Clinical Research

Interferon-gamma release assay and chest X-ray to classify intraocular tuberculosis among clinically undifferentiated uveitis

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ABSTRACT

BACKGROUND Tuberculosis (TB) is a common cause of intraocular inflammation in Indonesia. As no accurate biomarker can confirm the diagnosis, ophthalmologists often rely on systemic findings, such as tuberculin skin test, interferon-gamma release assay (IGRA), and chest X-ray (CXR) for TB suspicion. This study aimed to evaluate IGRA and CXR in classifying intraocular TB among patients with a clinically undifferentiated cause of uveitis.

METHODS This cross-sectional study included 116 patients (a total of 163 affected eyes) with a clinically undifferentiated cause of uveitis. IGRA and CXR were performed as part of the workup. Data on visual acuity, anterior chamber inflammation grade, and anatomical classification of uveitis were recorded. As there were no confirmed ocular tuberculosis (OTB) in our cases, eyes were classified into probable OTB, possible OTB, and unclassified.

RESULTS Overall, 93 patients (80.2%) with a clinically undifferentiated cause of uveitis had positive IGRA, whereas 10 (8.6%) had CXR results suggestive of TB. More than one-third of the patients were blind (visual acuity <3/60), and panuveitis was the commonest anatomical classification. A trend was identified in patients with panuveitis, who often showed ≥2+ cell anterior chamber inflammation (*p* for trend = 0.023), according to OTB criteria (probable OTB = 3/4, 75.0%; possible OTB = 44/67, 65.7%; unclassified = 2/9, 22.2%). Furthermore, the clinically undifferentiated uveitis cases were eligible to be stratified into probable (8.6%) and possible (75.0%) OTB categories after IGRA and CXR examinations.

CONCLUSIONS The combination of IGRA and CXR is valuable for classifying and diagnosing TB-related uveitis. A multidisciplinary approach is essential when the cause of uveitis is unknown.

KEYWORDS interferon-gamma release assay, tuberculosis, uveitis, X-ray

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (Mtb) that can affect body organs, including the eye,[1] which is called ocular tuberculosis (OTB). Uveitis is the most common manifestation of OTB,[1] particularly in developing countries such as Indonesia.[2,3] Besides the wide range of intraocular TB presentations,[4] isolating Mtb from ocular tissues is also challenging due to paucibacillary status with varying degrees of ocular inflammation.[1,5] Therefore, patients with suspected intraocular TB are often classified as a clinically undifferentiated cause of uveitis,[6] which can potentially hinder appropriate treatment of the causative pathogen.

Establishing a definitive diagnosis of intraocular TB in a resource-limited clinic poses a significant challenge. In Indonesia, direct examination of intraocular fluid using polymerase chain reaction (PCR) is not yet included in the national health insurance coverage

(*Jaminan Kesehatan Nasional*). Nevertheless, Gupta et al[4] proposed a classification system for OTB based on evidence from local and systemic TB infection, which classified OTB into "confirmed," "probable," and "possible".

Chest X-ray (CXR) and immunological evidence of TB infection, namely the tuberculin skin test (TST) or interferon-gamma release assays (IGRAs), are essential to support the diagnosis of OTB;[4] however, in endemic settings such as Indonesia, most of the population has received the Bacillus Calmette–Guérin (BCG) vaccination that will affect the TST results. IGRA is considered more reliable because the antigen has not been used in the BCG vaccine or environmental mycobacteria.[4,7] The IGRA test could identify latent TB infection (LTBI), which frequently happens with OTB.[8] In 2021, a consensus was reached to address the initiation of anti-tubercular therapy (ATT) in TB-related uveitis (intraocular TB) cases based on TB endemicity (the Collaborative Ocular Tuberculosis Study [COTS] consensus guideline);[9] however, the implementation of the intervention itself has not yet been evaluated in the Indonesian setting. Of note, the diagnosis and decision to start ATT rely on expert consensus alone, which comprises the bottom level of the evidence pyramid. This emphasizes the lack of high-quality evidence to support the diagnosis of intraocular TB.[10]

Currently, IGRA is considered important for classifying uveitis patients, especially those with clinically undifferentiated uveitis.[8,11] TST implementation has some practical issues, including the unavailability of TST reagents and the need for a second visit. Therefore, this study aimed to analyze the demographic and clinical characteristic data of patients with a clinically undifferentiated cause of uveitis, the use of IGRA and CXR examinations to narrow down the diagnosis based on the OTB classification system by Gupta et al,[4] and the clinical severity degree among probable, possible, and unclassified OTB cases.

METHODS

This cross-sectional study consecutively recruited patients who were newly diagnosed with a clinically undifferentiated cause of uveitis, aged ≥18 years, and had visited the Ocular Infection and Immunology Outpatient Clinic of Cipto Mangunkusumo Kirana Hospital, Jakarta, between January 2019 and September 2021. Patients who were HIV positive or had incomplete test results were excluded from the study. Uveitis cases with sputum smear-positive pulmonary TB or active extrapulmonary TB were excluded. Other suspected etiologies were treated carefully based on the ocular and systemic signs and symptoms.[12]

The patients underwent general ophthalmological examination during their first clinic visit, including best-corrected visual acuity testing, slit-lamp examination by the attending ophthalmology resident and consultant in charge, and ultrasound examination if the view of the posterior eye was obscured. The patient's clinical information was also documented at the first visit, including age, sex, visual acuity, anterior chamber cells grading, anatomical involvement, and laterality of inflammation. The anatomical classification of uveitis was based on the consensus of the Standardization of Uveitis Nomenclature (SUN) Working Group: anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis.[13] The grading scheme for anterior chamber cells was based on the SUN definition, and the examination was carried out using a slit-lamp with a field size of 1 mm × 1 mm slit beam.[13] The World Health Organization's criteria were applied to the visual acuity results.[14] Patients with bilateral uveitis were classified according to the best visual acuity from both eyes.[14] A tailored blood examination test was performed, including but not limited to complete blood count, erythrocyte sedimentation rate and/or C-reactive protein, HIV screening, liver function parameters, urea, creatinine, and serology for *Toxoplasma*, *Treponema* (including venereal disease research laboratory and *Treponema pallidum* hemagglutination), cytomegalovirus, and herpes simplex virus 1 and 2 infections. In line with the purpose of the study, patients with sputum smear-positive pulmonary TB or active extrapulmonary TB were excluded as they were clinically associated with confirmed TB. Uveitis was classified as undifferentiated based on the exclusion of other potential causes following the patient's workup.[6] Other diagnoses were made according to the established criteria. Diagnosis of Behcet's disease and Vogt-Koyanagi-Harada syndrome were made according to current diagnostic criteria.[15,16] Ocular toxoplasmosis was diagnosed based on active whitish-yellowish foci in the retina adjacent to an atrophic/pigmented chorioretinal scar and, when applicable, following positive serological results (specific IgM or IgG) and the resolution of ocular inflammation following antiparasitic drug

administration.[17] Diagnosis of cytomegalovirus retinitis was based on the appearance of typical lesions (whitish/yellowish retinal lesion with associated hemorrhage, variable small dot-like lesions [granular type], or rarely, retinal vasculitis with perivascular sheathing) in immunosuppressed patients.[18] Anterior uveitis presenting as unilateral granulomatous keratic precipitates, elevated intraocular pressure, and corneal lesion/hypoesthesia was managed as suspected viral anterior uveitis until proven otherwise.[19] Ancillary tests for those with a clinically undifferentiated cause of uveitis included targeted testing for TB such as IGRA, TST, and CXR. An aqueous tap for PCR was performed in selected cases and self-funded by the patients.

According to the manufacturer's manual (QuantiFERON®-TB Gold In-Tube [QFT]; Cellestis Inc., Australia), a 6 ml blood sample was drawn and tested for IGRA. The results were reported in three categories: positive (cut-off value of 0.35 IU/ml), negative, and indeterminate. The TST was performed using a standard dose of 0.1 ml tuberculin injected intradermally and read after 48–72 hours. An induration of ≥10 mm in diameter was considered positive.[20] The CXR obtained from the medical records was evaluated by the attending radiologist. A further evaluation was consulted with the outpatient internal medicine clinic in this hospital.

All patients were divided into $CXR^+/IGRA^+$, $CXR^+/IGRA^-$, $CXR^-/IGRA^+$, and $CXR^-/IGRA^-$ groups. OTB classification was based on the criteria by Gupta et al[4] regardless of the presence of clinical signs suggestive of OTB (broad posterior synechiae, retinal perivasculitis, multifocal serpiginous choroiditis, choroidal granuloma, optic disc granuloma, or optic neuropathy). A broader clinical presentation without being limited to those mentioned above was also adopted by the COTS group, which covered anterior, intermediate, posterior, and panuveitis.[9] Confirmed OTB was determined by microbiological confirmation of Mtb from ocular fluid/tissue. Probable OTB included (1) evidence of a CXR with TB infection, or clinical evidence of extrapulmonary TB, or microbiological confirmation from sputum or extraocular sites; and (2) at least one of the following: documented exposure to TB or immunological evidence of TB infection. Possible OTB was defined by either (1) a CXR not consistent with TB and no clinical evidence of extraocular and (2) at least one of the following: documented exposure to TB or immunological evidence of TB infection; or (3) evidence of CXR with TB infection or clinical evidence of extraocular TB but none of the characteristics listed in (2).[4]

Data analysis was performed using SPSS software version 25.0 (IBM Corp., USA) for Windows. The number of patients and eyes with uveitis were presented as percentages. The differences in visual acuity and anterior chamber cells grading among the four groups ($CXR^+/IGRA^+$, $CXR^+/IGRA^-$, $CXR^-/IGRA^+$, and $CXR^-/IGRA^-$) were analyzed by Kruskal–Wallis test. A Mantel–Haenszel test was used to assess the clinical severity degree trend in each group (a p-value <0.05 was considered significant).

Data of the samples were part of a larger prospective study entitled "Proportion of clinical improvement, comparison of interferon type 1 scores, and transcriptomic analysis in idiopathic uveitis with positive IGRA before and after anti-tubercular therapy (ATT): a prospective cohort study", which is currently in the follow-up period. This study was approved by the Ethics Committee of the Faculty of Medicine Universitas Indonesia (No. KET-796/UN2.F1/ETIK/PPM.00.02/2019) and adhered to the tenets of the Declaration of Helsinki.

RESULTS

Of 139 patients with a clinically undifferentiated cause of uveitis, 116 were included in the analysis. Ninety-three (80.2%) patients had positive IGRA, and none had a previous TB history. Five of 10 patients with a CXR suggestive of active TB proceeded to sputum examination (two smear examinations, one GeneXpert examination, one smear and GeneXpert examination, and one Mtb culture); however, none of these investigations confirmed the presence of Mtb in the sputum samples. After consulting with the internist, four individuals were subsequently diagnosed with active pulmonary TB with a negative sputum smear.

According to the best visual acuity, 44/116 patients (37.9%) were already blind at the first visit. From the inflammatory cells in the anterior chamber, half of the patients in the $CXR^+/IGRA^+$ group had a 4+ grade of inflammation (Table 1). The $CXR^+/IGRA^-$, $CXR^-/IGRA^+$, and $CXR^-/IGRA^-$ groups showed no significant differences in visual acuity and anterior chamber cells grade (Kruskal–Wallis test, p = 0.209 and p = 0.535, respectively).

Table 1. Baseline characteristics of patients with a clinically undifferentiated cause of uveitis according to IGRA and CXR

Characteristics	$CXR^+/IGRA^+$, n (%)	$CXR^+/IGRA^-$, n (%)	$CXR^-/IGRA^+$, n (%)	$CXR^-/IGRA^-$, n (%)	Total, n (%)
Patient's characteristics (number)	N = 9	N = 1	N = 84	N = 22	
Age (years), mean (SD)	43.33 (18.77)	56.00 (0)	41.04 (12.02)	37.73 (12.59)	40.72 (12.73)
Male sex	5 (56)	1 (100)	34 (40)	13 (59)	53 (46)
Laterality					
Unilateral	5 (56)	1 (100)	49 (58)	15 (68)	70 (60)
Bilateral	4 (44)	0 (0)	35 (42)	7 (32)	46 (40)
Visual acuity classification					
Mild visual impairment	2 (22)	0 (0)	29 (35)	7 (32)	38 (33)
Moderate visual impairment	2 (22)	0 (0)	21 (25)	6 (27)	29 (25)
Severe visual impairment	1 (11)	0 (0)	3 (4)	1 (5)	5 (4)
Blindness					
Category 3	0 (0)	0 (0)	6 (7)	4 (18)	10 (9)
Category 4	3 (33)	0 (0)	18 (21)	4 (18)	25 (22)
Category 5	1 (11)	1 (100)	7 (8)	0 (0)	9 (8)
Eye's characteristics (number)	N = 13	N = 1	N = 119	N = 30	
Anatomical classification					
Anterior uveitis	2 (15)	0 (0)	13 (11)	2 (7)	17 (10)
Anterior–intermediate uveitis	0 (0)	0 (0)	4 (3)	1 (3)	5 (3)
Intermediate uveitis	0 (0)	0 (0)	2 (2)	1 (3)	3 (2)
Posterior uveitis	2 (15)	0 (0)	17 (14)	7 (23)	26 (16)
Panuveitis	9 (69)	1 (100)	83 (70)	19 (63)	112 (69)
Anterior chamber cells grade* (number)	N = 4	N = 1	N = 63	N = 10	
0.5+ (1–5 cells)	0 (0)	0 (0)	15 (24)	4 (40)	19 (24)
1+ (6–15 cells)	1 (25)	0 (0)	13 (21)	2 (20)	16 (21)
2+ (16–25 cells)	0 (0)	0 (0)	16 (25)	1 (10)	17 (22)
3+ (26–50 cells)	1 (25)	0 (0)	13 (21)	0 (0)	14 (18)
4+ (>50 cells)	2 (50)	1 (100)	6 (10)	3 (30)	12 (15)

CXR=chest X-ray; CXR^+=chest X-ray result suggestive of tuberculosis; CXR^-=chest X-ray result not suggestive of tuberculosis; IGRA=interferon-gamma release assay; $IGRA^+$=interferon-gamma release assay with value ≥0.35 IU/ml; $IGRA^-$=interferon-gamma release assay with value <0.35 IU/ml; SD=standard deviation
*Anterior chamber cells obtained in 78 eyes

Panuveitis was the most common anatomical classification in patients with a clinically undifferentiated cause of uveitis in this study (112/163 eyes with uveitis, 68.7%). Eighteen patients underwent TST examination following their IGRA test, with 17 (94.4%) had positive results. All patients with a positive TST also had a positive IGRA. PCR analysis of aqueous fluid was performed on four eyes with uveitis; however, there was no evidence of Mtb presence, and no eyes were classified as confirmed intraocular TB. Considering the results of CXRs, IGRAs, and TSTs, all patients were classified into different categories of intraocular TB,[4] namely probable and possible OTB. Those who did not meet the criteria were classified as undifferentiated (Table 2). Most patients (123 eyes from 87 patients; 75.5%) fell into the category of possible OTB.

Subsequent analysis found that eyes in the probable and possible intraocular TB cases tended to present with ≥2+ anterior chamber cells, although this finding was not statistically significant (probable OTB = 3/4, 75.0%; possible OTB = 52/86, 60.5%; unclassified = 4/12, 33.3%; Mantel–Haenszel test of trend $p = 0.074$). In particular cases with panuveitis, however, the classification of OTB was significantly associated with anterior chamber cells grade ≥2+. Eyes in the unclassified group tended to have a lower grade of

Table 2. Classification of OTB based on the affected anatomic location in undifferentiated uveitis cases

Anatomical classification	Classification of OTB		
	Probable OTB, n (%) (N = 10)	Possible OTB, n (%) (N = 87)	Unclassified, n (%) (N = 19)
Anterior uveitis	1 (10)	10 (11)	2 (11)
Intermediate uveitis	0 (0)	2 (2)	1 (5)
Anterior-intermediate uveitis	0 (0)	4 (5)	1 (5)
Posterior uveitis	3 (30)	12 (14)	5 (26)
Panuveitis	6 (60)	59 (68)	10 (53)

OTB=ocular tuberculosis

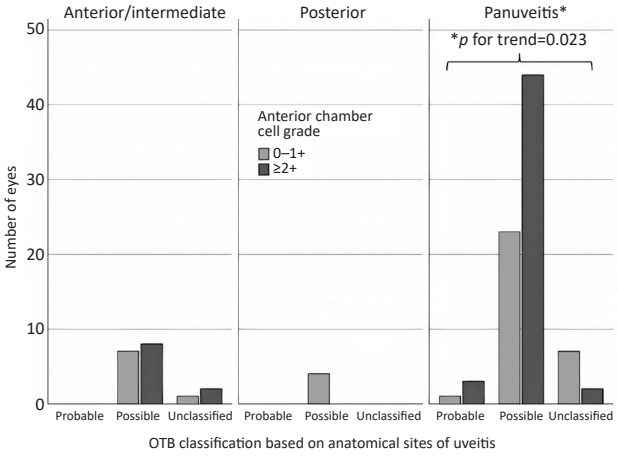

Figure 1. Number of eyes based on anterior chamber cell grade associated with the anatomical classification of the uveitis and OTB criteria. OTB=ocular tuberculosis

inflammation (probable OTB = 3/4, 75.0%; possible OTB = 44/67, 65.7%; unclassified = 2/9, 22.2%; Mantel–Haenszel test of trend $p = 0.023$; Figure 1). Ultimately, 5/11 eyes (four patients) with probable OTB and 72/123 eyes (51 patients) with possible OTB were treated with ATT. Only 1/26 eyes (one patient) in the unclassified group received ATT.

DISCUSSION

More than one-third of the patients with a clinically undifferentiated cause of uveitis presenting to the tertiary eye hospital were blind. The severity of their condition made diagnosis challenging, as the clinical presentation is often atypical and can sometimes be accompanied by secondary complications.[21] Moreover, the poor visual condition of these patients is likely to have a detrimental effect on their quality of life and economic productivity, particularly as they are, on average, of productive age.[22]

The high rate of 80% IGRA positivity among patients is caused by the high exposure to Mtb in the community,[23] which confirms Indonesia as an endemic country. A similar rate of IGRA positivity has also been reported in South Africa, another country with a high TB burden.[24] This study showed that most uveitis cases of unknown origin could be due to LTBI, which is hypothesized as one of the pathomechanisms of OTB.[25] Immunological evidence of Mtb infection could also be provided from the TST results; however, this test is less specific than IGRA for diagnosing intraocular TB.[4] Unfortunately, the current use of IGRA in Indonesia remains low as it is not widely feasible. This could potentially hamper the national program in combating TB,[26] particularly those related to the latent infection.

This study found no association between the IGRA and CXR results and the visual acuity and severity of inflammation (as measured by the anterior chamber cells). These results are consistent with Agrawal et al[8] who found that the patient's clinical features are not exclusively associated with TB infection. Several results were also related to the most common type of intraocular TB anatomical classification. Testi et al[5] found that choroiditis is the most common manifestation, followed by panuveitis. In contrast, Shakarchi et al[1] concluded that posterior uveitis is the most common presentation. In this study, panuveitis was the most prevalent. Even after considering the results of IGRAs, TSTs, and CXRs, the cohort of probable and possible intraocular TB was still dominated by panuveitis. This result is similar to those reported by studies from Saudia Arabia[27] and Iraq[28].

The COTS concluded that PCR assay of intraocular fluids might have low sensitivity for diagnosing intraocular TB.[29] This could be due to the low sample volume, the paucibacillary nature of the disease, or both.[30] Although most eyes with uveitis in this study matched the possible intraocular TB criteria,[4] particularly with the widespread use of IGRA at the center, daily clinical decision to initiate ATT was not strictly based on the implementation of OTB criteria. Therefore, those presenting with probable and possible TB are sometimes dilemmatic. The OTB spectrum does not correlate well with the treatment outcomes, whether it is treated with ATT alone, ATT combined with a systemic corticosteroid,

or with systemic corticosteroid alone, due to a lack of prospective studies with a high level of evidence on this subject.[31] In addition, recommendations on the use of IGRA to further identify those who might benefit from ATT are conflicting.[8] Of note, the panuveitis type has more severe inflammation according to the associated intraocular TB criteria; however, no consensus has yet been reached for initiating ATT, which depends solely on the IGRA result combined with the CXR for panuveitis TB.[9] The only strong consensus for initiating ATT is currently for the panuveitis type with IGRA, TST, and CXR suggestive of TB infection.[9] Interestingly, Pandey et al[32] also found that panuveitis is the predominant type of suspected intraocular TB in Nepal. All patients responded well to ATT, although they only recruited 12 suspected intraocular TB patients, and it was a retrospective study. Hence, intraocular TB validation requires prognostic markers and criteria to determine the appropriate time to initiate ATT in uveitis of unknown cause.

Ultimately, 26 eyes with uveitis (16%) remained unclassified. This is possibly because the rate of false-negative results in the workups, given the low sensitivity of CXR (15%)[33] and the relatively low sensitivity of IGRA (80% for QFT test)[34] for detecting LTBI; however, our results offer a substantial reduction in the rate of unclassified (or idiopathic) uveitis, as we investigated the possibility of TB-related uveitis in most cases of the clinically undifferentiated cause of uveitis. Furthermore, a multidisciplinary collaboration involving an ophthalmologist, pulmonologist/internist, radiologist, and clinical pathologist is essential for uveitis management.

This study was limited by the interpretation of the CXRs by only one radiologist. Moreover, using more advanced imaging techniques, such as computed tomography, could potentially improve the ability to diagnose systemic TB; however, experts agree that CXR is more applicable in many settings and remains the current recommendation for imaging.[9] In addition, we did not repeat IGRA testing in patients with indeterminate results and excluded them from the study, as this is recommended for those patients to help clarify their IGRA results.[23]

Given the dilemma of ocular TB diagnosis, clinical response to ATT has sometimes been considered a factor in confirming the earlier presumptive diagnosis.[35] Both IGRA and CXR are the valuable investigations included as a workup for the clinically undifferentiated cause of uveitis at the beginning to help narrow down the differential diagnoses into OTB. Our findings could affect our approach on ancillary examination to be performed in cases with clinically undifferentiated uveitis, especially in panuveitis, which poses difficulties in assessing the inflammation at the back of the eye. We may succumb to circumstances where IGRA testing is unavailable and costly; however, its use in uveitis cannot be underestimated. Even though we did not specifically address its comparative diagnostic utility with TST, we depicted that four fifths of the patients with a clinically undifferentiated cause of uveitis had a positive IGRA, and three quarters met the criteria for possible intraocular TB. Moreover, IGRA testing, which only needs one-time blood sampling, may also offer convenience to the patient. The results of this study could also be a basis for further prospective research addressing prognostic factors/scoring systems used to determine the initiation of ATT and the results of ATT management in patients with possible OTB.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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