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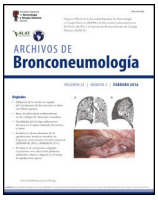

Scientific Letters

Aspergillus fumigatus Empyema☆

Empiema por Aspergillus fumigatus

To the Editor,

Pleural empyema caused by *Aspergillus* is a rare, potentially fatal invasive fungal infection,[1] resulting generally from a complication of aspergilloma, chronic necrotizing pulmonary aspergillosis, or surgical resection of these diseases.[2] Its incidence among cancer patients has increased in recent years, probably due to the increasingly complex immunosuppressive treatments and surgical procedures used.[3] Due to its low prevalence, there is uncertainty surrounding the diagnosis and management of invasive fungal infection, and the situation is particularly problematic in patients with underlying malignancy.

We report a case of *Aspergillus fumigatus* pleural empyema in a patient with T-cell acute lymphoblastic leukemia, treated in our hospital. This was a 19-year-old man who had been diagnosed 7 months previously with intermediate-risk cortical phenotype T-cell acute lymphoblastic leukemia. He received induction, consolidation and reinduction therapies, according to standard protocols, and achieved complete remission. Complications associated with the various treatments included vitamin K deficiency, hypofibrinogenemia, pancytopenia (with hemolytic anemia requiring transfusions), hyperglycemia, and hypertransaminasemia.

Thirty days after reinduction therapy, he was admitted to the hematology department for loss of vision in the right eye, odynophagia, and fever. Vital signs showed temperature 37.5 °C, blood pressure 110/60 mmHg and heart rate 100 bpm. Breathing at rest was normal, and notable findings on physical examination included pallor of the skin and mucosa, Cushingoid facies, bronchial breath sounds in the base of the left hemithorax, with crackles reaching the middle field, edema of the lower limbs, and exudative ulceration of the foreskin. Abdominal examination was normal and no peripheral lymphadenopathies were palpated.

The most relevant additional examinations included blood tests: hemoglobin 8.2 g/dl, hematocrit 24.9%, leukocytes $1\times10^3/\mu1$ (62% neutrophils, 35% lymphocytes), platelets $24\times10^3/\mu l$, total proteins 4.5 g/dl, GOT 117 IU/l, GPT 524 IU/l, GGT 268 IU/l, alkaline phosphatase 424 IU/l, LDH 999 IU/l, triglycerides 371 mg/dl and cholesterol 320 mg/dl. Bone marrow aspirate confirmed remission. A chest computed tomography was performed, showing a pulmonary consolidation in the left base with lucent foci suggesting cavitation, bilateral multiple pulmonary micronodules measuring less than 1 cm associated with cavitation, and left pleural effusion. Abdominal ultrasonography revealed 2 hypoechogenic hepatic lesions with echogenic centers consistent with abscesses. Brain magnetic resonance imaging showed multiple cerebral and cerebellar focal lesions, with fine peripheral enhancement, central necrosis, and a perilesional halo of edema, consistent with abscesses. The ophthalmologic examination revealed severe right endophthalmitis, requiring vitrectomy. Cerebrospinal fluid and blood were positive for galactomanan antigen. After vitrectomy, the vitreous humor showed abundant septate hyphae; *A. fumigatus* was cultured. The pleural effusion was not loculated, and had a purulent appearance with pH 7.34, leukocytes $3.6\times10^3/\mu l$ (69% segments, 31% lymphocytes), glucose 87 mg/dl, total proteins 3.6 g/dl, C-reactive protein 3.08 mg/dl, procalcitonin 0.3 ng/ml, LDH 894 IU/l, adenosine deaminase 8 U/l, interleukin-6 70 393 pg/ml. Fungal hyphae were observed and *A. fumigatus* was obtained on culture. A thyroid abscess was aspirated, and hyphae were observed. Enterococcus faecalis was isolated from culture of the foreskin, and trimethoprim–sulfamethoxazole sensitive Stenotrophomonas maltophilia from 2 sputum cultures, obtained 2 months after admission.

The clinical situation was interpreted as T-cell acute lymphoblastic leukemia with late post-chemotherapy bone marrow aplasia and disseminated aspergillosis (*A. fumigatus*) during the reinduction phase, with ophthalmic, cerebral, pulmonary, pleural (empyema), hepatic, and thyroid involvement with bacterial coinfections.

During admission, the patient received various courses of antifungals (amphotericin, voriconazole [up to 9 mg/kg/12 h depending on blood levels, as well as 8 intravitreal doses], AmBisome® and caspofungin), antibacterials (meropenem, vancomycin, linezolid, cotrimoxazole, levofloxacin, amikacin, and clindamycin), and dexamethasone, and a chest tube was placed (16F, 3 days then resolution). The patient progressed slowly, except for the pleural involvement, until voriconazole was administered at doses much higher than recommended in the package insert, and plasma levels within the therapeutic range were achieved. The patient was discharged after 3 months, having remained afebrile for the last month.

A diagnosis of fungal pleural empyema poses a clinical dilemma that is especially worrying in the setting of severely immunocompromised cancer patients. Our patient met the criteria for diagnosis of proven invasive fungal disease,[4] *A. fumigatus* on this occasion, and is one of the few cases in which pleural fluid has been infected by *Aspergillus* in an immunocompromised patient.[5]

A recent study reported a high percentage (16%; 111/708) of cultures positive for fungi in pleural fluid from cancer patients. This appears to be due to a higher incidence of invasive fungal infection in cancer patients, and improved detection of fungi by microbiological techniques. *Aspergillus* spp. were, in terms of percentages, the predominant microorganism in leukemia patients (the disease presented by our patient), suggesting that the type of cancer may be one of the risk factors for developing *Aspergillus* empyema.

Voriconazole is the recommended antifungal for the treatment of invasive aspergillosis in most patients.[7] Although this drug

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achieves high concentrations in pleural fluid,[8,9] pleural empyemas caused by Aspergillosis are usually treated with a combination of various antifungals[5] due to the high mortality rate (34%–75%, depending on when it is evaluated).[1,6] Intrapleural administration has been described in isolated cases,[1,10] and more studies are required to support this strategy. Treatment for all empyemas requires chest drainage, and if the patient presents life-threatening hemoptysis, lung resection surgery should be considered.[11]

In summary, in an immunocompromised cancer patient with pleural empyema, cultures in the appropriate media should be performed to rule out fungal infection. Treatment must consist of chest drainage and the long-term administration of a combination of various antifungals, including voriconazole, since mortality in these infections is high.

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Is a Respiratory Day Hospital Useful in Patients with Severe Disease?☆

¿Es útil un hospital de día de enfermedades respiratorias en pacientes graves?

To the Editor:

Respiratory day hospitals (RDH) are a useful alternative form of hospitalization.[1] However, no studies are available that demonstrate their suitability for managing exacerbations in patients with severe respiratory disease. In this communication, we report our experience in this area.

Between December 2013 and November 2014, we performed an observational, longitudinal, quasi-experimental study (patients were their own controls) of all patients who attended the RDH (2 or more admissions/emergency visits due to decompensation of an underlying respiratory disease in the previous year). All patients were followed for 1 year, and data from the previous year were obtained from their clinical records. The study was approved by the Ethics Committee (no. 2016/424). Widely accepted criteria were used to establish the diagnosis of COPD, asthma, and bronchiectasis, and to determine levels of physical activity, dyspnea grade, deterioration of state of health, BODE index, 6-minute walk test, classification of COPD patients, and definition of sepsis.[2–12]

A descriptive analysis was conducted of patient characteristics, and visits to the emergency department/hospitalizations between the year prior to and the year after the patient's first visit to the RDH were compared using the Wilcoxon non-parametric test for paired data, and variables associated with hospitalization were studied. It was estimated that the mean annual number of events (emergency visits and admissions) in these patients would be 9–10, and that after implementation of the RDH this rate could be reduced by 25%. To achieve a power of 85%, 125 patients would be needed to detect significant differences ($p<0.05$) between the number of events before and after RDH.

During the study period, 1053 visits to the RDH for exacerbations were recorded in 129 patients (COPD [87], bronchiectasis [12], asthma [7], and others [23]). Fig. 1 shows the level of physical activity (low/moderate in 112/129) (Fig. 1A), dyspnea grade (mMRC 34 in 71/129) (Fig. 1B), 6-minute walk test (42/129 walked < 250 m) (Fig. 1C), and FEV1 (84/129 < 50%) of the overall study population (Fig. 1D). Among COPD patients, 57/87 had a BODE index > 4 (Fig. 1E), 82/87 were GOLD stage D (Fig. 1F), 76/87 had a GesEPOC exacerbator phenotype (Fig. 1G), 76/87 had CAT ≥ 10, 5/87 had a body mass index < 21, 5/87 had alpha-1 antitrypsin deficiency, and 16/87 were receiving BiPAP home oxygen therapy (Fig. 1H). In total, 8.6% of visits (91/1053) required hospital admission, mainly due to the need for intravenous antibiotics (25; 27.5%), acute respiratory failure (21; 23.1%), and failure of previous outpatient therapy (12; 13.2%). When the year prior to and the year after the first visit to

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