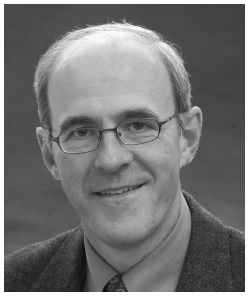
Editorial

Positron Emission Tomography/Computed Tomography for the Diagnosis and Assessment of Giant Cell Arteritis: When to Consider It and Why



Large-vessel involvement is now well recognized in patients with giant cell arteritis (GCA). While exact numbers vary, a recent study demonstrated that up to 67.5% of patients with biopsy-proven GCA have large-vessel disease at the time of diagnosis[1]. On occasion, large-vessel arteritis may occur in isolation, without classical features such as headache and scalp tenderness, making a clinical diagnosis difficult[2]. Recognition, however, remains important, as mortality in this subset of patients is significantly increased[3].

While temporal artery biopsy remains the diagnostic gold standard in GCA, it may be falsely negative in 42% of patients with isolated large artery disease[2]. In such cases, imaging studies are necessary to confirm large-vessel vasculitis. Angiography is suboptimal because of its invasive nature, risks of contrast allergy and nephropathy, and ability to detect only late anatomical changes such as stenosis or aneurysm. Positron emission tomography/computed tomography (PET/CT) is an alternative, offering the ability to detect both structural lesions and active inflammation.

When inflammatory cells become activated, they undergo a "respiratory burst" and metabolize large amounts of glucose[4]. (^{18}F) fluorodeoxyglucose (FDG) PET is a nuclear medicine scan that uses a glucose analog labeled with radioactive fluorine-18, which is taken into cells through the glut-1-transporter. This tracer mimics the distribution of glucose, thereby identifying conditions with high glucose metabolism, such as malignancy, infection, and inflammation[5]. Current PET scans are often combined with a low-dose CT scan for enhanced anatomical localization of isotope. While used most commonly for oncologic detection and staging, PET/CT is gaining popularity for use in a number of inflammatory diseases, and has notable advantages for the diagnosis of large-vessel arteritis.

PET/CT identifies active inflammation within the arterial wall, potentially leading to an earlier diagnosis of GCA. Studies of small numbers of patients with GCA have reported such abnormalities in the large vessels, with sensitivities of 77%– 92% and specificities of 89%–100%[6,7,8]. The most commonly affected large vessels are the subclavian arteries (74%), the aorta (> 50%), and femoral arteries (37%)[8]. Most studies suggest that large-vessel involvement in GCA is very common, affecting 50% to 80% of patients[7,8,9,10,11].

Vascular uptake on PET/CT scan correlates with clinical and laboratory markers of inflammation, in particular C-reactive protein (CRP). This was best demonstrated in a series of 26 patients with newly diagnosed GCA and Takayasu arteritis, where visual grade I uptake on PET corresponded to a CRP of 4 mg/l (normal < 10 mg/l), grade II to CRP 37, and grade III to CRP of 172 ($p = 0.007$). When CRP was < 12, overall sensitivity of PET was < 50%, as compared to 95.5% when CRP was elevated[9]. Abnormal scans, however, have also been reported in the subset of GCA patients with near-normal inflammatory markers[12].

Because of its ability to visualize the entire vascular tree with one scan, PET/CT is useful in laboratory investigations of atypical patients, including those with fever of unknown origin[13], and in polymyalgia rheumatica (PMR), where perisynovitis of the shoulders[8] and subclinical vasculitis[14] may be detected. The latter is supported by a prospective study showing large-vessel FDG uptake in 31% of patients with isolated PMR (based on negative temporal artery biopsy and absence of cranial symptoms)[15], and by the finding of similar inflammatory cytokine profiles in temporal artery specimens from patients with GCA and PMR[16].

In addition to diagnostic yield, PET/CT may also provide prognostic information in GCA. In a study by Blockmans, *et al*[17], FDG uptake at diagnosis correlated with increased aortic diameter (as measured by CT) after a mean of 46.7 months followup, adjusting for age, sex, hypertension, diabetes, cholesterol levels, erythrocyte sedimentation rate, and CRP. On multivariate analysis, only thoracic FDG uptake at baseline remained significantly associated with increased thoracic aortic diameter ($p = 0.039$). Such information may help identify patients who are at risk for poor outcomes, notably aortic dissection.

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The role of PET/CT in patients receiving treatment for GCA continues to evolve. In new-onset disease, a recent study noted a decline in the diagnostic accuracy of PET for GCA from 93.3% to 64.5% after the institution of steroids or immunosuppressives[18]. Sensitivity was similarly reduced from 99.6% to 52.9%. Overall, PET remained a useful test, increasing diagnostic accuracy from 54.1% to 70.5% ($p = 0.04$). It is unknown whether the reduction in FDG uptake seen in treated patients represents rapid resolution of inflammation, or the inhibitory effect of glucocorticoids on peripheral glucose uptake by reducing the expression of glut-transporters on the surface of skeletal muscle cells[19]. Further study in this area is required.

Similarly, issues arise regarding the use of PET/CT for followup. An initial study reported improvement in vascular uptake scores after 3 months of therapy but no further improvement at 6 months, despite maintained clinical remission. This result raises the question of whether persistent FDG uptake represents vascular remodeling due to neovascularization within the arterial wall or persistent active arteritis[8]. This is an area of debate, because postmortem data have previously reported persistent evidence of microvascular inflammation in the arterial wall of patients with GCA even after 7 years of treatment[20]. In contrast, a recent study followed 10 patients with GCA with serial PET/CT scans over an average of 36.8 months. This study reported ongoing improvement and even normalization of vascular scores in patients with a clinical response[21]. Relapse in 1 patient at 21 months was accompanied by a dramatic increase in FDG uptake. Similar findings have been reported elsewhere[10,22,23]; however, it remains unclear whether persistent vascular uptake on PET/CT at followup represents continuing active arteritis or chronic remodeling.

There are a number of limitations with PET/CT. The spatial resolution is poorer than that of other modalities, detecting vessels > 4 mm diameter only[24]. For this reason, PET/CT is unable to visualize the temporal arteries and cannot replace temporal artery biopsy as a direct indicator of vessel wall inflammation[7]. Similarly, it has limitations for investigating the small-vessel vasculitides[5]. The accompanying low-dose CT routinely used for anatomical localization of FDG uptake is suboptimal for detecting luminal abnormalities compared to other anatomical imaging counterparts, although many PET/CT scanners are capable of performing a diagnostic-quality CT if required. Other limitations are that access is confined to select medical centers, and cost (about CDN $2000/scan).

PET/CT may result in false-positive scans, because FDG uptake does not necessarily equate to active arteritis, but may highlight any metabolically active tissues, including malignancies, infection, or idiopathic sources of inflammation. In particular, uptake may be increased in nonarteritic inflammatory lesions, most notably atherosclerosis. Distinguishing features include the distribution, pattern, and intensity of FDG uptake: atherosclerosis is more likely to affect the internal carotid artery (vs the external), have a ring-shaped morphology (vs linear), and demonstrate mild uptake (vs the intensely FDG-avid arteritis)[25]. These subtle differences highlight the requirement for an experienced nuclear medicine specialist to interpret PET/CT scans.

Magnetic resonance imaging (MRI) offers an alternative for assessing the large vessels in patients with GCA. It has remarkable spatial resolution, to the submillimeter level. When used with gadolinium, it can detect active inflammation manifested by arterial wall edema and mural enhancement. Unlike PET/CT, it can visualize changes in both the temporal arteries and the large thoracic vessels, carries no risk of ionizing radiation, and is considerably less expensive. MRI may not be an option for patients with certain metallic implants such as pacemakers and for some with claustrophobia.

Several small comparative studies have shown PET/CT and MRI to be equivalent for the diagnosis of large-vessel vasculitis. However, because it scans the entire body, PET/CT reliably images more regions of active arteritis[13,22]. It has superior correlation with clinical and laboratory measurements, and is more accurate for assessing response to treatment[10,22,23]. In 8 patients with GCA, both modalities were performed at diagnosis and followup. With treatment, 11 (55%) of the original 20 pathologic regions noted on PET/CT normalized, in keeping with clinical and laboratory findings, whereas 14/15 (93%) original vascular lesions detected by MRI remained unchanged[22]. These results may reflect MRI's superior ability to image anatomical lesions such as stenoses and aneurysms, features of permanent damage due to previous vasculitis, rather than ongoing active disease. In contrast, PET/CT is superior for imaging areas of increased metabolic activity, and may be able to detect reversible inflammatory disease in the vessel wall. The major advantages and disadvantages of these 2 modalities are summarized in Table 1.

Table 1. Major features of PET/CT versus MRI/MRA in patients with GCA.

Feature	MRI/MRA	PET/CT
Detection of vascular inflammation	++	+++
Detection of vascular structural changes	+++	++
Spatial resolution	< 1 mm	> 4 mm
Visualization of temporal arteries	Yes	No
Location of large arteries visualized	Head, neck, thoracic regions	Whole body
Outcome treatment measure	No proven role	Possible role
Radiation exposure	No	Yes
Presence of renal failure	Contraindicated	No issue
Cost of procedure	+	+++

PET/CT: positron emission tomography/computed tomography; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography; GCA: giant cell arteritis.

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Large-vessel involvement in GCA is increasingly recognized as a cause of morbidity and mortality. In patients with atypical presentations or with negative temporal artery biopsies, PET/CT is a reasonable second-line investigation, with a moderate sensitivity and high specificity for large-vessel involvement. When choosing between PET/CT and MRI it is important to consider both study-specific and patient-specific factors, including the stage of disease being assessed. A number of important questions remain, such as the usefulness of PET/CT in patients taking corticosteroids and immunosuppressives, and the imaging modality's ability to assess treatment response and to predict major long-term complications such as aortic dissection.

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