial cells) and adenosine deaminase (ADA) 51 UI/L]. Pleural effusion culture was negative for bacteria. PCR detection for *Mycobacterium tuberculosis* in pleural effusion was negative.

Serum *Cryptococcus neoformans* antigen (CrAg) was tested, detecting titers of 1/64. Treatment with amphotericin B and flucytosine was initiated. A lumbar puncture was practiced ruling out central nervous system infection, allowing treatment simplification to fluconazole in monotherapy. We initiated antiretroviral therapy with bictegravir, emtricitabine and tenofovir alafenamide, and pneumocystis prophylaxis with trimethoprim – sulfamethoxazole.

Finally, *C. neoformans* isolation in pleural effusion culture provided the definitive diagnosis, exhibiting a strain with minimum inhibitory concentration (MIC) 8 μg/ml for fluconazole and 0.06 μg/ml for voriconazole. Based on these results, we switched treatment to voriconazole. The organism was detectable after 82 h of incubation. Subsequently bronchoalveolar lavage was also positive for *C. neoformans* (Fig. 1C).

The patient showed clinical and laboratory improvement, being discharged to complete outpatient treatment with voriconazole and follow-up by the infectious disease department. Eight months after the diagnosis a thoracic CT scan was made, showing mainly a thin-walled cavitated lesion in the apical posterior segment with bronchial communication and resolution of the pleural effusion (Fig. 1D).

Discussion

Cryptococcosis infection is caused mainly by *C. neoformans*, an opportunistic fungal infection that became worldwide relevant when the HIV era started.[1,2] The most common clinical presentations include neurological and pulmonary involvement.[3] Nevertheless, the cryptococcal pleural infection remains rare, with about 50 cases reported in the literature.[4]

In our patient, differential diagnosis based on cavitary pulmonary lesions and lymphocytic pleural effusion was made. Because cryptococcosis may also present an elevated ADA in pleural effusion, it can easily be misdiagnosed as tuberculosis, a far

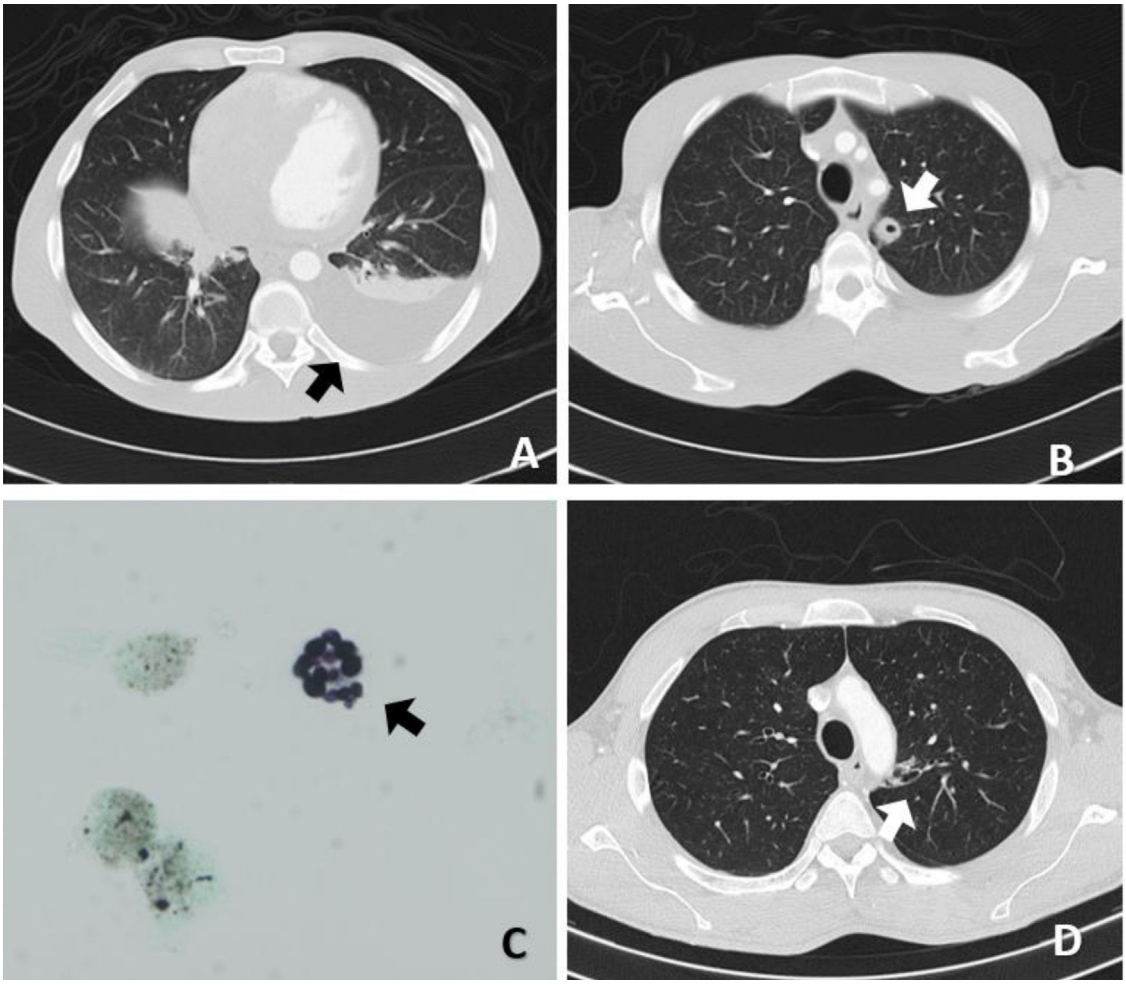

Fig. 1. (A, B) Computed tomography scan showing a thick-walled cavitated nodule in the left superior lobe with ipsilateral pleural effusion. (C) *Cryptococcus neoformans* in bronchoalveolar lavage (silver staining, 600×). (D) Computed tomography scan showing a thin-walled cavitated lesion in the apical posterior segment with bronchial communication; no pleural effusion was found.

more common entity, and be initially treated with tuberculostatic therapy.[5]

Pleural effusion and bronchoalveolar lavage cultures lead to the definitive diagnosis. Pleural effusion cultures for *Cryptococcus* may be negative due to the small number of microorganisms in pleural fluid. It has been postulated that the release of the antigen is the responsible for a pleural inflammatory response that leads to pleural effusion rather than the microorganism by itself.[4]

Regarding the treatment, over the past decade there has been an increase in reports describing *C. neoformans* with increased MICs for fluconazole. Nowadays there is still no consensus on the cut-off point or its clinical relevance.[6] Recent studies define MICs $\leq$ 8 μg/ml as susceptible, 16–32 μg/ml as dose-dependent susceptible, and $\geq$64 μg/ml as resistant.[7] Nonetheless, the EUCAST guidelines state that the clinical breakpoint is not yet determined.[8]

In conclusion, atypical presentations of cryptococcus infections should be considered in the differential diagnosis of pleural effusion in HIV patients. Additional research is needed to define the relevance of the antifungal susceptibility in *C. neoformans* infection and its possible clinical implications.

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Conflict of interests

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Jimena Del Risco Zevallos[a,*], Carlos Torres Quilis[b], Gemma Issus Olive[c], Felipe García[d,e]

[a] *Nephrology and Renal Transplantation Department, Hospital Clínic de Barcelona, Barcelona, Spain*
[b] *Internal Medicine Department, Hospital Sant Pau i Santa Tecla, Tarragona, Spain*
[c] *Radiology Department, Hospital Clinic Barcelona, Barcelona, Spain*
[d] *Infectious Diseases Department, Hospital Clínic de Barcelona, Barcelona, Spain*
[e] *AIDS Research Group, Hospital Clínic-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). University of Barcelona, Barcelona, Spain*

* Corresponding author.
E-mail address: jdelrisco@clinic.cat (J. Del Risco Zevallos).

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Ecthyma gangrenosum, beyond *Pseudomonas aeruginosa*☆

Ectima gangrenoso, más allá de Pseudomonas aeruginosa

Dear Editor,

Ecthyma gangrenosum is an uncommon skin manifestation of systemic infection that generally affects immunocompromised patients.[1]

We present the case of a 63-year-old female patient with a history of acute myeloid leukaemia on active treatment with carboplatin and etoposide after progressing from first-line and second-line treatment (idarubicin-cytarabine and the FLAG-IDA regimen: fludarabine + cytarabine and idarubicin and granulocyte-colony stimulating factor).

On day +7 of the first cycle, the patient experienced an episode of fever, coughing and dyspnoea, as well as pancytopaenia. She was admitted to hospital and administered broad-spectrum antibiotic therapy with piperacillin/tazobactam in combination with amikacin and granulocyte-colony stimulating factor. Complementary tests were also performed.

The pulmonary auscultation performed on physical examination revealed decreased breath sounds and scattered rhonchi.

An erythematous macule measuring 8 × 12 mm with a necrotic annular centre was observed on the outer part of the patient's right knee (Fig. 1a).

The complementary tests performed are described below.

A chest CT scan was conducted, which showed diffuse alteration of the pulmonary parenchyma with bilateral 'cobblestone' pattern and multiple bilateral pulmonary nodules with surrounding halo of ground-glass attenuation and area of left perihilar consolidation (Fig. 1b).

The bronchoscopy showed thickening of the left bronchial tree and erythaema of the mucosa at the entrance to the lung base that prevented the passage of the bronchoscope. Bronchoalveolar lavage (BAL) was performed, finding no malignant cells.

The skin biopsy of the lesion identified fungal structures (spores and hyphae) in the connective tissue of the skin and subcutaneous cellular tissue, as well as in the vessels of the superficial and reticular dermis and of the subcutaneous cellular tissue. Intravascular thrombi were also observed in many of the small and medium-sized blood vessels (Fig. 1c).

The skin biopsy culture revealed growth of *Fusarium proliferatum*.

Two of the four blood cultures were positive for *Fusarium proliferatum*.

Despite changing the patient's antibiotic therapy and starting a loading dose of intravenous voriconazole 200 mg every 12 h, she died a week after the onset of symptoms.

Ecthyma gangrenosum has often been associated with *Pseudomonas aeruginosa*,[1] although on rare occasions it is caused by other infectious pathogens. The literature points to a broader bacterial spectrum with Gram-negative bacteria such as *Escherichia coli, Citrobacter freundii*, *Klebsiella pneumonia* and *Morganella morganii*. Moreover, some fungi, such as species of *Candida, Aspergillus* and *Curvularia*, have been reported to cause clinically similar lesions.[2]

Some authors define the disease according to its aetiological agent, while others define it by its clinical characteristics. However, the name attributed to the disease rarely reflects a fungal infection. This confusion may mask a much broader prevalence of ecthyma gangrenosum-like infections that might otherwise have been reported in a broad spectrum of fungal diseases.

The species *Fusarium* is an opportunistic fungal pathogen that causes disseminated infections in immunocompromised patients.

Given the high mortality rate associated with this infection, making a definitive diagnosis in suspected cases is important. Skin involvement is the first sign of disseminated fusarium infection in most cases, and it often manifests early in the disease. Multiple painful papular or macular erythematous lesions are reported in 70% of cases. The lesions tend to have a necrotic centre similar to ecthyma gangrenosum and are described as ecthyma gangrenosum-like lesions.[3]

In immunocompromised patients, fusarium infection often spreads and is usually accompanied by lung involvement, resulting in a high mortality rate that can exceed 50%.[4]

That is why detecting each individual skin lesion in patients with haematological malignancies and pancytopaenia, performing a skin biopsy and administering antibiotics and antifungals early, together with neutrophil-stimulating factors for rapid recovery, is absolutely vital.

In conclusion, this is one of the few documented cases in the literature of an ecthyma gangrenosum-like lesion caused by *Fusarium proliferatum*. We stress the need to conduct a dermatological examination in these patients and the importance of an early skin biopsy of any lesion in order to make a correct diagnosis and initiate treatment as early as possible.

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