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Original research article

Large vessel vasculitis

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ARTICLE INFO

Article history:
Received 10 June 2017
Received in revised form
9 September 2017
Accepted 16 September 2017
Available online xxx

Keywords:
Large vessel vasculitis
Takayasu's arteritis
Temporal arteritis
Giant cell arteritis
Halo sign

ABSTRACT

Vasculitis represents a heterogeneous group of immunopathological diseases, characterized by the inflammation of blood vessels leading to destruction of the vascular wall, subsequent proliferation and constriction, or even blockage of the lumen. According to their range, inflammatory changes cause various severe systemic manifestations such as loss of appetite, weight loss, fever of unknown origin, and night sweats; locally causing ischemia of areas supplied by the affected artery. The aim of our paper is to highlight the fact that vasculitis pose significant danger for patients, who may encounter significant delays in getting the correct diagnosis and management of their condition; and also for doctors, as vasculitis is relatively rare disease, its etiology is often unknown and pathophysiology has not been fully understood.

Introduction

Although, in general, we comment on Takayasu's arteritis and Horton's disease here, we would mainly like to focus on "a new" nosological unit – giant cell arteritis with predominantly extracranial involvement of the large arteries, which is somewhat a "hybrid" of both of the above mentioned types that does not meet the diagnostic criteria of either of them. In the second part of our paper, we present a few case reports from the file of patients examined at the Department of Internal Medicine in Písek Hospital (catchment population 70 000 people) since the beginning of 2013 with suspicion of large vessel vasculitis that was subsequently confirmed. The subgroup, including solely the patients with arteritis predominantly affecting extracranial arteries, currently consists of 8 patients (2 males + 6 females). One separately presented case report describes a patient with simultaneous involvement of extracranial arteries and the temporal artery, thereby documenting possible overlap of the two units in some cases. Yet the involvement of the temporal artery seems to be key in some way. If the extracranial arteries are affected but the temporal artery is not, we, doctors, often lack the clue – though it is within our reach – that would lead us to accurate diagnosis during the first assessment. At the end, we include an extra case report of a young female patient with Takayasu's arteritis and striking differences in the velocity of blood flow in the coeliac trunk depending on the phase of respiration.

Classification

According to their etiology, vasculitides are divided into primary, whose underlying cause is unknown, and secondary

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http://dx.doi.org/10.1016/j.crvasa.2017.09.003

that accompany other conditions (e.g. oncological, infectious, etc.).

Classification of vasculitides is not united and varies according to different criteria. Chapel Hill Consensus Conferences (in 1994 and 2012) are a pair of international conferences that addressed the need of standardized classification system for vasculitides. They resulted in classification which takes into consideration vessel caliber, histopathology, pathogenesis, and serology. According to the caliber of the affected arteries, we distinguish between large, medium, and small vessel vasculitides. The aorta, its major branches and analogically the corresponding veins are referred to as large vessels; the main visceral arteries and veins and their initial branches are referred to as medium vessels; and the intraparenchymal arteries and veins, arterioles, capillaries and venules are referred to as small vessels [1]. Serology can define two groups – vasculitides associated with the occurrence of autoantibodies against antigens in the cytoplasm of neutrophils (ANCA – anti-neutrophil cytoplasmic antibodies) and vasculitides without such antibodies [2]. There are several mechanisms in the pathogenesis of vasculitides. For most of the secondary vasculitides, immune complexes and the inflammatory response they trigger, are involved in tissue damage. In ANCA-associated vasculitides, these are autoantibodies that affect various functions of neutrophils. They stimulate the neutrophils to produce oxygen radicals and to release lysosomal enzymes causing the damage to the surrounding tissue; they simultaneously inhibit their bactericidal functions and thereby contribute to patients' increased susceptibility to infections (particularly staphylococcal). Cell-mediated immunopathological response (e.g. in Takayasu's arteritis and Horton's disease) or cytotoxic mechanism of damage mediated by anti-glomerular basement membrane antibodies (e.g. Goodpasture syndrome) applies in some vasculitides.

Historically, only two types of arteritides belong to group of large vessel vasculitis – Takayasu's arteritis and giant cell temporal arteritis (Horton's). However, Horton analogous arteritis that mainly affects large extracranial arteries has appeared in this group recently. Another subset of large vessel vasculitis is represented by aortitis.

Diagnostics

Elevated erythrocyte sedimentation rate (ESR), CRP, anemia of chronic diseases and leukocytosis are typical laboratory findings in patients with vasculitis; some isotypes of immunoglobulins (particularly IgG), proinflammatory cytokines and values of extracellular matrix metalloproteinases may be raised as well. However, there is no laboratory marker specific for vasculitis, which would be clearly diagnostic.

CT or MR angiography that displays segmental stenoses up to occlusions of large arteries or aneurysms are conclusive imaging methods. PET/CT is a very useful examination, whose significance has grown recently as it became more available. It detects raised metabolic activity of inflammatory process in the arterial wall before we can detect structural changes by ultrasonography. It is used to assess activity of the disease during follow-up. Ultrasonography plays a significant role in the diagnostics of vasculitis. It is broadly available and, in the hands of an experienced physician, it is fast, inexpensive, and it does not burden the patient. The method has its limits in the elderly patients, where it can be sometimes difficult to differentiate between inflammatory changes of the arterial wall and atherosclerotic changes. Sonographic signs of ongoing inflammation are an increase in intima-media thickness (IMT), echogenic line in the thickened intima-media and a halo sign; and in the late stage confirmation of stenoses/occlusions can be detected. As the halo sign we call a hypoechogenic rim around the perfused artery lumen with a diameter of 0.3–2 mm that corresponds to swelling of the vascular wall. This can, however, be also found in patients with malignancies or infectious diseases and thus specificity of this finding is not fully diagnostic for vasculitis. Stenosis in an ultrasound image is characterized by segmental increase in blood flow velocity (two times higher speed in the region of the constriction than before stenosis), turbulent flow and persisting color flow signal during diastole. Acute arterial blockage manifests in complete absence of the color flow signal in the affected artery segment. Ultrasound is also very useful in identification of the correct place for possible biopsy and for monitoring the effect of treatment. After introduction of successful therapy, halo sign disappears within 14 days [3,4] (CRP drops to reference levels after approx. 42 days and ESR after approx. 28 days) although a certain degree of vascular wall thickening may persist even in patients who are in full remission.

Management

The standard management of vasculitis includes in the first line corticosteroids, either in monotherapy, or in combination with other immunosuppressive agents including cyclophosphamide, azathioprin, methotrexate or ciclosporin. In case of intolerance, poor therapeutic response or relapse, targeted (biological) therapy has been investigated. The biologics effect immune mechanisms on different levels both in cells and tissues. They block cytokines or their receptors and effect T-cell and B-cell subpopulations. From group of cytokine inhibitors or their receptors were in the management of refractory Takayasu's arteritis inhibitors of tumor necrosis factor (infliximab and etanercept) investigated. The first report of using monoclonal antibody against interleukin-6 in the management of 20-year-old female patient with refractory Takayasu's arteritis was reported in 2008. Since adequate therapeutic response to conventional therapy had not been achieved, the Ethics Committee in Osaka University Hospital approved the use of tocilizumab (the optimum dose to maintain adequate blood levels is 8 mg/kg every 4 weeks) [5]. Other promising agents investigated in the management of vasculitis include inhibitor of T-cell co-stimulator – abatacept, and anti-CD20 monoclonal antibody causing CD20+ B-cell depletion – rituximab [6,7].

Non-pharmacological approach is used to manage occlusions and stenoses, utilizing interventional radiology service – percutaneous transluminal angioplasty, and surgical – vascular bypass. However, unless the inflammation is not suppressed by simultaneous immunosuppressive therapy,

Please cite this article in press as: L. Zavadilová, L. Gergely, Large vessel vasculitis, Cor et Vasa (2017), http://dx.doi.org/10.1016/j.crvasa.2017.09.003