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Commentary: The proinflammatory soluble CD40 ligand is associated with worse outcomes after pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension

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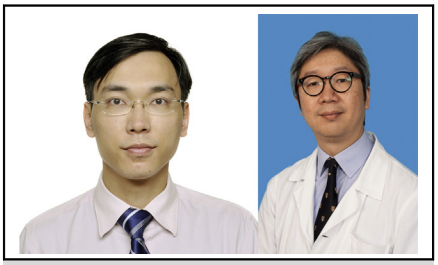

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CENTRAL MESSAGE

Elevated preop sCD40L levels are associated with low CI, high PVR, and poor surgical outcomes after pulmonary endarterectomy in CTEPH. Its utility as a biomarker and the mechanism needs further study.

Inflammatory thrombosis has been proposed as one of the pathophysiologic components in chronic thromboembolic pulmonary hypertension (CTEPH), where excessive inflammation contributes toward thrombus nonresolution.[1,2] In patients who underwent pulmonary endarterectomy (PEA), plasma levels of both C-reactive protein (CRP) and D-dimer at the time of diagnosis are independent and significant predictors of outcomes in CTEPH.[3] The French national CTEPH registry study showed that the preoperative CRP level is independently associated with prolonged catecholamine support after PEA.[4]

CD40L is a type II transmembrane protein that belongs to the tumor necrosis factor superfamily. It is highly expressed on activated T cells and platelets. The free and soluble form of CD40L (sCD40L) is released from the different cell surfaces into the circulation, and platelets are the major source of sCD40L. The proinflammatory sCD40L is involved in platelet activation, aggregation, and platelet–leucocyte conjugation and thus associated with inflammation, atherogenesis, and thrombosis.[5] Besides atherosclerotic cardiovascular diseases, sCD40L was found to have enhanced release or reduced clearance in the pulmonary vasculature and was involved in the inflammatory processes observed in pulmonary arterial hypertension.[6]

In this issue of the *Journal*, Shigeta and colleagues,[7] from Chiba, reported their single-center retrospective review of 90 cases of PEA spanning 19 years and showed for the first time that in patients with CTEPH, preoperative levels of sCD40L are associated with lower cardiac index, greater pulmonary vascular resistance, and poorer surgical outcomes after PEA.

The authors suggested that preoperative sCD40L levels could be a promising biomarker to identify high-risk patients undergoing PEA. As acknowledged by the authors, there is no validation cohort, and further study is needed. The reported discriminative power for poor surgical outcome was modest, with an area under the curve of 0.7586. Sensitivity and specificity were 79.3% and 67.3%, respectively, meaning false-positive and false-negative rates were 32.7% and 20.7%, which are not trivial. Thus the role of sCD40L as a single predictive parameter for poor surgical outcome may be limited. Whether it works

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better as part of a panel of serological biomarkers, for example, with CRP and D-dimer, requires further investigation.

The exact mechanism linking elevated sCD40L levels and poor surgical outcome remains unclear. The association of sCD40L with inflammatory processes provides biological plausibility, given the concept of inflamed thrombosis in the pathophysiology of CTEPH. This could be related to residual distal pulmonary microvasculature disease not amendable to PEA. Although there were no Jamieson type 4 cases in the cohort, data on anatomical correlation with post-PEA VQ scan or pulmonary angiogram reassessment, as well as serological correlation with postoperative sCD40L level at the time of reassessment right heart catheterization, were not available and would be useful to further delineate the correlation with persistent elevated pulmonary vascular resistance and low cardiac index post-PEA and residual distal disease as a contributing factor for poor PEA outcome.

Given there have been advances in pharmacotherapy for CTEPH in the past 19 years, it would also be useful to know the use of pulmonary targeted vasodilatory therapy for patients before and after PEA, especially for patients with persistent elevated pulmonary vascular resistance after PEA, which was not reported in the present study.

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