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Visceral leishmaniasis in a type 1 diabetic patient with isolated pancreas transplant☆

Leishmaniasis visceral en un paciente con diabetes tipo 1 y trasplante aislado de páncreas

Isolated pancreas transplant (IPT) is a treatment allowing for long-term normalization of carbohydrate metabolism in patients with type 1 diabetes mellitus (T1DM). It is currently indicted for patients with labile T1DM with frequent and severe acute metabolic complications and preserved kidney function.[1,2]

We report below the case of a 31-year-old male patient with T1DM starting 16 years before who showed poor metabolic control, highly variable blood glucose levels, acute diabetic complications (repeated severe undetected hypoglycemic episodes and frequent episodes of ketosis and ketoacidosis), and chronic complications (proliferative retinopathy, established nephropathy with preserved glomerular filtration rate, peripheral and autonomic sensorimotor neuropathy: gastroparesis requiring jejunostomy for feeding and neurogenic bladder with daily self-catheterization and recurrent urinary tract infection). Patient attended the endocrinology department of another hospital and was referred to our center to be assessed for IPT. He was treated with rapid-acting insulin analogues and insulin glargine using a basal-bolus regimen, and had glycosylated hemoglobin (HbA$_{1c}$) levels ranging from 10% to 12%. Despite treatment optimization with an integrated system of continuous glucose monitoring and continuous subcutaneous insulin infusion, recurrent undetected hypoglycemia

persisted, and IPT was therefore performed on November 2008. Patient had an uneventful postoperative course, and although insulin therapy could not be discontinued (insulin detemir at approximately 30 IU/day continued to be given), controls showed stable blood glucose levels, hypoglycemia did not recur, and tests showed HbA$_{1c}$ values around 5.5% and C peptide levels of 1.5 ng/mL.

Four months after transplant, patient reported malaise, fever up to 40 °C with chills, irritative cough, watery diarrhea, and weight loss for the past 20 days. He was taking immunosuppressants (prednisone, mycophenolate mofetil, and tacrolimus), trimethoprim–sulfamethoxazole at prophylactic doses, insulin detemir, and antihypertensives (losartan, atenolol, manidipine, furosemide, and doxazosin). On admission, patient was conscious and oriented, with a moderately impaired general condition, tachycardia, fever, and mild skin and mucosal pallor. Small pustular lesions were seen in right nostril mucosa. Cardiorespiratory auscultation was normal. No changes were found in abdomen and limbs. Supplemental tests on admission showed the following results: hemoglobin 8.5 g/dL, hematocrit 27%, platelet count 62,000/L, WBC count 1800/L (absolute neutrophils 1300/L, absolute lymphocytes 290/L), and creatinine 2.9 mg/dL; results of all other biochemical tests, including liver profile, were normal.

Blood, urine, sputum, nasal exudate, and catheter tip cultures were all negative. Cytomegalovirus, Epstein–Barr virus, parvovirus B19, and herpesvirus 6 viral loads were all negative. An echocardiogram and a Doppler abdominal ultrasound of the graft were normal, and computed tomography (CT) of the chest only showed a mild pericardial effusion. An abdominal CT revealed an enlarged spleen with infarction of 50% of its volume, no pancreatic graft changes, and no abdominal collections. Patient was initially treated with broad spectrum antibiotic therapy, with no response of fever. Bone marrow aspiration was performed because of the presence of pancytopenia and splenomegaly, showing

amastigotes in monocytes consistent with visceral leishmaniasis.

Treatment was started with intravenous liposomal amphotericin B at 5 mg/kg for one week, followed by weekly booster doses of 3 mg/kg for one month in an outpatient setting. Gradual improvement occurred after the first week of treatment, with disappearance of fever and symptoms. A serologic test for *Leishmania* performed on a pre-transplant blood sample was negative. While serology of *Leishmania* in the donor is unknown, transmission of infection through the pancreas appears unlikely, because this organ has no phagocytic mononuclear system. Infection was probably acquired after transplant, because the patient leaves in an area where leishmaniasis is endemic (Murcia) and has a dog (which is a common host of the parasite).

Recurrence of leishmaniasis was not found during follow-up. Once leishmaniasis was cured, insulin was discontinued and patient remained stable for approximately two months. He subsequently experienced viral meningitis which required hospital admission and was probably associated to reduction of immunosuppression during the intercurrent infections, and finally experienced graft rejection which required graft removal eight months after transplant.

The term leishmaniasis encompasses several clinical syndrome caused by strict intracellular protozoa of the *Leishmania* genus. Leishmaniasis is endemic to Central and South America, the Mediterranean basin, Africa, India, and China.[3] Its overall prevalence is estimated at some 12 million cases worldwide, with an incidence of two millions cases annually.[4] Incidence is increasing mainly in South European countries due to immunosuppression associated with infection by the human immunodeficiency virus and to other situations such as immunosuppressive treatment in cancer and transplant patients.[5]

Visceral leishmaniasis is usually caused by microorganisms of the *Leishmania donovani* complex,[3] which are transmitted by the bite of the sandfly (*Phlebotomus* or *Lutzomyia* genus), although transmission through blood transfusions, infection of a transplanted organ, or needles shared by intravenous drug users has also been reported.[6,7] In mammalian hosts, *Leishmania* spp. organisms are strict intracellular pathogens which infect hematopoietic cells of the monocyte/macrophage line.

Leishmaniasis is an uncommon disease in transplant patients and may occur in three ways: patient develops *de novo* infection after transplant, latent infection is reactivated in a patient infected before transplant, or patient becomes infected through the transplanted organ or blood transfusions.[6,8] In a literature review, in 2008 Antinori et al.[6] found 81 cases of visceral leishmaniasis reported in transplant patients. Most of them had occurred in endemic areas with a high number of transplant patients (Spain, France, and Italy). A majority of cases were associated with kidney transplant (77%), and less commonly to liver transplant (9%), heart transplant (8%), lung transplant (8%), combined pancreas–kidney transplant (one patient), hematopoietic stem cell transplant (one patient), and bone marrow transplant (one patient). Torregrosa et al.[9] reported visceral leishmaniasis in a patient undergoing kidney–pancreas transplant in Spain one year after surgery, and Aardema et al.[10] reported in The Netherlands another case of visceral leishmaniasis in a patient undergoing kidney–pancreas transplant who had travelled to Greece 17 months before the condition occurred.

Clinical signs of visceral leishmaniasis in transplant patients are similar to those seen in immunocompetent subjects, and fever is the most common symptom. Diagnosis may be delayed for months because of the low suspicion index. Microscopic analysis of a bone marrow aspirate is considered to be the procedure of choice for documenting the disease. Leishmaniasis is fatal if left untreated, and its course depends on when diagnosis is made and treatment is started. Cure rates of 84% have been reported in transplant patients with visceral leishmaniasis. These rates are similar to those found in immunocompetent subjects. Liposomal amphotericin B is considered as the first-line drug to treat leishmaniasis.[6]

Visceral leishmaniasis should therefore be included in the differential diagnosis of transplant patients with fever and pancytopenia. This is the first case of visceral leishmaniasis reported in a patient with an isolated pancreas transplant in our environment.

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Unusual characteristics and fatal outcome of a malignant struma ovarii. Case report and literature review☆

Características insólitas y resultado fatal de struma ovarii maligno. Informe de caso y revisión de la literatura

Struma ovarii is an uncommon teratoma of the ovary that contains over 50% of thyroid tissue. This tumor accounts for 0.2–1.3% of all ovarian tumors and for 2–4% of all teratomas. Malignancy is reported in 5–37% of patients with struma ovarii, with metastases occurring in few cases.[1–3] This article reports a patient with some unusual features, including malignancy, metastases, hormone production, and a fatal outcome. Literature is reviewed, and significance of appropriate treatment and follow-up of these patients is emphasized.

A 38-year-old woman was referred to our hospital in 1994 for a second opinion regarding management of a struma ovarii. The disease had been diagnosed at another center in 1981, when she was 25 years old, after right salpingectomy and partial oophorectomy for a right ovarian cyst. At that time, pathological study showed a struma ovarii with no signs of malignancy. In 1993 (at the age of 37 years), patient underwent a left salpingo-oophorectomy and completion of right oophorectomy because of detection of an 8-cm left ovarian mass. Multiple peritoneal nodules were found during surgery, and pathological study found a struma ovarii with positive immunohistochemistry for thyroglobulin. A ^{131}I scan revealed physiological accumulation of iodine in the thyroid gland and pathological deposits in abdomen. Total thyroidectomy and ^{131}I ablation therapy were proposed, but the patient refused them.

When patient attended our center in 1994, abdominal computed tomography (CT) showed nodules throughout the peritoneal cavity, and a ^{123}I scan revealed high uptake in the right iliac bone. A bone biopsy identified metastasis from a follicular carcinoma, reporting malignancy for the first time. The patient again refused thyroidectomy and ^{131}I ablation therapy, but continued to return for follow-up visits.

Between 1994 and September 2008, thyroglobulin levels varied from 600 to 1600 mcg/L (normal <60 mcg/L) and peritoneal lesions increased in number and size. In September 2008, a whole body positron emission tomography showed lung extension, with several nodules in the right lobe and invasion of thoracic lymph nodes (Fig. 1). A transbronchial biopsy was consistent with a poorly differentiated carcinoma and immunohistochemistry was non-conclusive. The patient finally agreed to total thyroidectomy, and the pathology laboratory reported a hyperplastic thyroid gland.

In November 2008, she was admitted for right transverse sinus thrombosis and multiple cerebral infarction from which she recovered completely; no etiology was found. One month later, the patient was readmitted to our center with dyspnea and no symptoms of infection. Chest X-rays showed a bilateral micronodular pattern (Fig. 2), serum thyroglobulin level was 6393 mcg/L, and TSH level was 3.15 mIU/L without thyroid replacement therapy. As the rapid spread of the disease in the lungs was considered the most probable cause of her current condition and thyroidectomy had already been performed, she was treated with 100 mCi of [131]I. Twenty-four hours later, patient experienced left hemiparesia, dysarthria, anosognosia and hemianopsia. A brain CT ruled out hematoma, and a second cerebral ischemic event was diagnosed. Over the following days, patient experienced respiratory insufficiency and worsening of X-ray signs, and finally died.

Struma ovarii is typically diagnosed before menopause. Benign lesions usually occur in the 4th decade of life, and malignant tumors in the 5th decade. The disease generally occurs as a unilateral mass, but up to 6% of cases are bilateral.[2,4] Most patients are asymptomatic or have nonspecific signs or symptoms such as pelvic pain, menstrual cycle changes, or an abdominal mass.[3–5] Like other ovarian tumors, struma ovarii may also cause ascites and hydrothorax, an indolent condition called pseudo-Meigs syndrome.[3,6] Hyperthyroidism appears in 5–8% of struma ovarii patients and is more frequent in benign lesions; however, when hyperthyroidism occurs in a malignant lesion, metastases are present in up to 83% of cases and are usually large.[2,7,8]

Diagnostic imaging techniques such as ultrasonography, CT, or magnetic resonance imaging with gadolinium show a heterogeneous ovarian tumor. Pathological study is the only way to confirm diagnosis of struma ovarii. Gross appearance is a large, green-brown, solid-cystic tumor with other features typical of teratomas.[1] Microscopically, hyperplastic foci, thyroiditis, adenoma, or carcinoma may be seen.[2,8] Immunohistochemical staining for thyroglobulin, chromogranin, and more recently with TTF-1 (thyroid transcription factor-1) is crucial for diagnosis of struma ovarii and helps