Comment on: Clinicopathological characteristics of severe aortic valve regurgitation caused by Behçet's syndrome

Sir,

We read with great interest the study by Zhang *et al*. describing the clinicopathological characteristics of severe aortic regurgitation (AR) caused by Behçet's syndrome (BS) (1). Given the rarity and clinical complexity of cardiovascular involvement in BS, such analyses are of substantial value. Nevertheless, several methodological aspects warrant further clarification to enhance the interpretability of the findings.

First, while the pathological assessment is comprehensive, the lack of comparator groups limits the ability to determine whether the observed inflammatory patterns are specific to BS or reflect advanced inflammatory AR in general. Inclusion of one or more reference populations, such as BS patients without aortic involvement, individuals with non-BS aortitis, or patients undergoing valve surgery for degenerative AR, could have strengthened the disease-specific interpretation of the histopathological features. This distinction is particularly relevant given that neutrophilic and lymphocytic infiltrates may occur across various inflammatory conditions affecting the aortic root (2).

Second, several clinical and biochemical confounders that may influence tissue inflammation were not fully addressed. Preoperative treatments such as corticosteroids, immunosuppressants, colchicine, and biologic agents can significantly modulate inflammatory cell dynamics (3). The exact dosing, duration and timing of these therapies were not specified. Additionally, the potential contribution of subclinical infection, including culture-negative endocarditis, was not discussed, despite its capacity to produce neutrophil-rich infiltrates (4). Common cardiovascular comorbidities (*e.g.*, hypertension, diabetes, smoking history), which affect vascular remodelling and adventitial neovascularisation, were also not reported. Given that ESR and CRP were used to define activity states, providing information on measurement timing and coexisting inflammatory conditions would enhance the reliability of group stratification.

Third, the absence of radiological correlations may have created a lack of integrated interpretation explanation. In contemporary vasculitis evaluation, aortic wall thickness, enhancement characteristics on CT/MRI, or PET-CT uptake values provide important complementary information. Similarly, echocardiographic quantification of AR severity and structural involvement (vena contracta, pressure half-time, annular measurements) would have allowed a more integrated clinicopathologic interpretation. The findings related to biologic therapy are of particular interest. However, the specific biologic agents administered were not detailed. Anti-TNF, anti-IL-1, and anti-IL-6 treatments have distinct immunologic profiles and may influence inflammatory cell infiltration differently (5). Aggregating these agents into a single category may obscure agent-specific effects and complicate interpretation of their association with reduced inflammatory infiltration.

Finally, while the authors performed between-group comparisons, the absence of multivariable adjustment limits the ability to ascertain whether the observed associations persist independent of confounding factors such as age, disease duration, baseline inflammatory markers, treatment exposure, and comorbidities. Incorporation of multivariable modelling, recommended in prior analyses of BS-related cardiovascular disease, would refine causal inference and strengthen the overall conclusions.

In summary, the study offers valuable insights into the pathological spectrum of severe AR associated with BS. Addressing the points above, particularly confounder control, radiologic-pathologic integration, clarification of therapeutic exposure, and greater methodological transparency, could further strengthen the conclusions and help delineate more precisely the pathological profile of Behçet-related aortic regurgitation.

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