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The dilemma of diagnosing fever of unknown origin: large arteries vasculitis revealed by ^{18}F-FDG PET/CT imaging. A case report

A. DE GIORGI, F. FABBIAN, M. PALA, V. BAGNARI*, R. TISEO, C. MOLINO, M.R. TRAPASSI, A. BOCCAFOGLI, F. PORTALUPPI, N. PRANDINI**, L. FEGGI**, R. MANFREDINI

Institute of Medical Clinic and Institute of Rheumatology; Department of Nuclear Medicine**, University of Ferrara (Italy)*

Abstract. – Fever of unknown origin (FUO) is an uncommon disease, and its underlying etiology may include a number causes, i.e., infections, malignancies, autoimmune conditions. Diagnosis is often a difficult task, and usually physician spend time and money in order to define the etiology of FUO. We report a case of patient who presented with FUO and headache, and positron emission tomography (PET) with 2-deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F-FDG) allowed to reveal the presence of a large vessel vasculitis. ^{18}F-FDG PET may represent an useful tool in patients with FUO, since it can early depict an hypermetabolic activity due to inflammation and so help to achieve a final diagnosis in some cases of FUO.

Key Words:

Fever of unknown origin, Diagnosis, Positron emission tomography.

Introduction

Fever of unknown origin (FUO) is an uncommon disease, identified since 1961, and defined as fever ≥38.3°C of unknown origin, persisting for more than 3 weeks, without a clear cause[1]. In 1991, Durack et al[2] distinguished FUO in 4 difference types: classical, nosocomial, neutropenic and HIV-associated. The etiology of FUO includes infections, malignancies, autoimmune conditions, and miscellaneous. Infectious diseases represent the most important causes of FUO (13-43%), especially regarding the upper respiratory tract and the lung and due to bacteria, mycobacteria, virus or fungi[3]. Autoimmune or collagen vascular diseases, and neoplasms represent also important causes of FUO (54% of cases)[4], but even in Western countries about 25% of FUO cases remain undiagnosed[5].

In 2005, Wagner et al[6] proposed a diagnostic work-up that included evaluation of history, physical examination, duplex ultrasonography of the arteries, biopsy of temporal artery, magnetic resonance imaging (MRI) and [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET).

We here report a case of patient who presented with FUO and headache, in whom ^{18}F-FDG PET/CT allowed to reveal the presence of a large vessel vasculitis.

Case Report

A 62 year-old woman was admitted in our Department with complaints of fever (max 38°C), frontal-orbital headache, visual disturbance, and polyarthralgias. One year before, she underwent surgical percutanous correction of oval foramen. Her home medication list included anticoagulants, antibiotics, and non-steroidal anti-inflammatory drugs (NSAID).

Physical examination did not show any cardiac, pulmonary, or abdominal abnormalities. Adenopathies were absent. Routine laboratory tests revealed high platelet count (642,000/μL), prolonged coagulation time (INR=2.7) and high fibrinogen levels (784 mg/dl), associated to hypoalbuminemia (27.5 g/dl). Erythrocyte sedimentation rate (ESR) was 74 mm/h, and C-reactive protein (CRP) 18 mg/dl (normal reference value <0.5 mg/dl). Blood, urine and oropharynx

Corresponding Author: Roberto Manfredini, MD; e-mail: roberto.manfredini@unife.it

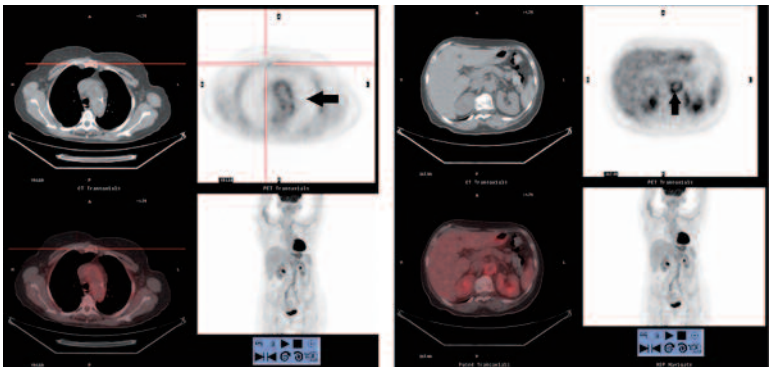

Figure 1. Uptake of FDG-PET in the aortic arch and in the thoraco-abdominal aorta.

tampon cultures were negative, and the other laboratory examinations, including antinuclear antibobies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-nDNA antibodies (anti-nDNA), anti-myeloperoxidase and anti proteinase 3-anti-neutrophil cytoplasmic antibodies (ANCA-MPO – ANCA-PR3), cardiolipin-IgG and antiphospholipid antibodies, carcinoembryonic antigen (CEA), Ca125, Ca15.3, Ca19.9, α-fetoprotein, complement (C3-C4) levels, and angiotensin-converting enzyme (ACE) were normal. Tuberculosis was excluded by skin testing with purified protein derivative (PPD) and quanti-FERON-TB. Test for hepatitis and other infections, such as HIV, *Borrelia burgdorferi, Bordetella, Cytomegalovirus, Salmonella typhi, Listeria monocytogenes, Clamidia thracomatis* were also negative. The temporal artery biopsy was negative for inflammatory lesions.

Imaging techniques, such as chest radiography, abdominal ultrasonography, transthoracic and transesophageal echocardiography, cerebral and abdominal computed tomography (CT) were negative. Therefore, ^{18}F-FDG PET/CT was carried out, and it demonstrated a diffuse FDG uptake by thoracic and abdominal aorta, epiaortic vessels, axillary and iliac arteries bilaterally (Figure 1). Thus, diagnosis of large arteries vasculitis was done, and treatment with intravenous methylprednisolone (1 mg/kg) was started.

Body temperature progressively normalized. The magnetic resonance imaging (MRI) identified two parietal thickenings on the left side of the aortich arch and descending aorta at the thoraco-abdominal junction (maximum thickness: 2.5 mm), in the absence of enhancement after gadolinium administration (Figure 2).

Discussion

According to the American College of Rheumatology[7], our patient presented the classical clinical picture of giant cell arteritis (GCA). However, the diagnostic pathway was difficult since it required a step-by-step search for possi-

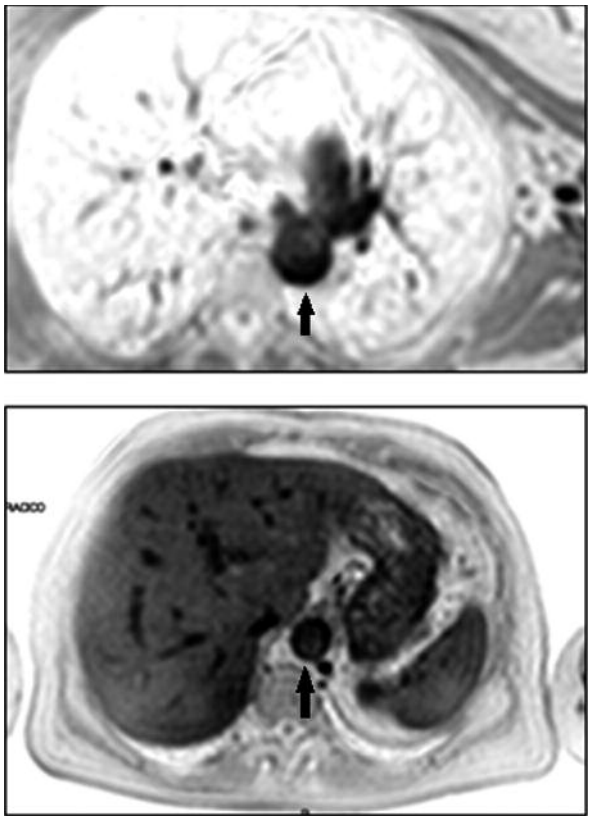

Figure 2. MRI imaging: thickening on left side of the aortic arch and descending aorta at the thoraco-abdominal junction.

ble clinical causes. First, we excluded infectious diseases, that represent a likely cause of FUO[8]. Although our patient presented only a CRP peak of 18 mg/dl, this is much less than the accepted cut-off for infectious diseases[8]. Again, autoimmune diseases should be considered as possible cause, since they occur in 17% of patients, and temporal arteritis is the most important cause of FUO in the elderly, although temporal artery biopsy is negative in 42-57% of cases[9].

The use of nuclear medicine investigation for FUO diagnosis was suggested by Blockmans et al[10], and recent studies showed that PET has contributed to the diagnosis in 35-55% of cases[11-12]. PET is a imaging technique based on the uptake of FDG in the region with major metabolism of glucose in order to quantify the activity of inflammation. The diagnostic power of FDG-PET is increased by the computer tomography (CT), since FDG-PET/CT combines the metabolic informations acquired by PET with the morphological imaging. Thus, it increases its sensibility, with an overall helpfulness for final diagnosis of 57% compared to 39% of PET alone[12]. For this reason, allowing an accurate anatomical localization of the lesions, it is also particularly valuable for applications in oncology[13].

Moreover, PET is more specific than CT, MRI or ultrasound imaging since it provides information on the entire body and allows also the identification of inflammatory from non-inflammatory lesions. Blockmans et al[10] compared the utility of PET with gallium scintigraphy, and concluded that FGD-PET was the best technique for the diagnosis of FUO. In fact, it was found to be clinically helpful in at least 33% cases of FUO, with the exception of cases with normal ESR and CRP[14]. However, the utility of PET in the diagnosis of FUO secondary to vasculitis is reduced in the case of small calibre vessels vasculitis, since a false negativity is possible in arteries smaller than 4 mm[15]. MRI may increase diagnostic power of FDG-PET, since it highlights the presence of parietal thickening, and in patients with FUO the chance of reaching the diagnosis was increased from 7% to 42%[6]. The utility of MRI is particulary important in elderly patients, in whom the FDG used for PET technique imaging can be uptaken by the atherosclerosis lesion or lamina muscolaris[16]. In these patients, MRI provides anatomical informations of specific part of the body, and can detect the atherosclerosis lesions. Moreover, MRI can be used in the follow-up of large artery vasculitis during the immunosuppressive therapy for evaluation the inflammatory process and vascular thickening[10].

In our patient the clinical symptoms were reduced by the use of corticosteroid therapy, that is the adequate therapy in 60% of FUO[17]. In fact, the long-term corticosteroid therapy is the basic approach to reduce the inflammation in affected vessel[18], and the utility of this therapy can be confirmed by the PET. In fact, Webb et al[19] observed a reduction of FGD uptake after corticosteroid therapy in patients with Takayasu arteritis.

In conclusion, FDG-PET may represent a very useful tool in patients with FUO, expecially in the early phase of inflammatory disease, due to its possibility to detect hypermetabolic and inflammatory activity. Although this kind of examination is highly expensive, in selected cases it could allow to speed up the final diagnosis, reducing the hospital length of stay and related economic burden.

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