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BRIEF REPORT

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Necrotizing cervical lymphadenitis due to disseminated *Histoplasma capsulatum* infection

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Disseminated histoplasmosis (DH) is usually associated with intense exposure to *Histoplasma capsulatum* or defective cellular immunity [1]. Described here is the case of an immunocompetent patient with necrotizing cervical lymphadenitis as an unusual presentation of chronic DH.

A 36-year-old Surinamese woman was transferred to our hospital with a 4-month history of progressive painful swelling of the cervical lymph nodes, fever, dysphagia, and weight-loss. Ten years earlier she had immigrated to The Netherlands from Surinam, and she had last visited her country of origin 3 years prior to presentation. Her medical history included panuveitis duplex of unknown origin since 1982, with refractory secondary glaucoma that eventually led to blindness. On admission, the patient had a temperature of 39.9°C, her blood pressure was 130/80 mmHg, and her heart rate was 122 beats per minute. Physical examination revealed extensive asymmetrical enlargement of the lymph nodes in the posterior triangle of her neck with firm induration and two draining fistulas, a shallow ulcer at the right side of the mouth, a pronounced swelling of the buccal mucosa, trismus (Fig. 1), and hepatomegaly. Laboratory examination showed microcytic anemia, due to heterozygotic ß-thalassemia in combination with iron deficiency caused by hypermenorrhea. CD4+ and CD8+ cell counts were normal. HIV serology was negative.

During hospitalization, the patient developed leukopenia and thrombocytopenia, and her hepatic enzymes and bilirubin levels became elevated. Computed tomography examination of the neck revealed edematous swelling of the right nasopharyngeal wall, suppurative retropharyngeal lymphadenitis, and multiple enlarged lymph nodes throughout the neck with encasement of the right carotid artery, compression, and probable thrombosis of the right internal jugular vein (Fig. 2). Computed tomography scan of the chest was normal. Abdominal ultrasound showed hepatosplenomegaly. Cultures of cervical and retropharyngeal pus and a lymph node sample grew *H. capsulatum* 12 days following inoculation. Eventually, a blood culture performed to detect mycobacteria also grew *H. capsulatum*.

Histological examination of the lymph node revealed necrotizing lymphadenitis with disintegrated cells, nuclear debris, and an influx of histiocytes and neutrophils. No

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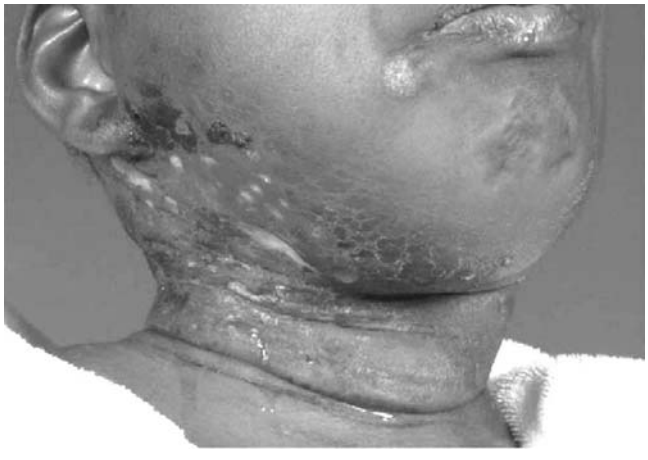

Fig. 1 Asymmetrical enlarged lymph nodes with draining fistulas in the posterior triangle of the neck in a patient with disseminated histoplasmosis. Note the shallow ulcer near the right corner of the patient's mouth and pronounced swelling of the cheek

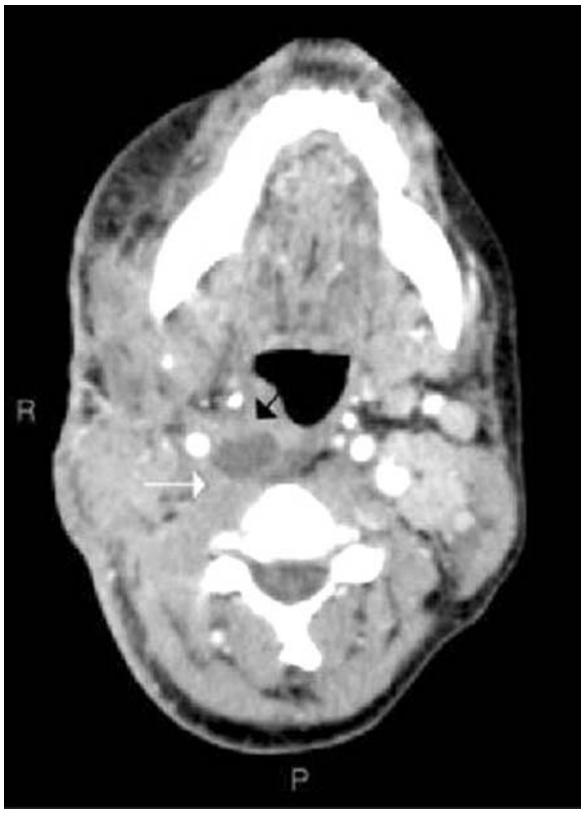

Fig. 2 Axial computer tomography scan of the neck showing (i) nonhomogeneous enhancing mass on the right side of the neck with infiltration of surrounding fat and thickening of the overlying skin, (ii) encasement of the right carotid artery and the internal jugular vein with compression and probable thrombosis of the jugular vein (*white arrow*), (iii) a rim-enhancing cystic mass surrounded by soft tissue swelling in the retropharyngeal space (*black arrowhead*) indicative of suppurative retropharyngeal lymphadenitis, and (iv) enlarged lymph nodes on the left side of the neck

granulomas were seen. In the periodic acid-Schiff (PAS) and Giemsa stain, sporadic intra- and extracellular oval structures without budding (diameter ± 5 μm) were found that were consistent with *H. capsulatum* var. *capsulatum*. Treatment with itraconazole (200 mg b.i.d.) resulted in the normalization of the patient's body temperature after 11 days and gradual improvement of her clinical condition. After 5 months of treatment, the cervical lymphadenitis had subsided significantly.

Histoplasmosis is a fungal infection caused by *H. capsulatum*, a thermally dimorphic fungus that grows in soil. In nature, *H. capsulatum* manifests in mycelial form with macro- and microconidia, whereas a yeast form is observed in infected human tissue. Two varieties of *H. capsulatum* are known to infect humans: var. *capsulatum* and var. *duboisii*. The latter is seen in tropical Africa [2], while the former is the most prevalent variety. Conditions that favor growth include a moderate climate, humidity, and specific soil characteristics. Bird and bat excrement enhance the growth of *H. capsulatum* by accelerating sporulation [1, 2]. These growth requirements explain, in part, the geographic distribution of areas endemic for *H. capsulatum*; these include the southern and central regions of the USA, Central America, the Caribbean, and a large part of South America [2].

Infection with *H. capsulatum* develops when infectious microconidia or small mycelial fragments are inhaled and deposited within the distal airspaces. Here, *H. capsulatum* rapidly converts to the yeast form, multiplies in macrophages, and spreads to draining lymph nodes and distant organs rich in mononuclear phagocytes, such as the liver and spleen [2, 3]. Persistence of *H. capsulatum* can result in DH, primarily in individuals with underlying immunosuppressive disorders or those at the extremes of age [1, 2]. However, in up to two-thirds of cases no identifiable risk factors are recognized [4].

The clinical presentation of DH varies from an acute fatal illness with septic shock and multiorgan failure [1, 2] to a chronic progressive form characterized by fever, night sweats, and weight-loss. Commonly, the latter presentation is accompanied by respiratory symptoms, hepatosplenomegaly, lymphadenopathy and, less frequently, skin or mucosal lesions. Oropharyngeal lesions can be a presenting feature and may remain the only localization for a long time [2, 5]. Cervical lymphadenitis is an extremely rare manifestation of DH in adults. Our review of the English-language literature revealed only one published case of DH in a nonimmunocompromised patient, with the DH presenting as a neck mass extending into the anterior mediastinum [6]. The absence of well-circumscribed granulomas and the presence of macrophages and scattered lymphocytes, as seen in the lymph node biopsy of our patient, is commonly found in progressive DH and is indicative of a 'perturbed cellular immune response' [2].

Other pathogens that should be considered in the differential diagnosis of necrotizing cervical lymphadenitis are mycobacteria, *Coccidioides immitis*, *Bartonella henselae*, *Francisella tularensis*, *Chlamydia trachomatis* L2, *Yersinia pseudotuberculosis* or *Y. enterocolitica*, herpes simplex, and parvovirus B19 [7]. The detection by microscopic examination of single budding yeast-like cells of 2–5 μm in diameter in clinical materials should raise strong suspicion that the fungus is *H. capsulatum* var. *capsulatum*; in contrast, var. *duboissi* typically has a diameter of up to 15 μm. However, the finding is not specific since other organisms, such as *Cryptococcus neoformans*, *Penicillium marneffei* or *Sporothrix schenckii*, can mimic the intracellular forms of *H. capsulatum* [8].

The yeast is poorly visualized by hematoxylin-eosin staining and is more apparent by using the Giemsa or PAS stain. The most useful stain, however, is either Gomori methenamine or Grocott's silver stain [2]. The definitive diagnosis of histoplasmosis relies on the isolation and identification of *H. capsulatum* by culture. Cultures are incubated at 30°C for up to 6 weeks, and more than 90% of cultures exhibit fungal growth within 7 days [2]. In cases of DH, cultures of blood and bone marrow have the highest diagnostic yield [3].

The mortality rate for untreated DH is 80%, but with antifungal therapy the mortality rate can be reduced to <25%. Amphotericin B (0.7–1.0 mg/kg/day) is recommended for all patients with severe DH [1, 9], but

in patients with mild-to-moderate manifestations, and for those whose condition has improved in response to amphotericin B, itraconazole (200 mg once to twice daily for 6–18 months) is the treatment of choice.

In conclusion, the case presented here underscores that histoplasmosis should be included in the differential diagnosis of suppurative necrotizing cervical lymphadenitis in the presence of an appropriate geographical history. Both clinical and laboratory vigilance are required to accurately identify this fungal infection in time.

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