Causa rara de nódulo pulmonar

A rare cause of pulmonary nodule

Ana Aráujo, Míriam Magalhães, Clara Brito, Pedro Soares, Diana Fernandes, Luisa Teixeira, Leonel Pinto, Renato Saraiva

Resumo

O Histoplasma capsulatum é um fungo com dimorfismo térmico, causador de micose sistémica chamada Histoplasmose. Esta é a micose endémica mais comum, sendo no entanto uma doença rara na Europa. Os autores descrevem o caso clínico de um doente de 48 anos de idade com queixas de dor torácica em cinturão, mialgias e parestesias dos membros inferiores com um mês de evolução cuja longa investigação clínica levou ao surpreendente diagnóstico de histoplasmose pulmonar sob a forma rara de histoplasmoma sem nunca ter viajado para regiões endémicas.

Palavras chave: Histoplasma Capsulatum, histoplasmoma.

Abstract

Histoplasma capsulatum is a thermally dimorphic fungus, causing systemic fungal infection called Histoplasmosis. This is the most common endemic mycosis, which is a rare disease in Europe. The authors describe a case of a 48-year-old patient with complaints of chest pain as a tight belt, myalgia and leg paresthesia evolving for a month. The long clinical investigation led to a surprising clinical diagnosis of pulmonary histoplasmosis in the form of rare histoplasmoma in a patient who had never traveled to endemic regions.

Key words: Histoplasma capsulatum, histoplasmoma.

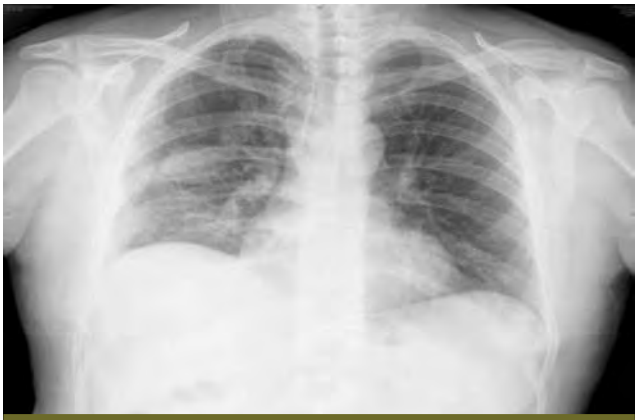
INTRODUCTION

There are two variants of *Histoplasma capsulatum*: *capsulatum* and *duboisii*.[1] The distinction between them is only possible through a direct exam: the *capsulatum* variant is developed *in vivo* measuring around 2-4 µm whilst the *duboisii* variant has a diameter reaching 12-15 µm.[2] In their saprophyte stage they are indistinguishable. The *capsulatum* variant, present in contaminated soils, is found in high concentration in endemic areas close to birds and bats habitats. It does not cause infection in birds, as its consumption does not transmit the disease.[3,4] However, its feces are a good culture medium favoring its viability and propagation for years.[3,4] As bats are mammals they become hosts, and might disseminate the fungus in their habitat through contaminated feces.[4] Endemic histoplasmosis, widely spread in the American continent is rare in Europe.[5] However, occasional cases have been identified in Southern Europe namely in Italy.[1] After inhaled, the capsulatum variant of the Histoplasma capsulatum proliferates in the cells of the lung macrophage-lymphoid system, reaching the perihilar and mediastinal lymph nodes with a subsequent systemic dissemination through hematic route and activation of the cellular immune response of the type Th1.[1] It expresses itself in many ways, from an asymptomatic and disseminated way, being life threatening if not treated in immunocompromised individuals namely those transplanted under immunosuppression, patients in high doses of corticotherapy, with congenital immune deficits, lymphomas or infected by the human immunodeficiency virus (VIH).[1,4,6]

CASE REPORT

48-year-old patient, male, born and residing in Leiria, a locksmith by trade, looked for help at the Emergency Service (SU) of Hospital de Santo André (HSA) in Leiria due to constant thoracic complaints, as a tight belt of low intensity with mechanical characteristics, paresthesia and myalgia of the lower limbs and gait ataxia evolving for a month. This patient had no relevant medical history with exception of a recent hospitalization due to atypical pneumonia on the right basis. No medication or smoking habits only mentioning a moderate consumption of alcoholic drinks. From the epidemiologic study, it should be highlighted the patient contact with active pulmonary tuberculosis and with animals namely pigeons and dogs.

Medicine 1 Service of Hospital de Santo André - EPE, Leiria
Received for publication on the 8th February 2011
Accepted for publication on the 23rd October 2011



Thorax radiography.

FIG. 1

Relevant in the physical examination were gait ataxia tending to lean to the left and patellar and cutaneous-plantar hyporeflexia. The neurologic exam did not show evidence of other changes namely motor or sensitivity deficit. No inflammatory signs or deformation in the joints were seen either.

In a first approach, tests were carried out in the Emergency Service, including hemogram, kidney and liver function, ionogram and C reactive protein (CPR) dosage, electrocardiogram (ECG) and cranial-encephalic CT scan, showing no changes, as well as thorax X-ray (*Fig. 1*) showing an infiltrate on the right base with fissure pleural effusion and a suspected opacity on the lateral medium third.

Admitted subsequently in the Medicine I Service for study, he underwent additional diagnosis tests (ADT) resumed on Table no. 1. Among these, just some of the image results have shown abnormalities with clinical meaning. Thorax CT scan (*Fig. 2*) has identified in the apical segment of the lower right lobe an oval form of undefined contours with around 2.5 cm in diameter suggesting an expanding process. In the dorsal magnetic nuclear resonance (NMR) it was observed an image suggesting a pulmonary neoplasm which would extend itself from D5 to D6-D7 invading the pediculum, right transverse apophysis, lamina and right rib on D6 and the right pediculum, joint processes and D5 lamina with invasion of the right intervertebral foramen in D5-D6 and a discreet epidural extension. The spine CT Scan (*Fig. 3*) has shown that the referred lesion in the NMR presented an osteolytic component involving the right inter-

TABLE I

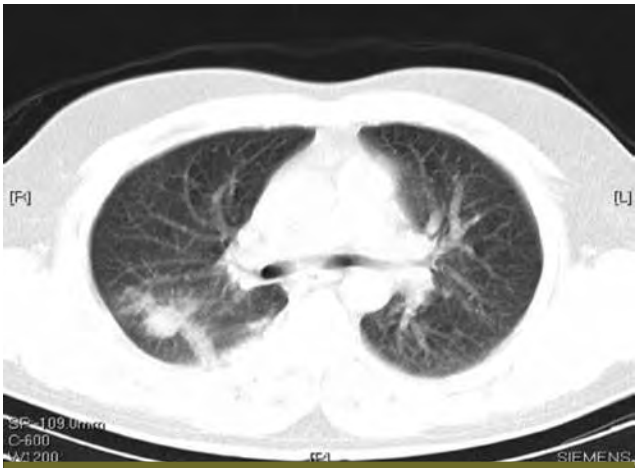
Exames complementares de diagnóstico

- Serologies (serum):
  - TORCH Group
  - *Clamydia psitacci*
  - *Borrelia burgdorferi*
  - *Mycoplasma Pneumoniae*
  - *Chlamydophila Pneumoniae*
  - *Legionella Pneumophila*
  - HIV 1 and 2
  - HCV
  - HBV
- Dosage of vitamin B12 and folic acid
- Dosage of ANCA, ANA, C3, C4 and CH50
- Dosage of SACE
- CSF Study:
  - Cell count, protein dosage, LDH and glucose
  - Culture
  - protein immunoelectrophoresis and research of oligoclonal bands
  - VDRL
  - ADA dosage
  - PCR Research of HSV1/2, EBV, CMV and enterovirus
  - serology of Chlamydophila Pneumoniae, Borrelia Burgdoferi, Mycoplasma Pneumoniae and Legionella Pneumophila
- Thorax CT Scan
- Spine CT Scan

Table I: Diagnosis additional tests
TORCH: toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus and others, ANCA: anti-neutrophil cytoplasmic antibodies, ANA: anti-nuclear antibodies, C: complement, SACE: serum angiotensin-converting enzyme, ADA: adenosine deaminase, VDRL: venereal disease research laboratory, PCR: poly chain reaction, EBV: Epstein-Barr virus, CMV: cytomegalovirus, HSV: herpes simples virus, HIV: Human immunodeficiency virus, HBV: hepatitis B virus, HCV: hepatitis C virus.

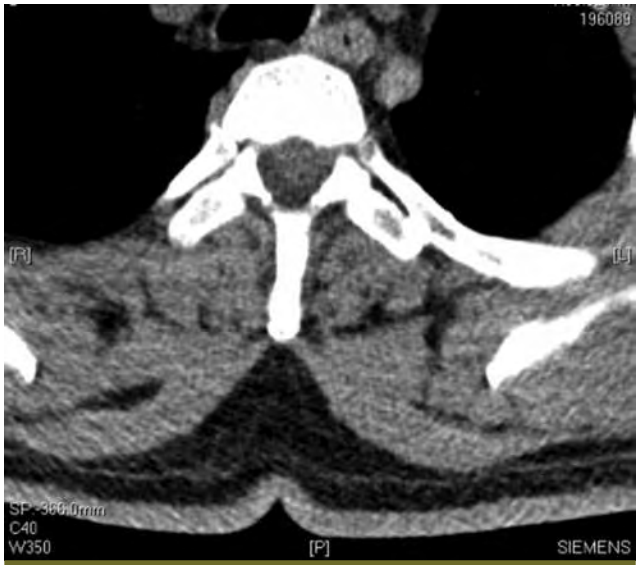
-apophysaire articular mass in D5-D6 and D6 transverse apophysis.

As the results of the clinical investigation pointed to a pulmonary neoplasm, the study was continued in order to confirm the diagnosis on one hand and to proceed to the staging of the malignant process on the other hand. For such purpose, a bronchofibrescope was carried out, which has denied the evidence of infiltrates or neoformations with a final view of pneumonia in remission or peripheral pulmonary neoplasm. The pathoanatomical study of the bronchial aspirate did not confirm the presence of malignant cells mentioning only the existence of fungi groups which were not identified. The research and culture of bacilli acid alcohol resistant



Thorax CT Scan.

FIG. 2



Spine CT scan .

FIG. 3

(BAAR) in the gastric fluid and in the bronchial aspirate were negative, as well as the aerobic culture. A transthoracic biopsy driven by CT scan was also carried out and the histological evaluation has denied again the presence of any malignancy, showing only fibrosis of the support of the fibro vascular axis with lymphocytic inflammatory infiltrate and the existence of macrophages. Osteo-articular scintigraphy has enabled to value hyperactivity on D6 border and D5 – D6 joint with a discrete extension on the contiguous extremity of the sixth costal arch as potential of secondary lesion. The dosage of different tumor markers was normal as well as abdominal ultrasound.

These new data did not allowed to exclude safely the existence of a malignant neoplasm, reason why the patient was referred to Coimbra Hospital Center (HSA reference hospital) to carry out an open biopsy of the pulmonary lesion. The report of the surgical procedure has confirmed the presence of a round formation, at the fissure level, involving both the upper and lower lobe with a fistula trajectory towards the thorax wall (without a visible transcutaneous drainage) draining purulent material. The histological assessment of the piece removed has shown numerous small organisms; the morphological aspect observed, expressed a fibrinoid inflammatory lesion with the formation of abscesses followed by a granulomatous tissue reaction suggesting a fungal infection compatible with *Histoplasma capsulatum*.

Once established the diagnosis of pulmonary histoplasmosis, the patient was subject to an antifungal target therapy and cortical therapy. At the induction stage, he was treated with liposomal Amphotericin B on a 4mg/kg dosage for the first seven days and 0.8mg/kg for the following seven days. At the consolidation stage, he was treated with itraconazole on a daily dosage of 400 mg divided in two daily intakes for nine months.

The patient follow-up has revealed a clear improvement of the clinical condition with remission of pain and neurologic complaints. These were gradual demanding symptomatic treatment with gabapentine. The image control has shown a resolution of the inflammatory process with a persistence of the posterior pleural thickening on the right.

DISCUSSION

As it has been mentioned before, histoplasmosis evolves in individuals who live or have traveled to endemic regions. As a matter of fact, near contaminated soils, there are numerous spores flowing in the air.[4] *Histoplasma capsulatum* var. *capsulatum*, after establishing itself, persists indefinitely in the soil even after the birds have migrated. Most spores can be found in the superficial layers therefore they are easily taken by the wind[4] to miles away[5] and brought to non-endemic areas by Travelers, attached to their

TABLE II

Immunology Tests

Immunodiffusion and Complement fixation:
- (+) in 80% of patients or more
- False positive (Cross reaction with Blastomyces dermatidis and Coccidioides immitis)
- False negative (Immunodepressed, widespread disease)
- Titer of 1/32 suggest active infection

Imunoprecipitation:
- Detection of anti-glycoproteins H and M antibodies (Ab)
- Anti-M Ab (+) in 50 to 80 % of patients, detectable for years
- Anti-H Ab (+) in 10 to 20% of patients, undetectable to 6 months

Antigen detection (histoplasmin):
- Technique applicable in the CSF, blood, urine and respiratory secretions
- (+) in the serum of 85% of those infected
- (+) in the urine of 95% of those infected
- Skin tests do not distinguish a recent from an old infection (not recommended)

(+): Positivity

shoes.[7] The fact that this patient used to breed pigeons can be the cause for having developed a good culture environment for spores. It is also known that decomposing wood can shelter the fungi and spread it in the air when it is sawn[8] reason why his occupation as a blacksmith may have also provided his exposure. It is not known how the spores were inhaled by the patient, and there is no record of such symptoms with his relatives and co-workers.

Its transmission is mainly in the air, with other infection routes (cutaneous and gastrointestinal) being very rare.[9] Conidia are inhaled reaching pulmonary alveoli where they will trigger a primary infection. There are a number of clinical manifestations depending on the size of the inoculate, the hosts response and the pulmonary vitality.[1,3,4,10] Massive exposure can lead to a severe breathing failure kneeling treatments. In such cases radiologic changes have a slow resolution.

The diagnosis of such diseases relies on viewing directly the fungi as happened in the case report we presented or in positive cultures and/or serology (*Table II*).[1,3] It should be pointed out that in the acute respiratory form, it is seldom possible to confirm the diagnosis because it is difficult to observe and make a culture of the microorganisms in secretions (in around 15% of cases).1,3

In the current situation, the difficulty on the diagnosis has been due mainly because the disease was not suspected. As a matter of fact, the patient´s epidemiologic background and because it rarely occurs in Europe led to a situation where histoplasmosis was never raised as a diagnosis hypothesis when approaching the patient. In a first medical evaluation, the patient presented essentially the clinical and neurologic condition compatible with a spine transverse commitment on D6 – D7 area inducing diagnosis hypotheses related with spine aggression on the mentioned region. Throughout the investigation, to visualize a pulmonary node invading the spine has changed the diagnosis approach. The pulmonary nodes, with different etiologies, are divided in two main groups: malignant including primary and secondary neoplasms and the benign which includes granulomatous infections as tuberculosis or histoplasmosis, arteriovenous malformations, inflammatory affections as rheumatoid and benign neoplastic nodes as lipoma or fibroma. The vital impact of malignant neoplasms and the characteristics of the node found, namely its spiky and invasive aspect they have imposed the exclusion of a malignant neoplasm as first target. The high incidence of tuberculosis in Portugal prompts also its study as the most frequent cause of benign node.

A *posteriori*, it seems logical to associate the first time the patient was hospitalized to the acute expression of such mycosis as the massive spore inhaling leads to the development of an acute pulmonary infection evolving with the clinical condition overlapping pneumonia, and able to show an infiltrate with an interstitial or reticular nodular pattern in the thorax X-ray.[5]

Histoplasmoma, pulmonary granulomatous nodes, are related with the healing of the primary lesion with an excessive fibrotic response and slow growth reaching a diameter of 3 to 4 cm in 10 to 20 years.[11] They seldom happen and are usually diagnosed after surgical removal through the piece histopathological exam.[12] Unis et al.[10] have also observed that they are located predominantly in the lower lobe and in the right lung as it happens with our case report.

The surgical ablation is usually curative in cases of histoplasmoma.[1] However, our patients neurological complaints during the after surgery period reason

why it was chosen to implement an antifungal target therapy and cortical therapy with a view to prevent potential fibrosis whilst reducing the associated immune/inflammatory reaction.

CONCLUSION

Histoplasmosis is a very rare entity in Portugal. This case enhances the importance of taking into account such pathology in patients with pulmonary nodular lesions differential diagnosis, even if they have a negative epidemiological background. It should be remembered that the high human mobility is responsible for the cages observed in Europe. ■

References

1. Ferreira MS, Borges AS. Histoplasmose. Rev da Sociedade Brasileira de Medicina Tropical 2009: 42 (2): 192-198.

2. Vieira R, Botelho MM, Lima C, Lázaro A. E Martins ML. Intra-abdominal abcess: A clinical manifestation of African Histoplasmosis. Journal de Mycologia Medicale 2009;19: 134-137.

3. http://emedicine.medscape.com/article/299054 (access in September 2010).

4. Martins EML, Marchiori E, Damato SD, Pozes AS, da Silva ACG e Dalston M. Histoplasmose pulmonar aguda: relato de uma microepidemia. Radiol Bras 2003; 26 (3).

5. Filho AD, Wanke B, Cavalcanti MAS, Martins LMS e Deus ACB. Histoplasmose no Nordeste do Brasil. Relato de três casos. Rev Port de Pneumol 2009; XV (1): 109-114.

6. Kauffman CA. Diagnosis of Histoplasmosis in immunosuppressed patients. Current opinion in Infectious Disease 2008; 21:421-425.

7. Outbreak of histoplasmosis among travelers returning from El Salvador-Pennsylvania and Virginia. Morb Mort Wkly Rep 2008; 57(50):1349-1353.

8. Davies SF. Colbert, R. L. Concurrent human and canine histoplasmosis from cutting decayed wood. Annals of Internal Medicine 1990;113 (3) : 252-253.

9. Wheat J. Histoplasmosis: Recognition and treatment. Clin Infect Dis 1994; 22, (supl2): 19-27.

10. Unis G, Severo LC. Chronic pulmonary histoplasmosis mimicking tuberculosis. J. Bras Pneumol 2005; 31 (4): 318-324.

11. Unis G, Pêgas KL, Severo LC. Histoplasmoma Pulmonar no rio Grande do Sul. Ver. Da Sociedade de Medicina Tropical 2005; 38 (1): 11-14.

12. Severo LC, Rizzon CFC, ROesch EW, Porto NS. Histoplasmose pulmonar aguda: episódio em casal de adultos. Revista da Associação Médica do Rio Grande do Sul 1993;37:281-283.