JOURNAL OF CASE REPORTS 2014;4(1):20-25

The Role of F-18 FDG PET in the Diagnosis of Visceral Leishmaniasis: Two Case Reports

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Abstract:

Visceral leishmaniasis (VL) is endemic in Mediterranean countries. Among immunosuppressed patients, the disease can manifest with atypical clinical features. An unusual clinical manifestation of the disease is fever of unknown origin (FUO). F-18 fluorodeoxyglucose positron emission tomography-computed tomography (F-18 FDG PET) may be useful for detecting inflammatory foci by observing increased metabolism in activated granulocytes and macrophages. We report two cases of PET/CT total body imaging showing a diffuse increase of reticuloendothelial metabolic activity in the spleen and vertebral bodies in two patients diagnosed with VL by direct detection of amastigotes in bone marrow biopsy.

Key words: Leishmaniasis, Fever of Unknown origin, Bone marrow, Positron Emission Tomography, Spleen, Fluorodeoxyglucose F18.

Introduction

Leishmaniasis is considered to be endemic in 88 countries over four continents. There are an estimated 12 million cases worldwide. Among immunosuppressed patients the disease can manifest with atypical clinical features which can lead to delay in diagnosis. Moreover, VL is a life-threatening disease when it occurs in immunocompromised patients, and if untreated typically leads to death within 2 years. An unusual clinical manifestation of the disease intriguing the diagnosis may present as fever of unknown origin (FUO). We report two cases of PET/CT total body imaging, showing a diffuse increase of reticuloendothelial metabolic activity in the spleen and in vertebral bodies, of two patients diagnosed with VL by direct detection of amastigotes in bone marrow biopsy.

In the absence of specific findings, particularly in endemic countries, VL should be kept in mind as a potential cause of unexplained long-standing fever. F-18 FDG PET may help in detecting inflammatory foci by detecting an increased metabolism of activated granulocytes and macrophages.

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Received: November 5, 2013 | **Accepted:** January 8, 2014 | **Published Online:** January 15, 2014

Conflict of interest: None declared | **Source of funding:** Nil | **DOI:** http://dx.doi.org/10.17659/01.2014.0006

Case reports

Case 1

A 53-year-old Filipino woman who moved to Italy ten years earlier in June 2007 received renal transplantation from a cadaveric donor after 11 months on hemodialysis. She had end-stage renal disease (ESRD) of unknown cause. After transplantation, she had immediate diuresis and recovery of renal function. She was managed with antithymocyte globulin, methyl-prednisolone, cyclosporine, and mycophenolate mofetil. She was discharged with good renal function and no acute rejection.

Eleven months after surgery, she presented with fever due to Cytomegalovirus (CMV) infection. Eighteen months after transplantation, she suffered leukopenia (white blood cells 3.3 x 10^9/L, normal: 4.0–10 x 10^9/L) with a T-CD4 lymphocyte count of 202/μL. Three months later, she presented with high fever, asthenia, and general malaise. Laboratory studies showed worsened leukopenia (white blood cells 2.6 x 10^9/L), mild thrombocytopenia (platelet count 133 x 10^9/L; low-normal 140 x 10^9/L), increased C-reactive protein (CRP) (CRP 8.3 mg/dL, normal 0.0 - 0.5 mg/dL), and worsening kidney function (creatinine 1.34 mg/dL, normal 0.50-1.10 mg/dL); the results of the remaining routine blood tests were within normal limits. She was treated empirically with ciprofloxacin and ganciclovir.

Two years after transplantation she presented with high fever and worsened leukopenia; she was successfully treated empirically with vancomycin, amikacin and ganciclovir. Thirteen days after discharge, the patient presented to hospital complaining of high fever. Laboratory studies showed worsened leukopenia (white blood cells 2.3 x 10^9/L), anemia (hemoglobin 10.6 g/dL, normal 12.0-16.0 g/dL), thrombocytopenia (platelet count 72 x 10^9/L), increased CRP (10.9 mg/dL), and worsening kidney function (creatinine 2.4 mg/dL); the results of the remaining routine blood tests were within normal limits. Plasma CMV viral load was negative. A serological test for Leishmania and for other infectious diseases was negative. Cultures from blood and urine were negative.

On abdominal ultrasound (US) and on contrast-enhanced abdominal computed tomography (CT), the spleen was moderately enlarged, with a cranio-caudal length of nearly 15 cm. F-18 FDG PET/CT images showed diffuse increased FDG uptake in an enlarged spleen [Fig.1].

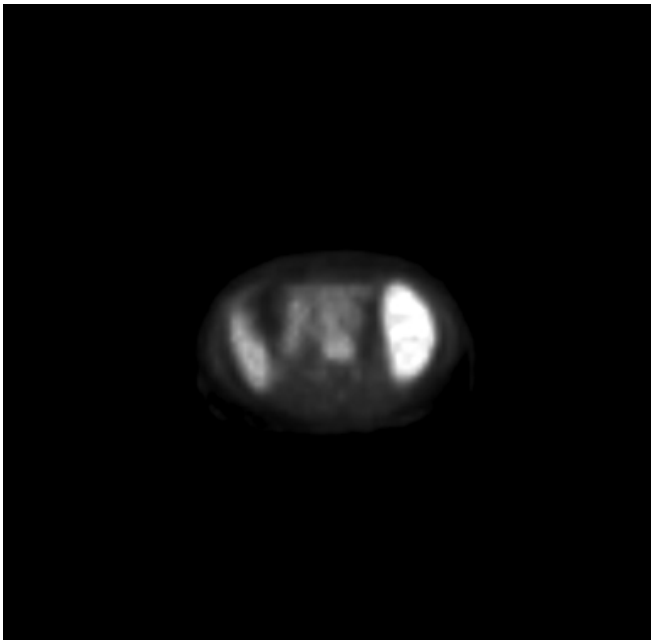

Fig.1: PET-CT showing very marked radioactive uptake in a moderately enlarged spleen. She was injected with 222 MBq (6 mCi) F-18 FDG.

A bone marrow biopsy (BOM) was performed 10 days later after F-18 FDG PET/CT and revealed numerous leishmania amastigotes within macrophages in Giemsa-stained bone marrow smears. After three relapses of VL, she was definitively cured using high-dose liposomal amphotericin B (AmBisome) (total dose, 5500 mg).

Case 2

The patient was a 45-year-old man from Sicily, Italy, and has been Human Immunodeficiency Virus (HIV) positive for the past 15 years. Following his HIV diagnosis, he was started on highly active antiretroviral therapy, but he had discontinued administration for more than three years. His past medical history included insulin-dependent diabetes mellitus. He was referred to the hospital because of discomfort, progressive weight loss, nausea, and episodes of vomiting after meals. Upon physical examination, he was found to be afebrile.

At admission, his T-CD4 lymphocyte count was 9/μL and HIV viral load was 602,531 copies/mL. Initial laboratory studies showed anemia (hemoglobin 11.6 g/dL), leukopenia (white blood cells 3.57 x 10^9/L), thrombocytopenia (platelet count 73 x 10^9/L), moderately increased CRP (5.7 mg/dL), hyperglycemia (fasting blood sugar 218 mg/dL, normal range 70-110 mg/dL), and increased glycated hemoglobin (HbA1c) (HbA1c 8.6% HbTot, normal range 4.0-6.0% HbTot). The results of other routine blood tests were within normal limits.

Ten days after admission, he presented with undulant fever (up to 39°C) and sweats. Serological tests for leishmania, syphilis, HBV, HCV, legionella pneumophila, chlamydia pneumoniae, rickettsia, borrelia burgdorferi, and the Quantiferon®-TB Gold test were all negative. Plasma CMV viral load was 1155 copies/mL. Cultures of blood, bronchoscopic lavage, cerebrospinal fluid (CSF), urine, and stool were negative. PCR of CRF for diagnosis of virus-associated opportunistic diseases of the central nervous system was negative. Parasite tests were all negative. An esophago-gastro-duodenoscopy showed gastroduodenal normal mucosa. Abdomen ultrasound and CT scanning of the abdomen revealed a diffusely enlarged spleen of 15 cm long at the largest axis. F-18 FDG PET/CT images showed diffuse increased FDG uptake in an enlarged spleen and diffuse uptake in the spine [Fig.2]. Bone marrow aspiration revealed leishmania amastigotes confirming the diagnosis.

The treatment was started with liposomal amphotericin B (4 mg/kg/day) for five days, and subsequently once per week for five weeks. Next, he was transferred to a hospital near his home for further management.

Discussion

Visceral leishmaniasis (VL) is a neglected but typically fatal vector-borne protozoan disease of the reticuloendothelial system caused by the protozoan leishmania, which is endemic in South America, India, Northeast Africa, and the Mediterranean basin [1]. The incubation period of leishmania is typically 3–6 months, but can be months or years, and onset of the disease is related

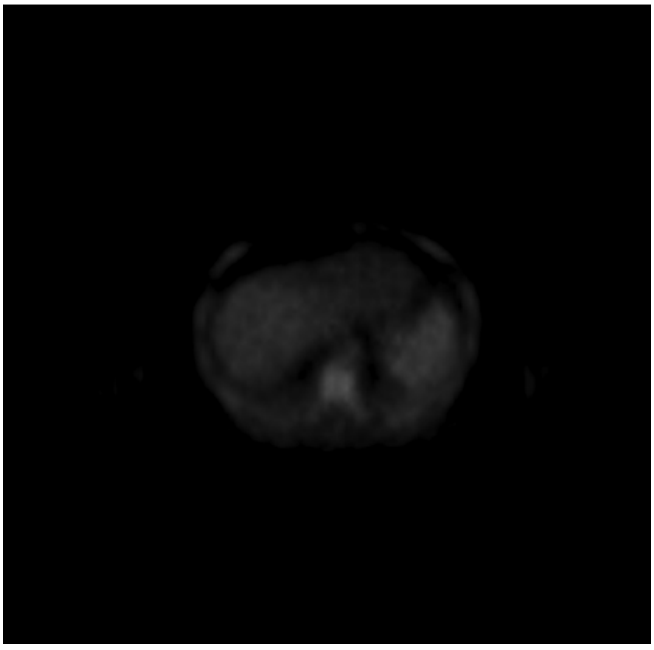

Fig.2: PET-CT showing diffuse uptake in a moderately enlarged spleen; moderate hypermetabolism in all vertebral bodies. He was injected with 296 MBq (8 mCi) F-18 FDG.

to clinical outcome of the asymptomatic infection following changes in the immune system [2].

Although it normally involves immunocompetent individuals in endemic areas, the disease primarily affects immuno-depressed patients with HIV infection, neoplasia, transplants, and long-term steroid or monoclonal antibody treatments, with HIV infection being a major risk factor [3,4]. Clinical signs of VL include fever, splenomegaly, and hepatomegaly caused by reticuloendothelial cell hyperplasia. Other findings include anemia, leucopenia, thrombocytopenia, and hyper-gammaglobulinemia. Moreover, VL can also manifest itself atypically, mostly in patients infected with HIV, transplants, and elderly immunocompetent patients [4-6].

Gold standard diagnosis of the disease relies on the detection of amastigotes within macrophages in an aspirate of the spleen, bone marrow, or lymph nodes after routine hematoxylin and eosin or Giemsa staining [7]. Moreover, the histopathological diagnosis of VL can be established in tissue sections from unusual implantation sites. Other diagnostic tools include isolation of promastigotes by Novy-McNeal-Nicolle (NNN) culture; serological tests to detect antileishmanial antibodies which are 80–100% sensitive in patients with VL and not infected with HIV; PCR testing that is available in specialized institutes, which offers rapid identification of leishmania, is highly sensitive and specific, and on peripheral blood has been recommended as a non-invasive first-line screening test for both immunocompetent and immunocompromised patients [8-10].

The first case presented describes an atypical clinical presentation of VL in a renal transplant patient. Among transplant cases reported in the literature, leishmaniasis is predominantly described with kidney transplantation. Leishmaniasis typically occurs as a late complication after transplantation, with a median delay of 18 months between transplantation and onset of disease [10]. During the previous 6 months, our patient likely experienced a gradual insidious onset of the disease (irregular fever, with transitory fall to subfebrile levels) that was difficult to diagnose. The misdiagnosed VL led to increased leukopenia and contributed to cumulative immunosuppression and secondary infections. At the last admission to our institution, the patient showed a more classic presentation with high fever, asthenia, anemia, leukopenia, moderate splenomegaly, and increased C-reactive protein. Moreover, as symptoms had previously been refractory to broad-spectrum antibiotic therapy, the presence of concomitant opportunistic infections needed to be considered and ruled out.

The second case we described shows an example of atypical presentation of leishmaniasis in an HIV patient. In HIV infection, VL coincides with serious immunosuppression, and most patients have fewer than 200 CD4+/μL. Moreover, in severely immunocompromised hosts (<50CD4+/μL), leishmania amastigotes are more frequently found at atypical locations, less often affecting the spleen and more present in gastrointestinal, pulmonary, or laryngeal regions [11]. The patient presented with symptoms of possible duodenitis. Additionally, if at the beginning there was no fever and only moderate splenomegaly, VL should have been considered since the gastrointestinal location is relatively common in HIV-positive individuals [11]. However, in 90% of patients with acquired immunodeficiency syndrome, the location is duodenal and causes dysphagia, diarrhea, or abdominal pain [12-14].

We should have performed biopsies as esophago-gastro-duodenoscopy endoscopy showed gastroduodenal normal mucosa; previous studies stressed that 45% of biopsies taken in “apparently normal mucosa” at endoscopy in HIV-infected patients with digestive tract

symptoms revealed leishmaniasis infection [12,16]. Interestingly, in both cases marked splenomegaly, hypergammaglobulinemia and serum anti-leishmania antibodies were absent. The diagnosis of VL was achieved by the demonstration of numerous amastigotes in macrophages on bone marrow aspiration.

In both cases presented here, we acquired F-18 FDG PET/CT total body images showing a diffuse increase of reticuloendothelial metabolic activity. F-18 FDG PET/CT may significantly contribute to the recognition of causes of fever of unknown origin, which is difficult to diagnose using conventional modalities. Metabolic total body imaging may be of help in detecting inflammatory foci when clinical evaluation or conventional imaging features cannot identify the source of prominent local symptoms. The role of F-18 FDG-PET has not been extensively studied and the literature search revealed few findings [16,17].

VL systemic pathology with diffuse macrophage activation may determine peculiar PET patterns; unexpected PET/CT localization of focal F-FDG uptake may contribute to draw the clinician's attention to focal illness (atypical locations of leishmania). Cases with problematic interpretation can be solved appropriately by supplementary immunity assessment or with targeted biopsy.

Conclusion

Visceral leishmaniasis can have atypical presentation in immunocompromised patients. F-18 FDG PET may be used as a second-line tool in VL patients with FUO because it may be of help in detecting inflammatory foci.

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