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Editorial

Navigating the Diagnostic Labyrinth of Difficult Sarcoidosis

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Sarcoidosis, an enigmatic multisystem granulomatous disorder, has forever posed unique diagnostic challenges for clinicians in daily practice. It is identified by the presence of non-caseating granulomas in affected organs, most commonly the lungs. Diagnosis is never secure and usually done when the probability likelihood alternative diseases is extremely low by a detailed differential diagnostic assessment [1-4]. Yet, its diagnosis often requires traversing a labyrinthine process, especially when the manifestations are atypical, isolated single organ involvement at the initial setting, and patients with stage 0 disease.

Definitive diagnosis of sarcoidosis can create a dead end for clinicians. The manifestations of sarcoidosis can span multiple systems, from pulmonary to cutaneous, ocular, or neurological involvement. The multisystemic involvement in sarcoidosis may lead to misinterpretations, especially when patients exhibit atypical symptoms without lung involvement. Sarcoidosis has long been called the "great mimicker" because of its capacity to imitate other diseases such as interstitial lung diseases, granulomatous or malignant disorders. Furthermore, sarcoidosis is neither an infectious, autoimmune, vasculitic, or malignant disorder leading to a diagnostic stalemate for clinicians in daily practice. Its variable presentation, the nonspecific nature of symptoms frequently shared by other diseases, lack of pathognomonic clinical features, and absence of a definitive diagnostic test frequently confounds even the most astute clinician. This clinical profile usually leads to a diagnostic dilemma that entails a keen clinical acumen, advanced imaging techniques, and sometimes invasive procedures. Diagnosis requires pathologic evidence of non-caseified granulomatous inflammation in at least two organs with exclusion of other disease with similar histopathology. Consequently, misdiagnosis and overdiagnosis is quite common in sarcoidosis [5]. Diagnostic confidence level of sarcoidosis have changed from definite highly probable, probable, possible, or to unlikely because absolute identification accuracy or precision may not be achievable in sarcoidosis [6].

Several obstacles that to a diagnostic impasse of sarcoidosis include heterogeneity of presentation, absence of specific laboratory manifestations or biomarkers, lack of specific imaging findings, and overlap with disease such as tuberculosis, lymphoma, and other granulomatous or infectious disorders. High-resolution CT scans are pivotal for detecting early pulmonary changes, while PET/CT scans can help in detecting metabolically active disease sites, assisting not only in diagnosis but also in directing biopsy sites. ^{68}Ga-citrate PET/CT may yield a high diagnostic yield in sarcoidosis patients [7] while the presence of other granulomatous diseases will reduce the diagnostic yield of nuclear imaging modalities as a triangulation point. Conditions such as tuberculosis, lymphoma, and certain fungal infections can present with granulomas similar to those in sarcoidosis. Discriminating between these ailments requires a combination

of clinical, radiological, and sometimes, microbiological assessment. Histopathologic diagnosis of sarcoidosis is required in at least two organs along with compatible clinical setting, and a detailed differential diagnosis.

Non-caseified granulomas are the pathologic hallmark of sarcoidosis. At the heart of sarcoidosis lies the formation of granulomas with compact collections of inflammatory cells, notably macrophages, and T-lymphocytes. Though granulomas can be observed in various other conditions such as tuberculosis, fungal infections, and foreign body reactions, the non-caseified granulomas of sarcoidosis have unique features making them distinct. For a definite sarcoidosis diagnosis, biopsies of involved tissues, such as the lungs, skin, or lymph nodes, often prove crucial in at least two organs. While non-caseified granulomas are characteristic, they are not pathognomonic for sarcoidosis. Other conditions can present with similar granulomas, emphasizing the need for a comprehensive work-up. Special stains to rule out mycobacterial and fungal infections are paramount in such cases. This attention to detail ensures that the granulomas of sarcoidosis are not mistaken for those of another condition. Pathologic findings, while essential, must always be interpreted in conjunction with the clinical picture. Clinical findings, such as hypercalcemia or bilateral hilar lymphadenopathy, when paired with appropriate histologic findings, can solidify the diagnosis.

The forgotten diagnostic tool the Kveim test appears to be the hallmark of diagnosis. Primary drawbacks to the current use of the Kveim test are difficulties in reagent storage, transmission of infectious agents, lack of a standard application and assessment protocol. Despite all its disamenities, the Kveim test has achieved a diagnostic accuracy approaching 80% displaying a significant diagnostic yield of sarcoidosis compared to currently utilized conventional laboratory methods. In sarcoidosis patients with stage 0, single organ disease, or without lung involvement, the Kveim test is the hallmark of diagnosis. Diagnostic yield increases furthermore nearly approaching 100 per cent when the Kveim test is collaborated with the conventional laboratory methods (unpublished data by Tetikkurt and Yanardag).

It is well-known that diagnosis of sarcoidosis is never secure. Collaboration between clinicians and pathologists is integral to the accurate diagnosis of sarcoidosis. Despite the advanced imaging modalities hold promise they may yield equivocal findings particularly in stage 0, single organ disease, and in patients without lung involvement. The road ahead for an accurate final sarcoidosis diagnosis lies in the collaboration between clinicians and pathologists. Assessment of all laboratory and imaging modalities together in a compatible clinical setting is the sine qua non for a definitive sarcoidosis diagnosis.

Author Contributions

Cuneyt Tetikkurt wrote the manuscript.

Halil Yanardag prepared diagnostic laboratory findings.

Seza Tetikkurt wrote pathologic assessment of sarcoidosis.

Conflicts of Interest

The authors declare that they do not have not any conflicts of interest to declare associated with this study. We as authors state explicitly that any kind of potential conflicts do not exist.

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