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Review Article

Clinically isolated aortitis: pitfalls, progress, and possibilities☆

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ABSTRACT

Non-infectious aortitis may be caused by several distinct systemic rheumatologic diseases. In some patients, aortitis is identified either pathologically or radiologically in the absence of clinical evidence of a systemic vasculitis. By consensus nomenclature, such cases are referred to as clinically isolated aortitis (CIA). Some systemic disorders may initially present as CIA including giant cell arteritis (GCA), IgG4-related disease, infectious aortitis, and granulomatosis with polyangiitis. CIA most commonly occurs in women of European descent over the age of 50 and, thus, mirrors the gender, age, and geographic distribution of GCA. CIA most often demonstrates a granulomatous/giant cell pattern of inflammation (GPI), and CIA-GPI is pathologically indistinguishable from aortitis due to GCA. In many cases, CIA may be a manifestation of extracranial GCA. CIA is being identified both pathologically in resected aortic tissue and radiologically by computed tomography scanning, magnetic resonance imaging, and fluorodeoxyglucose positron emission tomography. However, there appears to be significant differences between pathologically defined CIA and radiologically defined CIA. Multiple studies have shown that patients with CIA are at increased risk for subsequent aortic events (new aneurysms or dissections) and thus it is recommended to monitor these patients with periodic aortic imaging. While the data is currently limited, there is increasing evidence that at least some patients with CIA may benefit from immunosuppressive therapy.

Contents

1. Introduction

Aortitis is a group of disorders leading to inflammation in the aorta, and may be caused by either infectious or non-infectious etiologies [1–3]. Systemic diseases associated with noninfectious aortitis include

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giant cell arteritis (GCA), Takayasu arteritis, rheumatoid arthritis, systemic lupus erythematosus, Cogan's syndrome, Behçet disease, ankylosing spondylitis, and IgG4-related disease (IgG4-RD) [4–12]. Infectious aortitis can be caused by both bacterial and fungal infections [13–16]. In some patients, aortitis is identified without clinical features of a systemic vasculitis, and such cases are referred to as clinically isolated aortitis (CIA) [1,17–33]. While CIA is the terminology for this condition that was recently endorsed by international consensus, the disorder has also been referred to in the literature by various other names including idiopathic aortitis, isolated aortitis, and non-syndromic aortitis. When CIA involves the ascending aorta, it has been referred to as isolated ascending aortitis [20,22]. By revised Chapel Hill vasculitis nomenclature, CIA would be considered a single-organ vasculitis, which presumes it is truly isolated to the aorta [34]. CIA as an entity emerged largely coincident with the advent of aortic surgical pathology, with surgical pathologic case series reporting CIA as early as 1977 [17].

Currently, CIA can be diagnosed in two distinct settings. Traditionally and most commonly, the disorder is diagnosed pathologically following surgical resection of an aortic segment for aneurysm or dissection, and the patient is clinically found to have no other signs or symptoms of vasculitis. Pathologically defined CIA is typically a non-infectious form of aortitis, since infectious aortitides with a suppurative pattern of inflammation would usually be excluded from such case series. CIA may also be identified radiologically, most often by magnetic resonance imaging (MRI) or computed tomography (CT) scan with or without fluorodeoxyglucose positron-emission tomography (PET). In contrast to pathologic CIA, radiologic CIA may be either infectious or non-infectious in etiology.

It is also becoming clear that some patients initially felt clinically to have CIA actually have a systemic form of vasculitis, which fully manifests at a later time. Thus, often it has been unclear whether patients with CIA truly have a vasculitis that is completely isolated to a specific aortic segment, such as the ascending aorta, or if in fact they have a smoldering systemic vasculitis that is subclinical in other locations at the time of presentation. Managing patients with CIA can be difficult, as there are conflicting long-term follow up studies, and no general consensus on the role on immunosuppression. This review will highlight our current understanding of this disorder focusing on long-term follow up studies, and the heterogeneity of the disease as diagnosed in different settings.

2. Pathology of clinically isolated aortitis

The pathology of aortitis is best classified into four patterns of inflammation: granulomatous/giant cell pattern of inflammation, lymphoplasmacytic pattern of inflammation, suppurative pattern of inflammation, and the mixed inflammatory pattern [1]. Each inflammatory pattern is associated with specific systemic diseases. The granulomatous/giant cell pattern of inflammation is characterized by the presence of large epithelioid macrophages with or without giant cells and compact granulomas and is seen in GCA, Takayasu arteritis, rheumatoid vasculitis, sarcoidosis, granulomatosis with polyangiitis (GPA), and mycobacterial and fungal infections. An accompanying lymphoplasmacytic infiltrate is often present. The lymphoplasmacytic pattern consists of lymphocytes and plasma cells without a granulomatous/giant cell component, and occurs in the setting of IgG4-RD, syphilitic aortitis, lupus erythematosus, and ankylosing spondylitis, and also with under-sampling of an aortitis with one of the other inflammatory patterns, particularly the granulomatous/giant cell pattern [1,35]. The mixed inflammatory pattern is an uncommon pattern characterized by a mixture of inflammatory cells including lymphocytes, plasma cells, macrophages, neutrophils, mast cells, and eosinophils, and is seen in Cogan syndrome, relapsing polychondritis, and Behçet disease. The suppurative pattern is characterized by a marked neutrophilic infiltrate with extensive necrosis and is seen in some forms of infectious aortitis, such as infections with Gram-positive cocci, *Salmonella*, and *Pseudomonas*.

Since CIA is defined in part by the lack of clinical signs and symptoms of systemic vasculitis, essentially any of the four histologic patterns of inflammation could be present in this disorder, particularly when identified radiologically. However, when CIA is identified pathologically, cases with a suppurative pattern of inflammation will usually be defined as infectious aortitis rather than CIA, which often implies a non-infectious etiology. Thus pathologic CIA may have a granulomatous/giant cell, lymphoplasmacytic or mixed inflammatory pattern.

Understanding the pathology of CIA has been hindered by the fact that in some case series, detailed pathologic information was not reported. In addition in some series, the full spectrum of pathology that may be encountered in the granulomatous/giant cell pattern of inflammation was not considered and only the presence of giant cells was reported. Furthermore it is understood that under-sampling can hinder the identification of the granulomatous giant cell pattern of inflammation. However, in spite of these limitations, in most case series of the ascending aorta, the majority of cases of CIA show a granulomatous/giant cell pattern of inflammation (CIA-GPI) that overlaps considerably with that seen in giant cell arteritis (Fig. 1) [28]. Overall from 9 separate studies from the United States, Europe and Asia, CIA-GPI accounted for at least 150 (66%) of 226 cases of CIA [17–21,25,29,30,32]. The majority of the remaining cases appear to have a lymphoplasmacytic pattern of inflammation, and as discussed above, many of these may represent under-sampled cases with a granulomatous/giant cell pattern of inflammation.

There have been efforts to determine if the histologic features of CIA, beyond the type of inflammatory pattern, differ from those of aortitis occurring in the setting of systemic rheumatologic disorders [20,22,29,31,32]. One study reported that CIA may have a distinctive pathology, with so-called medial laminar necrosis being present in 39 (89%) of 44 CIA cases but only 4 (50%) of 8 systemic aortitis cases [22]. A subsequent study echoed this observation, in which so-called laminar medial necrosis was present in 50 (86%) of 58 CIA cases compared with 3 (23%) of 13 systemic aortitis cases [32]. It should be stressed that many of the areas being presented as necrosis in these studies are unlikely to be acute necrosis and are best interpreted as zones of medial smooth muscle cell nuclear loss or simply medial smooth muscle cell loss [36]. In contrast to these two studies, three studies did not find histologic features in aortitis, such as the presence of necrosis, to be helpful in differentiating CIA from aortitis associated with systemic diseases [20,29,31]. Together in these three studies, so-called necrosis was present in 32 (55%) of 58 CIA cases and in 26 (65%) of 40 systemic disease cases. Interestingly, in the studies reporting a specific association of "necrosis" with CIA, CIA accounted for 83% of the aortitis cases compared with only 59% of the aortitis cases ($P=.0001$) in the studies not finding such an association. This marked difference suggests that lack of clinical history and follow-up may be contributing in part to the purported association of CIA with "necrosis" being observed in some studies.

In a follow-up study of CIA-GPI of the ascending aorta, all 15 cases in the study contained this so-called laminar medial necrosis, and 7 of the 15 patients suffered subsequent distal aortic events, indicating that so-called laminar medial necrosis was not useful in identifying which cases of aortitis were limited to the ascending aorta [28]. Thus, it would appear that the presence of so-called laminar medial necrosis should not be used to conclude that an aortitis is isolated to the ascending aorta, and that at present there appears to be no clear and reliable histologic feature that allows accurate distinction of CIA from a clinically systemic disorder.

3. Systemic disorders that may present as clinically isolated aortitis

Since CIA is defined by the absence of clinical evidence of extra-aortic involvement and is thus dependent on the quality of the clinical workup and the degree of follow-up, essentially any systemic vasculitis