

Histoplasmosis as a Late Infectious Complication Following Heart Transplantation in a Patient with Chagas' Disease

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Case Report

Infectious complications following heart transplantation are an important cause of morbidity and mortality. Generally, bacterial infections are predominant; however, fungal infections can be responsible for up to 25% of infectious events.

We report the case of a patient who presented with histoplasmosis as an infectious complication five years after heart transplantation due to a chagasic cardiopathy. This association has rarely been reported in the international literature.

Infectious events constitute an important cause of morbidity and mortality following heart transplantation, being responsible for 17% to 40% of deaths¹⁻³.

Usually, a predominance of bacterial infections exists, with peak incidence in the first month. The lungs are the main site of attack, and lung infections the predominant type of hospital infections. After the 6th month posttransplantation, with the reduction in immune-depression intensity, the predominant out of hospital infections are similar to those observed in immune-competent persons.

In the literature, reported fungal infections in patients who undergo heart transplantation ranges between 10% and 25%⁴, with the peak incidence in the first and second months, although some infections may occur after the 6th month. Deep mycosis is usually associated with greater mortality³.

The occurrence of histoplasmosis in patients who undergo heart transplantation is rare, with few reports published in the literature. Our purpose is to report such a unique association.

The patient is a 37-year-old Caucasian male transplanted five years ago due to a chagasic cardiopathy. He is under ambulatory follow-up at the Congestive Heart Failure and Heart Transplantation Unit of the Instituto do Coração (InCor), and is taking 200mg/day of cyclosporin, 50mg/day of azathioprine, 5mg/day of prednisone, and 90mg/day of diltiazem. Approximately one month earlier, the patient experienced sporadic, uncontrolled fever, associated with intense holocranium headache, diffuse myalgia, and a decline in general status. Laboratory examinations conducted during the patient's first appointment showed: leukocytes 3,400/mm³ (18% band forms and 58% segmented) and low platelets (126,000/mm³). Empirical therapy was initiated with 500mg of ciprofloxacin every 12 h, for 10 days; azathioprine was discontinued and ambulatory re-evaluation was scheduled. After the use of the antimicrobial, the patient reported an improvement in fever; however, he mentioned that he had experienced the onset of coughing with white sputum, a loss of 4kg of weight in one month, and a vesicular eruption on the lower lip. During a routine follow-up examination of the transplanted patient, a mild diffuse hyperconcentration in the pulmonary fields and a focal hypercaptation area of a moderate degree on the left supraclavicular region was revealed in the cardiac scintigraphy with gallium 67, where the presence of lymphatic ganglion was investigated. The study for an active cardiac inflammatory process was negative (figure 1).

Because the patient remained febrile, with low leukocytes (2,700/mm³) and platelets (113,000/mm³) and with lesions on the lower lip, we chose to admit the patient to investigate the cause of the fever.

The physical examination on admission revealed the following: the patient was hydrated, and eupneic; his blood pressure was 130/90mmHg, and his heart rate was 120bpm. Examination of the oral cavity revealed gum hypertrophy, in addition to the presence of hematic cicatricial lesions on the

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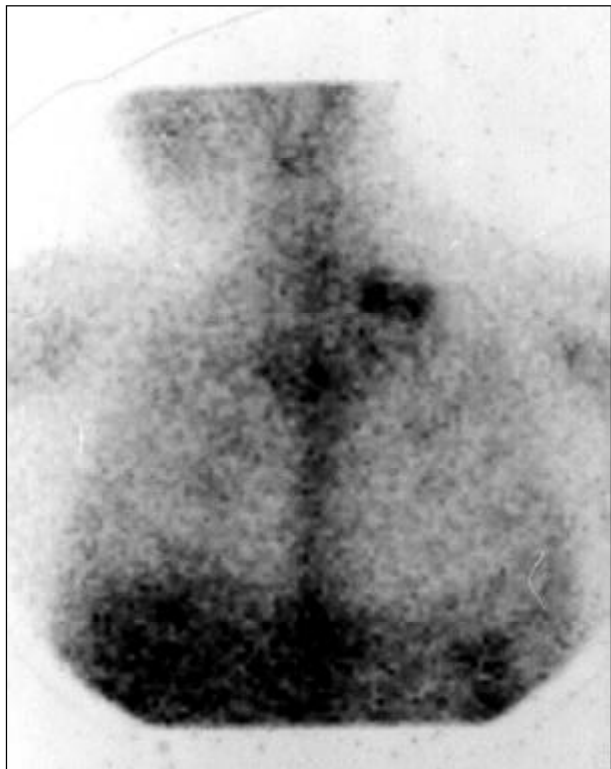


Fig. 1 - Scintigraphy with gallium revealing a diffuse hyperconcentration of the tracer in the pulmonary fields and a moderate degree focal hypercollection area on the left supraventricular region. An abnormal radioligand concentration in cardiac area projection was not observed.

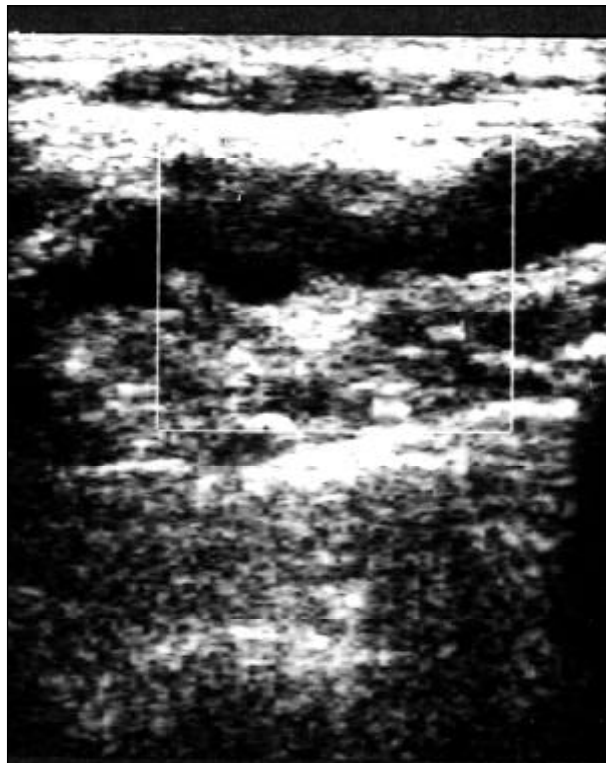


Fig. 2 - Ultrasonography of the left supraventricular region revealing the presence of confluent adenomegaly.

lower lip. No alterations were noted at the neurological examination. The abdomen had mild splenomegaly. Cervical palpation showed ganglion in an anterior chain of approximately 1.5cm, elastic and attached to deep planes. During hospitalization, the patient experienced two febrile peaks (38.4°C and 38.8°C).

Five pairs of blood cultures were collected, which did not reveal bacterial growth. It is important to emphasize that the cultures were followed for only five days according to the usual protocol, and were not examined for fungal growth.

The thoracic radiography was normal. No bacterial growth was discovered in the urine culture. Thoracic tomography was performed and did not reveal alterations in the pulmonary parenchyma. Ultrasonography of the left supraclavicular region revealed three solid nodules, hypoechogenic and confluent, measuring up to 2.2cm (Fig. 2).

A biopsy of the cervical lymphonodus was performed, revealing a sinusoidal histiocytic reaction, with the numerous rounded fungi of uniform size present, measuring 2.2 µm in diameter and histoplasma sp. morphology (Fig. 3). The histochemistry study of bacteria and BAAR were negative. Histological slides of the lymphonodus were submitted to immunohistochemistry investigation with polyclonal and monoclonal antibodies for *T. cruzi*, with negative results. The indirect xenodiagnosis was negative. A diagnosis of histoplasmosis was then made, and therapy with amphotericin B was started.

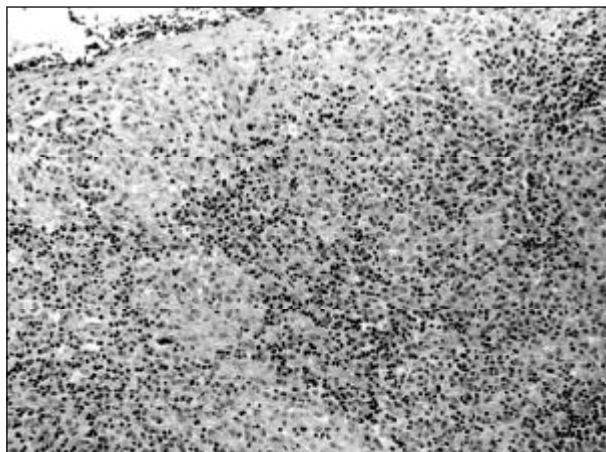


Fig. 3 - Biopsy of cervical lymphonodus.

Ten days after the onset of treatment, the patient showed significant improvement in his general condition and appetite.

Discussion

The signs of infection after heart transplantation are extremely variable according to the criteria adopted; however, infections are responsible for up to 40% of the deaths. Bacterial infections occur most frequently, especially in the first month after the transplantation. The frequency of fungal infections is also variable, although a reduction in the number

and severity of these events has been reported⁴. Histoplasmosis in patients who undergo heart transplantation is rare. Uip et al.⁴ reported in a series of 100 patients, that 47 had fungal infections, with just one single episode of histoplasmosis.

In the present patient, the differential diagnosis was performed to eliminate reactivation of Chagas' disease and lymphoproliferative disease.

Investigation of Chagas' disease reactivation is of fundamental importance, because it can produce graft dysfunction and, due to its systemic character, leads to death⁵⁻⁷. It can simulate rejection and must be differentiated from other infectious diseases. It may evolve asymptotically and produce nonspecific symptoms, such as a decline in general condition, anorexia, anemia, icterus, long-term fever, liver involvement, central nervous system impairment, with headaches and localized signals. *T. cruzi* may invade the bone marrow and cause cytopenias. Cutaneous assault is also characteristic, with the presence of hard, painful subcutaneous nodes and the likely presence of phlogistic signs. For the diagnosis of reactivation of *T. cruzi* infection, the parasite must be demonstrated. Xenodiagnosis may also be efficiently used to demonstrate the parasite, where the indirect method is preferred⁸. In the present case, both indirect xenodiagnosis and immunohistochemistry investigation of *T. cruzi* in the lymphonodus were negative, excluding the possibility of Chagas' disease reactivation.

A higher incidence of neoplasias occurs in patients who undergo heart transplantation, especially cutaneous and lymphoproliferative neoplasias; the diagnosis is made by a biopsy of the tumoral mass, detected by the clinical examination or imaging methods. In the present case, despite the presence of lymphonodemegaly in the cervical chain, the anatomic-pathological examination of the lymphonodus ruled out the possibility of lymphoma.

Histoplasmosis occurs by inhalation of fungi conidium, which reach the alveolus and undergo phagocytosis, initiating a process of multiplication inside the alveolar macrophages. Through the lymphatic passage, the parasites reach regional lymphonodus where they produce a new

inflammatory focus, thus forming the primary pulmonary and ganglionic complex. In this phase, the hematogenous dissemination of the fungi may occur determining the formation of new focuses. After a variable period of 10-18 days, activation of cellular immunity determines an intense inflammatory reaction, with formation of granuloma with clot necrosis, fibrotic encapsulation and, eventually, calcification. This primary infection, generally regressive, usually occurs in immune-competent patients⁹.

In immune-compromised patients, the primary infection or the re-infection may assume a progressive character, with variable severity from patient to patient, without formation of granuloma, solely with a histiocytic reaction, as in the present case.

In Brazil, numerous inquiries with histoplasmin have demonstrated expressive levels of positiveness in the study population, with a higher prevalence occurring in the Southeast region of the country^{9,10}. Clinical manifestations of histoplasmosis are variable, from light symptomatology, confused with flu symptoms in the regressive forms, to extremely severe situations in disseminated progressive forms. Our patient probably had the chronic disseminated form, which is more prevalent in immune-compromised subjects, with concomitant oropharynx or larynx lesions in up to 70% of the cases. Sometimes, lips, gums, tongue, pharynx, or larynx lesions constitute the only manifestation of the disease, which is accompanied by low and intermittent fever, asthenia, and weight loss.

The definitive diagnosis is obtained in the laboratory by means of mycological, histological, or immune techniques, where the culture is individually the most sensitive diagnostic tool. In the present case, however, the diagnosis was made exclusively by the anatomic-pathological examination. The response to treatment and the prognosis are generally good, but depend fundamentally on the patient's immune condition^{11,12}.

We conclude that in the evaluation of heart transplant patients who are febrile, a thorough clinical investigation must be performed, aiming at an early diagnosis and immediate onset of treatment, avoiding the expressive morbidity and mortality of infectious events in these patients.

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