Utility of imaging studies in assessment of vascular inflammation

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Imaging studies used in vasculitis can be divided into isotopic, ultrasonographic, and radiographic studies. The most important role of nuclear medicine in systemic vasculitis is the use of inflammation-specific agents to monitor the inflammatory activity of the disease.[1] The agents in clinical use today to target inflammation are leukocytes, labeled with technetium (Tc)-99m or with indium (In)-111, gallium-67 and 18-fluorodeoxyglucose (FDG). Ultrasound examinations allow the noninvasive diagnosis of temporal arteritis.

Radiographic studies (classic and magnetic resonance angiography) are used in those forms of vasculitis in which it is difficult to obtain histologic proof, due to difficulties in performing biopsies on affected organs. Examples of these diseases are Takayasu's arteritis, classical polyarteritis nodosa (PAN) and isolated cerebral vasculitis. Pulmonary vasculitic involvement, eg, in Wegener's granulomatosis, can be seen on a plain x-ray of the lungs or on the much more sensitive high-resolution computed tomography (CT). (Para)nasal involvement in Wegener's disease patients or periaortic inflammation in periaortitis are also best appreciated on CT scan.

■ ISOTOPIC STUDIES

Labeled leukocytes

The effective ingredient in a labeled leukocyte preparation is the neutrophil, since lymphocytes are too sensitive to ionizing radiation, which prevents them from recirculating normally through the lymphoid system within hours of labeling.[2] This limits the use of labeled leukocytes in vasculitis, in which the chronicity of inflammation and its neutrophilic content may vary widely. The normal distribution of Tc-99m and In-111 labeled leukocytes is the reticulo-endothelial system, but Tc-99m can also be seen in the urinary tract, gall bladder, and gut.

Isotopic studies with labeled leukocytes in small-vessel vasculitis were reported for patients with Wegener's granulomatosis and microscopic polyangiitis. Splenic photopenia on In-111–labeled leukocyte scintigraphy was described in a Wegener's granulomatosis patient due to splenic necrotizing vasculitis with granuloma formation.[3]

In a retrospective study of 12 patients with systemic vasculitis (six each with Wegener's granulomatosis and microscopic polyangiitis), all with renal disease, Jonker et al observed increased diffuse lung radioactivity soon after the injection of In-111–labeled granulocytes or Tc-99m–labeled leukocytes in all patients with Wegener's granulomatosis and in three with microscopic polyangiitis. The majority of patients with systemic vasculitis had scintigraphic evidence of abnormal splenic function (2 with splenic defects, 7 with an increased labeled cell uptake). Focal nasal uptake was seen in Wegener's granulomatosis patients, but renal disease was scintigraphically apparent in only one patient.[4]

In a large retrospective study on 50 patients with systemic vasculitis (Wegener's granulomatosis in 32, microscopic polyangiitis in 12, Churg-Strauss syndrome in 4, and temporal arteritis in 2), leukocyte imaging was useful for detecting unsuspected sites of disease and monitoring disease activity. Scintigraphy was superior to conventional radiography or CT scanning for detecting and monitoring vasculitic involvement of the respiratory tract. Nasal uptake on leukocyte scans could differentiate between Wegener's granulomatosis and microscopic polyangiitis. Also in this study, the scans were not sensitive in detecting renal vasculitis.[5]

In-111–labeled leukocytes were also used in large-vessel vasculitis. Fink et al described three patients with nonspecific features, including unexplained fever due to aortitis, which was diagnosed by this isotopic technique. The final diagnoses were periaortitis in Wegener's granulomatosis, aortic dissection in giant-cell arteritis, and streptococcal aortitis with impending rupture.[6] In Takayasu's arteritis, In-111 mixed leukocyte scans had a low sensitivity for active disease (25% only, increased vessel uptake in two of eight scans). Possible explanations are the size of the vessels involved, the small volume of the cellular infiltrate at any one site of inflammation, and the lymphocytic predominance in the cellular infiltrate.[7]

Gallium-67 scintigraphy

Gallium-67 citrate binds to the transferrin receptor expressed on the surface of activated macrophages.[8] In 1988, Yuasa et al reported that granulomatous involvement of the lungs in a Wegener's granulomatosis patient could be detected on gallium scintigraphy.[9] Other case reports de-

scribe gallium uptake in cutaneous lesions of periarteritis nodosa.[10,11] In a large study of 46 consecutive infants and children with Kawasaki disease, clinically suspected myocarditis could be demonstrated in 63% using imaging with gallium-67 citrate by planar imaging and even in 80% by single photon emission CT imaging.[12]

Gallium scintigraphy was performed in 4 patients with Takayasu's arteritis. Vascular uptake was noted in 3 patients before therapy. After total lymphoid irradiation, gallium scans returned to normal.[13] Significant gallium-67 uptake in the distribution of the aortic arch and great vessels was reported in several case reports.[14-16]

Généreau et al evaluated temporal gallium-67 uptake in a prospective study on 24 patients with temporal arteritis, which was biopsy-proven in 19 cases. Compared to 18 elderly controls undergoing gallium scans for various inflammatory diseases, the gallium uptake in the temporal region was significantly higher in biopsy-proven and biopsy-negative temporal arteritis patients. The specificity of a gallium-uptake ratio >0.4 (compared to a parietal region of interest) was 94% and its predictive positive value was 90%, while its sensitivity reached only 38%. Gallium uptake ceased during remission (six months after diagnosis, not with short-duration steroid treatment, <38 days). The authors concluded that gallium scintigraphy may contribute to the diagnosis in temporal artery biopsy-negative patients.[17]

FDG-positron emission tomography (PET)

FDG is a glucose analogue which is transported across the capillary and sarcolemmal membranes in proportion to the rate of glucose uptake. Increased FDG-uptake can be observed in cells with high metabolic requirements, such as inflammatory and tumor cells.

In 1996, we undertook a prospective study in order to compare FDG-PET scintigraphy with gallium-67 scanning in the workup of patients with fever of unknown origin.[18] In some of these patients, we saw a very profound FDG-uptake in the large thoracic vessels. These patients later on turned out to suffer from giant-cell arteritis. In view of these findings, we started a second prospective study in which all consecutive patients who presented to our department with a clinical picture compatible with giant-cell arteritis and/or polymyalgia rheumatica underwent a temporal artery biopsy and FDG-PET scintigraphy before eventual therapy with steroids was started. Owing to high uptake in the brain, the small diameter of the vessel, and the relatively high background of the skin, direct evaluation of the temporal arteries is not possible on whole-body PET investigation. A preliminary series of 5 patients with polymyalgia rheumatica, 6 patients with giant-cell arteritis, and 23 age-matched control patients was published in 1999.[19] Vascular FDG-uptake in the thoracic vessels and in the upper legs was seen significantly more in the temporal arteritis and polymyalgia patients than in the controls. Thoracic vascular FDG-uptake especially was very specific for temporal arteritis and/or polymyalgia rheumatica since it was encountered in only 1 control patient compared to 8/11 patients. In 4 patients, FDG-PET scan was repeated under steroid treatment, at a time when all symptoms had disappeared and inflammatory parameters had normalized. Vascular FDG-uptake had clearly decreased at that time.[19] A larger series on the use of FDG-PET scintigraphy in patients with giant cell arteritis (n = 25) and polymyalgia rheumatica (n = 13) was published in 2000.[20] Thoracic vascular FDG-uptake had a sensitivity for the diagnosis of giant-cell arteritis or polymyalgia rheumatica of 56%, a specificity of 98%, and a positive predictive value of 93%. Vascular FDG-uptake in the legs had a slightly higher sensitivity of 64% but a lower specificity of 77%. The highest yields were obtained in patients with predominant systemic symptoms, such as fever, weight loss, or general malaise.[20] These studies confirmed former clinical reports that giant-cell arteritis affects not only the temporal arteries, but also the aortic arch, the abdominal aorta, the subclavian and even the femoral arteries. Recently, other groups reported similar FDG-PET findings in single patients.[21-23] Rare false-positive FDG-PET scans may be due to severe atherosclerosis,[24] although we could not find a correlation with clinical atherosclerosis in our controls with false-positive upper leg vascular uptake.[19]

In April 2000, we included our first patient with giant-cell arteritis/polymyalgia rheumatica into a new prospective study with the intention to see if vascular FDG-uptake in these disorders has any influence on the relapse rate. All patients got a FDG-PET scintigraphy before treatment with steroids was started, at 3 months (if the initial PET scan showed vascular FDG-uptake) and at 6 months (whenever the PET scan performed at 3 months was still positive). Patients with isolated polymyalgia rheumatica were treated with methylprednisolone 12 mg/day, which was then gradually tapered and stopped after 6 months of therapy. Patients with temporal arteritis received 32 mg of prednisolone/day as an initial treatment, which was then also gradually diminished and stopped after 1 year of treatment. At this moment (December 2001), 20 patients with isolated polymyalgia and 20 patients with giant-cell arteritis were enrolled. In the 20 patients with isolated polymyalgia (temporal artery biopsy performed in 18, always negative), vascular FDG-uptake was visible in only 3 (15%). Eighteen out of 20 (90%) showed intense FDG-uptake in their shoulders and hips. Today, 13 patients finished their 6 months of steroid treatment, but 10 of them relapsed, most frequently when taking 2 mg methylprenisolone/day or a few weeks or months after stopping treatment. Since only a few patients showed vascular FDG-uptake and almost all showed (peri)articular FDG-uptake, we cannot make any statement about the possible predictive role of vascular FDG-uptake in isolated polymyalgia at this moment. It is clear, however, that a 6-month treatment for isolated polymyalgia is too short, since most patients relapsed.

In patients with giant-cell arteritis (which was biopsy-proven in 18 out of 20), intense FDG-uptake in the large vessels was seen in 16 (80%). Fourteen of these 16 already underwent a second FDG-PET scan after 3 months of steroid treatment (while they were taking 16 mg methyl-prednisolone/day). FDG-uptake had disappeared in 7 and had diminished but was still detectable in another 7. Six

patients thus far of those with residual uptake at 3 months underwent a third FDG-PET scan at 6 months of treatment (taking 8 mg methylprednisolone). There was no clear further decrease in FDG-uptake at 6 months compared to 3 months of steroid treatment. All these patients are still taking methylprednisolone at this moment (December 2001), but it will be interesting to see if they will have more relapses of their vasculitis, compared to those whose FDG-PET scan normalized. A typical sequence of FDG-PET scintigraphy before the start of steroid treatment, at 3 months, and at 6 months is shown in **Figure 1**.

Large-vessel inflammation in Takayasu's arteritis could also be demonstrated using FDG-PET scintigraphy.[25-27] Meller et al had 3 patients with Takayasu's arteritis in their series of FUO patients. The thoracic aorta was positive on transaxial FDG tomography in these 3 patients, while gallium-67 scintigraphy was negative in 2. In one patient, FDG scintigraphy was repeated following 3 months of glucocorticoid therapy; it had normalized by that time.[26]

During the past 2 years, we had the opportunity to study several patients with idiopathic periaortitis, both at thoracic and abdominal level, with FDG-PET scintigraphy. There was always a high FDG-uptake in the inflamed aortic tissue, which normalized during steroid therapy.[28,29]

Few patients with medium-sized vasculitis (Churg-Strauss syndrome, PAN) underwent FDG-PET scintigraphy. No vascular FDG-uptake was detected.[27] In small-vessel vasculitis, internal organ involvement can be visualized with FDG-PET scintigraphy, especially in the lungs and the nose (in case of Wegener's granulomatosis).[27,30]

■ ULTRASONOGRAPHIC STUDIES

In a prospective study on 30 patients with temporal arteritis (biopsy-confirmed disease in 21), Schmidt et al reported that color duplex ultrasonography showed a dark halo around the lumen of the temporal arteries in 22 patients (73%). These halos disappeared after a mean of 16 days of treatment with corticoids. No halos were identified in 37 patients with isolated polymyalgia rheumatica nor in 45 control patients, which makes it a very specific sign. Stenoses or occlusions of temporal artery segments were found in 24 patients (80%) compared to only 6 patients (7%) with polymyalgia or other diseases. Twenty-eight temporal arteritis patients (93%) had stenoses, occlusions, or a halo.[31] Lauwerys et al, in contrast, reported thickening of the vessel wall in only 2 out of 11 temporal arteritis patients, but they found a significantly lower peak systolic velocity compared to the velocities measured in 21 polymyalgia patients and 32 controls. Follow-up with color Doppler sonography in 6 patients with giant-cell arteritis under treatment produced evidence of a significant increase in the mean peak systolic velocity.[32]

We are using color duplex ultrasonography in a prospective way to study the temporal arteries of all patients suspected of having giant-cell arteritis. Until now, 95 patients were studied, of whom 19 indeed had temporal arteritis, as evidenced by temporal artery biopsy. The typical halo, described by Schmidt et al, was found in 14

of these 19 patients and in only 3 of the 76 patients with isolated polymyalgia or with other diseases. Therefore, sensitivity of the halo sign for giant-cell arteritis was 74%, its specificity 96%, its positive predictive value 82%, and its negative predictive value 94% (Guy Beyens et al, unpublished data).

■ RADIOGRAPHIC STUDIES
Angiography

Visceral arterial aneurysms were already noted in the original description of PAN by Kussmaul and Maier in 1866[33] and were first demonstrated angiographically by Fleming and Stern in 1965.[34] The angiographic findings in classical PAN include aneurysms, irregular beading, stenoses and/or occlusions of medium-sized vessels, usually best seen in the renal and hepatic vascular territories. The presence of aneurysms is generally associated with more severe disease and hypertension.[35] When typical arterial changes are present in the right clinical context, the diagnosis of PAN can usually be made, although slight dilatations have also been encountered in Wegener's granulomatosis, Churg-Strauss syndrome, and vasculitis look-alikes such as infective endocarditis.[36]

In Takayasu's arteritis, angiography is now being replaced by magnetic resonance imaging (MRI) and magnetic resonance angiography (see below). Indeed, angiography can only visualize alterations of the vessel lumen, eg, stenoses, occlusions, or aneurysm formation. This is at a stage when the disease has already progressed considerably, while MRI can detect earlier alterations in the vessel wall. Angiographically, stenoses and occlusions are found in the thoracic and abdominal aorta (with aneurysm formation as well), the subclavian and renal arteries, and also in the pulmonary arteries. Embolization of hypertrophied bronchial arteries, which can develop as a result of pulmonary infarction, can be lifesaving in case of severe hemoptysis.[37]

Primary angiitis of the central nervous system is usually suspected clinically and recognized by angiography, but a definitive diagnosis still requires tissue documentation of the presence of a true vasculitis.[38] CT scan and MRI of the brain will frequently show alterations, but these are very unspecific for vasculitis. A brain biopsy is of course very invasive, and rather frequently one has to be satisfied with a compatible angiography. Sensitivity of a high-probability angiogram is less than 40% in histologically confirmed cases (and 100% in reports not supported by histology), whereas its specificity lies around 20% since atherosclerosis, vasospasm, and infection can give very similar images.[39]

Magnetic resonance imaging

Conventional x-ray angiography has played a prominent role in the evaluation of large- and medium-sized vessel vasculitis. Recently, noninvasive magnetic resonance methods have been introduced for the evaluation of large-vessel vasculitis. Magnetic resonance provides high-resolution anatomic information, including lumen configuration and vascular wall thickening, and physiologic data, such as measurements of the degree of wall en-
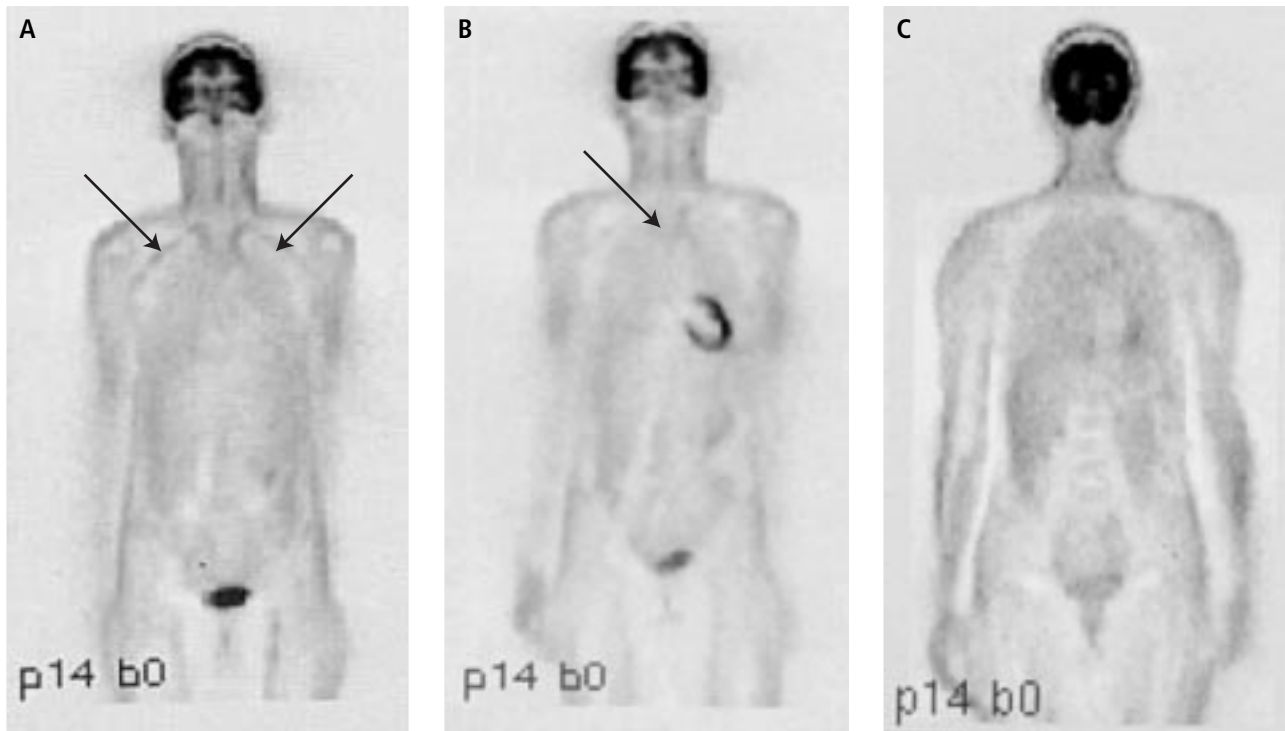
Figure 1. (A) Increased FDG-uptake at both subclavian arteries (arrows) in a patient with GCA, before therapy with steroids was started. (B) Same patient, 3 months later during steroid treatment (methylprednisolone 16 mg/day). Almost complete disappearance of vascular FDG-uptake (arrow). (C) Same patient, at six months of steroid therapy (methylprednisolone, 8 mg/day). There is no FDG uptake visible any more at the large thoracic arteries.

hancement and the presence of edema.[40] Using breath-hold three-dimensional magnetic resonance angiography, Yamada et al demonstrated a 100% sensitivity and specificity for the diagnosis of Takayasu's arteritis in a prospective study on 30 people suspected of having the disease.[41] Choe et al suggested that strong enhancement on MRI of the thickened aortic and carotid artery walls, equal to or greater than myocardial tissue signal, correlates with active inflammation in Takayasu's arteritis.[42] Vascular wall thickening is an important finding in the acute phase of Takayasu's arteritis, subsiding after appropriate therapy.[43] Mural edema is a characteristic pattern of active and progressive Takayasu's arteritis, but it is absent in the chronically active state.[44]

■ CONCLUSIONS

Most forms of vasculitis can be readily diagnosed through a combination of clinical symptoms, biochemical parameters, and radiographic and/or bioptic findings. Probably the most difficult diagnosis in the field of the vasculitides remains primary angiitis of the central nervous system, since angiography is not very specific and brain biopsy is very invasive. For those patients with very aspecific complaints (eg, only fever or weight loss) who suffer from large-vessel vasculitis, FDG-PET scan can reveal giant-cell arteritis or periaortitis. Large thoracic vessel FDG-uptake is a very specific sign for giant-cell arteritis (nearly 100%), and its sensitivity approaches 80%. In isolated polymyalgia rheumatica, synovial FDG-uptake in the shoulders and hips is the most frequent finding, but this picture cannot differentiate from other (peri)articular inflammatory disorders.

In the follow-up of ANCA-related vasculitides, serial ANCA-titer determinations are useful as a measurement of disease activity. Flare-ups of giant-cell arteritis or polymyalgia are characteristically accompanied by increases in sedimentation rates and CRP levels. These inflammatory parameters normalize very rapidly upon the start of steroid treatment and hence cannot be used really to guide therapy in order to prevent relapses. Perhaps FDG-PET scan, which can remain pathologic even after 6 months of steroid therapy, may be a more helpful determinator of treatment duration or dosage.

In the diagnosis of Takayasu's arteritis, nuclear magnetic resonance angiography has replaced the more invasive classic angiography. In the assessment of the activity of the disease, MRI of the aortic wall (its thickness and presence of edema) has proven to be valuable.

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