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How many organs need to be involved to diagnose sarcoidosis? An unanswered question that, hopefully, will become irrelevant

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Introduction

This issue of our journal contains an article describing the WASOG sarcoidosis organ assessment instrument that is a vastly updated version from the previous ACCESS (A Case Control Etiology of Sarcoidosis Study) effort (1). The purpose of these instruments is to establish criteria for specific organ involvement with sarcoidosis to a) develop universal consistency in clinical trials and b) offer the clinician guidance concerning clinical scenarios where a clinical diagnosis of sarcoidosis organ involvement could be considered without performing a confirmatory biopsy. Although this has not yet been subjected to study, we believe that, similar to the previous ACCESS instrument, a clinical scenario classified as "probable" or "highly probable" would strongly suggest sarcoidosis involvement of an organ if other potential causes had been reasonably excluded.

The WASOG instrument differs from the previous one in that new diagnostic laboratory tests were included (e.g. MRI scanning), all organs were included by adding an "other organs" category, and the criterion for organ involvement were determined by a vote of international sarcoidosis experts rather than by the opinions of very few individuals. The WASOG instrument still has several inherent limitations that are well outlined in the article.

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The WASOG instrument is the culmination of more than one year's effort by more than 40 individuals in the Americas, Europe, and Asia. During this process, an unexpected controversy came to light that we address here in this editorial. Specifically, there was significant and passionate disagreement among the group as to whether the diagnosis of sarcoidosis requires evidence of disease in one or multiple organs. Sarcoidosis has been described as a multisystem granulomatous disease of unknown cause (2). This definition implies that sarcoidosis is not confined to one organ. The fact that sarcoidosis often develops in organ allografts that have been transplanted into sarcoidosis patients (3-5) also provides strong evidence that the disease has no organ boundary.

The exclusion of patients in whom a second organ has not been defined may lead to misclassification of potential sarcoidosis patients. It is not unusual for patients to develop noncaseating granulomatous inflammation that is clinically apparent in only one organ such as the brain, and these patients are often given a clinical diagnosis of sarcoidosis if alternative causes of granulomatous inflammation have been reasonably excluded (6) It is possible that such patients have occult granulomatous disease elsewhere that cannot be clinically detected. This has been clearly demonstrated in the case of cardiac (7, 8) and hepatic sarcoidosis (9, 10). In the ACCESS trial, half of the patients had involvement of only one organ identified at time entry into the study (11). Some of these patients developed second or more organ involvement during a two year follow up, but not all cases had clear cut second organ involvement (12). In some cases, the presentation of single organ involvement is quite supportive of the diagnosis of sarcoidosis, such as a patient with bilateral

hilar adenopathy and a lung biopsy demonstrating granulomas. In addition, serum markers showing elevated angiotensin converting enzyme, chiotripidase, and/or soluble IL-2 receptor are quite supportive of the diagnosis (13, 14).

However, it should be pointed out that there are several well defined conditions with granulomatous involvement limited to a single organ. This includes idiopathic hepatitis (15) and granulomatous uveitis such as Vogt-Koyanagi-Harada syndrome (16). It is important to keep in mind that not all idiopathic granulomatous conditions are sarcoidosis, since that may prevent the discovery of truly different diseases. For example, Blau's syndrome can be mistaken for juvenile sarcoidosis (17, 18). However, the genetic abnormalities observed in Blau syndrome are not found in sarcoidosis patients (19, 20).

It is also possible that an alternative cause of granulomatous inflammation was not identified that may cause granulomatous inflammation in only one organ. One example of this situation is chronic beryllium disease, a condition which be radiologically and pathologically indistinguishable from pulmonary sarcoidosis, and has been misdiagnosed as pulmonary sarcoidosis up to 40 percent of the time (21). But finally, is it also possible that some of these patients truly have sarcoidosis confined to one organ? This issue reaches the point of circular reasoning, because the diagnosis of sarcoidosis is not clearly defined: If the diagnosis of sarcoidosis requires multiple organ involvement, then granulomatous inflammation in an isolated organ cannot be sarcoidosis, unless our diagnostic criteria for sarcoidosis are faulty.

We would argue that at this point, the issue of whether one or multiple organ involvement is required for a diagnosis of sarcoidosis cannot be answered until the immunopathogenic mechanisms of sarcoidosis are understood to the point where a test can confirm its presence. We look forward to the day when we develop such understanding to make this controversy irrelevant.

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