Pre- and post-therapy $^{18}$F-FDG PET/CT of a patient affected by non-HIV multicentric IgG4-related Castleman disease

TO THE EDITOR: Multicentric Castleman disease (MCD) is usually a progressive systemic disease that has a worse prognosis than the unicentric form. The treatment of MCD is based on systemic therapies, such as chemotherapy and monoclonal antibodies. Imaging procedures play an important role in defining the response to treatment. However, no radiologic linchpins exist, due to the lack of evidence.

Castleman disease (CD) is a rare lymphoproliferative disorder first described by Benjamin Castleman, a pathologist at the Massachusetts General Hospital. CD may be unicentric or multicentric. Unicentric CD (UCD), the most common form, is localized and may often be successfully treated with local therapies. MCD is a systemic disease, occurs most commonly in the setting of human immunodeficiency virus (HIV) infection, is usually progressive, and has a worse prognosis. The management of MCD may be carried out by systemic therapies. In the past, the diagnostic imaging of CD has largely been supported by conventional structural imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), as well as by traditional nuclear medicine examinations, such as $^{67}$Gallium scan. In the past two decades, $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET/CT) has become an established imaging tool in oncology. In addition, PET/CT has been generating increasing interest in the areas of infectious diseases [1] and fever of unknown origin [2], as well as with lymphoproliferative disorders such as CD [3, 4] particularly in individuals with HIV infection [5]. Here, we present the case of a patient affected by MCD who underwent PET/CT for staging and restaging of the disease. In the diagnostic setting, PET/CT contributed to the identification of the most appropriate node to select for biopsy, whereas it provided objective information regarding the early response to therapy during the restaging.

CASE

In June 2012, a 50-year-old man presented to our hospital with a pruritic papular skin rash of the lower limbs, xerostomia associated with a 6 kg weight loss, asthenia, weakness of the lower limbs, and dyskinesia. The preliminary laboratory tests showed hypergammaglobulinemia, elevated liver enzymes, and values suggestive of an inflammatory state. Bilateral laterocervical and inguinal lymph nodes were observed on the medical evaluation. Additional tests revealed that the hypergammaglobulinemia was polyclonal with a prevalence of the immunoglobulin G (IgG) cluster (50 g/L) and increases in the light kappa and lambda chains. Moreover, C3 and C4 complement proteins were decreased, whereas beta-2 microglobulin was increased. The serology tests for cryoglobulin, antinuclear antibody (ANA), anti-mitochondrial antibody (AMA), anti-extractable nuclear antigen (ENA), antineutrophil cytoplasmic antibody (ANCA), anti-deoxyribonucleic acid (DNA), lupus anticoagulant (LAC), HIV, Hepatitis B virus (HBV), Salmonella, Brucella, Leishmania, Parvovirus, Strongyloides Stercoralis, Bartonella, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) were negative. The CT scan showed slightly enlarged lymph nodes in the mediastinum, retroperitoneum, and iliac regions. Electromyography (EMG) reported mild sensorimotor neuropathy.

PET/CT scanning (Siemens Biograph PET/CT scanner) was performed from the base of the skull to the upper
thighs nearly one hour after the intravenous administration of 370 MBq of $^{18}$F-FDG and after 6 hours fast. Emission data were acquired for a 3 min per bed position. PET demonstrated the presence of multiple foci of increased radio-pharmaceutical uptake corresponding to adenopathies in the Barety, aortopulmonary, subcarinal, hilar, celiac, para-aortic, right common iliac, and bilateral inguinal spaces (Fig. 1). The PET findings well matched both the diagnoses of a low-grade lymphoma or an inflammatory granulomatous disease. The inguinal lymph node biopsy revealed presence of capsular fibrosis, histiocytosis, plasma cell infiltration, and interfollicular plasmacytosis with large CD30 positive cells. Immunohistochemistry showed the prevalence of mature IgG positive plasma cells with a significant presence of IgG4 positive cells. The pathological diagnosis was the plasma cell variant of MCD.

The patient underwent weekly administration of rituximab 375 mg/m$^2$ for a total of 700 mg/cycle for four cycles. The treatment resulted in an initial gradual reduction in most of the symptoms. PET/CT performed four weeks after the start of the therapy showed disappearance of the radio-pharmaceutical uptake in all the lymph nodes involved (Fig. 2). The patient’s symptoms completely disappeared roughly six weeks after the start of the treatment.

**DISCUSSION**

MCD is a very rare disease, associated with various clinical manifestations and systemic symptoms, sometimes severe enough to be life-threatening. A definite treatment for MCD is still lacking, due to its relative rarity and heterogeneity. On the other hand, as is almost inevitably for rare diseases, the infrequency of CD has hampered wide-ranging clinical studies. Unresectable or widespread diffuse MCD may be treated with external beam radiation therapy, chemotherapy, and steroid therapy. However, strong prognostic features that may be used for the selection of the treatment remain to be identified. Keeping in mind that there are several effective, but no established, standard treatment op-

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Bilateral Parotid MALToma: a sure shot for radiation

TO THE EDITOR: The concept of mucosa-associated lymphoid tissue (MALT) lymphoma was first proposed by Isaacson and Wright in 1983 and is now recognized as a distinct clinical-pathologic disease entity [1]. Between 60% and 70% of patients with MALT lymphomas present with localized (stage I or II) disease involving a non-lymphatic organ. MALT lymphoma arising from the salivary glands is rare; data in the literature are scarce, limited to small series and isolated case reports. Therefore, the characteristics and clinical outcome of this unusual presentation are largely unknown. Extranodal marginal zone lymphoma has a slight female preponderance and usually presents at a localized stage with a low incidence of widespread dissemination, thus requiring local treatment, such as radiation therapy (RT), rather than systemic therapy [2]. In the present case report, we describe a case of MALT lymphoma involving both salivary glands presenting with Sjögren’s syndrome and renal tubular acidosis.

A 42-year-old woman diagnosed with renal tubular acidosis type II, secondary to Fanconi’s syndrome, presented with swelling in the left cheek that was not tender but was progressively increasing in size (Fig. 1). Physical examination revealed palpable bilateral swelling in the region of the angle of the mandible measuring 5×5 cm on the left side and 3×3 cm on the right side. The swelling was firm and fixed to the underlying structures. There were no palpable cervical lymph nodes or any other swelling. Ultrasonography revealed a bulky heterogeneous lesion in the left parotid gland measuring approximately 10 mL, suggesting parotitis or a parotid gland abscess. She was given a course of antibiotics for a week but the swelling did not resolve after the treatment. Fine needle aspiration cytology (FNAC) of the swelling showed numerous small-sized lymphoid cells in varying stages of maturation along with histiocytes, indicating a parotid lymph node.

Contrast enhanced magnetic resonance imaging (MRI) of the face and neck revealed complete replacement of the entire left parotid parenchyma by a large, solid lesion involving both the superficial and deep lobes measuring 5.8×4.2×4.0 cm (Fig. 2). A similar lesion was visualized in the right parotid gland measuring 3×2×2 cm with enlarged cervical lymph nodes, which suggested the diagnosis of lymphoma or Warthin’s tumor.

A trucut biopsy of the left parotid gland swelling was performed, which revealed a moderate amount of sheets of monotonous lymphoid cells with round irregular nuclei, coarsely clumped chromatin and inconspicuous nuclei with eosinophilic cytoplasm with occasional mitotic figures, resembling monocytoid B cells. Immunohistochemically, the cells were positive for CD20 and Bcl-2, weakly positive for Bcl-6 with a Ki-67 proliferative index of 35%, suggestive of MALT lymphoma (Fig. 3).

There was no evidence of lymphadenopathy, extra-nodal spread or bone marrow involvement (stage IE). The serology test for hepatitis B virus & hepatitis C virus (HCV), were negative, and did not have past history suggestive of any autoimmune disorder.

In consideration of the limited stage disease, she was scheduled for localized radiation therapy with three-dimensional conformal radiation therapy. She received a total dose of 36 Gy in 12 fractions over 16 days to the right and left parotid area by utilizing paired tangential fields. She achieved a complete clinical and radiological response. She is being followed-up monthly and has been disease-free.