Potential Usefulness of a Combination of Inflammatory Markers in Identifying Patients With Sarcoidosis and Monitoring Respiratory Functional Worsening

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To the Editor

We read with interest the article that appeared in the Journal by De Smet and colleagues,1 who applied likelihood ratios (rather than a dichotomous interpretation) for different results intervals for 3 laboratory tests (the percentage of bronchoalveolar lavage fluid [BALF] lymphocytes, the BALF CD4/CD8 ratio, and the serum angiotensin-converting enzyme activity) to improve clinical interpretation for the diagnosis of pulmonary sarcoidosis. They also examined the allocation power of the 3 diagnostic tests combined together by means of logistic regression analysis.

The authors retrospectively evaluated the data for 153 subjects (36 with diagnosed sarcoidosis and 117 control subjects with clinical suspicion of sarcoidosis, but with diagnosis of other pulmonary diseases). The combination of the 3 laboratory tests allowed exclusion of sarcoidosis in 57 (48.7%) of 117 control subjects and confirmation of the diagnosis in 12 (33%) of 36 cases of pulmonary sarcoidosis.1

We strongly agree with the authors that the common practice of applying diagnostic tests by using strict cutoff values may result in a loss of information and a risk of an inappropriate interpretation of results, and we would like to give a further contribution to support their approach.

We analyzed the findings for 30 subjects with proven sarcoidosis and 34 with idiopathic pulmonary fibrosis (IPF) diagnosed by lung biopsy and/or according to European Respiratory Society/American Thoracic Society criteria for an IPF diagnosis.2 We examined BALF cellular profiles and BALF and serum concentrations of eosinophil cationic protein (ECP), myeloperoxidase, tryptase, procollagen

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III, soluble interleukin-2 receptor (sIL-2R), interleukin 6 (IL-6), and tumor necrosis factor α. At baseline, all participants underwent pulmonary function tests, radiologic investigations, and fiberoptic bronchoscopy for BALF acquisition. The study was approved by the local ethics committee (909/CE), and informed signed consent was obtained from all participants.

The linear predictor score (on the logit scale), based on the combination of BALF lymphocytes, CD4, CD8, and ECP was able to correctly allocate 29 patients with sarcoidosis (97% of correct classification; 95% confidence interval [CI], 84.4%-99.8%) and 28 with IPF (82% correct classification; 95% CI, 68.8%-92.2%). The area under the curve (AUC) was 0.93. None of the markers analyzed as a single variable reached a similar allocation rate: for lymphocytes, correct discrimination was obtained in 60% of sarcoidosis and 76.5% of IPF cases (95% CI, 43.7%-75% and 60.9%-87.5%, respectively); for CD4, the allocation rates were 76.6% for sarcoidosis and 79.4% for IPF (95% CI, 60.9%-88.3% and 64.1%-89.8%, respectively); using CD8, the allocation rates were 80% in sarcoidosis and 67.4% in IPF (95% CI, 64%-90.6% and 51.6%-81.2%, respectively); for ECP a correct distribution was reached in 86.6% of sarcoidosis and 70.6% of IPF cases (95% CI, 71.9%-95.3% and 54.7%-82.8%, respectively). The AUCs were 0.71, 0.80, 0.80, and 0.84, respectively.

In addition, in the effort of testing the accuracy of the combinational model in predicting the respiratory functional worsening, we analyzed pulmonary function of people with sarcoidosis after a 2-year follow-up period. At reevaluation 76% of participants had stable disease, and 24% experienced a worsening of respiratory function needing adequate corticosteroid treatment.3,4 Logistic regression (with pulmonary function worsening as the dichotomous outcome) was used to test the discriminatory effect of variables considered together in univariate and multivariate models.

The combination of BALF neutrophil percentage, ECP, and tryptase yielded a 100% correct classification of patients (95% CI, 90.6%-100%); the area under the curve was 1. We also examined the allocation rate obtained by each marker analyzed as a single variable: polymorphonuclear leukocytes exactly allocated 58% of worsenings (95% CI, 21.8%-87.5%) and 100% of stable (95% CI, 87.5%-100%) disease; for ECP, a correct classification was obtained in 42% of patients with progressive disease (95% CI, 12.5%-78.13%) and 92% with stable disease (95% CI, 75%-98.4%); finally, tryptase was not able to identify any of the patients with disease progression (95% CI, 0%-34.4%), while it correctly allocated 100% of patients with stable disease (95% CI, 87.5%-100%). The AUCs were 0.9, 0.66, and 0.58 respectively. For both combinational approaches, the attempt to remove each of the variables included in the panel resulted in a poorer outcome.

In addition, a dissatisfying discrimination was obtained using markers from peripheral blood.

We concur with De Smet et al1 that a correct diagnosis of sarcoidosis almost always requires tissue biopsy specimens, obtained in most of the cases through fiber bronchoscopy; sometimes, when fiber bronchoscopy does not yield a diagnostic result, more invasive surgical procedures are needed, with consequent delay and implications for the patient’s outcome. Currently, a histologic diagnosis cannot be replaced by other diagnostic tests, but we strongly believe that the approach showed in the study by De Smet and colleagues,1 and supported by our findings, could help the diagnostic process, reducing delay in establishing a diagnosis.

This combinational method, although with some shortcomings (an approach more complex than the usual threshold index, the limited number of patients, the possibility that different and newer molecules may be combined together), could be a valuable alternative to optimize the performance of the many biomarkers that every day are discovered in the effort to identify sarcoidosis and to predict its clinical course.5,6

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To the Editor

We read with interest the article by Panyasai and colleagues in which they identified spuriously increased levels of hemoglobin (Hb) A2 by capillary zone electrophoresis (CZE) in 11 patients heterozygous for Hb Hope. We have encountered the same type of false elevation in HbA2 any time there are 2 major peaks in adjoining zones, eg, S/D-Punjab, S/G-Philadelphia, A/Hope, A/Camden, and A/Athens-Georgia. The explanation for this is that in CZE, the baseline is integrated by the tangent method. In the electropherogram in the article by Panyasai et al (their Figure 1B), the nonblack area under both peaks (inverted V), which visually represents at least 30% of total hemoglobin, is not integrated into the total hemoglobin. This explains why the HbA2 is falsely elevated. However, if the baseline had been manually corrected, the HbA2 would be within the reference range.

This correction method, which is recommended by the manufacturer (Sebia, Norcross, GA), is illustrated in Figure 1 by electropherograms from a 79-year-old man who was heterozygous for Hb Athens-Georgia (HBB:p.40Arg>Lys) and also had severe iron deficiency. His Hb concentration

![Figure 1A](https://example.com/figure1a.png) shows that a large area (inverted V) is not integrated into the total percentages. This falsely elevates the A2 value.

![Figure 1B](https://example.com/figure1b.png) shows that when A and Athens-Georgia are brought to the baseline they are reported as a combined percentage, but an accurate A2 value is obtained.