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PET/CT for Diagnosis and Management of Large-Vessel Vasculitis

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Abstract

Purpose of Review This review aims to discuss the use of fluorodeoxyglucose (FDG) positron emission tomography (PET/CT) for diagnosis and management of patients with large-vessel vasculitis (LVV).

Recent Findings Incidence of LVV is likely underestimated, in part due to its non-specific symptoms. Nevertheless, early diagnosis of LVV is essential to initiate timely therapy in order to prevent vascular complications, such as stenoses and aneurysms. FDG PET/CT imaging has the ability to detect LVV during the acute phase, prior to edema and other vascular structural changes, with its high sensitivity for inflammatory activity. FDG PET/CT was shown to be a powerful prognostic marker by allowing identification of patients at risk of vascular complications. Additionally, preliminary data support the use of FDG PET/CT to follow therapy efficacy.

Summary FDG PET/CT allows early detection of inflammation, before morphological and irreversible vascular changes can be observed, allowing prompt diagnosis and treatment of LVV.

Keywords Positron emission tomography · Fluorodeoxyglucose · Large-vessel vasculitis · Giant cell arteritis (GCA) · Takayasu's arteritis · FDG

Introduction

Primary vasculitides are a group of relatively rare inflammatory diseases affecting the blood vessels. They are categorized based on the caliber of the affected vessels as small-, medium-, and large-artery vasculitis [1]. Large-vessel vasculitis (LVV) affects the aorta and its main branches and classically is divided into two entities: Takayasu's arteritis (TAK) and giant cell arteritis (GCA).

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Over the past few years, positron emission tomography (PET) imaging with the radiolabeled tracer ^{18}F-fluorodeoxyglucose (FDG), a glucose analogue, has emerged as a promising modality in the evaluation of patients with LVV. The ability of FDG-PET to detect early vascular inflammation, even before arterial narrowing occurs, and to monitor response to therapy contributed to the marked interest invested in this modality for LVV. This review will first present an overview of the pathophysiology and traditional investigation of LVV. Then, the technical aspects of FDG-PET imaging for LVV will be briefly discussed, followed by a review of its diagnostic performances, prognostic value, and role in evaluation of response to therapy.

Large-Vessel Vasculitis

Takayasu's Arteritis

TAK is a chronic idiopathic granulomatous autoimmune panarteritis affecting patients younger than 50 years old. TAK is rare, with an estimated incidence of 1 case per million person per year, typically affects women in childbearing age, and has a higher incidence in the Asian population [2]. In

TAK, the ascending aorta as well as the carotid, subclavian, renal, and splanchnic arteries are more frequently involved. Coronary artery involvement is seen in 15 to 25% of cases [3]. The disease is characterized by intimal hyperplasia, which leads to stenosis or occlusion in over 90% of cases while aneurysms are seen in roughly 25% of cases [4].

Two phases of TAK arteritis have been described: the acute (systemic) and chronic (occlusive) phases. The acute phase is characterized by constitutional symptoms associated with active vascular inflammation. In the chronic phase, vascular morphological abnormalities cause signs and symptoms, such as absent or weak peripheral pulses, claudication, and blood pressure discordance between the arms [4]. The diagnostic of TAK is usually delayed because of the non-specific presentation and low clinical suspicion, especially during the acute phase. Most frequently, the diagnosis is established during the chronic phase, once irreversible vascular damage has already occurred.

Giant Cell Arteritis

GCA is a chronic idiopathic granulomatous autoimmune vasculitis affecting medium and large arteries. It is the most frequent cause of LVV with a prevalence estimated between 1 and 33 cases/100,000 persons, depending on geographical location and ethnicity [5]. As opposed to TAK, GCA affects patients over the age of 50. Large-vessel GCA (LV-GCA) is part of the GCA clinical syndrome, which comprises a spectrum of overlapping phenotypes, including cranial GCA, LV-GCA, and polymyalgia rheumatica (PMR) [6]. Cranial GCA corresponds to the classical description of GCA, often referred to as temporal arteritis or Horton's disease, in which patients present with headaches, sudden changes in vision, and jaw claudication. At the other end of the spectrum, PMR is characterized by peripheral musculoskeletal symptoms, such as arthritis involving the neck, shoulders, hips, and knees; morning stiffness; pitting edema; and tenosynovitis. LV-GCA tends to affect younger patients compared with cranial GCA and PMR, with a marked female predominance [7]. In all three phenotypes, acute phase reactants and constitutional symptoms are often present. Importantly, the phenotypes are frequently overlapping, and large-vessel inflammation can develop in patients with apparently isolated PMR or cranial GCA [6–8]. In these patients, the prevalence of vascular complications is relatively high, emphasizing the need for large-vessel inflammation screening, especially in PMR [9].

Interestingly, reports dating back to the 1970s suggest that TAK, GCA, and PMR are different manifestations of the same disease [10]. This hypothesis is based on several similarities between those diseases. First, GCA/PMR and TAK have overlapping histopathological features, making it impossible to distinguish the two on tissue sampling alone [11]. In fact, differentiation between GCA/PMR and TAK usually relies on patient's age. Second, all three conditions present with similar clinical manifestation and both show drastic response to steroid therapy. Finally, one condition might precede the other. Hence, the investigations of patients with suspicion of TAK and GCA are very similar.

Investigation

Establishing the diagnosis of LVV is challenging for several reasons. The symptoms, especially in the early phase of the disease, are nonspecific. Additionally, because LVV is relatively rare, the diagnosis is often not suspected at presentation. Biomarkers, such as acute phase reactants (ESR and CRP), are neither sensitive nor specific and are not helpful to confirm or exclude the presence of LVV [12]. Various clinical criteria have been proposed to establish the diagnosis of GCA and TAK, with the 1990 American College of Rheumatology (ACR) criteria being the most frequently used [13, 14]. Such criteria are certainly useful in clinical trials to recruit homogeneous cohorts of patients but have major limitations when applied to the clinical practice. For instance, five out of six ARC criteria for TAK refer to signs or symptoms relating to arterial stenosis. Early diagnosis of vascular inflammation is of uttermost importance to initiate treatment promptly in the acute phase of disease and to reduce the risk of vascular complications [15]. When morphological changes are observed, the disease is already at a late stage and irreversible vascular damage occurred. Therefore, these criteria cannot correctly identify patients presenting in the acute phase of the disease. Similarly, ARC criteria for GCA are also flawed as they are heavily based on temporal artery involvement. Because temporal arteries are spared in approximately 40% of LV-GCA patients, these criteria are ineffective at detecting the disease in a large number of patients with LV-GCA [16].

Arterial biopsy is not frequently performed due to its invasive nature and associated complications. In GCA, temporal biopsy is no longer considered the diagnostic gold standard [17]. Indeed, temporal biopsies sample only a small portion of the artery, whereas the disease is often patchy, if present at all, in the sampled artery. Additionally, the availability of arterial biopsy is limited compared to most imaging modalities [18]. Catheter-based angiography has been considered the gold standard for the diagnosis of vasculitis for a long time. However, angiography does not allow evaluation of the vascular wall morphology, is not always readily available, and is associated with risk such as iatrogenic embolization and dissection. More importantly, vascular abnormalities occur late in the disease process and reflect irreversible changes associated with long-standing inflammation. With the increased utilization of non-invasive imaging modalities, angiography is now rarely performed unless vascular interventions are considered [19]. In fact, for patients with high clinical suspicion of LVV, a positive imaging result can confirm the diagnosis while for patients with low clinical suspicion, a negative imaging result makes the diagnosis unlikely [18]. Different imaging modalities have been used for the diagnosis of LVV, and each has their strengths and weaknesses (Table 1). Computed tomography angiography (CTA) is widely available and can identify vascular morphological abnormalities, such as stenosis, and can also show arterial wall thickening and contrast enhancement [7, 20]. Ultrasonography and magnetic resonance angiography (MRA) can also demonstrate morphological abnormalities of the artery with the added benefit of avoiding iodinated contrast and ionizing radiation. Additionally, MRA can detect vascular wall edema and thickening with dedicated sequences and gadolinium enhancement [21]. Unfortunately, abnormalities observed on MRI can persist even after successful therapy and resolution of the vascular inflammation [22]. As opposed to all other imaging modalities which rely on morphological changes, molecular imaging with FDG positron emission tomography/computed tomography (PET/CT) has the unique ability to detect vascular inflammation early in the disease process, prior to morphological alterations [23]. Because of this, PET/CT can play several key roles in diagnosis and management of LVV, including accurate diagnosis and monitoring of response to therapy (Table 2) [24].

Table 2 Potential role of FDG PET/CT imaging in large-vessel vasculitis

Potential roles of FDG PET/CT in vasculitis
Initial diagnosis
Guide biopsy
Evaluation of disease extent
Assessment of therapy efficacy and modulation of therapy
Exclusion of other causes of systemic symptoms
Surrogate end point in clinical trials

FDG PET/CT

FDG is a radioactive sugar labeled with the positron emitting isotope fluorine-18. FDG is extensively used in oncology for diagnosis and staging of numerous cancers. Additionally, it is used in a wide range of infectious and inflammatory disorders [23, 25–27]. As a glucose analogue, FDG crosses cell membranes with glucose transporter proteins (GLUT) before it is phosphorylated by glucose-6-phosphatase. Once phosphorylated, the FDG does not undergo further metabolism through the glycolysis pathway, as would glucose, and therefore accumulates in the cells [28]. FDG accumulation in tissue is proportional to glycolytic activity which can be associated with upregulation of GLUT, increased hexokinase activity, and reduced glucose-6-phosphatase activity. In inflammation, FDG accumulates mainly in macrophages due to their high glycolytic activity [29]. On histopathology, both GCA and TAK are characterized by activated macrophage infiltration [11], which accounts for the accumulation of FDG in the inflamed vascular wall. FDG PET/CT is a marker of active inflammation, as opposed to most imaging modalities, which show the chronic morphological changes secondary to inflammation. Indeed, FDG accumulates in various inflammatory diseases before morphological abnormalities can be identified on CT and MRI [30, 31].

Table 1 Strengths and weaknesses of the imaging modalities used for the diagnosis of large-vessel vasculitis

Modality	Strengths	Weaknesses
Catheter angiography	Percutaneous intervention possible	Invasive with risk of complications Ionizing radiation Provides no information about vascular wall morphology
Ultrasonography	Widely available No ionizing radiation Ability to assess the temporal artery	Suboptimal assessment of extracranial arteries Operator dependent
CTA	Widely available Enable assessment of vascular wall morphology	Inability to assess intracranial arteries Ionizing radiation Adverse effects of contrast agents Not suitable to monitor response to therapy
MRA	Ability to assess cranial and extracranial arteries No ionizing radiation High standardization of acquisition	Restricted availability Cost Adverse effects of contrast agents Not suitable to monitor response to therapy
PET	No contrast needed Ability to identify other causes of systemic symptoms Ability to monitor response to therapy	Restricted availability Cost Inability to assess cranial arteries Small patient radiation dose

Imaging Protocol

A fasting period of at least 6 h is necessary prior to radiotracer injection. Vigorous physical activity should be avoided during the 24 h preceding the test to avoid significant skeletal muscle uptake. Also, to minimize brown fat uptake, injection is performed in a temperature-controlled room, and warm blankets can be provided. Imaging is performed 60 to 120 min post-FDG injection. At time of injection, a serum glucose level of 7 mmol/L or less is preferable [32••]. Higher serum glucose levels can result in greater blood pool activity, limiting the ability to visualize the vascular wall uptake [33]. In the presence of significant blood pool activity, delayed images can be acquired 120 to 180 min post-injection and better visualize of the vessel wall [34•].

Whole-body PET/CT acquisition extending from the head to the knees is recommended. As there is significant overlap between GCA and PMR, identification of inflamed joints can be contributory to the diagnosis. Furthermore, whole-body imaging allows for identification of other pathology that could explain the symptoms of patients. A detailed description of the recommended imaging protocol has been proposed in a recent joint procedural recommendation paper (see [32••]). In patients investigated for fever of unknown origin (FUO) or if myocardial inflammation or endocarditis is suspected, a myocardial suppression protocol should be used to minimize physiological myocardial uptake. If coronary vasculitis is suspected, in addition to the myocardial suppression preparation, an ECG-gated acquisition should be obtained to minimize the blurring of the coronary vessels due to cardiac motion [3].

Interpretation Criteria

On FDG PET/CT, LVV often presents as diffuse increased uptake affecting the aorta and its branches (Fig. 1). Several interpretation criteria have been described to assess the presence of LVV. Some rely on visual interpretation while others use semi-quantitative or quantitative methods. Quantitative methods were shown to be more specific but less sensitive compared with semi-quantitative approaches [17]. Visual interpretation comparing vascular to liver uptake has been shown to have better diagnostic accuracy compared with various quantitative metrics [35•, 36••]. A standardized 4 point-scale system comparing vascular uptake to liver uptake is recommended. When using this 4 point-scale system, the study is considered positive for LVV when uptake is greater than liver (grade 3); when uptake is equal to liver (grade 2), it is indicative of LVV. Uptake less than liver (grade 1) or completely absent (grade 0) is considered negative for LVV. In addition to maximizing diagnostic accuracy, such standardized approaches have been shown to improve inter-observer agreement and facilitate comparisons of multiple studies [37].

Diagnostic Performance

In a meta-analysis of 21 studies totalizing 413 subjects, FDG PET imaging was shown to detect LVV accurately for both TAK and GCA. The pooled sensitivity and specificity obtained for GCA were 90 and 98%, respectively. Pooled sensitivity and specificity were slightly lower in patients with TAK, at 84% [36••]. Another meta-analyses assessing the diagnostic accuracy of FDG PET/CT for both TAK and GCA showed similar results with a pooled sensitivity and specificity of 83.9 and 92.4%, respectively [38]. These results have been confirmed in subsequent studies. For example, in a study comparing visual and semi-quantitative interpretation of FDG PET/CT in patients with LV-GCA, visual analysis alone was shown to be superior to other semi-quantitative methods. Using the standard visual interpretation comparing vascular uptake to liver activity, sensitivity and specificity were 83 and 91%, respectively [35•]. When excluding patients receiving glucocorticoid therapy, the sensitivity increased to 92%, while the specificity remained at 91% [35•]. This can be explained in part by the ability of FDG PET/CT to normalize with effective therapy. In another study of FDG PET/CT for GCA, both visual and semi quantitative methods were equivalent with positive and negative predictive values greater than 92% [39].

Different hypotheses have been proposed to account for the slightly lower accuracy of FDG PET/CT in TAK. For instance, in TAK, vascular inflammation is predominant in the early phase of the disease, and patients presenting during the chronic phase might have morphological abnormalities, such as stenosis and aneurysm with minimal to no inflammation. In those cases, FDG PET/CT will be considered a false-negative study, while in fact, there is no active inflammation to be detected. On the other hand, increased vascular uptake is sometimes observed in subjects without biological or clinical evidence of active disease. Although they are considered to be false positive studies, a subset of these cases likely represent early disease. Indeed, the diagnostic gold standard used in most studies is the ARC criteria, which are positive late in the chronic phase of the disease process as discussed above. Because macrophage accumulation in the vascular wall occurs early in the pathophysiology of LVV, before ARC criteria are met, FDG PET/CT can detect disease that does not meet the gold standard definition of the disease.

FDG PET/CT vs Other Imaging Tests

Prior to the accessibility of PET scanners, molecular imaging of LVV was performed with SPECT radiopharmaceuticals. FDG PET/CT was shown to be significantly more sensitive to detect vascular inflammation compared with SPECT

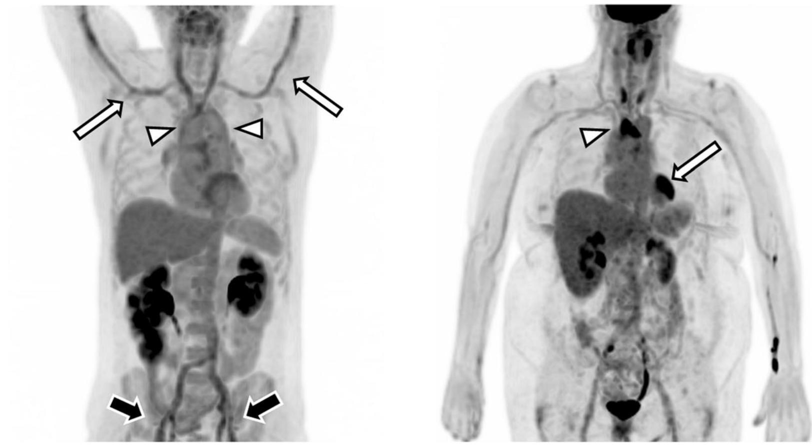

Fig. 1 Left: maximal intensity projection (MIP) image of a FDG PET/CT scan of a 54-year-old male with giant cell arteritis. There is increased uptake along the ascending aorta, aortic arch (arrow heads), subclavian arteries (white arrows), and carotid arteries. The intensity of the uptake is greater than liver activity (grade 3), compatible with vasculitis. There is also grade 3 uptake in the iliofemoral arteries, compatible with vasculitis (black arrows). Right: maximal intensity projection (MIP) image of a FDG PET/CT scan of a 58-year-old female who initially presented with an anterior ST elevation myocardial infarction (STEMI). Angiography (not shown) demonstrated tortuous coronary arteries, suspicious for coronary vasculitis. On PET/CT images, there is intense increased uptake along the transverse aorta, extending in the right common carotid, right subclavian, and brachiocephalic arteries (arrowhead). The intensity of the uptake is greater than liver activity (grade 3), compatible with vasculitis. The intense uptake projecting in the anterior wall of the left ventricle (arrow) is related to inflammation secondary to recent STEMI. Low-intensity uptake in the subclavian and iliac arteries (grade 1) does not represent active vasculitis

radiotracers, such as ^{67}gallium-citrate and white blood cells labeled with ^{99m}Tc or ^{111}In [40, 41]. At present, where available, FDG PET/CT is the molecular imaging modality of choice and recommended for investigation of LVV.

In patients imaged for initial diagnosis of GCA, both CTA and FDG PET/CT were shown to be able to detect the presence of LVV with excellent concordance and high sensitivity and specificity [42, 43]. However, on per segment analysis, FDG PET/CT detected a significantly higher number of involved vascular territories compared with CTA [42]. While sensitivity of the two modalities was comparable for the aorta, FDG PET/CT was superior at evaluating disease extent with higher sensitivity for detection of aortic branch involvement. Similar results were obtained in small studies, showing higher sensitivity of FDG PET/CT compared with MRA [22, 44]. In a recent larger prospective study comparing MRA and FDG PET/CT, the two modalities were shown to yield complementary information on the disease status; FDG PET/CT provides information on the disease activity, while MRI provides information on vascular damage [21, 45]. Because FDG PET/CT findings relate to an earlier and different stage of the disease, it should be viewed as complementary to other imaging modalities rather than an alternative [21, 46, 47].

Finally, FDG PET/CT is able to accurately detect other causes of systemic symptoms. Because patients investigated for LVV often have non-specific clinical presentations and systemic symptoms, underlying infection or neoplasia remains a possible diagnosis, which can be identified with whole-body FDG PET/CT.

Prognostic Value

Aortic complications, such as stenosis, dissection, and aneurysm, are dreaded consequences of LVV as they are associated with increased morbidity and mortality [48]. It is estimated that 8 to 25% of patients suffering from LVV will develop aortic complications, and identification of those who are at higher risk is challenging. Clinical symptoms, biomarkers, and ACR criteria cannot reliably predict the risk of arterial complications [49–51]. In GCA, large-vessel involvement established on various imaging modalities, including FDG PET/CT, CTA, and MRA, was shown to be the strongest independent predictor of aortic dilatation [52]. In multivariate analyses, the intensity of FDG uptake in the thoracic aorta was the only independent risk factor for aortic dilatation [53, 54•].

In a multicenter retrospective study including 130 patients, nine patients developed aortic complications and all of them had aortic inflammation on FDG PET/CT [54•]. In the same study, aortic inflammation as demonstrated by increased FDG uptake was associated with a statistically significant increase in aortic dilatation, aortic dissection, or both, regardless of whether the PET was performed at time of diagnosis or during follow-up. Remarkably, all other factors investigated, such as age, gender, height, cumulative corticosteroid dose, and time elapsed since diagnosis, did not correlate with rates of aortic complications. Specifically, factors that have been associated with increased risk of aortic dilatation or aortic dissection in the general population (male gender, dyslipidemia, hypertension, etc.) were not associated with increased risk of aortic complications in LVV [54•]. FDG PET/CT can therefore provide incremental information on the risk of developing vascular complications.

Evaluation of Response to Therapy

FDG PET/CT imaging has been shown to be useful in assessing disease activity and monitoring response to therapy in various inflammatory disorders, such as sarcoidosis [26, 28]. In an in vitro model of temporal arteritis, glucocorticoid therapy was shown to gradually reduce macrophage infiltration and inflammation over the course of 12 months [55], suggesting that FDG PET/CT could be useful to monitor therapeutic efficacy in vasculitis. Several small studies support this hypothesis by demonstrating decreased FDG uptake following successful immunosuppressive therapy [56–58, 59•, 60]. In a prospective study of 35 subjects with PMR, FDG uptake decreased significantly after 3 months of glucocorticoid therapy without additional reduction after 6 months of therapy [56]. In another prospective study evaluating the effect of high-dose glucocorticoid therapy, the sensitivity of FDG PET remained unchanged after 3 days of prednisolone 60 mg, with all patients demonstrating persistent increased FDG uptake [61•]. However, after 10 days of therapy, 64% of patients had visual normalization on PET imaging [61•]. On semi-quantitative analyses, the FDG uptake intensity decreased by 10 to 15% after 3 days and by 30 to 40% after 10 days of high-dose glucocorticoid therapy. Importantly, faint uptake is often seen several months following successful therapy, and complete normalization of uptake is seen in less than 20% of patients (Fig. 2) [62]. The exact nature of this persistent faint uptake is unclear, and it has been suggested that it could represent subclinical vasculitis [59•, 63]. Indeed, the presence of persistent low-grade uptake post-therapy is associated to an increased risk of relapse [59•]. The optimal timing at which follow-up imaging should be performed to assess response to therapy remains unknown, and further studies are required [32••]. Based on available evidence, one can expect FDG uptake to decrease in response to successful therapy between 4 to 12 weeks post-initiation of treatment. Further studies are required for definition of criteria for the assessment of vasculitis activity and remission on follow-up FDG PET/CT.

Limitations and Open Questions

One of the main limitations of FDG PET/CT is the non-specific nature of the tracer uptake. Vascular FDG uptake can be seen in different conditions, including atherosclerosis and graft infection [64, 65]. This was highlighted in a recent prospective study evaluating the clinical value of FDG PET in vasculitis [59•]. In this study, the authors obtained a significantly lower specificity compared with previous reports (83% vs 93%) [38]. This difference was attributed in part to the fact that a comparative cohort was used as controls rather than healthy volunteers. By doing so, more subjects in the control group had increased vascular uptake not related to LVV, with the main cause of false positive study being the presence of atherosclerosis. Even though vasculitis usually appears as smooth linear uptake and atherosclerosis classically presents with patchy discontinuous uptake, the two imaging pattern can overlap. This is especially true in the older population where abdominal aorta and iliofemoral artery uptake due to atherosclerotic disease can be observed [32••].

Several questions related to improvement in imaging techniques are still opened. For example, further studies are required to determine whether dual-time point imaging or utilization of hybrid imaging, such as PET/CTA and PET/MR imaging, can improve accuracy of FDG PET imaging. Moreover, standardization of visual and quantitative criteria is required to obtain uniform and reproducible interpretation of FDG PET. Although a joint position paper recently addressed some of these issues by recommending interpretation criteria, more studies are needed to support these recommendations [32••].

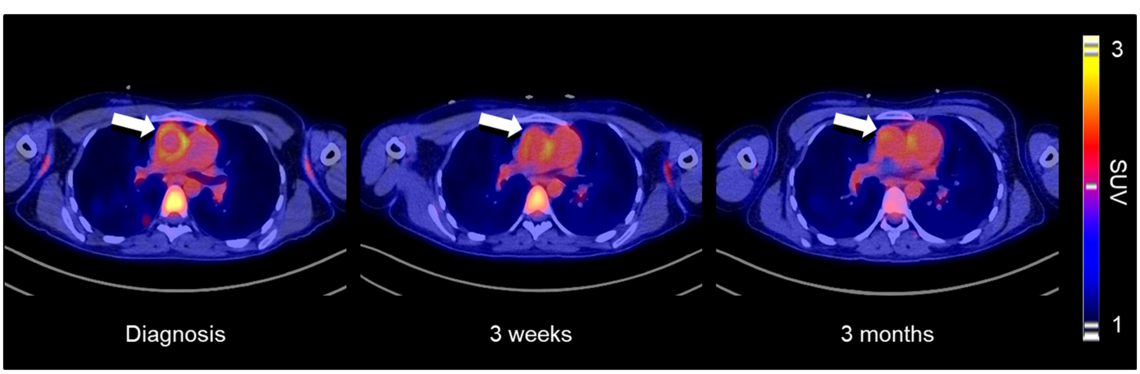

Fig. 2 Selected axial FDG PET/CT images of a 26-year-old female with Takayasu's arteritis. The initial image obtained at time of diagnosis (left) shows increased circumferential FDG uptake in the wall of the ascending aorta (white arrow), compatible with aortitis. Images of subsequent scans obtained 3 weeks (middle) and 3 months (right) after corticosteroid treatment show normalization of the aortic wall uptake (white arrows)

Many unresolved issues are also related to clinical aspects. How FDG PET/CT should be integrated in the current diagnostic algorithms of LVV and PMR remains to be established. Also, the exact role of FDG PET/CT in monitoring therapy remains an open issue, and the timing and frequency of follow-up imaging need to be clarified.

Conclusion

Accurate and timely diagnosis of LVV is of utmost importance to minimize complications related to untreated disease. Imaging has become the cornerstone of the investigation of patients with suspicion of LVV, allowing rapid and non-invasive assessment. FDG PET/CT emerged as a useful modality for the diagnosis of LVV, and evidence suggests that it provides independent prognostic information. FDG PET/CT can be used to monitor and modulate therapy. Further prospective trials are warranted to improve the level of clinical evidence.

Compliance with Ethical Standards

Conflict of Interest Matthieu Pelletier-Galarneau declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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