Temporal Artery Vascular Diseases

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The term “temporal arteritis” is sometimes used to refer to giant cell arteritis (GCA) but this term is not appropriate. In fact, GCA does not consistently affect the temporal artery (TA) and other types of vasculitis or non-inflammatory diseases may affect TA.

Temporal Arteritis | Giant Cell Arteritis | Vascular

1. Giant Cell Arteritis (GCA)

GCA remains of course the first cause of temporal arteritis. GCA is a granulomatous large vessel vasculitis involving large vessels, mainly the aorta and extracranial branches of the external carotid artery such as the TA [1]. GCA is the most common vasculitis in adults. It affects patients after 50 years, with a peak incidence between 70 and 80 years [2].

Two types of symptoms are distinguished in GCA. On one hand, systemic signs are frequent, unspecific, and related to systemic inflammation, and correlated to interleukin-6 (IL-6) production. Fever is usually low-grade and reaches 39 °C in only 15% of cases, usually without shearlings. It might be the only feature of GCA. Malaise, anorexia, and weight loss are also common. Around 40% of patients also experience polymyalgia rheumatica (PMR), which is characterized by aching and stiffness of the neck, shoulder, and pelvic girdles. The pain is bilateral and symmetrical, and usually radiates towards the elbows and knees, and predominates in the morning. On the other hand, patients have ischemic signs which are more specific to GCA and can cause morbidity and mortality. The type of ischemic signs directly depends on the topography of the arterial involvement and is the consequence of vascular remodeling that leads to thickening of the vascular wall and ultimately to stenosis or occlusion of the affected arteries [3]. Among them, a new-onset headache is the most frequent symptom, occurring in at least two-thirds of patients. The pain usually occurs over the temporal or occipital areas or diffuse and is poorly released by paracetamol. It can be so intense that it can cause insomnia. Widespread headache should be considered as the first symptom of GCA in patients with PMR [4].

Other cephalic ischemic signs include jaw claudication, scalp tenderness, and, more rarely, scalp or tongue necrosis. Transient or permanent vision loss may also occur. In most cases, it occurs in patients at diagnosis, exceptionally during a relapse, unless the disease has been poorly treated. The most frequent visual impairment is acute anterior ischemic optic neuropathy and more rarely the occlusion of the central retinal artery or posterior ischemic optic neuropathy. These conditions are the most severe form of GCA, as they constantly leave heavy visual sequelae [5]. Some patients may also present diplopia, transient or permanent, which is often linked to an

attack on the 3rd cranial pair [6]. In this case, patients often present with ptosis. Unlike other visual impairments, diplopia usually recovers after a few weeks of treatment with glucocorticoids. In 7% of cases, patients also present with a stroke that preferentially affects men and most often concerns the vertebrobasilar territory [7][8][9].

Two main phenotypes of GCA are usually distinguished and can be mixed together. Cephalic GCA was first described by Bayard Horton in 1932 [10]. It is the typical form of GCA that mainly affects extracranial branches of the carotid artery among which is the TA which is associated with the highest risk of vascular involvement [11]. Clinical examination of the TA typically shows an induration of the TA, which may be tender to palpation with occasional facing edema. The specificity for the diagnosis of GCA is then greater than 99% [2]. The temporal pulses may also be decreased or even abolished, but the diagnostic specificity of this clinical sign is lower [2].

In addition, recent advances in vascular imaging (angio-computed tomography [CT] scan, positron emission tomography [PET]-CT, angio-MRI) have demonstrated that 30–70% of GCA patients also have involvement of extracranial large vessels, in particular, the aorta and the subclavian or axillary arteries [12]. Its prevalence in GCA has increased with the increasing use of imaging [13][14][15] showing a halo sign by Doppler ultrasound, arterial wall thickening sometimes with contrast enhancement with a CT scan or an angio-MRI, and arterial wall uptake of ^{18}Fluoro deoxyglucose on a PET-CT [13][14][15][16][17].

Color Doppler ultrasound of the TA and supra-aortic arteries is the first-line examination in case of suspected GCA because it is less invasive, less costly, and has a lower rate of false negatives than a temporal artery biopsy (TAB) [18]. The halo sign, which is investigated by color Doppler ultrasound and is defined as a homogeneous, hypoechoic thickening of the arterial wall, visible in both the longitudinal and transverse planes and not compressible, has a sensitivity and specificity of 68% and 81%, respectively [19]. Thus, there are halo signs without GCA (false positives), with an estimated rate of 4.6% in the study by Fernandez-Fernandez [20]. Among 14 patients with a halo sign without GCA, 29% had PMR, 21% had atherosclerosis, and the remaining 50% had a wide variety of diagnoses (T-cell lymphoma, skull base osteomyelitis, multiple myeloma-associated amyloidosis, granulomatosis with polyangiitis, urinary sepsis, neurosyphilis, and angle-closure glaucoma). False positives may be related to a condition responsible for an increase in intima-media thickness that produces a true halo sign but is not the consequence of GCA. Hypoechoic thickening of the arterial wall may indeed be related to cellular infiltration of another nature, or to parietal edema, as is the case in ANCA-associated vasculitis, skull base osteomyelitis, neurosyphilis, or lymphoma [20]. Hypoechoic thickening may also be due to the deposition of inert material in the arterial wall, as in amyloidosis [21][22][23]. These false positives may also be due to errors in image interpretation (i.e., absence of halo sign) because there is a learning curve in the performance and interpretation of TA ultrasound. Indeed, the TABUL study showed that the sensitivity of TA Doppler ultrasound for the diagnosis of GCA increased from 45% to 62% after 10 TA Doppler ultrasounds were performed [24].

Some GCA patients are characterized by an isolated involvement of large vessels without cranial involvement and thus correspond to the second phenotype of GCA that is entitled “large vessel vasculitis (LVV)-GCA” [11]. These patients are usually younger than cephalic GCA and have a less ischemic complication (vision loss or stroke) but a higher risk of relapse [11]. They are also characterized by an increased risk of aortic complication or any

cardiovascular event [25][26][27]. The aorta is the artery most often affected in these patients. This does not usually cause any symptoms but can lead to complications in the long term, such as aneurysms and more rarely aortic dissection [16][28]. In patients with GCA, the risk of aortic aneurysm is indeed two times higher than in the general population [28]. Aortic aneurysms usually occur after several years of evolution, in a segment previously affected by the vasculitis, which is more frequently the thoracic aorta than the abdominal aorta, contrary to the general population [25]. After the aorta, the other most frequently affected vessels are: subclavian arteries (26–42.5%), carotid arteries (35–40%), femoral arteries (30–37%), and axillary arteries (14–17.5%), with frequencies varying according to the mode of recruitment and the imaging technique [17][29]. Patients with GCA have an increased risk of cardiovascular events: stroke, myocardial infarction, and lower limb arteritis [30]. Stroke is usually related to the involvement of the vertebrobasilar system by vasculitis [7][8][9]. Conversely, myocardial infarction is not related to coronary artery damage but to a mismatch between myocardial oxygen supply and demand that is probably related to systemic inflammation in these elderly patients [31].

There is no specific biological marker for GCA but patients almost always have elevated inflammatory proteins and increased sedimentation rates (ESR). Inflammatory anemia (hemoglobin <12 g/dL) is observed in 54.6% of cases and thrombocytosis in 48.8% of cases [32]. Nevertheless, ESR may be less than 50 mm/h in 10.8% of cases and its normality does not exclude the diagnosis [33], mainly in the case of ischemic signs [34].

The gold standard for the diagnosis of GCA is TA biopsy (TAB) that reveals a non-necrotizing granulomatous panarteritis, with an inflammatory cellular infiltrate composed of mononuclear cells (T lymphocytes and macrophages), sometimes giant cells, fragmentation of the internal elastic lamina (IEL), and destruction of the media and hyperplasia of the intima which induces the stenosis of the vascular lumen [35][36]. To confirm the diagnosis of GCA, the essential element is the presence of an inflammatory infiltrate within the media and/or intima. Elastophagy of the IEL and/or giant cells are pathognomonic but inconsistent. Intimal hyperplasia, which increases in frequency with age, and IEL dissociation are not specific to GCA. Isolated involvement of the adventitia and/or *vasa vasorum* is of uncertain diagnostic significance, as discussed below. The diagnosis of GCA may be retained even if the TAB does not show vasculitis lesions. Indeed, the sensitivity of TAB varies from 60% to 80% [2][37] and some patients have an extracephalic GCA that predominates on the aorta, subclavian, and/or carotid arteries so that, in this group of patients, only 52% of TAB are positive [38].

Glucocorticoids (GC) are the cornerstone of treatment for GCA. This treatment is remarkably effective but should be prescribed in high doses (40–80 mg/day prednisone-equivalent) at diagnosis for induction of remission and prevent ischemic complications [39][40][41]. In patients with GCA with acute visual loss or amaurosis fugax, the administration of 250 to 1000 mg intravenous methylprednisolone for up to 3 days should be considered [39][40][41]. Once remission is achieved, the dose of prednisone is then gradually reduced, first rapidly to a target dose of 15–20 mg/day within 2–3 months and then more slowly to target ≤5 mg/day after 1 year and to be stopped after two years [39][40][41].

When GC are tapered, about half of the patients will relapse, on average 7 months after diagnosis and at a mean dose of 7.5 mg/d of prednisone. These relapses are severe in only 3.3% of cases and it is exceptional to see

ischemic complications on these occasions. The risk of relapse increases in the case of large-vessel involvement and in the case of a rapid decrease in GC therapy [42][43]. These relapses are easily controlled by increasing the dose of GC but contribute to exposing these patients to high cumulative GC doses and thus increase the risk of GC-induced adverse events, such as osteoporosis, fractures, diabetes, cardiovascular disease, or glaucoma [44]. It is commonly estimated that 86% of patients will have at least one side effect from steroids after one year of treatment [44]. It is therefore important to reduce the total dose and duration of GC without increasing the risk of relapse in GCA. Methotrexate and tocilizumab, an anti-interleukin-6 (IL-6) receptor monoclonal antibody, are the two drugs used in patients with relapses or steroid-related side effects [45][46]. The efficacy of tocilizumab to induce and maintain remission of GCA and to significantly spare GC has been shown in two recent randomized controlled clinical trials [46][47]; so that recent American recommendations propose to use a combination of prednisone and tocilizumab as first-line therapy in new-onset GCA [40]. In patients receiving GC-sparing therapy, faster GC taper and earlier withdrawal of GC should be considered on an individual basis. Data on the efficacy of methotrexate in GCA are more contradictive and only focused on newly diagnosed GCA patients [48][49][50]. However, a meta-analysis showed that methotrexate reduced the risk of relapse and spared glucocorticoids with an effect size that appears to be smaller than that of tocilizumab but needs to be reassessed in a comparative study [45]. This is what the Multicenter, Randomized, Controlled Trial (METOGiA) trial (NCT03892785) is currently investigating in France. Other treatments have been investigated in GCA: anti-tumor necrosis factor-alpha [TNF-α] blockers are not effective [51][52][53], neither is azathioprine [54]. Abatacept, a fusion protein of extracellular part of cytotoxic t-lymphocyte antigen-4 (CTLA-4) and Fc fragment of an IgG that blocks T-cell activation, has been reported to have a mild efficacy to maintain remission in a phase 2 trial [55] and is currently under investigation in a phase 3 trial (NCT04474847). Ustekinumab, an anti-p40 subunit monoclonal antibody that targets IL-12 and IL-23 pathways, has been reported to spare glucocorticoids in cohort studies [56][57], which was not confirmed in a pilot study with a very rapid glucocorticoid tapering regimen [58]. Ustekinumab is currently evaluated in a phase 2 study in France (NCT03711448). Mavrilimumab (anti-Granulocyte Macrophage Colony Stimulating Factor [GM-CSF] monoclonal antibody) and secukinumab (anti-IL-17 monoclonal antibody) have also been reported as promising therapies for GCA in phase 2 trials whose results have been presented at international conferences [59][60]. Secukinumab is now evaluated in an ongoing phase 3 trial (NCT04930094). Current clinical trials are also evaluating upadacitinib (Janus activated kinase-1 [JAK1] inhibitor, NCT03725202) and guselkumab (anti p19 subunit, NCT04633447).

The pathophysiological mechanisms of GCA are becoming clearer but the triggering factor of this vasculitis has not been identified yet. It is likely that an agent, infectious or not, activates the Toll-like receptor of dendritic cells located in the adventitia and then leads to their activation and the recruitment of T cells and monocytes and finally to the formation of a granulomatous vasculitis with an intense vascular remodeling process [61]. Several infectious agents have been associated with the occurrence of GCA but none has been actually confirmed [62]. The most recent is the varicella-zoster virus, which is probably more consistent with another type of vasculopathy. A recent study has also reported on a defect in programmed cell Death protein ligand-1 (PD-L1) expression by vascular dendritic cells in GCA thus resulting in sustained activation of PD-1+ T cells and a loss of tolerance leading to vasculitis [63][64]. The involvement of this signaling pathway is highlighted by the description of a few cases of GCA occurring after treatment with immune checkpoint inhibitors (ICI) for cancer. The clinical presentation was mainly

ophthalmologic (transient diplopia, amaurosis, or blindness). In most cases, TAB confirmed the diagnosis of GCA by showing typical granulomatous vasculitis lesions [65][66]. ICIs are probably a trigger rather than a differential diagnosis of GCA [64]. Treatment is the same as for GCA with the addition of discontinuation of the ICI.

2. Others Temporal Artery Vascular Diseases

2.1. Post-Traumatic Complications of the Temporal Arteries

Trauma to the periauricular region can cause a false aneurysm or arteriovenous fistula of the TA [67][68][69]. A false aneurysm is a rare event occurring after a localized rupture of the vessel wall and consists of a blood bag communicating with the injured vessel and contained by the adjacent tissues. Doppler ultrasonography reveals an anechoic, circulating formation in contact with the TA and whose pertus is derived from the latter [69]. The arteriovenous fistula of the scalp can also be of congenital origin. These lesions of the TA cause the appearance of a pulsatile mass, associated with headaches or pulsatile tinnitus [67]. Treatment options include surgical excision, ligation of the feeding vessels, or the use of endovascular techniques (percutaneous embolization) [67][68][69].

The TA may be the site of arteriovenous malformations, which are rare, usually congenital vascular anomalies, composed of a complex network of interconnected arteries and veins. Up to 20% of arteriovenous malformations involving the scalp are associated with a history of trauma [70]. Arteriovenous malformations of the head and neck occur in 0.1% of the population and TA is involved in 75% of scalp arteriovenous malformations [71]. Clinically, the patient may present with headache, local pain, paresthesias, tinnitus, ischemic necrosis, or nidus ulceration and hemorrhage associated with *thrill* on palpation [71].

2.2. Atheromatous Disease

The existence of atheromatous lesions is almost constant at the age when GCA is revealed [2]. The Atheromatous disease leads to the appearance of more or less calcified atheromatous plaques in the arterial wall, which on ultrasonography are manifested by a thickening of the intima-media thickness, generally hyperechoic or isoechoic, more rarely hypoechoic. This appearance may be confused with a true halo sign. De Miguel et al. showed in a cohort of 40 patients over 50 years of age at high cardiovascular risk and without GCA, that an intima-media thickness at the level of the common carotid artery > 0.9 mm on Doppler ultrasound was associated with an increase in intima-media thickness at the level of the TA > 0.3 mm and could therefore be confused with a halo sign [72]. As a result, they proposed to retain the threshold of 0.34 mm of intima-media thickness in at least two branches of the TA (common, frontal, or parietal) to define a true halo sign. This threshold made it possible to exclude 97.5% of patients with atheromatous damage to the TA [72].

2.3. Calcifying Uremic Arteriolopathy (Calciphylaxis)

Calcifying uremic arteriolopathy (calciphylaxis) mainly affects patients with chronic end-stage renal disease and leads to the development of calcifications in arterioles and soft tissues. Arteriolar calcifications are the cause of an

obliterative vasculopathy leading to ischemia of the perfused territory (mainly dermis and hypodermis) and then to its necrosis. Clinically, the skin lesions are very painful, evolve towards ulceration, and are at high risk of infection. Histologically, calciphylaxis is a vasculopathy without vasculitis, characterized by calcification predominantly in the media with narrowing of the vascular lumen and the presence of fibrin microthrombi [73]. A few cases of calciphylaxis of TA have been described, mimicking GCA with ophthalmologic involvement (decreased visual acuity, sudden blindness, diplopia). An ophthalmologic examination may demonstrate authentic anterior ischemic optical neuropathy. Although GCA is more common in women, the majority of cases of TA calciphylaxis occur in men around 70 years of age, who are hypertensive and have renal insufficiency [74].

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