Laboratory investigations in uveitis: current practice and future directions

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ABSTRACT

Diagnosis and management of uveitis always remains a challenge to the treating ophthalmologists. Rapid diagnosis and timely initiation of appropriate, effective treatment in uveitis are the critical determinants that lead to good visual outcome and reduce the risk of ocular morbidity. In the last decade, significant progress has been made in molecular diagnostic modalities and in development of newer diagnostic tools, which included serological tests and imaging techniques. However, a tailored approach to laboratory investigations based on meticulous history and comprehensive ocular evaluation has been propounded as the gold standard for successful management of an uveitic entity. In this article, we review the laboratory diagnostic tests in uveitis as well as recent technological advances in laboratory science, which may be the future direction for diagnosis of uveitis.

In spite of tremendous progress made in the research of understanding the etiopathogenesis and management of various uveitic entities over last few years, laboratory diagnosis of uveitis continues to remain a challenge in our day-to-day clinical practice. Laboratory investigations in uveitis patients are essential to identify the primary cause of the intraocular inflammation to ensure proper, effective treatment and also to identify comorbid association of systemic diseases. Diagnosis of uveitic entities is dependent on analysis of various body fluids (e.g., serological tests, analysis of aqueous, vitreous), tissue analysis (e.g., chorioretinal biopsy, biopsy of lymph nodes), and to some extent on radiological and other ancillary investigations.

It is often a mammoth task on the part of a clinician to decide which laboratory tests should be performed. For example, examination of serum parameters for disease may contribute very little information on a localized pathology or disease process confined only to the eye. Also, because of devastating nature of the inflammatory process and its impact on visual function in uveitis, the clinicians are usually tempt to get as much information as possible from commercially available laboratory investigations. Lack of a tailored approach to laboratory investigations can have a huge impact on patients economically. While evaluating the cost-effectiveness of uveitis investigation by the ophthalmologists, Noble et al.[1] found that up to $75 per patient was spent as additional cost in the investigation of anterior uveitis.

Various studies have shown that a specific diagnosis of uveitis could be achieved only in 26%–40% of the patients with uveitis in tertiary eye care centres.[2,3] Also, the diagnosis of uveitis often remains diagnosis in evolution and requires longer follow-up and repeated clinical and laboratory evaluation to reach at a specific diagnosis.[3]

Many of the uveitic conditions have a plethora of presentations and one needs to have high index of suspicion, especially in cases with atypical presentations. Conditions such as masquerade syndromes can often mimic uveitis and can be associated with life-threatening neoplasms.[3] Detailed and meticulous ocular and systemic history before ordering any investigation plays a pivotal role in diagnosis of uveitis.[4] Multidisciplinary approach such as consultation with our rheumatology and pulmonology colleagues is often necessary and helps to narrow down the list of probable causes. There are certain forms of equivocal uveitic entities such as Fuchs uveitis, Vogt-Koyanagi-Harada syndrome, sympathetic ophthalmia, and uveitis after trauma, where laboratory investigation has a limited role and helps only to rule out any diagnostic uncertainty.

Laboratory Investigations of Sarcoidosis

Sarcoidosis is a multiorgan granulomatous disease of unknown etiology. Ocular involvement occurs in 30%–60% of the cases, and bilateral granulomatous uveitis is the most common presentation.[5–7] A diagnosis of sarcoidosis is usually considered in young or middle-aged adults with history of unexplained cough, shortness of breath, or constitutional symptoms. However, majority of the patients are usually asymptomatic and ocular disease may occur in the absence of systemic involvement, which makes the diagnosis of ocular sarcoidosis difficult.

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The First International Workshop on Ocular Sarcoidosis (IWOS) proposed international criteria for the diagnosis of ocular sarcoidosis, which included 7 clinical signs and 5 laboratory parameters.[8] In a retrospective analysis to validate these classification, Takase et al.[9] collected data from 370 patients with uveitis, which included 50 patients of biopsy-proven sarcoidosis and 320 control uveitis. They found that this classification has high predictive value for diagnosis of ocular sarcoidosis. Negative tuberculin skin test has been found to be an important biomarker for the diagnosis of ocular sarcoidosis, especially in countries where BCG vaccination is performed routinely.[8] Serum angiotensin enzyme (ACE) and serum lysozyme measure the same parameters (i.e., macrophage load secreted by sarcoid granuloma). Serum ACE is more commonly done than serum lysozyme in routine clinical practice. However, serum ACE can be raised in various other pathological conditions and in children. In a study by Kawaguchi et al.,[10] the combined sensitivity, specificity, positive, and negative predictive value of raised serum lysozyme was higher when compared with that of raised serum ACE.

Bilateral hilar lymphadenopathy (BHL) is the most common radiological finding in systemic sarcoidosis. A conventional chest radiograph is usually sufficient to establish the diagnosis of sarcoidosis. However, high-resolution chest computed tomography (HRCT) is now considered the gold standard, and it is undoubtedly superior to conventional chest radiograph in the diagnosis of atypical presentation and delineating pattern of pulmonary interstitial lesions. American Thoracic Society (ATS)/European Respiratory Society (ERS)/World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) expert consensus statement on sarcoidosis has recommended the use of computed tomography (CT) in the following situations in sarcoidosis: (*i*) atypical clinical or radiological findings; (*ii*) pulmonary complications such as bronchiectasis, aspergilloma, pulmonary fibrosis, traction emphysema, or a superimposed infection or malignancy; and (*iii*) a normal chest radiograph in the presence of high clinical suspicion of the disease.[11]

Gallium scintigraphy uses gallium 67, which is concentrated at the site of inflammation in sarcoidosis and some other diseases, such as Sjögren's syndrome and tuberculosis. Gallium scintigraphy has a low specificity for sarcoidosis but is highly sensitive. It has to be kept in mind that a confirmed diagnosis of sarcoidosis can be made only by biopsy demonstrating classic noncaseating granuloma. Bronchial or transbronchial biopsies and bronchoalveolar lavage (BAL) are usually recommended. Video-assisted thoracoscopic lung biopsy currently is en vogue, and in more than 90% cases a confirmatory diagnostic yield has been reported. Other possible sites are skin, lip, and superficial lymph nodes. Procedures such as blind biopsy of conjunctiva (i.e., biopsy in the absence of any visible lesions of conjunctiva) has also been reported with high diagnostic yield.[12] CD4/CD8 ratio in BAL fluid also has been used for diagnosis of sarcoidosis, and a CD4/CD8 ratio greater than 3.5 was reported to have a specificity of 94%. CD4/CD8 ratio of T lymphocytes in the vitreous samples of ocular sarcoidosis patients was reported to be significantly higher than that in the vitreous samples of nonsarcoidosis control group. According to a study by Kojima et al.,[13] the sensitivity and specificity of the CD4/CD8 ratio from vitreous for the diagnosis of ocular sarcoidosis were 100% and 96.3%, respectively. Sanz-Marco et al.[14] highlighted the diagnostic importance of CD4/CD8 ratio estimation from aqueous samples of ocular sarcoidosis patients.

Laboratory Biomarkers in the Diagnosis of Systemic Rheumatic Diseases

An ideal laboratory biomarker is expected to have several properties: it should be present in a biosample which will be used in a diagnostic test for the disease, with the help of a standardized and reproducible analytical methodology. Also, an ideal biomarker should enable one to differentiate between health and disease condition; high or low exposure to risk factors; and effectiveness of or no response to the specific therapy. Unfortunately, in spite of significant progress in the laboratory diagnosis of systemic rheumatic diseases over the last few decades, there is no such ideal biomarker available for most of the systemic rheumatic diseases. However, newer autoantibody detection technologies using computer-aided systems and multiplex proteomic technologies have a higher analytical validity than the previously used classical techniques, immunodiffusion, agglutination, and immunofluorescence. A major problem with such laboratory procedures is that they are expensive and the standardization of methods such as reference materials for the calibration and quality assessment of immunological assay are often difficult.

The presence or absence of any biomarker does not rule in or rule out diagnosis of a particular systemic rheumatic disease. Various cardinal criteria for the diagnosis of systemic rheumatic disease have highlighted the role of laboratory biomarkers in addition to the specific clinical findings. Thus, a thorough comprehensive ocular examination and multidisciplinary approach, such as consultation with other disciplines of medicine, are required rather than relying solely on the result of laboratory investigations. For example, positive antinuclear antibody (ANA) and the presence of anti–double-stranded DNA or anti-Sm antibodies constitute 2 of the 11 criteria for the diagnosis of systemic lupus erythematosus (SLE).[15] However, anti–double-stranded DNA or anti-Sm antibodies are highly suggestive of SLE, and the presence of anti-dsDNA antibody even in apparently asymptomatic patient may increase the likelihood of having subclinical SLE.

One should follow a tailor-based approach while advising laboratory investigations in patients with uveitis when