

bleeding, uncontrolled arterial hypertension, kidney failure, liver disease, anemia, concomitant use of antiplatelet agents, and regular use of anti-inflammatory agents.<sup>2,4</sup> An excessive antithrombotic effect (INR>3 or INR between 2 and 3 plus antiplatelet therapy) is known to favor bleeding. However, 20% of the major bleeds in an Italian series occurred in patients with INR<2, so it is important to take into account other factors that might increase the risk of bleeding.<sup>4</sup>

DOACs, such as oral Xa factor inhibitors (rivaroxaban, apixaban, and edoxaban) and an oral thrombin inhibitor (dabigatran), have been available since 2008. They were first used for the primary prevention of venous thromboembolic disease in adults undergoing elective hip or knee replacement surgery, and subsequently to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation, and in the secondary prophylaxis of venous thromboembolic disease. They are also indicated in other situations, for example rivaroxaban for secondary prevention in adult patients who have suffered an acute coronary syndrome with elevated biomarkers.<sup>2,3,6</sup> DOACs have certain benefits over AVKs, such as a faster onset of action, no need for routine monitoring, a more predictable dose-response relationship, a shorter plasma half-life, a low risk of adverse effects, few interactions with drugs and food, improved efficiency, and the availability of specific antidote (idarucizumab) in the case of dabigatran. Other antidotes are in the process of approval, including andexanet for the reversal of factor Xa inhibitors.<sup>2,4,7</sup> However, DOACs, like any anticoagulant treatment, always carry a risk of bleeding due to patient-associated factors, which may be increased in some situations, such as overdose, disease, or concomitant therapies that increase drug exposure, changes in hemostasis, or an urgent need for an invasive or surgical procedure.<sup>3,4</sup> In clinical trials with DOACs, bleeding rates were generally low and comparable to those produced by low molecular weight heparin or warfarin in the case of dabigatran and rivaroxaban, or significantly lower in the case of apixaban (in the ARISTOTLE study, the rate of major bleeds was 2.13% per year in the apixaban group compared with 3.09% per year in the warfarin group, RR: 0.69; 95% CI: 0.60–0.80;  $P<0.001$ ).<sup>3,8</sup> In this regard, current cardiology guidelines recommend the preferential use of DOACs over AVKs in patients with non-valvular atrial fibrillation.<sup>9</sup>

In conclusion, anticoagulation is a predisposing factor for the development of bleeds, including those that originate in the lung. Overdosing, in the case of AVKs, is a major risk factor for this complication, but other factors that may increase the risk of bleeding must also be taken into account. DOACs have advantages with respect to AVKs, but as with any anticoagulant treatment there is always a risk of bleeding due to patient-associated factors.

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Alicia Cerezo Lajas, María del Carmen Rodríguez Guzmán,  
Javier de Miguel Díez\*

Servicio de Neumología, Hospital General Universitario Gregorio  
Marañón, Madrid, Spain

\* Corresponding author.

E-mail address: [javier.miguel@salud.madrid.org](mailto:javier.miguel@salud.madrid.org) (J. de Miguel Díez).

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## Imported Acute Histoplasmosis in an Adolescent with Suspected Lymphoproliferative Syndrome<sup>☆</sup>



### Histoplasmosis aguda importada en un adolescente con sospecha de síndrome linfoproliferativo

To the Editor,

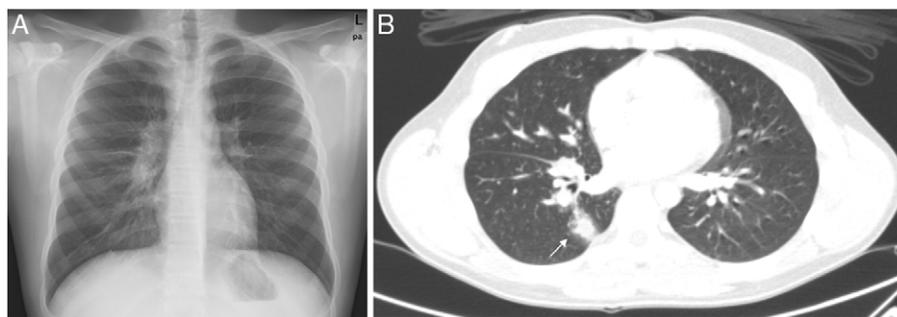
Histoplasmosis is an infection caused by *Histoplasma capsulatum*, a dimorphic fungus endemic to the Americas and parts of Africa and Asia. In Europe, it primarily occurs as an imported infection, although native cases have been reported in Italy and Turkey.<sup>1</sup> In recent years, due to increased travel to endemic areas and immigration, the diagnosis of histoplasmosis in non-endemic areas has increased, including in Spain.<sup>2</sup> Imported cases occur mainly in young adults, and very rarely in children or adolescents. In a Euro-

pean registry,<sup>1</sup> only 4 of 118 cases were diagnosed in individuals under the age of 20 years. We report the case of an immunocompetent teenager presenting with acute pulmonary histoplasmosis after a trip to Mexico.

This was a previously healthy 15-year-old male patient with a complete childhood vaccination schedule, who consulted due to a 9-day history of fever of up to 39.5 °C. He had returned 20 days previously from a 10-day holiday in Riviera Maya. He presented asthenia, hyporexia, generalized myalgia, headache, and mild cough without rhinorrhea. Physical examination was normal. The blood test showed discretely elevated acute phase reactants (CRP 2.8 mg/dL), with no other abnormalities, and a blood culture was sterile.

The study was expanded to include serology (Epstein-Barr virus, cytomegalovirus, hepatitis A and B, HIV, *Toxoplasma*, *Entamoeba histolytica*, *Brucella*, *Borrelia*, dengue, parvovirus B19, *Echinococcus*, *Leishmania*, syphilis, *Legionella*, and *Mycoplasma pneumoniae*), which was negative; malaria antigens, thick blood smear, QuantiFERON<sup>®</sup>, and cultures of blood, pharyngeal exudate, and urine were negative; viral culture of nasopharyngeal exudate was negative; Mantoux test 0 mm; peripheral blood smear normal. Zika virus serology was IgG+/IgM–, and Zika virus PCR in blood

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**Fig. 1.** (A) Chest X-ray: bilateral hilar and paratracheal lymphadenopathies. (B) Chest CT: mediastinal and hilar lymphadenopathies, predominantly right-sided. Right parenchymal nodule measuring 15 mm (arrow) with ground-glass halo and a tract connecting it with the hilum.

was negative. Endemic fungi serologies (*Blastomyces*, *Coccidioides*, *Histoplasma*, *Paracoccidioides*) were negative. The abdominal ultrasound was significant for splenomegaly 15.6 cm, and chest X-ray showed an increase in density in the right paracardiac region, consistent with pneumonic consolidation. Empiric treatment began with amoxicillin.

Due to the persistence of fever (total of 14 days), the patient was evaluated in cardiology (ECG and echocardiography) and ophthalmology (fundus), but no changes were observed. In addition to the initial symptoms, he developed profuse sweating mainly at night and a weight loss of 3 kg. Three weeks after the onset of the syndrome, endemic fungi serologies were repeated; chest X-ray showed bilateral and paratracheal hilar adenopathies (Fig. 1A), and abdominal ultrasound revealed splenomegaly increased to 17 cm and lymphadenopathies in the hilar region. A chest-abdominal computed tomography was performed (Fig. 1B), which showed a right parenchymal nodule, and bulky ipsilateral hilar and mediastinal lymphadenopathies (right paratracheal, aortopulmonary, subcarinal, and azygo-esophageal recess). In view of the possibility of a lymphoproliferative syndrome, bronchoalveolar lavage and bone marrow aspirate were performed 29 days after the onset of symptoms. The histopathological studies of both samples were normal, with no isolates on bacterial and fungal cultures, and negative panfungal PCR (18S rRNA) and negative specific PCR for *Aspergillus* and *Mycobacterium tuberculosis*. Finally, seroconversion of *Histoplasma* antibodies was observed on immunodiffusion in a second serum sample.

A diagnosis of acute histoplasmosis was made, and in due to the persistence of symptoms for more than 4 weeks, treatment with itraconazole was administered for 6 weeks. In the successive follow-up visits, the patient showed complete resolution of symptoms, along with normalization of the radiographic changes.

To our knowledge, this is the first case of pediatric histoplasmosis published in Spain. The infection occurs by inhalation of conidia during activities that involve contact with contaminated surfaces. Severity depends on the intensity of exposure and the host immune status, and the clinical spectrum is broad. Most immunocompetent cases remain asymptomatic. Symptomatic acute forms in immunocompetent patients usually consist of a flu-like illness, with fever and cough, which is self-limited to 2 weeks.<sup>3</sup> The radiological presentation is highly unspecific, with diffuse reticulonodular infiltrates and hilar and mediastinal lymphadenopathies. The most severe form is a progressive disseminated disease, which can occur after acute infection or reactivation of a past infection. It is caused by hematogenous spread of the fungus in immunocompromised individuals or at extreme ages of life.

In non-endemic areas, the infection may be seen in 2 types of populations with different clinical profiles: travelers and immigrants from endemic areas.<sup>4</sup> In Spain, most are from Central and South America.<sup>5</sup> In the case of travelers, it is common to identify

risk activities that involve exposure to the fungus (caving, construction, excavations, etc.). Subjects tend to be immunocompetent and, if they are symptomatic, the disease presents as an acute pulmonary infection starting within 2 months of exposure, that is not usually severe. It can occur in a cluster of several cases.<sup>6</sup> Our patient reported having made a tour to underground lakes during his trip, which could explain the risk exposure.

Diagnostic confirmation is obtained by isolating the fungus, although this is very rare in the acute forms. In these cases, microbiological diagnosis is usually based on serological testing. *Histoplasma* antibodies begin to be detectable 2–4 weeks after infection, reaching a sensitivity of 90%,<sup>7</sup> so in suspected cases with a first negative serology, such as ours, it is advisable to repeat the test later. Other diagnostic tests include histopathological studies, antigen detection (not available outside the US) or, more recently, PCR, available only in reference laboratories. Treatment depends on the clinical form, severity, and immune status of the individual. The Infectious Diseases Society of America (IDSA) recommends treatment in acute moderate or severe pulmonary forms and in mild forms when symptoms persist for more than 4 weeks.<sup>8</sup>

A diagnosis of histoplasmosis should be considered in travelers returning from endemic areas with fever and respiratory symptoms who have participated in risk activities, or after other companions are diagnosed. Due to its self-limited course, this infection is probably underestimated in non-endemic areas, so a high index of suspicion is required.

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Julia García Mancebo, David Aguilera-Alonso,\*  
Elena María Rincón-López, María Luisa Navarro

*Sección de Enfermedades Infecciosas Pediátricas, Servicio de  
Pediatria, Hospital General Universitario Gregorio Marañón, Madrid,  
Spain*

\* Corresponding author.

*E-mail address:* [davidaguilera1988@gmail.com](mailto:davidaguilera1988@gmail.com)  
(D. Aguilera-Alonso).

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