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Commentary

Leaving History Behind: CD4/CD8 Ratio as a Diagnostic Tool in Sarcoidosis

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The recent meta-analysis in *EBioMedicine* by Shen and colleagues is the first to report a systematic analysis of the diagnostic performance of bronchoalveolar lavage fluid (BALF) CD4/CD8 ratios in sarcoidosis (Shen et al., 2016). Their results are consistent with numerous studies and BAL guidelines over the last 2 decades which have shown that elevated CD4/CD8 ratios in BALF lack sufficient sensitivity and specificity needed to replace histologic confirmation of sarcoidosis (Meyer et al., 2012).

Where does the use of the BALF lymphocyte ratio fall in the diagnostic pathway for sarcoidosis? One could take the position previously suggested by Costabel in 1997, who argued that performing BAL as a first step could confirm the diagnosis in the majority of patients, and obviate the need for those patients to undergo more invasive and risky biopsy procedures (Costabel, 1997). However, based on the pooled specificity of 83% reported by Shen and colleagues, this approach fails to meet one of the primary tenets of diagnosing sarcoidosis, namely the exclusion of alternative diagnoses (Statement on Sarcoidosis, 1999).

More recently, the use of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has gained favor at most centers for the diagnosis of sarcoidosis. It has a low rate of adverse events, and a recent meta-analysis reported pooled sensitivity of 84% and specificity of 100% (Gupta et al., 2014; Trisolini et al., 2015). Although TBNA is superior to the performance of the CD4/CD8 ratio, it requires the presence of mediastinal lymphadenopathy. When a CD4/CD8 ratio is considered for cases in which EBUS is negative or not available, practitioners should be aware of factors that can alter BALF CD4/CD8 ratios, including active smoking and advanced age. In addition, BALF CD4/CD8 ratio is lower in more advanced radiographic stages of sarcoidosis (Danila et al., 2008).

Sarcoidosis is considered an orphan disease. However, compared to many other orphan diseases that have many diagnostic tools and treatments in development, sarcoidosis has a relative lack of guidelines, inconsistent clinical practice across institutions, and variation in study methodology. These have resulted in significant clinical trial heterogeneity. Of the 16 studies included by Shen, 1 was blinded, 5 were retrospective, and there was variability in CD4/CD8 ratio cut-points and sarcoidosis diagnostic criteria. Significant heterogeneity still existed when the authors performed a sensitivity analysis of prospective studies with low risk of bias.

For a path forward, the sarcoidosis scientific community should work for better diagnostic tools, a better understanding of pathogenesis that might alter therapeutic targets, and build consistent practices across centers. Collaboration and data sharing can then result in more reliable conclusions and progress in sarcoidosis. As we leave the CD4/CD8 ratio behind, the need for effective diagnostic biomarkers has never been higher.

Disclosure

The author declared no conflicts of interest.

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