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Case report

Disseminated histoplasmosis presenting as dental lesion in the absence of a vital organ, the thymus

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ABSTRACT

We present a case report of a patient who has rare anatomical anomalies and presented with an oral lesion that led to a diagnosis of disseminated histoplasmosis. The case brings forth important clinical considerations for a diagnosis of histoplasmosis.

Background

Histoplasmosis is a dimorphic fungal infection caused by *Histoplasma capsulatum* that is endemic to the Ohio and Mississippi river valleys in North America as well as some regions in Central America [1]. It commonly causes a self-limiting pulmonary infection in the immunocompetent individual, but in rare cases, it can cause disseminated infection that is fatal if not immediately treated. The disseminated form of Histoplasmosis is often found to affect immunocompromised hosts, including HIV positive individuals. Other important risk factors for developing histoplasmosis include living or recent travel to an endemic area or exposure to bat or bird droppings, especially while exploring caves or soil containing the microconidia [2].

One of the observed manifestations of disseminated histoplasmosis is oral lesions with a 25–45% incidence in an immunocompromised host [3]. Oral lesions can range from nodules to painful shallow or deep ulcers. Disseminated histoplasmosis with oral lesions is a rare presentation seen in HIV seronegative patients [4]. This is a case report of a patient who has rare anatomical anomalies and presented with an oral lesion that led to a diagnosis of disseminated histoplasmosis. The case brings forth important clinical considerations for a diagnosis of histoplasmosis.

Case presentation

A 36-year-old Caucasian male initially presented to oral maxillofacial surgery in the outpatient setting for a dental lesion that had been present for 3 months. He has a peculiar medical history of situs inversus totalis (see Supplementary Fig. 1) and neonatal cardiac surgery from which he recovered. Otherwise, no other pertinent medical history was reported. The oral surgeon's clinical impression of the dental lesion was necrotizing ulcerative gingivitis. A soft tissue dental biopsy was completed at the oral surgeon's office after which patient had instructions for a scheduled follow up.

Prior to following up with oral surgery clinic the patient presented to the hospital emergency department with complaints of acute shortness of air. He was noted to be febrile and cachexic. He reported a 16-kg unintentional weight loss over 3 months. Chest X-ray showed lesions in bilateral lower lobes, suggestive of multifocal infection. The soft tissue dental biopsy that was obtained at the oral maxillofacial surgeon's office was accompanied by a pathology report documenting microscopic findings of squamous mucosa with a diffuse lymphohistiocytic proliferation that extended from just beneath the epithelium to the depth of the biopsy in some areas, and into minor salivary glands. It was noted on hematoxylin and eosin staining that within many histiocytic cells there were small hyperchromatic organisms often surrounded by a clear halo (Fig. 1). Both Grocott Methenamine Silver stain and Periodic Acid-Schiff stains with appropriate controls were positive. Numerous organisms were noted with involvement of multiple oral sites. Chest CT showed multifocal pulmonary nodular opacities, greatest in left lower lobe with nodules measuring up to 1.3 cm (see Supplementary Fig. 2), suggestive of disseminated histoplasmosis. The lower section of the chest CT incidentally picked up abdominal lesions in the spleen (see Supplementary Figs. 3 & 4). This was followed by an abdominal ultrasound that showed hypoechoic foci that were suspicious for splenic microabscesses in the presence of presumed fungal infection. Due to the high suspicion of histoplasmosis based on soft tissue biopsy and radiology, liposomal Amphotericin B therapy was started empirically [5 mg/kg intravenous daily]. The diagnosis was further confirmed with positive urine

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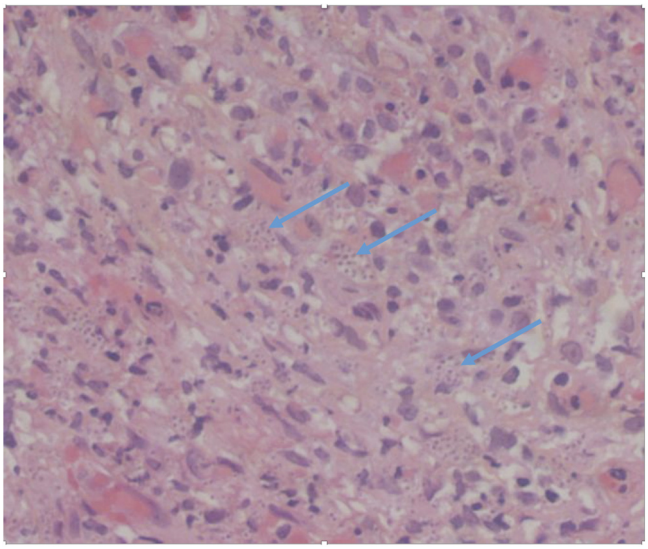

Fig. 1. H&E stain of oral biopsy, arrows pointing at small hyperchromatic organisms often surrounded by a clear halo.

Histoplasma Antigen level at 3.79 ng/ml (MiraVista Laboratories, Indianapolis, IN, > 0.6 ng/ml interpreted as positive) and a positive serum (1,3)-B-D-Glucan Assay level that was > 500 pg/ml (<60 pg/ml interpreted as negative). During course of infection, his *Coccidioides* IgM Ab was also found to be positive. Intravenous Amphotericin B liposomal was administered for 12 days with improvement of symptoms. Subsequently, we switched antifungal treatment to Itraconazole orally and recommended at least 1 year prescription of antifungal therapy [Itraconazole 200 mg orally twice daily for 12 months].

Our patient denied any recent travel history, exposure to bird or bat droppings, caves or large amounts of soil that could have potentially contained microconidia. Due to the rarity of disseminated histoplasmosis in immunocompetent individuals, an extensive immunodeficiency workup including HIV 1/2 antibody and p24 Antigen was obtained: the results were negative. There was also concern for chronic variable immunodeficiency or Hyper IgM syndrome, but this was ruled out with serum IgG and IgM levels that were within normal limits. With a known history of situs inversus, Kartagener's Syndrome was considered; however, it was felt this was unlikely because the patient has 7 children and no history of recurrent respiratory infections. There was no recent history of corticosteroid use, which can also increase susceptibility to disseminated fungal infection. Interestingly, patient had a CD4 T-cell count of 432 cells/mm3 (490–1740 cells/mm3) with normal CD8 T-cell count of 358 cells/mm3 (180–1170 cells/mm3). While this patient did not have an overt immunodeficiency state, his CD4 + cell count was noted to be in the lower limits without a clear etiology. Given the self reported, non-specific cardiac surgery history on admission, underlying T-cell deficiency state from thymic hypoplasia or Digeorge syndrome was considered. Historical records were obtained and revealed that the patient had neonatal cyanotic heart disease. He had severe Tetralogy of Fallot anomaly and had undergone a Waterston procedure with a Gore-tex graft and Blalock type shunt surgeries. He also underwent a neonatal thymectomy with a dissected thymus measuring 5 cm × 3 cm × 1 cm. Gross pathology description of tissue was described as a of pale, rubbery soft tissue. Microscopic pathology was not available.

We suspect the patient had a higher risk profile for infection that made him susceptible to disseminated histoplasmosis. He was at higher risk for infection due to his under-developed cell mediated immune response competency secondary to his neonatal thymectomy.

Discussion

Early thymectomy is sometimes performed in newborns that undergo surgical correction of congenital heart defects to facilitate surgical access. The procedure has been associated with T-cell lymphopenia, a less diverse T cell receptor repertoire, and a skewed autoantibody profile [5]. However there have been a paucity of studies examining the long term consequences of neonatal thymectomy into adulthood.

The thymus plays a major role in lymphocyte maturation process. A neonatal thymectomy removes the environment for the functional maturation of lymphocytes, leaving T cells in a newborn locked in the same stage before the thymectomy and limiting the possibility of achieving immune competence. Furthermore, the thymus plays a role in T-cell selection, meaning only cells that recognize potential antigens are activated, resulting in clonal T cell replication. Larger quantities of T-cell recognizing specific antigens prepare the body for a more competent lymphocytic response to a pathogen [6]. In primary histoplasmosis infection, T cells play an integral role in host resistance and response to Histoplasmosis. It is known that CD4 + T cells are needed critically for survival and CD8+T cells are necessary for clearance [7,8]. Unfortunately, studies that have been conducted to study immune system response to histoplasmosis capsulatum organisms are mostly conducted on on murine lungs and could not be accomplished in humans because pulmonary parenchyma is difficult to obtain [7].

Nonetheless, mouse studies examining congenital athymic mice when compared to mice with functioning thymus showed that athymic mice developed a rapid fatal disseminated infection and transplantation of thymic tissue into those mice diminished the severity and mortality by about 50% [9]. The importance of T cell protective role is further supported by the higher incidence and mortality rates of disseminated histoplasmosis in AIDS patient population [10].

Conclusions

This case is unique in presentation, anatomical anomalies and clinical considerations. It was an atypical presentation of oral lesions with biopsy that led to a diagnosis of disseminated histoplasmosis. Typically, histoplasmosis is diagnosed with a presentation of pulmonary symptoms such as cough, shortness of air, and nonspecific symptoms such as chills, fever, malaise, anorexia, and weight loss [2]. After literature review by the methods described below, even though murine experimental studies have already demonstrated biological plausibility for immunodeficiency after neonatal thymectomy [9], to our knowledge this is the first case report exploring disseminated histoplasmosis in the setting of neonatal thymectomy in humans. The co-existence of the two congenital conditions, Situs Inversus Totalis & Tetralogy of Fallot is also rare. Literature review by methods described below only revealed 9 reported cases, with the first reported in 1963 [11–19]. For literature review methods see supplementary material.

The case introduces the topic of immunocompetency in patients who have congenital heart disease and are athymic. Neonatal cardiac surgery is a particular medical history consideration that literature on clinical diagnosis does not specifically prompt us to inquire about. Literature however, does prompt us to consider cellular immunodeficiency in patients without underlying risk factors, which should be followed by T cell subset

quantification. In vitro testing could include measure of interferon gamma responses to *H. capsulatum* antigens [20].

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.idcr.2019.e00635.

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