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Review

Discrepancies between vascular and systemic inflammation in large vessel vasculitis: an important problem revisited

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Abstract

A lack of absolute correlation between systemic inflammation parameters and ongoing vascular disease activity is an important problem in some patients with large vessel vasculitis, especially Takayasu arteritis (TAK). Systemic and vascular wall inflammation in TAK are obviously interrelated, but sometimes they may act independently. There are clear discrepancies between these two types of inflammation, including cytokine patterns and responses to treatment. Vascular and systemic inflammation may also be discordant in two subgroups of giant cell arteritis. The first subgroup is mainly characterized by severe systemic inflammation mostly associated with IL-6-driven immunity, while in the second subgroup there is less systemic inflammation but prominent neuro-ophthalmic ischaemic complications characterized mostly by IFN-γ-mediated effects. Although no definite boundaries exist, it may be suggested that the IL-6/Th17/IL-17 pathway primarily drives systemic inflammation while the IL-12/Th1/IFN-γ pathway dominates in vascular wall inflammation both in TAK and giant cell arteritis. Immunosuppressive treatment of TAK (especially corticosteroids) initially suppresses systemic inflammation, while longer treatment duration is required for the suppression of vascular inflammation. Therefore, evaluating only the systemic inflammation may be misleading. Vascular wall inflammation is currently evaluated using expensive imaging methods, which are not feasible for repetitive use. Although pentraxin-3 is superior to erythrocyte sedimentation rate and CRP, we need more reliable biomarkers to reflect vascular wall inflammation in patients with TAK.

Key words: Takayasu arteritis, inflammation, giant cell arteritis

Rheumatology key messages

- In large vessel vasculitis, there may be clear discrepancies between systemic and vascular wall inflammation.
- In Takayasu arteritis, vascular wall inflammation may persist despite suppression of systemic inflammation.
- Besides currently used imaging methods, reliable biomarkers for detecting vascular wall inflammation are needed.

Introduction

A lack of absolute correlation between systemic inflammation as assessed from acute phase responses and ongoing vascular disease activity is an important problem in large vessel vasculitis, especially Takayasu arteritis (TAK). In other words, systemic inflammation in TAK does not always reflect the degree of vascular wall inflammation and arterial specimens of some patients with TAK may show histological signs of active or smouldering vasculitis despite normal ESR and/or serum CRP levels [1–3]. On the other hand, vascular and systemic inflammation may also be discordant in two subgroups of giant cell arteritis (GCA). The first subgroup is mainly characterized by severe systemic inflammation mostly associated with IL-6-driven immunity, while in the second subgroup there is less systemic inflammation but prominent neuro-ophthalmic ischaemic complications characterized mostly by IFN-γ-mediated effects [4].

It is not clear why measures of systemic inflammation do not always reflect vascular inflammation and disease activity in TAK. Although these two types of inflammation are

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obviously interrelated, sometimes they may act independently and there are discrepancies between the systemic and vascular wall inflammation seen in TAK. Although there are still many unknown issues and controversies in TAK, recent publications have contributed much to our current understanding of its pathogenesis [5–8]. As summarized below, inflammation in TAK initially arises in the vascular wall [9], and it may be speculated that systemic inflammation develops subsequently. Immunosuppressive (IS) treatment of TAK probably suppresses systemic inflammation initially, while the suppression of vascular inflammation requires a longer treatment duration.

In the present review we discuss the current evidence supporting the discrepancies between systemic and vascular wall inflammation in large vessel vasculitis, with renewed focus on the problem of the unreliability of systemic inflammation in reflecting ongoing vascular disease activity, especially in some patients with TAK. We begin with a brief overview of the pathogenesis of vascular wall inflammation in TAK, followed by an examination of the differences in cytokine production patterns in circulation and vasculitic lesions. We continue by discussing evidence of discordance between vascular and systemic inflammation in some subgroups of GCA and the effects of IS treatment on inflammation (including limited histopathological data) in TAK, as well as differences from GCA. Finally, we summarize current approaches to the evaluation of vascular wall inflammation, relate some disappointing results obtained with pentraxin-3 (PTX-3) and discuss the challenging but necessary next step of finding more reliable biological markers for detecting vascular inflammation.

Brief overview of the pathogenesis of vascular wall inflammation in TAK

Inflammation originates in the adventitia via the vasa vasorum [9], and the earliest inciting event in the pathogenesis of TAK is likely to be the activation of resident vascular dendritic cells (vasDCs) within the adventitia. Later on, these vasDCs transform, increase in number and distribute throughout the wall [10, 11]. In addition to vasDCs, the vascular inflammatory cell infiltrate is composed predominantly of Th1 and Th17 subsets [7] plus cytotoxic T cells, $\gamma\delta^+$ T cells, NK cells, macrophages, monocytes and giant cells [12–14]. Recently, Kong *et al.* [8] showed that there were more $CD4^+$ T cells than $CD8^+$ T cells in the areas of vascular inflammation in TAK. $CD4^+$ T cells also initiate and maintain granuloma formation by releasing IFN-γ [15]. Seko *et al.* [13, 14] analysed the expression of T cell receptor transcripts of infiltrating cells in the aortic tissue of patients with TAK and found that the repertoire of these gene transcripts had an oligoclonal profile, which is typical for antigen-induced proliferation.

Recently, Saadoun *et al*. [7] demonstrated marked increases in the expressions of Th1 and Th17 cells in vascular inflammatory infiltrates of patients with TAK, correlating with disease activity. They concluded that both Th1 and Th17 immunity played important roles in driving TAK-related vascular and systemic inflammation. In another recent study, Kong *et al.* [8] showed extensive production of IL-6, IL-17, IL-12 and IFN-γ in vascular lesions of TAK. Given that IL-6 promotes the differentiation of T cells towards the IL-17-producing Th17 cells [16] and IL-12 produced by vasDCs promotes the differentiation of T cells towards the IFN-γ-producing Th1 cells [17], the findings of Kong *et al.* support the role of both Th1 and Th17 cells in vascular wall inflammation in TAK. On the other hand, O'Neill *et al.* [6] suggested that the IL-6/Th17/IL-17 pathway mainly sustains systemic inflammation both in TAK and GCA, while the IL-12/Th1/IFN-γ pathway may be predominant in vascular wall inflammation.

However, the role of IFN-γ in TAK pathogenesis is generally extrapolated from reviews and original studies concentrating mainly on GCA [4, 18–20] and on atherosclerosis [21–24]. These studies showed that IFN-γ caused smooth muscle cell proliferation and seemed to be responsible for driving vascular remodelling of stromal cells and intimal hyperplasia. Recently, Saadoun *et al.* [7] also demonstrated the presence of IFN-γ-, IL-6-, and IL-17A-producing T cells in vascular inflammatory infiltrates in patients with TAK. Furthermore, they reported a positive correlation between IFN-γ and vascular disease activity. Based on these observations, O'Neill *et al.* [6] suggested that IFN-γ not only induced the activation of macrophages and differentiation of T cells but also contributed to luminal stenosis and occlusion of the large arteries in both GCA and TAK. Since peripheral blood mononuclear cell expression of IFN-γ was also reported to be significantly higher in patients with TAK compared with GCA [7], O'Neill *et al.* [6] further speculated that this might account for increased vessel stenosis in TAK *vs* GCA. However, we believe that IFN-γ is not the only cytokine causing vessel narrowing and stenosis in TAK. IL-6 and IL-17, which are markedly produced and abundant in vascular lesions [8], may also contribute to vascular stenosis in TAK. Other factors contributing to vascular damage and stenosis in TAK are the release of growth factors such as VEGF and PDGF by IFN-γ-activated macrophages, NK and $\gamma\delta$ T cells and pro-apoptotic pathways [5, 12]. Furthermore, MMPs cause the degradation of elastic fibres within the arterial wall, leading to fragmentation of the internal and external elastic laminae [25, 26].

Differences in the cytokine production patterns in circulation and vasculitic lesions in TAK

Serum levels of IL-6 [8, 26–29], the chemokine RANTES (regulated on activation, normal T cell expressed and secreted) [27], IL-8 [29, 30], IL-18 [28, 29] and TNF-α [28] were reported to be higher in patients with TAK. Among these cytokines, serum IL-6 [28] and IL-18 [28, 29] levels were significantly elevated in TAK patients with active disease compared with those with inactive disease. On the other hand, serum levels of IFN-γ [28], GM-CSF [29], IL-10 [29] and IL-23 [29] were found to be similar to those of healthy controls.

The data are rather confusing for IL-12. Serum levels of IL-12 were reported to be similar between patients with TAK and healthy controls in a previous study [28]. However, Verma *et al.* [31] reported that plasma concentrations of IL-12 were not only significantly increased in TAK compared with healthy controls, but were also associated with disease activity. Similarly, Kong *et al.* [8] recently reported that serum IL-12 levels were higher in patients with TAK. Kong *et al.* [8] also reported that serum IL-10 levels tended to be slightly higher, while IL-4, IL-17 and IFN-γ levels were lower in patients with TAK. In contrast , Tripathy *et al.* [32] studied pro-inflammatory cytokine transcripts of peripheral blood mononuclear cells and found that patients with TAK had higher mRNA gene expression of TNF-α, IFN-γ, IL-2, IL-3 and IL-4.

Unfortunately, histopathological studies investigating local vascular cytokine expressions are limited in TAK. In other words, a paucity of tissue data available in patients with TAK is an important problem. Recently Kong *et al.* [8] studied tissue samples from nine TAK patients and nine patients with atherosclerosis as a control group and showed that IL-6, IL-17, IL-12 and IFN-γ were markedly produced and abundant in local vascular lesions in TAK. It was striking that the vascular expression levels of IFN-γ and IL-17 were also high, despite low serum levels, showing that cytokine levels in the peripheral blood were not always in accord with those in vasculitic lesions. The authors speculated that the discrepancy between serum IL-17 levels and tissue IL-17 signals might contribute to the migration of T cells from peripheral blood to local vascular tissues and subsequently to activation *in situ* [8]. They also speculated that excessive production of IL-17 in aortic tissues might result from enhanced expression of IL-6 [8]. Similarly, Saadoun *et al.* [7] showed that the aortic inflammatory infiltrates in three patients with active TAK showed strong expression of IFN-γ and IL-6 compared with three patients with TAK in remission and three patients with atherosclerosis.

While evaluating the data for serum cytokine levels and local vascular cytokine expression in TAK, it should be kept in mind that these results were obtained from different studies that were not necessarily linked. Besides, patients included in these studies were in different stages of disease activity, had different disease durations and were on different treatment regimens.

Are there subgroups of GCA that exhibit discordant vascular and systemic inflammation?

TAK and GCA have been considered to be two separate large vessel vasculitides based on a number of differences, including age of onset, ethnic discrimination, clinical features and vascular distribution. However, these two diseases also have striking similarities, such as the role of cell-mediated immunity in their pathogenesis, similar pathological findings in the vessel wall and high serum levels and vascular expression of certain cytokines, including IL-6 and IL-17 [6, 33]. Recently a metachip analysis including both GCA and TAK patients revealed IL-12B as the most prominent genetic factor for both diseases [34].

Although there is an ongoing debate concerning whether TAK and GCA may represent a spectrum of the same disease [6, 33, 35], two subgroups of GCA with two different dominating immunopathologies deserve special attention [4]. The first subgroup is mainly characterized by severe systemic inflammation mostly associated with IL-6-driven immunity, while in the second subgroup there is prominent vaso-occlusion sustained by a less inflammatory but more tissue-remodelling process [4].

The background of these observations goes back to 1998, when Cid *et al.* [36] retrospectively investigated 200 consecutive patients with biopsy-proven GCA in a multicentre study and found that 32 patients who developed irreversible cranial ischaemic complications had significantly lower acute phase responses. The authors reported that the presence of a strong acute phase response defined a subgroup of patients at very low risk of developing cranial ischaemic complications, while low systemic inflammatory response correlated with a high risk for such complications. Two years later, Gonzalez Gay *et al.* [37] also reported that GCA patients with visual ischaemic complications had lower clinical and laboratory biologic markers of inflammation, based on their series of 161 patients. They observed a lower incidence of constitutional symptoms and higher haemoglobin values in those patients and pointed out that a higher inflammatory response might be a protective factor against the development of cranial ischaemic events. In 2005 Salvarani *et al.* [38] confirmed this observation. They investigated the frequency of and risk factors for visual manifestations in an Italian population-based cohort of 136 patients with biopsy-proven GCA. They reported that patients with low inflammatory response had a higher risk of visual loss. In 2009 the same group extended their data and confirmed that low systemic inflammatory response was associated with a higher risk of developing severe cranial ischaemic events [39].

The exact reason for the lower systemic inflammatory response in GCA patients presenting with ischaemic complications remains unknown. IFN-γ production is higher in GCA patients with prominent cranial symptoms compared with patients who have only systemic manifestations [40]. Therefore variations in cytokine production may indeed account for different disease expression patterns in patients with GCA [36]. A close association between neuro-ophthalmologic complications and intimal hyperplasia on biopsy has also been demonstrated [41]. On the other hand, acute phase reactants like haptoglobin may promote neovascularization in patients with a higher inflammatory response. Therefore Cid *et al.* [36] suggested that lower systemic inflammation, that is, lower haptoglobin levels, may increase the likelihood of ischaemic complications in GCA.

In summary, vascular and systemic inflammation may also be discordant in some patients with GCA. In

particular, there is a subgroup of GCA that is characterized by less systemic inflammation and increased neuro-ophthalmic ischaemic complications [4, 36, 40]. Evidence supporting discordance between vascular and systemic inflammation in TAK and in GCA is summarized in Table 1.

Effects of immunosuppressive treatment on inflammation in TAK and differences from GCA

The data regarding the effect of corticosteroid (CS) treatment on various T cell subsets in different types of large vessel vasculitis seem to be controversial. Saadoun *et al.* [7] reported that production of Th1 cytokines (IFN-γ, TNF-α and IL-2) was adequately suppressed by CS treatment in patients with TAK, while Th17 cytokines (IL-17A and IL-23) were found to be CS resistant. On the other hand, in GCA the Th17 pathway was reported to be important in early disease and was rapidly suppressed by CS therapy, while the Th1 axis, that is, IFN-γ production, was relatively CS resistant and implicated in ongoing vascular inflammation [18, 42]. However, it should be kept in mind that the data in GCA represent temporal artery histological findings before and after CS treatment, thereby reflecting the effects of CS treatment on vascular wall inflammation [18, 42]. However, TAK data reflect the effect of CS treatment on systemic inflammation [7]. The differential effects of systemic IS treatment in TAK and GCA are summarized in Table 2.

Since histological evaluation of vascular wall inflammation in TAK is not possible except for surgical specimens, there is a paucity of data showing the effects of systemic IS treatment on T cell subsets and cytokine expression in vascular inflammatory lesions. In a recent study, Kong *et al*. [8] demonstrated that IL-6 staining was strongly positive in three vascular layers of pathological specimens independent of vascular changes, while other cytokines, such as IFN-γ, IL-12 and IL-17, were mainly positive in sites with inflammatory cell infiltrates. They showed that vascular IFN-γ expression disappeared, whereas staining for IL-6 and IL-12 remained positive in two TAK patients treated with CS. They speculated that vascular IL-6 and IL-12 may be more resistant to CS treatment and these two cytokines may be responsible for ongoing vascular pathology and the development of chronic vascular fibrosis in TAK, despite suppressed systemic inflammation [8]. However, the histopathological data of only two TAK patients are not sufficient to draw firm conclusions.

Various conventional IS agents such as MTX, AZA and LEF also seem useful in uncontrolled series in TAK [43]; however, further controlled studies are necessary to determine whether they can replace CS therapy.

Tocilizumab (TCZ) is an IL-6R inhibitor widely used for active and/or treatment-resistant TAK [44, 45]. TCZ treatment seems to be effective for TAK in uncontrolled case series [46, 47]. However, there are case reports of silent vascular progression detected via imaging despite normalized acute phase reactants during TCZ treatment [48, 49]. These observations also support the hypothesis that systemic and vascular inflammations may be discordant in TAK and may have two basic implications: first, vascular IL-6 expression may be more resistant to TCZ, and second, persistent vascular IL-12 activity despite IL-6 inhibition may be responsible for ongoing vascular inflammation during TCZ treatment.

Given that vascular inflammation in TAK is granulomatous and vascular expression of TNF-α is abundant, biologic agents inhibiting TNF-α may also be effective in controlling both systemic and vascular wall inflammation in TAK. In support of this, anti-TNF agents have been shown to be effective in TAK in a large number of case series [50, 51]. However, anti-TNF agents seem to be ineffective in patients with GCA [52–54]. Although the reason remains unknown, it has been proposed that TNF-α may be more functional in TAK than in GCA [6].

A Disappointing Pentraxin Story in TAK

Due to the discordance between systemic and vascular wall inflammation in TAK, in clinical practice, suppression

Table 1 Evidence supporting that sometimes vascular and systemic inflammation may be discordant in large vessel vasculitis

Discordant parameter	Definition of the discordance	Reference(s)
Laboratory parameters (TAK)	Normal ESR and serum CRP levels despite ongoing vascular inflammation in TAK	[1, 2, 48]
CRP *vs* pentraxin-3 (TAK)	While serum CRP levels more accurately reflect the burden of systemic inflammation, serum PTX-3 may identify vascular inflammation better in some patients with TAK	[57]
Cytokine patterns (TAK)	IL-6 and IL-17 levels high both in serum and vascular lesions in TAK; IL-17 and IFN-γ levels low in serum but high in vascular lesions in TAK	[8, 26–29]
Th1 and Th17 pathways (TAK and GCA)	In both TAK and GCA, the IL-6/Th17/IL-17 pathway mainly directs systemic inflammation, while the IL-12/Th1/IFN-γ pathway may dominate in shaping vascular wall inflammation	[6]
Severe systemic inflammation *vs* prominent cranial vascular ischaemia (GCA)	A subgroup of GCA is mainly characterized by severe systemic inflammation mostly associated with IL-6-driven immunity, while the second subgroup is characterized by less systemic inflammation, but more prominent vaso-occlusion driven by IFN-γ	[4, 36–41]

Table 2 Differences between TAK and GCA with regard to treatment responses

	TAK	GCA
Response to corticosteroid treatment	Serum levels of Th1 cytokines adequately suppressed while Th17 cytokines were not [7]	Th17 pathway rapidly suppressed, while the Th1 pathway (IFN-γ production) was relatively resistant and responsible for ongoing vascular inflammation (temporal artery biopsy data) [18, 42]
Response to anti-TNF agents	Favourable response [50, 51]	Inadequate response [52–54]

of vascular inflammation is evaluated by imaging methods such as magnetic resonance angiography and/or PET [1, 3, 55]. To identify effective new biomarkers, we need inflammatory molecules that are locally produced at sites of vascular inflammation and are expected to better reflect the degree of vascular wall inflammation. Therefore plasma PTX-3, which acts as the humoral arm of innate immunity and is involved in the maintenance of vascular homeostasis [56], was suggested as a more reliable and promising biomarker to reflect vascular disease activity in TAK [57–59]. Tombetti *et al.* [57] showed that PTX-3 may identify vascular progression only in a subgroup of TAK patients not receiving anti-cytokine treatments, while levels of CRP more accurately reflect the burden of systemic inflammation. However, in other patients with TAK, including those receiving anti-cytokine treatments, even plasma PTX3 levels were shown to be normal despite ongoing smouldering vascular inflammation [57]. In other words, although PTX-3 certainly had some advantages compared with CRP, it unfortunately could not solve the problem of detecting smouldering vascular wall inflammation in TAK.

Conclusion

Although systemic and vascular wall inflammation are clearly related with each other, there are obvious discrepancies between these two types of inflammation in TAK and they may also exhibit differences in cytokine production patterns and response to IS treatment. Vascular and systemic inflammation may also be discordant in two subgroups of GCA, evidenced by severe systemic inflammation mostly associated with IL-6-driven immunity in the first subgroup, whereas the second subgroup features less systemic inflammation but prominent neuro-ophthalmic ischaemic complications resulting primarily from IFN-γ-mediated effects. It is likely that treatment of TAK with CS and IS agents initially suppresses systemic inflammation, while longer treatment duration is required for the suppression of vascular inflammation. Therefore evaluating only the systemic inflammation may be misleading. Currently magnetic resonance angiography or PET may be used to follow vascular wall inflammation, but these expensive techniques are not feasible for repetitive use. Reliable biomarkers are obviously needed to reflect vascular wall inflammation in patients with TAK. However, identifying these biomarkers is very challenging and may be accomplished only by means of prospective, multicentre studies utilizing repetitive imaging together with serial serum samples for biomarker studies in a cohort of newly diagnosed TAK patients.

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