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Something not so new for lymphangioleiomyomatosis: is VEGF-D a glass half empty or half full?

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An isolated lung cyst on an HRCT scan of the chest is usually just an incidental finding with no relevant clinical significance[1]; however, one only needs to find a few more cysts for it to become a real diagnostic puzzle. HRCT, alongside a thorough clinical assessment, is actually an essential first-step tool for trying to narrow down the broad range of differential diagnoses, but in several patients with diffuse cystic lung disease (DCLD) a definitive diagnosis still cannot be achieved without further investigation.[2]

Lymphangioleiomyomatosis (LAM) is a rare low-grade neoplastic disease that mainly affects women of reproductive age in its sporadic form or associated with tuberous sclerosis complex. LAM is characterized by diffuse small regular well-defined thin lung cysts on HRCT, and imaging has become an essential modality in the diagnosis of the disease. Nonetheless, the diagnosis of LAM can only be established in the presence of extrathoracic accompanying features, otherwise it may require histopathological confirmation.[3] Even when a "typical" tomographic presentation of LAM could be considered, alternative and less common diagnoses, such as bronchiolitis, have been proven to be possible.[4]

Serum VEGF-D quantification has emerged as a potential diagnostic tool with great specificity and reasonable sensitivity to differentiate LAM from other DCLD and from healthy controls.[5-7] Additionally, since the first prospective assessment of VEGF-D, it has been shown to carry prognostic information and to be useful as a biomarker of disease severity and treatment response.[7-9] An important implication of elevated VEGF-D concentrations in the approach of DCLD is to obviate the need for lung biopsy, which has led the American Thoracic Society/Japanese Respiratory Society in their clinical practice guidelines,[10] despite their moderate confidence, to strongly recommend the use of this biomarker as a diagnostic tool in suspected LAM before tissue sampling. Well, the matter seems to be settled then—but it is not all roses.

First, the optimal threshold of serum VEGF-D level is yet to be determined. Currently, a cutoff value ≥ 800 pg/mL has high specificity and is recommended as a diagnostic parameter for LAM, but median values are extremely variable, and using this threshold to discriminate LAM patients from non-LAM patients lacks sensitivity: it might leave almost half of truly LAM patients with a false-negative result.[6] Our group[7] has also described a cohort of Brazilian patients with LAM with serum VEGF-D concentrations somewhat lower than those in previous reports.[5,6] Although such variations in VEGF-D levels might be attributable to true differences in intrinsic population characteristics, they may also be partially explained by discrepancies in laboratory analysis, such as sample collection, storage, and processing; time from diagnosis; and other individual patient features, such as lymphatic involvement, which is associated with higher VEGF-D levels.[7] Greater disease severity and faster disease progression associated with elevated baseline VEGF-D levels have been shown in some studies, but these findings could not be replicated in others.[3] Furthermore, treatment with sirolimus may lead to a decrease in serum VEGF-D levels,[8] but the magnitude of decline is not well correlated with functional improvement.[11]

In this issue of the *Jornal Brasileiro de Pneumologia*, Li et al.[12] shed additional light on the matter. The authors have conducted a rigorous systematic review and meta-analysis of VEGF-D diagnostic performance for LAM. Ten studies conducted between 2009 and 2019 were included in the meta-analysis, yielding a total of almost one thousand individuals, a number probably unachievable otherwise in the setting of a rare disease. The findings might sound expected, but are yet somehow reassuring. The study showed an excellent diagnostic performance of VEGF-D with great overall accuracy, including an AUC of 0.98. No effect on the adopted threshold, control group composition, or site location was observed, inferring reasonable generalizability of the findings. However, the quality of the results was considered low based on the GRADE system, mainly due to a high risk of bias and heterogeneity among the studies. Also, although specificity barely reached unity, sensitivity was lower and showed greater variability, with a wider confidence interval.

Such news might not be new, since VEGF-D has already been recommended as a standard diagnostic tool, but by revisiting established concepts with the addition of fresh evidence, especially in the setting of conflicting findings, doubts regarding optimal values and the extent of the conclusions drawn from previous work are definitely very welcome.

The study by Li et al.[12] confirmed the utility of VEGF-D as a biomarker to avoid an invasive procedure in several patients with LAM and ratified an albeit conservative cutoff value of 800 pg/mL as the greatest possible accuracy within variability. The direct clinical implication of such a safe intervention justifies the fact that the authors[12]

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have strongly recommended the use of serum VEGF-D quantification in the suspicion of LAM. On the other hand, the study reinforces that, even with the determination of serum VEGF-D levels, a number of patients will still need to undergo lung biopsy to confirm the diagnosis of LAM. The incorporation of VEGF-D in clinical practice is also far from feasible for most health care professionals, since wide availability and access to standardized testing with controlled quality are yet to be within reach, even in referral centers.[3]

Finally, the role of serum VEGF-D in the diagnosis of LAM seems to be well established, with its strengths and weaknesses corroborated by that study.[12] After all, is VEGF-D still the best diagnostic method for the approach of patients with suspected LAM without other confirmatory clinical and tomographic features? The answer is yes, but there are relevant limitations and issues that still need to be addressed. That is, the glass remains half full or half empty. Therefore, the assessment of emerging biomarkers in serum or in BAL fluid, perhaps in combination with VEGF-D, is warranted and should be further explored in the approach of LAM and other DCLD as an aid to diagnosis, prognosis, and treatment response.

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