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Review Article

Assessment of disease activity in Takayasu's arteritis

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ABSTRACT

Takayasu's arteritis (TA) is a large vessel vasculitis of unknown etiology, more common among Asians. Since it is a smoldering, chronic disease, assessment of disease activity is a challenge. Acute phase reactants, erythrocyte sedimentation rate and CRP, imperfectly correlate with disease activity on histopathology. The earliest clinical criteria to assess disease activity were the NIH criteria, taking a composite of clinical features, inflammatory markers, and imaging to assess disease activity in TA. Of late, clinical scoring systems like DEI.Tak (Disease Extent Index in TA), derived from the BVAS scoring for small vessel vasculitis, and the ITAS2010 and ITAS-A, derived from DEI.Tak, have been validated. Serum biomarkers like matrix metalloproteinases 2, 3, and 9, pentraxin-3 and soluble receptor for advanced glycation end products hold promise in assessing disease activity. Recently, endothelial microparticles have been shown to correlate with active TA. Evidence suggests wall edema, and contrast uptake in the vessel wall on angiography may suggest active TA. Scoring systems assessing angiographic extent of TA are a work in progress, validation of which shall help quantify extent of vascular involvement in TA, and serial follow-up might prove valuable for assessment of disease activity. PET-CT is useful to diagnose prepulseless TA; however, its utility in patients on immunosuppression is debatable. Analysis of serum metabolites using nuclear magnetic resonance spectroscopy is a promising exploratory approach towards identifying new biomarkers in TA. There remains an unmet need for a composite index, taking into account clinical features, serial radiography, and circulating biomarkers, to assess disease activity in TA.

1. Introduction

Takayasu's arteritis (TA) is a granulomatous large vessel vasculitis of unknown etiology, common in young Asian women.[1] Patients are classified as having TA as per the 1990 ACR criteria if they have at least 3 out of 6 of the following features: age of onset less than 40 years, decreased pulse in the upper limb, limb claudication, blood pressure inequality between limbs greater than 10 mm Hg, bruits on auscultating

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the subclavian arteries or aorta, and angiographic abnormalities consistent with TA.[2] Vascular inflammation in TA leads to fibrosis and stenosis slowly over a number of years. This vascular occlusion manifests clinically as limb claudication, stroke, or hypertension due to renal hypoperfusion. Often the manifestations of the disease do not become apparent until significant damage resulting in vascular stenosis has resulted. Hence, delay in diagnosis is an important consideration in patients with TA.[3]

Assessment of disease activity and damage is important in vasculitis to identify manifestations of active disease that are possibly amenable to therapy vis-à-vis those due to scars left behind by prior disease activity, viz., damage. In ANCA-associated small vessel vasculitis (AASV), assessment of disease activity is well established, through the Birmingham Vasculitis Activity Score.[4] Features in various organ systems, which are new or worse in the past 3 months, are scored, and a score greater than or equal to one at any time suggests active disease. Since the manifestations of AASV are relatively acute, it is easier to distinguish active disease or damage. Due to the low-grade vascular inflammation prevalent in TA, the assessment of disease activity is challenging in these patients. We shall review the assessment of disease activity in patients with TA.

2. Clinical assessment of activity in TA

The NIH criteria were the first to assess disease activity in TA. Patients who had new onset or worsening in 2 or more of the following abnormalities were classified as having active disease: presence of systemic features like fever or malaise, erythrocyte sedimentation rate (ESR) greater than 20 mm/h, features suggestive of vascular involvement like limb claudication, carotidodynia, pulse loss, asymmetry of blood pressure, vascular bruits, and angiographic abnormalities consistent with TA.[3] These criteria suggest that the longitudinal course of the disease is the most important reflection of disease activity. Using these criteria, new onset abnormalities on clinical examination or angiogram alone can suggest active disease irrespective of the ESR. Indeed, in the same study, 72% patients with active disease and 44% with clinically inactive disease had elevation of ESR.[3] Other studies correlating histopathology with ESR elevation have demonstrated presence of vascular inflammation in aortic biopsies of patients with TA obtained during vascular bypass procedures in spite of normal ESR. Hoffman reported presence of active vasculitis in aortic biopsies of 44% patients with clinically inactive TA at the time of surgery.[5] Cong et al. reported 12 patients with clinically inactive disease who had aortic biopsies. Seven of these patients had active inflammation on biopsy specimens despite ESR within normal range.[6] These clearly elucidate the limitations of relying on an acute phase reactant to assess disease activity in TA.

Considering these limitations of the NIH criteria or inflammatory markers to indicate active TA, the Indian Rheumatology Core Group for Vasculitis (IRAVAS) devised the DEI.Tak (Disease Extent Index in TA)[7] on the template of the Birmingham Vasculitis Activity Score (BVAS),[4] an established tool to assess disease activity in small vessel vasculitis. This score quantifies extent of disease at assessment, considering features present in the past 6 months, whether new or persistent, with a maximum score of 75. Various domains assessed include: systemic, cutaneous, mucous membranes, eyes, ENT (ear, nose, and throat), chest, abdomen, renal (including hypertension), nervous system, genitourinary, and cardiovascular. A weighted score is given in the presence of cardiovascular features, viz., the presence of bruits, pulse inequality, pulse loss, or claudication. Importantly, the DEI.Tak score is a composite score taking into consideration features that could be due to either disease activity or damage. Aydin et al.[7] compared the DEI.Tak to the NIH criteria and found an agreement of 94% between the two criteria for detecting patients with active TA. When compared with the physician global assessment for activity, NIH criteria had an agreement of 74% compared to 68% for the DEI.Tak. The superiority of the NIH criteria could be accounted for by their inclusion of radiology in the assessment of disease activity. The DEI.Tak, like the NIH criteria, is sensitive enough to reflect changes in disease activity over time. However, unlike the NIH criteria, it uses a much more comprehensive set of clinical manifestations in making a decision as to whether TA is active or not. Moreover, the DEI.Tak has been validated in a cohort of Turkish patients.[7]

Considering the fact that TA is a large vessel vasculitis, a spectrum different from the small vessel vasculitides, for which the BVAS was devised, and from which the DEI.Tak was derived, there was a need to devise a new scoring system to assess disease activity in TA. Hence, Misra et al.[8] devised a clinical scoring system, the Indian Takayasu Clinical Activity Score (ITAS2010), and the ITAS2010 modified to include acute phase reactants (ITAS-A), to assess disease activity in TA. Features of large vessel vasculitis were derived from the erstwhile DEI.Tak. ITAS2010 score features, which are new or worse in the past 3 months in the following domains: systemic (malaise, weight loss greater than 2 kg, fever, myalgia, arthralgia, arthritis, headache), abdomen (severe abdominal pain), genitourinary (abortions), renal (systolic hypertension greater than 140 mm Hg, diastolic hypertension greater than 90 mm Hg), nervous system (stroke, seizures, syncope, and dizziness) and cardiovascular system. Cardiovascular features account for 33 of the 44 features considered. The cardiovascular features include bruits, pulse inequality, new loss of pulses, claudication, carotidodynia, aortic regurgitation, congestive cardiac failure, cardiomyopathy, myocardial infarction, or angina. Features of diastolic hypertension, stroke, new pulse loss, bruits, pulse inequality, claudication, and carotidodynia are weighted to reflect a higher score. A maximum score of 51 is possible. ITAS2010 score of 4 or more is considered active. The ITAS-A is a modification of the ITAS 2010 to reflect acute phase reactants with additional score of 0–3 given based on acute phase reactants (ESR, if not available CRP is used). ESR (mm/h) of <20 is scored 0, 21–39 scored 1, 40–59 scored 2, and greater than 60 scored 3. Similarly, CRP (mg/L) of <6 scored 0, 6–10 scored 1, 10.1–20 scored 2, and greater than 20 scored 3. The score was validated in 143 Indian patients from two different centers. The score was significantly higher in patients with active TA compared to those with grumbling or inactive disease as rated by the physician global assessment. With immunosuppressive therapy, the ITAS2010 came