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TAFRO Syndrome on ^{18}F-FDG-PET/CT: An Appealing Diagnostic Tool

Ayoub Jaafari [1,*], Nadim Taheri [2], Sohaib Mansour [3], Saif-Eddine El Bouhali [4] and Rachid Attou [4]

[1] Department of Nuclear medicine, H.U.B Hospital, Brussel, Belgium; Ayoub.jaafari@ulb.be
[2] Department of Rheumatology, C.H.U Brugmann, Brussel, Belgium; nadim.taheri@gmail.com
[3] Department of Internal medicine, C.H.U Brugmann, Brussel, Belgium; sohaib.mansour@chu-brugmann.be
[4] Department of Intensive Care Unit, C.H.U Brugmann, Brussel, Belgium; saif.elbouhali@gmail.com; rachid.attou@chu-brugmann.be
* Correspondence: Ayoub.jaafari@ulb.be

Abstract: TAFRO syndrome (TS) is a rare variant of idiopathic multicentric Castleman's disease (iMCD) characterized by a confluence of symptoms: thrombocytopenia (T), anasarca (A), fever (F), reticulin myelofibrosis (R), and organomegaly (O). First described in Japan in 2010, the pathogenesis of the disease remains unclear. Due to its heterogeneous presentation and potential life-threatening delays in diagnosis, precise diagnosis is essential. According to the literature, no specific imaging modality has been recommended for the work-up of patients with suspected TS. Here, we report a case of TS and its management using 18F-FDG-PET/CT imaging as an attractive complementary diagnostic tool.

Keywords: TAFRO syndrome; multicentric Castleman disease; iMCD; 18F-FDG-PET/CT

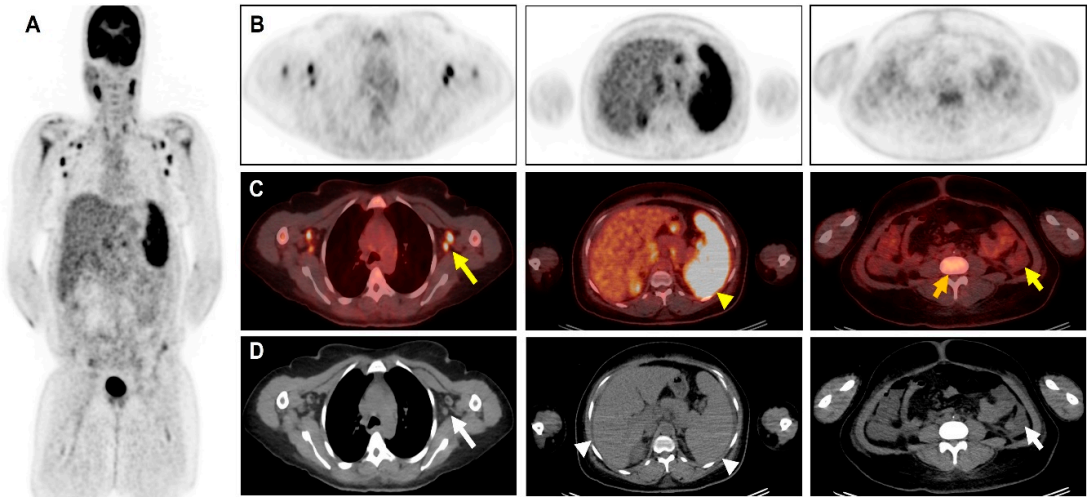

Figure 1. ^{18}F-FDG-PET/CT of the patient: (**A**) Maximum Intensity Projection image (MIP) of the chest, upper and lower abdomen respectively (left to the right), (**B**) PET images, (**C**) fused PET/CT images, (**D**) CT-images. A 44-year-old Mauritanian woman without significative pre-existing medical and recent traveling history presented with tiredness, and febrile non-bloody diarrhoea for 3 weeks. No other complaints. Physical examination revealed left cervical adenopathy, anasarca, and mild splenomegaly. Laboratory tests showed non-regenerative anaemia (5.5g/L), hypoplakettosis (23,000/µL), elevated serum concentration of C-reactive protein (121mg/dL), direct Coombs positive without acute haemolysis. Extensive work-up for infections (viral, bacterial, and fungi) and autoimmune diseases were also negatives. A thoracoabdominal scanner was realized and showed slightly enlarged cervicothoracic adenopathy (large white arrow), hepatosplenomegaly (head white

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arrow), and ascites (small white arrow). The bone marrow was initially explored via a sternal marrow puncture showing a dry tap, with inconclusive results (Figure 2A). An ensuing bone marrow biopsy was performed and exposed reticulin myelofibrosis, and numerous megakaryocytes bordering dilated sinusoids (Figure 2B). Metabolic imaging with ^{18}F-FDG-PET/CT was achieved to assess underlying causes and identify the most active lymph node for biopsy. MIP (**A**) and fused images show increased and diffuse FDG uptake in the cervicothoracic lymph nodes (large yellow arrow), spleen (yellow head arrow) ascites (small yellow arrow), and vertebral medulla (orange arrow). Lymph node biopsy revealed rare follicles, atrophy of germinal centers, proliferation, hyperplasia of blood vessels, and plasma cells suggestive of Castleman's disease (Figure 2C-D). Tests for herpes human virus-6 (HHV-6), HHV-8, and human immunodeficiency virus (HIV) were negative. These results, alongside the biological, CT-images and ^{18}F-FDG PET/CT findings, suggest a diagnosis of TAFRO syndrome (TS). She was successfully treated with corticosteroid and immunotherapy (Interleukin-6 inhibitors) with a clinical and biological improvement. First described by Takai et al. in 2010, TAFRO syndrome (TS) is a rare inflammatory lymphoproliferative disease characterized by a highly heterogeneous clinical presentation and potential life-threatening implications [1]. As of now, the exact pathogenesis remains unclear, and it is regarded as a distinct clinicopathological variant of idiopathic multicentric Castleman's disease (iMCD) [2–4]. While the majority of reported TS cases have originated in Japan, the syndrome has increasingly been recognized in non-Asian patients worldwide [5]. According to existing literature, no specific imaging modality has been universally recommended for the evaluation of suspected iMCD or TS cases. Typically, computerized tomography (CT-scan) reveals nonspecific multiple lymphadenopathies that may indicate other differential diagnoses such as lymphoproliferative disorders or granulomatosis [6]. Consequently, determining the highest metabolic activity using 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography combined with computed tomography (18F-FDG-PET/CT) in enlarged lymph nodes potentially facilitates the identification of suitable biopsy targets, leading to earlier diagnosis. Moreover, certain disease features like myelofibrosis are challenging to detect on CT imaging alone, but 18F-FDG-PET/CT can demonstrate diffuse uptake in the marrow (orange arrow), capturing key findings of TS [7,8]. Additionally, uptake in hepatosplenomegaly provides supplementary information by reflecting sites of secondary hematopoiesis, aiding in diagnosis [7]. Identifying the cause of ascites poses a challenge due to its association with various pathologies, ranging from non-malignant conditions like chronic liver disease and heart failure to malignant neoplasms [9]. In our case, observing hypermetabolism in ascites is particularly intriguing. While ascites are generally present in all TS cases, different studies have described varying sensitivity and specificity values of 18F-FDG-PET/CT for its characterization [10,11]. Furthermore, combining metabolic imaging with tumor biomarkers such as interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) levels in effusions and serum can provide valuable insights for investigating TS [12–14]. To date, only a few TS cases have been reported, and the utilization of 18F-FDG-PET/CT as a complementary diagnostic tool remains limited. Given the heterogeneous presentation of the disease and potential life-threatening delays in diagnosis, accurate diagnosis is crucial to initiate appropriate treatment. In conclusion, 18F-FDG-PET/CT holds promise as a complementary tool for providing characteristic findings of TS. We suggest considering the diagnosis when a combination of PET/CT results, such as thrombocytopenia, fever of unknown origin, diffuse FDG uptake in the bone marrow, hepatosplenomegaly with elevated splenic FDG uptake, and lymphadenopathy with increased FDG uptake, is observed in a patient.

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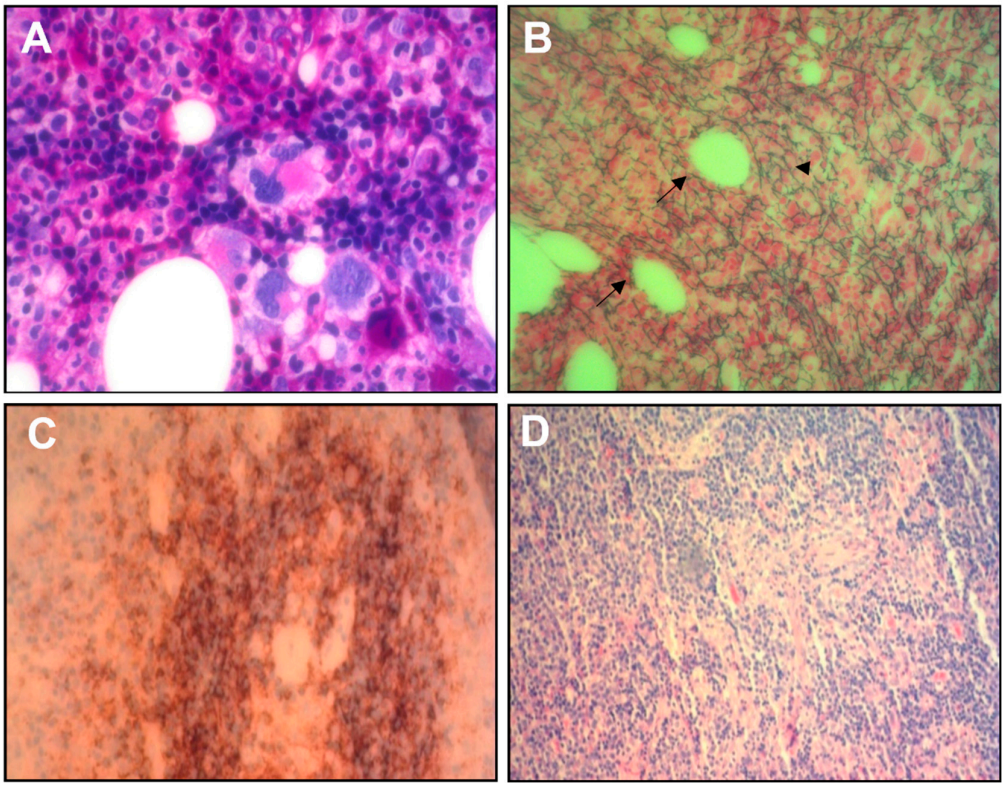

Figure 2. (**A**) 100x hematoxylin- and eosin-stain of the marrow puncture showing a "dry tap" characterized by slightly hypercellular marrow with increased megakaryocytes. (**B**) Reticulin stain of bone marrow biopsy showed reticulin myelofibrosis (head arrow, green fibers), and numerous megakaryocytes bordering dilated sinusoids (arrow). Lymph node biopsy showed rare follicles, atrophy of germinal centers (**C**), proliferation, and hyperplasia of blood vessels (**D**).

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Institutional Review Board Statement: This study did not receive ethical review and approval due to the nature of the research (case report).

Informed Consent Statement: Written informed consent was obtained from the patient. The consent form was obtained on 01.03.2024.

Data Availability Statement: The data used and analyzed in this study are available from the corresponding author on reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

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