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LETTER TO THE EDITOR

Potential value of FDG PET-CT in diagnosis and follow-up of TAFRO syndrome

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Dear Editor,

Beginning in 2010, Takai and other Japanese physicians described a group of patients with a common set of clinical features, including thrombocytopenia (T), ascites (A), myelofibrosis (F), renal dysfunction (R), and organomegaly (O), hence TAFRO [1]. The majority of initial case reports were reported from Japan [2–4]. More recently, TAFRO syndrome has been reported in non-Asian patients around the world. TAFRO syndrome is considered to describe a sub-type of idiopathic multicentric Castleman disease (iMCD) that shares common symptoms and laboratory abnormalities due to a cytokine storm [5]. Whereas human herpes virus-8 (HHV-8) drives the hypercytokinemia in a cohort of immunocompromised patients, the etiology of HHV-8-negative MCD is not known, hence idiopathic MCD (iMCD) [6]. Patients present with heterogeneous clinical features and often deadly multiple organ dysfunction. Lack of familiarity with the disease is a major challenge for clinicians often resulting in delay or lack of proper treatment leading to death [7].

Imaging modalities, such as 18F-Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), CT, and ultrasound, are commonly used as part of the work-up in these patients to reach a diagnosis; however, no specific imaging diagnostic criteria have been suggested. Herein, we present the first-reported Hispanic case and a Caucasian case of TAFRO syndrome with iMCD. Both cases received PET-CT as a part of their work-up and evaluation. We discuss findings and potential benefits of PET-CT over CT.

Case 1

A 33-year-old Hispanic male who had initially been diagnosed as atypical hemolytic uremic syndrome (HUS) in an outside facility for which he had received Eculizumab and plasmapheresis. Due to acute renal failure, he had also undergone dialysis. Given no improvement in his condition, he was transferred to our hospital in July 2013. At presentation, he had anasarca, abdominal pain, leukocytosis, anemia, thrombocytopenia, hypoalbuminemia, and multi-organ failure. A bone marrow biopsy had been performed and reported as myelofibrosis. Needle aspiration of an axillary node was performed and was nonspecific. Ultrasound showed moderate splenomegaly and large ascites with a patent portal vein. Non-contrast CT was positive for pericardial effusion, ascites, diffuse subcutaneous edema, hepatosplenomegaly, and generalized lymphadenopathy. Nodal size was overall mildly increased, the largest node measuring 2.1 cm in short axis. Based on CT findings, an initial differential diagnosis of lymphoma versus CLL was entertained. Following 24 days of hospitalization and work-up, patient was discharged in "fair" condition with diagnosis of myeloproliferative neoplasm, most consistent with myelofibrosis. He was advised to follow up with hematology and nephrology.

He was in his usual state of health until approximately 2 months later when he noticed a dark scab on his lower right abdomen which ulcerated. The area of the discoloration and

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wound grew in size. He was re-admitted 10 days later to an outside facility with 7/10 abdominal pain and distension, and discharge and bleeding around the wound. He received a total of 16 units of packed red blood cells and 4 units of pooled platelets before being transferred back to our institution.

During his 45-day hospitalization, his condition got complicated with pneumonia. CT scan during this stay showed small pericardial and pleural effusions, large ascites, marked anasarca, hepatosplenomegaly, and lymphadenopathy. He left the hospital in fair condition and was lost to follow up until March 2015 when he was admitted with daily epistaxis and anasarca, 10/10 abdominal pain, nausea, and vomiting. He stated that he had had several visits to outside hospital emergency room in the meantime and had been hospitalized once, when he received 3 units of packed RBC and was restarted on eculizumab. At the time of presentation, he had already completed 4 weekly doses of eculizumab; however, his symptoms had only worsened. As part of the work-up and to assess lymphadenopathy, a PET-CT was ordered in April 2015, which showed anasarca, extensive cervical, axillary, mediastinal, retroperitoneal, and inguinal lymphadenopathy (Fig. 1). The nodes were only mildly enlarged, the largest measuring 2.4 cm in short axis. Intensity of FDG uptake was variable across the nodes, the highest Max SUV being 2.8 in a cluster of left cervical nodes. Given the constellation of findings and the clinical presentation, a diagnosis of TAFRO syndrome was entertained and biopsy of nodes with higher FDG uptake was recommended. An axillary node was biopsied which showed findings compatible with HV-type Castleman disease. Tests for HHV6, HHV8, and HIV were negative.

The multicentric nature of lymphadenopathy with consistent histopathology and clinical features were suggestive of iMCD with TAFRO syndrome. The patient responded well to IL-6 inhibition with siltuximab, IL-6 levels dropped from 4800 to 19 pg/mL (normal <5), repeat PET-CT showed significant improvement (Fig. 2), and symptoms dramatically improved.

He has had one recurrence since, for which he has received four cycles of R-CVP.

He is currently on sirolimus 2 mg daily, and is doing well.

Case 2

A 36-year-old Caucasian gentleman, originally from Eastern Europe (Poland), who was transferred to our facility on 02/12/13 with diffuse abdominal pain, nausea, chills, night sweats, and weakness. Lab results included platelet count 406×10^3/uL, CRP 200 mg/L, albumin 3.7 g/dL, creatinine 3.6 mg/dL, and gamma-globulin 82 g/dL. On initial CT ascites, pleural effusion, and extensive lymphadenopathy were noted. Biopsy of the liver, omentum, and an inguinal lymph node were obtained, none of which showed specific changes. Extensive work-up for infections and autoimmune diseases was also negative. Over time, renal function deteriorated with creatinine rising to 3.6 mg/dL. A PET-CT was ordered for evaluation of a possible underlying malignancy. It was positive for widespread mildly enlarged nodes, the largest being 1.4 cm in short axis (Fig. 3). Max SUV across the nodes was 6.3. Biopsy of hypermetabolic lymphadenopathy showed changes consistent with iMCD, HV type. No immunoclonality was observed by staining for kappa/lambda light chains. Patient was negative for HIV and HHV-8. The multicentric lymphadenopathy with iMCD histopathology and clinical features indicated that this patient had iMCD with TAFRO syndrome. He was started on IL-6 inhibitor tocilizumab, yet continued to have elevated

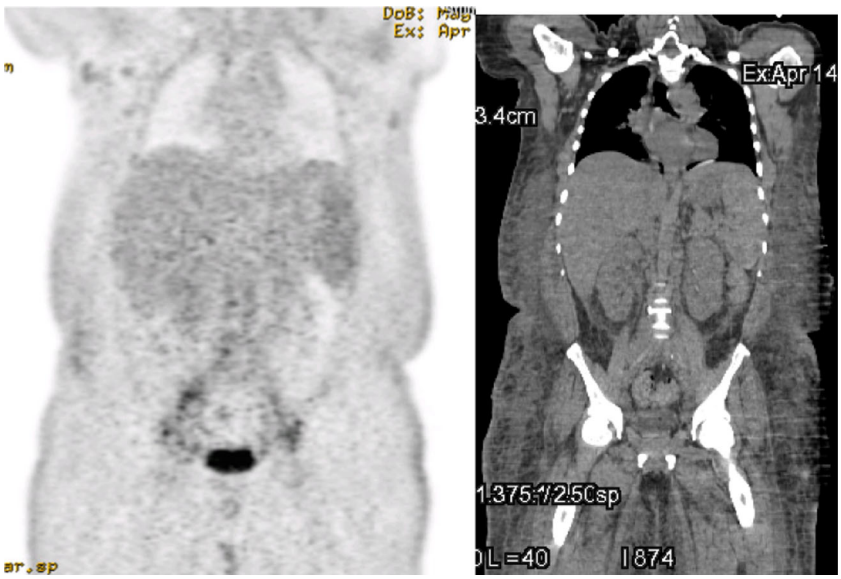

Fig. 1 Coronal image of the initial PET-CT, 4/14/15. Note anasarca with retention of the radiotracer. Mildly increased uptake (max SUV OF 1.9) in bilateral axillary nodes is seen. Biopsy of a hypermetabolic right axillary node helped reach the diagnosis of iMCD with TAFRO syndrome

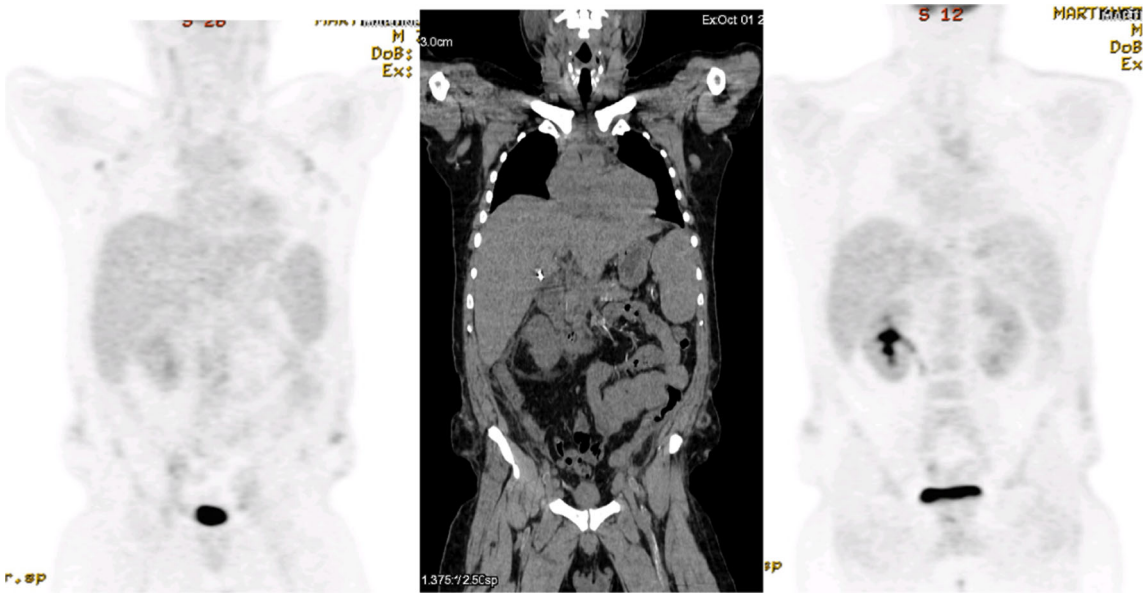

Fig. 2 On the left, first follow-up PET-CT, 5.5 months later, following IL-6 inhibition. Ascites and anasarca have greatly improved, resulting in decrease of weight from 117 kg at presentation to 81 kg. There is still residual disease. Note right axillary lymph node uptake of FDG. The coronal PET on the right was obtained 5 months later and shows resolution of FDG avid lymph nodes

inflammatory markers and progression of lymphadenopathy on restaging CT scan of chest and abdomen. At this time, cytoreductive chemotherapy was deemed appropriate. Patient showed significant improvement after 6 cycles of DA-EPOCH + R. He is currently on maintenance dose of siltuximab every 3 weeks and rituximab every 9 weeks and is stable.

Discussion

No specific imaging modality has been previously recommended in the work-up of patients with suspected MCD or TAFRO syndrome. Ultrasound shows nonspecific splenomegaly, pleural and pericardial effusion, ascites, and lymphadenopathy. CT can help to differentiate UCD versus MCD,

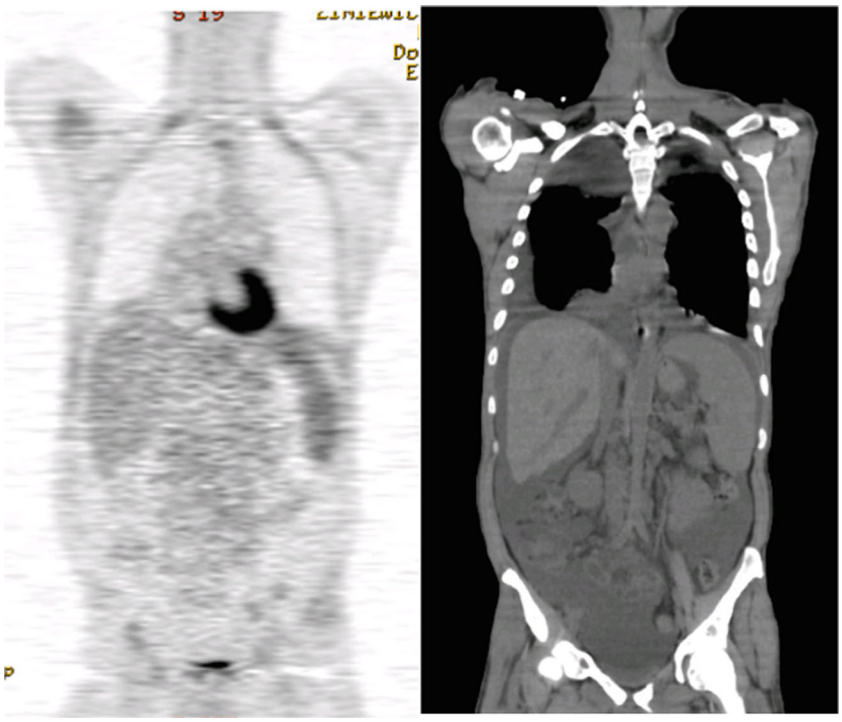

Fig. 3 Initial PET-CT dated 3/4/2013 showing ascites, splenomegaly, and right pleural effusion. Only mild FDG uptake (SUV OF 2.1) was seen in non-enlarged nodes

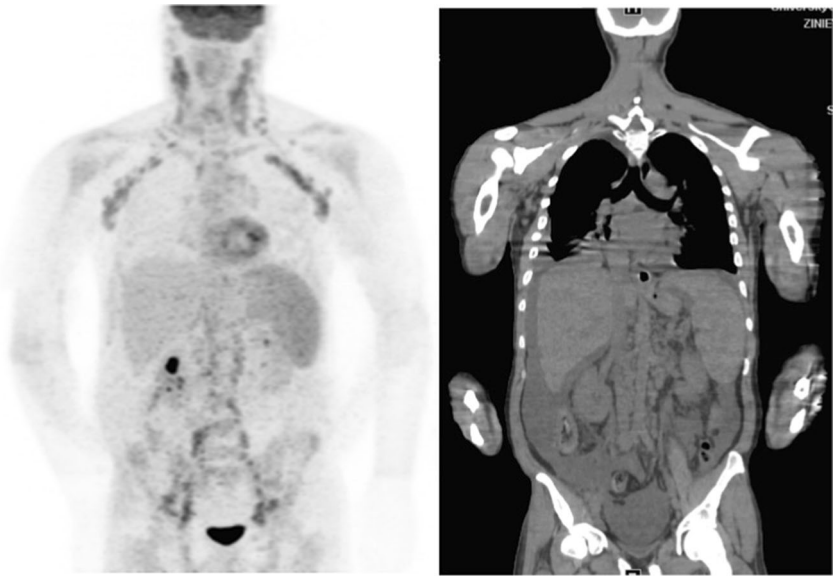

Fig. 4 Follow-up on 6/25/2013 shows extensive lymphadenopathy with increased FDG uptake. Ascites, pleural effusion, and splenomegaly are unchanged. Diffusely increased splenic uptake is likely due to anemia. Biopsy of a hypermetabolic right axillary node showed HV type iMCD. No follow-up PET-CT has been ordered

but findings are nonspecific as well. Moreover, due to universally poor renal function, iodinated contrast cannot be administered. FDG PET-CT, although not specific, shows the main findings of splenomegaly, ascites, pleural and pericardial effusion, and lymphadenopathy (Fig. 4). Determining highest metabolic activity in enlarged nodes potentially helps with identification of the appropriate target for biopsy, which will lead to earlier diagnosis. We used a combination of histopathological findings, clinical manifestations, laboratory data, and imaging to diagnose both cases with iMCD and TAFRO syndrome. Case 1 is an important example where the initially biopsied lymph node, selected based on size and ease of access, was not able to confer an iMCD diagnosis. The second biopsied node, which was selected based on FDG avidity, was able to reveal iMCD. Expedient diagnosis is essential because untreated, iMCD results in death. Patients can respond well, sometimes dramatically, to appropriate treatments. However, a large number of patients will not respond to the only FDA-approved treatment for iMCD [7]. We suggest use of PET-CT to assess response to therapy and to decide whether or not additional therapies are needed. Furthermore, recurrences are common in iMCD and TAFRO, and malignancies are diagnosed at an increased rate [7], so PET-CT could also be used for surveillance against relapse and malignancy. Though we expect survival to improve with the advent of anti-IL-6 therapies, utilization of all available tools, including PET-CT, is essential as approximately 35% of iMCD patients die within 5 years of diagnosis [8].

Compliance with ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Conflict of interest Dr. Fajgenbaum has received a research grant/funding from Janssen pharmaceuticals. The authors Drs. Behnia, Elojeimy, and Matesan declare that they have no conflict of interest.

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