Role of imaging in diagnosis of and differentiation between vasculitides

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Improving quality and increased use of magnetic resonance imaging, computed tomography, ultrasonography, positron emission tomography and angiography for the diagnosis of vasculitis leads to a greater number of patients with the diagnosis of vascultis and a growing detection of involved anatomic areas. Imaging is important to determine the extension and involvement of organs in small-vessel vasculitides. Furthermore, these techniques offer characteristic findings, particularly for large- and medium-vessel vasculitides, and, therefore, play an important role for establishing the diagnosis. Classification and diagnostic criteria for polyarteritis nodosa, Kawasaki disease and Takayasu arteritis include imaging. New imaging techniques, such as magnetic resonance imaging and ultrasonography, delineate characteristic homogeneous wall swelling in temporal arteritis, large-vessel, giant-cell arteritis and idiopathic aortitis. Positron emission tomography demonstrates that large-artery involvement is much more common in temporal arteritis and polymyalgia rheumatica than previously thought. Furthermore, positron emission tomography may become an interesting new tool for follow-up examinations.

Keywords: angiography, computed tomography, magnetic resonance imaging, polyarteritis nodosa, positron emission tomography, Takayasu arteritis, temporal arteritis, ultrasonography, vasculitis, Wegener's granulomatosis

Vasculitides may be primary or secondary to infections, drugs or other rheumatic diseases. They may affect small, medium or large vessels. Wegener's granulomatosis (WG), microscopic polyarteritis (MPA), Churg–Strauss syndrome (CSS), Henoch–Schönlein purpura, cryoglobulinemic vasculitis, leucocytoclastic vasculitis, primary cerebral vasculitis and secondary vasculitides usually affect small vessels, although involvement of larger arteries has been occasionally described. Polyarteritis nodosa and Kawasaki disease are vasculitides of medium-sized arteries. Large arteries are involved in giant-cell arteritis (GCA; temporal arteritis), Takayasu's arteritis, Behçet's disease, large-vessel GCA and idiopathic aortitis. The latter two entities have recently attracted particular attention due to increased use of modern imaging techniques.

Experience with angiography exists for decades. Newer imaging methods depict vessel walls, are less invasive and there is less or no exposure to radiation. A lot of scientific work on magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), ultrasonography (US), computed tomography (CT), CT angiography (CTA) and positron emission tomography (PET) has been published within the last few years. The increased use of these new imaging techniques generated improvement in diagnosis of and differentiation between vasculitides.

The new imaging techniques offer characteristic findings, particularly for large- and medium-vessel vasculitides, which became the basis for establishing the diagnosis together with characteristic clinical findings. Imaging is also important to determine the extension and involvement of organs in small-vessel vasculitides [1].

Imaging studies in small-vessel vasculitis

Imaging is particularly important for the evaluation of ear, nose, throat, pulmonary and cerebral manifestations. It describes the extent of the disease and detects adequate regions for biopsy. The diagnosis of small-vessel vasculitis should still be confirmed histologically.

Ear, nose & throat manifestations

WG often occurs with granulomatous vasculitis of the nasal mucosa, paranasal sinuses, mastoid and, less frequently, the orbits. In many patients, this is the first or only organ manifestation of WG. Allergic rhinitis, sinusitis and polyposis are common in CSS.

MRI depicts mucosal thickening of the nasal cavity and the paranasal sinuses as high-intensity lesions on T2-weighted spin-echo sequences. Granulomas in the paranasal sinuses and orbits are characterized as low-signal intensity lesions on T1- and T2-weighted spin-echo sequences [2]. CT is superior to MRI in detecting bony lesions [3,4]. The combination of bone destruction and bone formation is regarded as specific for WG. The value of conventional radiography for the detection of vasculitic lesions is low because of lack of sensitivity.

Subglottic tracheal stenosis occurs in WG. Conventional radiography, CT and MRI demonstrate the diameter of the stenosis. In addition, MRI depicts edema and increased vascular perfusion.

Pulmonary manifestations

Pulmonary manifestations are common in WG, MPA and CSS. Findings on chest radiography include granulomatous nodules, which may cavitate, and alveolar, diffuse or pleural opacities. CT scanning is helpful in disclosing minor opacities, and cavities in opacities that are not seen in plain chest radiographs. Asymptomatic patients may only reveal minor changes in CT and not in conventional radiography. CT is superior to MRI in delineating pulmonary changes.

Nodules occur more frequently in WG, infiltrates are more typical for MPA. Nevertheless, patients with WG may have infiltrates, particularly in case of pulmonary hemorrhage [5–7]. Two studies, each with approxiamtely 30 patients, investigated patients with active pulmonary disease in WG with CT. They described nodules in 61 and 90%, respectively, and ground glass opacity in 23 and 44%, respectively [5,6]. Patients with MPA may develop pulmonary fibrosis. Infiltrates are also common in CSS, usually without nodules or hemorrhage. The main CT findings of CSS consist of air space consolidation or ground-glass opacities, septal lines and bronchial wall thickening because of the presence of eosinophilic infiltration of the air spaces, interstitium and airways, and interstitial edema [8].

CNS involvement

Vasculitis may occur as primary cerebral vasculitis. In WG, CNS involvement is found in less than 10% of cases. Chronic hypertrophic pachymeningitis, pituitary involvement and cerebral vasculitis have been described [9]. Usually, the diagnosis of WG is well established before the disease is complicated by CNS manifestations. MRI is sensivitive for the detection of pathologies, but it lacks specificity in case of cerebral vasculitis [10]. Angiography often fails to detect small-vessel vasculitis due to the small diameter of involved vessels. Furthermore, typical angiographic findings of primary angiitis of the CNS are often associated with other specific pathologic diagnoses [11]. There is no indication for angiography if MRI and spinal tap are normal.

Practical issues

For staging in small-vessel vasculitis, we perform chest radiography in two planes, abdominal US including search for pleural effusions, and echocardiography. If patients are symptomatic or findings are ambiguous, we perform MRI of the cerebrum and the ENT region, and chest CT.

Imaging studies in medium-sized vessel vasculitis

Classic polyarteritis nodosa and Kawasaki disease are vasculitides that affect medium-sized arteries. The detection of aneurysms is part of classification/diagnostic criteria of both entities.

Kawasaki disease

Kawasaki disease is an acute self-limiting vasculitis of childhood. It is characterized by fever, polymorpheous exanthema, conjunctivitis, membranous desquamation of fingertips, mucositis and unilateral cervical lymphadenopathy. Aneurysms occur in coronary arteries in approximately 25% of untreated cases and in other arteries. Vasculitis of coronary arteries may lead to coronary artery occlusion and impaired left ventricular function. Coronary aneurysms can be detected by transthoracic echocardiography, angiography, MRA [12] or CTA [13]. Echocardiography has a sensitivity and a specificity above 90%, compared with angiography. Intracoronary US reveals increased thickness of the arterial intima–media complex [14].

Echocardiography is initially recommended followed by stress testing if coronary stenosis is suspected. Stress testing can be either combined with echocardiography or with scintigraphy [15]. Angiography still has a role in interventional therapy and when the results of noninvasive techniques remain ambivalent. MRA and CTA are new alternatives for noninvasive imaging. Intracoronary US remains a research tool at the moment because of its invasiveness.

Polyarteritis nodosa

Several medium-sized arteries may be involved, representing a great variety of possible symptoms and complications. Positive abdominal angiography is one of the American College of Rheumatology classification criteria for polyarteritis nodosa. Only approximately 50% of patients with polyarteritis nodosa exhibit aneurysms of abdominal arteries. Occlusions are more frequent (in more than 90% of patients; [16]). The superior mesenteric artery is most frequently involved [17]. Multiple small aneurysms also

occur in other vasculitides, such as in WG or in secondary vasculitis due to systemic lupus erythematosus. Furthermore, aneurysms of abdominal arteries may be observed in patients with drug abuse, after liver trauma, infectious arteritis, fibromuscular dysplasia and viral infection [18].

New methods, such as MRA, CTA or even color Doppler US of the abdomen may replace angiography in the future, but little experience exists until now with these imaging studies in polyarteritis nodosa because of the low prevalence of this disease [19].

Angiography revealed occlusion of muscle arteries in 32% of cases with polyarteritis nodosa [16], but only a few patients present with a generalized myopathy and elevated CK, which can be suggestive of polymyositis. Reviewing the published data, muscle biopsy was necessary to establish the diagnosis of polyarteritis nodosa and to exclude polymyositis [20].

Imaging studies in large-vessel vasculitis

Temporal arteritis and Takayasu arteritis are listed in the Chapel Hill nomenclature of primary vasculitides as large-vessel vasculitides. Large-vessel GCA and idiopathic aortitis have recently attracted particular attention owing to increased use of modern imaging techniques.

Temporal arteritis

Vasculitis occurs most frequently in the temporal arteries, but also in other arteries, such as the occipital and facial arteries, and in the vasculature of the eye. Diagnosis is sometimes difficult as only 74% of patients complain of headache, and only 64% exhibit tender temporal arteries with reduced pulse [21]. Temporal artery histology has been the gold standard for diagnosis for decades, but it is only positive in approximately 80–90% of cases who are diagnosed with GCA because of clinical findings, including evaluation of response to corticosteroid therapy and follow-up visits. The specimen may have been taken from an unaffected segment of a temporal artery.

Duplex US of temporal arteries displays a hypoechoic (dark) edematous wall swelling in temporal arteritis that disappears with corticosteroid treatment after 2–3 weeks. Furthermore, stenoses and/or acute occlusions are frequently found [22]. According to a meta-analysis of 23 studies, the sensitivity of temporal artery duplex US is 87% with regard to the clinical diagnosis. The specificity is 96% [23]. In our center, which has a long-standing experience with temporal artery US, sensitivities and specificities are even higher (88% sensitivity; 99.5% specificity; and 95% sensitivity with regard to histology) [24]. In contrast to histology, US enables the whole length of the superficial temporal arteries, but it is not possible to detect minor histological pathologies. It is also possible to assess occipital and other arteries with US. We detected pathologies of the temporal arteries by duplex US in 7% of patients with pure polymyalagia rheumatica (i.e., polymyalgia rheumatica without clinical signs of temporal arteritis) that led to the diagnosis of temporal arteritis [25]. Routine temporal artery biopsy is not recommended in patients with pure polymyalgia rheumatica.

Promising results have been published on contrast-enhanced MRI of temporal and occipital arteries [26]. Although the resolution for superficially localized structures is below that of US, modern 1.5–3 T high-field MRI scanners provide good image quality.

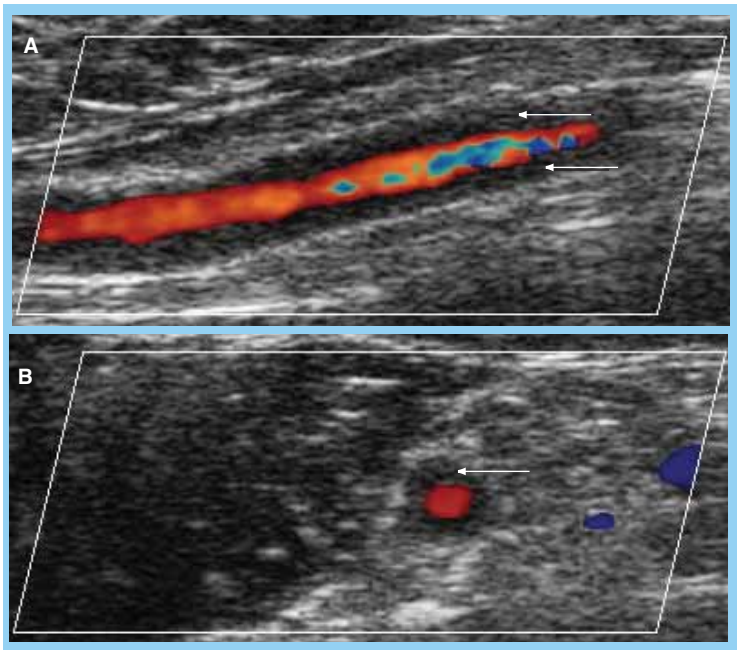
Sensitivities and specificities of the MRI examinations appear to be comparable to those of temporal artery US. Further scientific evaluation of temporal artery MRI from more than one center is needed.

Angiography of temporal arteries has been evaluated decades ago. As angiography does not depict artery walls, sensitivities and specificities were too low as to justify this invasive test with a reasonable risk for complications.

Single-photon emission computed tomography (SPECT) displayed positive findings in nine patients with active temporal arteritis [27]. Larger studies are needed before this method can be recommended for clinical practice. Positron emission tomography (PET) can only detect signals in arteries greater than 4 mm. The lumen of the branches of the common superficial temporal arteries is only approximately 0.7 mm. The temporal arteries are too close to the skin surface, and the enhancement of the brain is too strong to enable any diagnostic benefit from PET [28].

Although US and MRI detect characteristic patterns of temporal vasculitis by delineating homogeneously thickened artery walls, they do not distinguish between giant cell arteritis and other, rare causes of temporal artery vasculitis. In approximately 1% of patients with the clinical presentation of temporal arteritis, histology reveals another disease, such as WG, polyarteritis nodosa or CSS. In general, the patients have clinical features of these other vasculitides, such us pulmonary infiltrates, persistent bloody rhinorrhea or glomerulonephritis. On the other hand, temporal artery histology may also fail to

Figure 1. Color Doppler ultrasonography of the right axillary artery in a 62-year old male with large-vessel giant cell arteritis with hypoechoic (edematous) wall swelling.



(A) Longitudinal view. **(B)** Transverse view. The patient had arm pain, but no clinical signs of temporal arteritis. Nevertheless, temporal artery ultrasonography and histology were also positive.

reveal typical patterns of another vasculitis, such as granulomata in WG [29]. We demand a detailed history and clinical examination as well as testing for ANCA, renal, pulmonary, ENT and neurologic involvement if the diagnosis of temporal arteritis is established by imaging without histological examination.

Large-vessel GCA

Patients with large-vessel GCA exhibit vasculitis of the subclavian, axillary and proximal brachial arteries. They are slightly younger than those with classic temporal arteritis (66 vs 73 years), and approximately 86% are female. Approximately 50–60% have positive findings by duplex US or by histology of the temporal arteries (Unpublished Data).

Large-vessel GCA can be assessed with several imaging techniques, such as US, angiography, MRI, MRA, CT, CTA and PET. Although the greatest experience exists for angiography, there is no golden standard. Angiography displays smooth stenoses. It is invasive, but it enables central blood pressure to be measured and to perform procedures, such as arterioplasty and stenting, US, MRI and CT depict characteristic homogeneous wall swelling. US is very easy to perform at axillary, brachial, carotid and subclavian arteries, except for the proximal left subclavian artery (Figure 1). Transthoracic US can only delineate short segments of the thoracic aorta. MRI and CT provide better images of the thoracic aorta (Figure 2). MRA does not delineate the vessel wall, but it provides a good overview. Radiation is high with CT and angiography.

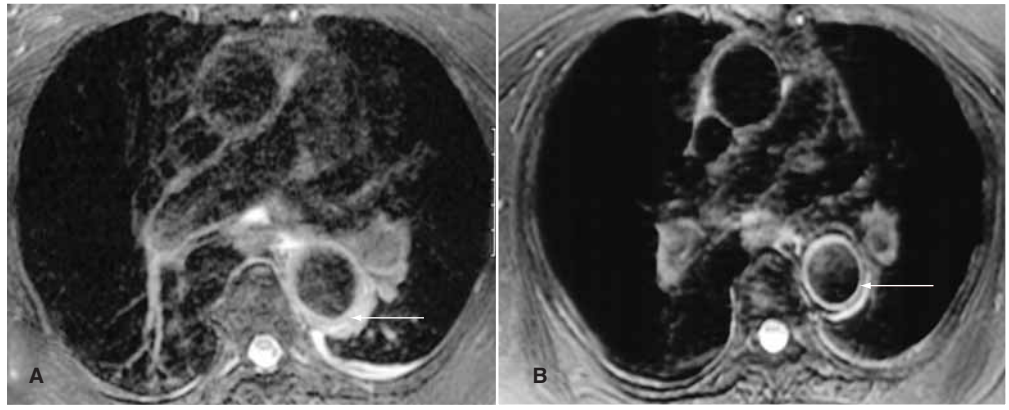
PET shows vascular fluorodeoxyglucose (FDG) uptake of the aorta, brachiocephalic, the subclavian, or the axillary arteries in 56–83% of patients with acute temporal arteritis, but only in few controls and less frequently in patients with polymyalgia rheumatica [30–32]. The uptake decreases within months with corticosteroid treatment [31]. Uptake at the iliofemoral arteries can also be observed in some patients. One study demonstrated complete agreement in the anatomical distribution of changes between PET and US [33]. The visibility of pathologies with PET decreases beyond the distal region of the subclavian arteries because of smaller vessel size. FDG-PET was used as a second-line examination in fever of unknown origin (FUO). It was better than Ga^{67}, due to the ability of PET to detect large-vessel vasculitis as a cause of fever [34].

Since we perform US of the subclavian and axillary arteries in all patients with suspected temporal arteritis, polymyalgia rheumatica, FUO and arm claudicatio, the percentage of patients with large-vessel GCA increased to 40% of all patients with GCA within the last 4 years. Addition of thoracic MRI to a standardized work-up program for FUO significantly increased the diagnosis of systemic vasculitis as the underlying cause of FUO [35]. To date, the routine use of PET scanning in patients with FUO, temporal arteritis and polymyalgia rheumatica is limited in most countries, owing to costs and problems with reimbursement. We suggest that chest radiography be performed at diagnosis and every 12 months to exclude aortic aneurysm, as patients with temporal arteritis are at a 17-fold increased risk for developing thoracic aneurysms.

Takayasu arteritis

Takayasu arteritis is a vasculitis of large arteries that principally occurs in young females. The first symptoms are malaise and low-grade fever. In most cases, the diagnosis is not established before stenoses are found. The subclavian arteries are most frequently affected (Figure 3), followed by the aorta and the carotid arteries. Vasculitis often also involves the renal, mesenteric, pulmonary and several other arteries. As for large-vessel GCA,

Figure 2. T2-weighted MRI images of the thoracic aorta of a 68-year old female with large vesssel giant-cell arteritis presenting originally with fever of unknown origin.

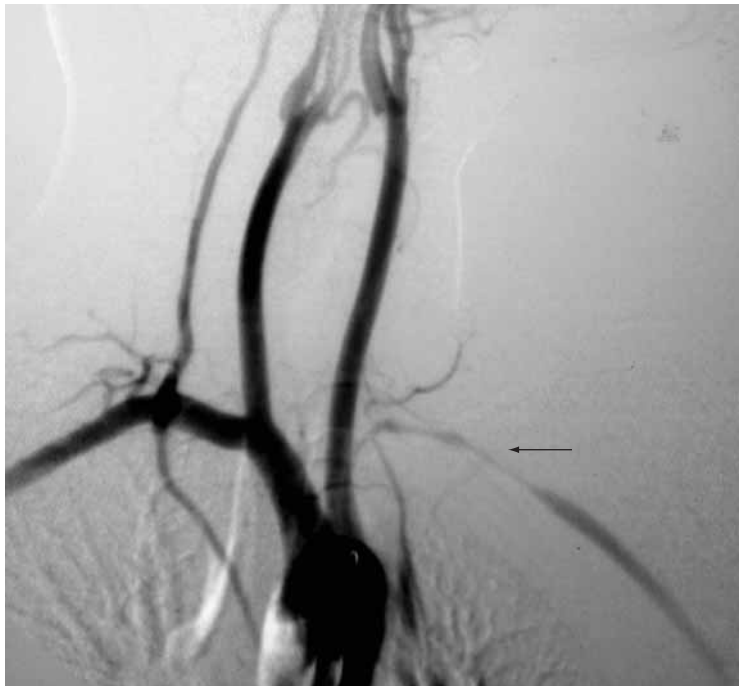


(A) Significant edema and increase in wall thickness of the descending aorta (as indicated by white arrow). **(B)** Wall morphology returned to normal after 3 months of corticosteroid treatment (as indicated by white arrow).
MRI: Magnetic resonance imaging.

angiography, MRI, MRA, CT, CTA, PET and US have been studied for Takayasu arteritis [36].

US delineates a more hyperchoic wall swelling in Takayasu arteritis than in large vessel GCA, probably due to a lower degree of edema in a more chronic course of the disease. A hypoechoic wall swelling is occasionally found in severe acute flares. Transesophageal echocardiography may reveal cirrcumferential wall thickness, dilated segments and a global impairment of elastic properties of the thoracic aorta of patients with Takayasu arteritis [37]. Transthoracic echocardiography frequently delineates left ventricular concentric hypertrophy, adnormal wall motion, aortic or mitral regurgitation and pulmonary hypertension [38].

Figure 3. Digital subtraction angiography of a 26-year-old female with Takayasu arteritis with smooth stenosis of the left subclavian artery and no flow in the left vertebral artery.



Black arrow indicates the region of smooth stenosis of the left subclavian artery.

Positive results of angiography are part of the American College of Rheumatology classification criteria for Takayasu arteritis. Angiography still plays a role in interventional therapy [39], but it fails to detect minor changes as only US, MRA and CT depict the vessel wall. The sensitivity and specificity of MRA compared with angiography for the diagnosis of Takayasu arteritis were both 100%. In few cases, stenoses may be overestimated by MRA [40]. Inconsistencies in the presence or absence of artery wall edema and subsequent anatomic changes have cast doubt on the utility of edema-weighted MRI as a sole guide to disease activity and treatment in Takayasu arteritis [41].

PET may gain more importance for follow-up examinations, although less experience exists with PET in Takayasu arteritis than with large-vessel GCA [42].

Idiopathic aortitis

Imaging sometimes reveals isolated inflammation of the aorta in patients that may not be classified as Takayasu arteritis, particularly if they are older than 40 years at disease onset. Aortitis may be part of

another vasculitis, such as GCA or WG. The differential diagnosis includes infectious diseases, such as syphilitic aortitis and mycotic vasculitis due to bacterial endocarditis. Infectious aortitis is often complicated by early aneurysms. The aforementioned imaging techniques aid in assessing the extent of vasculitis and establishing the diagnosis.

Conclusion

Imaging has become an important tool for diagnosing vasculitides and assessing their distribution. To date, MRI is very important for detecting cerebral and nasal pathologies. CT is important for detecting pulmonary changes in small-vessel vasculitis. Furthermore, MRI, CT and echocardiography are now used in the diagnosis of medium-vessel vasculitis. US, MRI and CT delineate characteristic homogeneous wall swelling in large-vessel vasculitis. MRA and CTA provide a less invasive method to provide a good overview of a greater number of vessels. PET is a more sensitive method to demonstrate large-vessel vasculitis in more arterial regions than expected before.

Executive summary

Ear, nose & throat manifestations in small-vessel vasculitis

- Magnetic resonance imaging (MRI) is the imaging method of choice for detecting mucosal swelling.
- Computed tomography (CT) may reveal a combination of bone destruction and formation, which is regarded as specific for Wegener's granulomatosis (WG).
- The value of conventional radiography for the detection of vasculitic lesions is low.

Pulmonary involvement in small-vessel vasculitis

- Conventional radiography should be performed first in the search for pulmonary involvement.
- CT should be performed if smaller lesions are suspected
- Nodules are typical for WG. Infiltrates are more frequently detected in microscopic polyarteritis (MPA) and Churg–Strauss syndrome (CSS).

CNS involvement in small-vessel vasculitis

- MRI is sensivitive for the detection of pathologies, but it lacks specificity in case of cerebral vasculitis.
- There is no indication for angiography in search for cerebral involvement in primary vasculitis if MRI and spinal tap are normal.

Kawasaki disease

- Echocardiography is recommended initially to detect coronary aneurysms.
- Anigiography has still a role in interventional therapy and for ambivalent cases.
- Magnetic resonance angiography (MRA) and CT angiography (CTA) are new alternatives for noninvasive imaging.

Polyarteritis nodosa

- Occlusions of abdominal arteries are more frequent than aneurysms.
- Aneurysms of abdominal arteries may also be observed in patients with other diseases.
- To date, little experience exists with other imaging studies.

Giant-cell arteritis

- Temporal artery ultrasonography (US) delineates characteristic homogeneous wall swelling, stenoses and occlusions with high sensitivities and specificities according to a meta-analysis.
- Similar images of temporal and occipital arteries are found by MRI.
- Large-vessel, giant-cell arteries (GCA), particularly with vasculitis of the subclavian and axillary arteries, occurs more frequently than previously thought, as demonstrated by studies with US, MRI and positron emission tomography (PET).

Takayasu arteritis

- MRI, MRA, CT, CTA, PET and US enable typical images in Takayasu arteritis.
- Homogeneous wall swelling is found similar to GCA.
- PET may be an interesting imaging method for follow-up investigations.

Future perspective

- Cardiac MRI and MRA will be more widely used to evaluate patients with suspected Kawasaki disease.
- US of temporal and axillary arteries will be widely used for diagnosis of GCA. More studies of MRI of temporal and occipital arteries and, perhaps, a meta-analysis of studies will be published, as it has been done for temporal artery US. Temporal artery biopsy will be performed only in ambivalent cases.
- PET scans will be cheaper and more widely available. Physicians wil be reimbursed for PET in developed countries. This method will be used for screening and follow-up of large-vessel vasculitis.

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