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Presentation of histoplasmosis as mononucleosis syndrome in an immunocompetent patient

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ABSTRACT

Histoplasmosis is a fungal disease usually occurring in endemic areas that can affect immuno-impaired patients in whom pulmonary involvement is the rule. We present the case of an 18 year-old immunocompetent, male patient, resident of the State of Florida, who showed signs of mononucleosis syndrome that included odynophagia, cervical adenomegaly, sporadic fever and rash; however, no pulmonary involvement or visceromegaly were present. Faced with this atypical and unexpected clinical picture, histoplasmosis infection was eventually diagnosed following cervical lymph-node biopsy. Disseminated histoplasmosis may have unexpected manifestations, as is pointed out in the case described below.

1. Introduction

Immunocompromised patients are frequently struck by infections, including histoplasmosis [1]; however, this disease rarely appears in immunocompetent patients, but when either immunocompromised or immunocompetent patients are infected, histoplasmosis will eventually evolve into a systemic disorder, affecting the lungs first. In its advanced stage, lesions appear in the esophagus, the oral-pharyngeal cavity and the oral cavity; however, these localizations are uncommon in immunocompetent patients. The case described herein is that of an HIV-seronegative patient diagnosed for infectious mononucleosis, but ultimately for disseminated histoplasmosis. Symptoms at time of initial diagnosis included oropharyngeal lesions and cervical lymphadenopathy, but no detectable pulmonary involvement. The patient, a Colombian national residing in the United States, acquired the disease during an unexpected (reverse) migration course.

2. Case

An 18-year old male patient, from Bogota, Colombia, who had been residing in the State of Florida for one year, exhibited initial clinical signs of progressive odynophagia, accompanied by bilateral cervical lymphadenopathy. Both symptoms gradually advanced and were eventually coupled with fever and weight loss. Patient had received first level medical care in Miami, including laboratory exams, and was consequently prescribed antibiotics after presumptive diagnosis for "Neck masses, infectious mononucleosis vs. lymphoproliferative disease"; patient could not remember which antibiotics the doctor had prescribed; patient recalled buying the prescription drugs, taking them over a 5-day period; nonetheless, rash appeared two days after starting antibiotics (Fig. 1) and severe adynamia; at that time, he arrived in Bogota.

Challenged by progressive disease, patient arrived at our hospital in Bogota, (day 0) where he reported a 6 kg weight loss, bilateral cervical adenomegaly with conglomeration in the right submandibular region that upon palpation caused no pain, small adenomegaly in the posterior cervix, fever of up to 38.5 °C and pharyngeal exudates. Maculopapular rash covered entire body, including arms, hands, chest and abdomen. Mobile, non-confluent, bilateral inguinal adenomegaly were also observed during initial physical examination. Chest x-ray was normal, but neck ultrasound revealed all cervical terminals had multiple, enlarged, bilateral, oval-shaped, hypoechoic lymph nodes, some of which exhibited loss of hilum; Doppler color exam showed scant vascularization; largest lymph node measured 46 × 21 mm; thyroid gland and submandibular parotid glands had no lesions and were in normal locations. Fibreoptic naso-laryngoscopy revealed predominately right-sided amygdalin hyperplasia, but no lesions were observed in the larynx, pharynx or nasal and oral cavities during initial hospital exam. Abdominal ultrasound exam verified the absence of hepatosplenomegaly.

WBC contained 9% monocytes; no atypical lymphocytes were present. Additional serological/virological studies and their results

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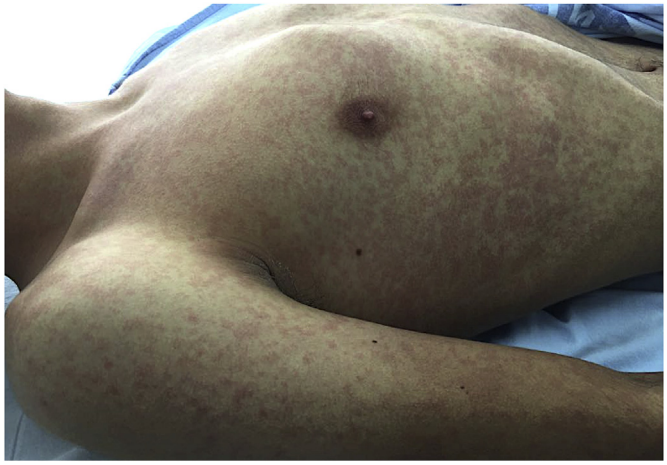

Fig. 1. Widespread skin rash.

included (day two): Epstein-Barr Virus, IgG positive; IgM negative; IgG Herpes Virus, positive and IgM, negative; HIV, negative (duplicated).

Approximately at 8 weeks from appearance of symptoms, patient continued losing weight (more than 10% of previous weight). Tests were carried out for Parovirus B19 and Herpes Virus 6. The presence of Still's disease and lymphoproliferative disease were also considered; however, hepatic and renal tests produced normal results, and rheumatoid factor tested negative; blood culture also tested negative. CT scans of the neck, chest and abdomen revealed multiple adenopathy, some with necrotic centers; pulmonary parenchyma showed no abnormalities. During same period, low-grade fever persisted, and patient's progressive odynophagia led to acute eating disability, including severe palatal pain upon liquid intake. Supplementary WBC tests revealed CD4 lymphocytopenia.

Further examination exposed total involvement of left-side lymph chain; consequently, a cervical lymph-node excisional biopsy was sent to histopathology lab for anatomopathological and infectious study, at day 30th. Lab results described an approximately 6 cm-wide, whitish, rubber-like mass, with bloodied surface and whorled interior; histological study delineated a lymph node with markedly distorted architecture caused by epithelioid granulomas and profuse necrosis; histochemical staining confirmed the presence of intracytoplasmatic granules compatible with fungi (Fig. 2) (preliminary results at day 31st), histochemical morphology analysis identified Histoplasma capsulatum, a fact subsequently confirmed by tissue culture results (day 94th: Histoplasma capsulatum s.p.).

The paragraph was completed: Treatment began with Amphotericin B (1 mg/kg, intravenous infusion, 20 hours per day for 9 days (days 30th to 39th), to which patient responded favorably; this was then followed by a year-long regimen of oral-dose itraconazole (oral solution itraconazole 200mg (20 cc 3 times a day for one year) (say 40th to 405th).

At one year, Histoplasma capsulatum tested negative on antigenuria assay; chest x-ray and neck CT results were normal; CD4 lymphocyte count had reached normal levels, thus indicating the presence of reactive rather than idiopathic lymphopenia.

3. Discussion

Infectious mononucleosis appears frequently in young male adults [3–5]; symptoms include asthenia, pharyngitis and diffuse lymphadenopathy; fever and rash are also other common symptoms. Diagnosis is based up clinical picture and test results for atypical lymphocytes taken from peripheral blood sample. Some authors consider hepatosplenomegaly to be an additional diagnostic sign. Microorganisms commonly found in clinical picture include: Epstein-Barr virus (EBV), cytomegalovirus, Herpes virus 6, Parvovirus B-19 and human immunodeficiency virus type I [3,9]. Other series have also included: Coxsackie B3 and B4 viruses, Rickettsia rickettsii, Brucellosis, Leptospirosis, Hepatitis B, Herpes 8 and Toxoplasma gondii. In most patients, latency period for infectious mononucleosis is two weeks; after which time, symptoms begin to appear [10].

Due to similarity with clinical picture for infectious mononucleosis syndrome, infectious streptococcal pharyngitis is among possible differential diagnoses, despite the fact that the latter, unlike the former, usually causes less fatigue and is not associated with splenomegaly; other differential diagnoses include Rubella, lymphoma, and some drug treatments (phenytoin, carbamazepine, sulphonamides and minocycline) [11]. One of the least frequently mentioned etiologies is fungus infection, such as that diagnosed in our patient after having received various negative test results, as well as confirmatory biopsy results.

Histoplasmosis is a disease caused by the dimorphic fungus, Histoplasma capsulatum [1], which contains two pathogenic varieties in humans: Histoplasma capsulatum var. capsulatum and H. capsulatum var. duboisii [12]. This fungus is frequently found in bird and bat droppings, especially in caves, farmyards, and wherever poultry are raised. Humans are usually infected by breathing in fungal spores [1], that later germinate in the lungs, thereby causing pneumonitis “in patches”; shortly afterwards, usually within two weeks, hematogenous dissemination takes place. The resulting clinical picture will be influenced by exposition intensity, as well as by host's immunological status. Three clinical histoplasmosis syndromes have been recognized: acute pulmonary histoplasmosis, cavitary histoplasmosis, and progressive disseminated histoplasmosis. However, histoplasmosis infections, of any kind, are infrequent in immunocompetent patients. Clinical appearance of disseminated histoplasmosis can be acute, subacute or chronic; acute disease may begin abruptly with fever and general feeling of illness, adenopathy occurs in 30% of patients; yet, pulmonary symptoms, such as cough and difficulty in breathing, are rare [3], even if patient is HIV+, involvement of the larynx and pharynx is also uncommon [25], occurring in less than 20% of cases [27,29]. But, in cases of chronic disseminated histoplasmosis, these anatomical sites tend to show greater involvement; and, from onset, may be the source of the only recognizable symptoms [15], as was the case of the patient described herein. In a Mayo Clinic study of 111 patients, the most frequently documented symptoms were fever (63%), respiratory ailments (43%), and weight loss (37%) [18]. In cases of oral histoplasmosis infection in concomitant HIV + patients, the most commonly affected sites are tongue, palate and oral mucosa [19]; in cases of disseminated histoplasmosis, oral involvement ranges from 25 to 45% [20]. Furthermore, when histoplasmosis symptoms appear in non-endemic areas, diagnosis is a challenge [21]; proper diagnosis must necessarily rely on histologic studies [18]. Even though cervical compromise is generally

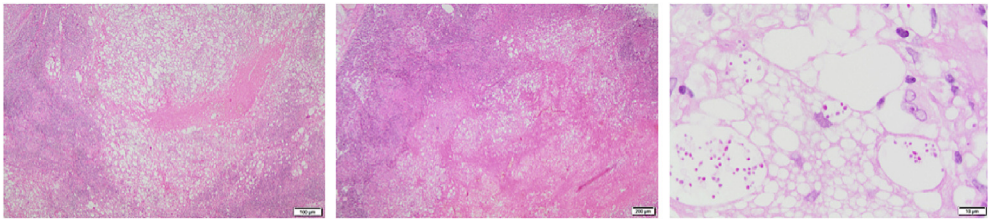

Fig. 2. *Histological study: Left: lymph node with markedly distorted architecture; middle: epithelioid granulomas and profuse necrosis; right: intracytoplasmatic granules compatible with Histoplasma capsulatum.*

regarded as the exclusive symptomatic indicator of histoplasmosis, other, atypical symptoms can occur, thus complicating diagnosis. Our patient's unexpected histoplasmosis diagnosis was produced in spite of a background of no immunity disorders and no signs of pulmonary involvement, both common factors to be considered during primary infection stage; in our patient's case, laryngeal, pharyngeal, and later on, palatal involvement, predominated; eventually, dissemination took place, but in the absence of splenomegaly or pulmonary involvement.

In South America, fungi have been widely reported in Brazil [25], Ecuador, Costa Rica, Nicaragua, Perú, Guatemala, Venezuela y Colombia [5,25]. The hypothetical contagion site of the case described herein was the State of Florida. In the United States, H. capsulatum infection is prevalent in the Mississippi and Ohio River Valleys [14], where it is has been classed as the most common, endemic pulmonary mycosis in that country [18,30]; particularly in states such as Minnesota or Wisconsin [3] however, during his residence in North America, our patient had visited no Mid-Western US states. In Colombia, endemic histoplasmosis areas are found near fresh water sources in temperate zones where daily temperatures range from 19 to 22C°, as well as in subtropical and tropical rainy regions; however, our patient had not visited any such sites before moving to the United States; nonetheless, infrequent cases have been reported in Bogota, where the patient is originally from Ref. [30]. While living in Florida, patient often hiked through woods and swamplands, where wild ducks abound. Interestingly, other cases of disseminated histoplasmosis have been reported in southern Florida [16,31].

Accurate diagnosis of histoplasmosis infection continues to pose a challenge, even more so when patients are immunocompetent. It is important to keep in mind that even though pulmonary involvement may be absent and no clear instance of exposure exists, particularly in non-endemic areas, mononucleosis syndrome can result as differential diagnosis. In this light, our case of a Latin American patient with deep mycosis infection, imported from the United States, also proved difficult to diagnose.

Ethical Form

Please note that this journal requires full disclosure of all sources of funding and potential conflicts of interest. The journal also requires a declaration that the author(s) have obtained written and signed consent to publish the case report from the patient or legal guardian(s).

The statements on funding, conflict of interest and consent need to be submitted via our Ethical Form that can be downloaded from the submission site www.ees.elsevier.com/mmcr.

Declaration of competing interest

None of the authors has any potential or actual interests relevant to the topics discussed in this manuscript. This paper has been financed by the Pontificia Universidad Javeriana, Hospital Universitario San Ignacio in Bogota, Colombia.

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