The utility of routine tuberculosis screening in county hospital patients with uveitis

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ABSTRACT

Background/aim To evaluate the utility of tuberculosis (TB) screening in diagnosing ocular TB in uveitis patients in a government-funded hospital.

Methods The charts of 142 consecutive patients seen during August 2011–July 2012 at the Los Angeles County Hospital uveitis clinic were reviewed for manifestation/laterality of uveitis, purified protein derivative (PPD) test results, interferon γ release assay, chest x-ray, birthplace, treatment history and diagnosis. 'Presumed TB-uveitis' was diagnosed when patients had positive TB screening and favourable response to anti-TB therapy, and definite ocular TB when *Mycobacterium tuberculosis'* presence was demonstrated. Post-test probabilities were determined.

Results TB screening was positive in 21.1%. Six patients were diagnosed with TB-related uveitis: one definite, four presumed and one systemic TB with uveitis. With regard to PPD positivity, being foreign-born was the only statistically significant factor with OR of 2.26 (95% CI 1.01 to 5.13; p<0.01) if born in Mexico and 4.90 (95% CI 1.74 to 13.83; p<0.01) if born in other foreign countries. The post-test probabilities of a positive PPD in a uveitis patient showed a 17.2% (overall) or 30.3% (foreign-born patients) chance of ocular TB.

Conclusions PPD skin test plays an important role in the diagnosis of TB-associated uveitis in high-risk groups, such as immigrants from TB endemic regions.

Tuberculosis (TB) affects a third of the world's population. In the USA, 10 521cases (incidence 3.4 per 100 000) were reported in 2011, the lowest since 1953[1] and greater than the average yearly 3.8% decline between 2000 and 2008.[2] A resurgence of TB coincided with the HIV epidemic and increased immigration between 1985 and 1992;[3] however, the decline since 1992 was limited to US-born persons.[4] Foreign-born persons are affected disproportionately with 12 times higher incidence.[1]

Most cases are pulmonary infections with a small fraction representing extrapulmonary dissemination. Intraocular TB can present in the absence of pulmonary disease and poses significant morbidity.[5] Many factors hamper diagnosis, including variability in presentations, often-absent non-ocular symptoms, poor history of exposure and risk in obtaining specimens.

Ophthalmologists often have only their clinical judgment, the results of a skin test, a chest x-ray and therapeutic response. As no confirmatory test for intraocular TB exists, no reliable prevalence data exist.[5]

Two tests are available for TB detection: purified protein derivative (PPD, or 'Mantoux') skin test and interferon γ release assay (IGRA). The Centers for Disease Control and Prevention (CDC) regard the sensitivity of IGRA 'statistically similar to that of the [PPD] for detecting infection in persons with untreated culture-confirmed tuberculosis.'[6]

Based on analysis of results from routine PPD tests on large groups, a previous study opposes routine PPD testing in uveitis due to low positive predictive value (PV Pos) in the general US population.[7]

As the utility of PPD screening in uveitis patients is highly debated, we undertook a retrospective review at a large referral clinic with both immigrant and indigent populations, assessing factors associated with positive screening tests and their value in predicting a diagnosis of ocular TB.

MATERIALS AND METHODS

Participants were consecutive patients seen at the uveitis clinic at the Los Angeles County + University of Southern California Medical Center (LAC +USC), a hospital serving an uninsured, urban population, between August 2011 and July 2012. The Institutional Review Board at the USC approved the protocol, and procedures conformed to the Health Insurance Portability and Accountability Act and Declaration of Helsinki. Exclusion criteria were <6 months follow-up or being lost to follow-up. The data collected included age, sex, birthplace, Snellen visual acuity, laterality and major manifestation of uveitis, TB screening test results (PPD and/or IGRA), chest x-ray, ophthalmic imaging, TB-treatment history, and final diagnosis.

The PPD test was performed by trained personnel by intradermally injecting five tuberculin units raising a 6–10 mm weal.[8] After 48–72 h, induration was positive if >10 mm. Positive PPDs within a 2-year period were counted.

IGRAs were obtained using QuantiFERON –TB GOLD (Cellestis, Carnegie, Australia) in selected cases at the treating physician's discretion. Positive results were determined according to CDC guidelines.[6] Because these guidelines and other studies[9–11] indicate that IGRA can be used in place of and in conjunction with PPD, IGRA and PPD were regarded as equivalent.

Positive TB tests were referred for further evaluation and for management of anti-TB treatment (ATT) by TB control clinic pulmonologists. To capture all positive responses, the response to ATT by four-drug therapy (rifampicin, isoniazid, pyrazinamide and ethambutol; RIPE) was considered positive if the degree of uveitis decreased over a 2–

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4-month follow-up period,[5] as specified by the SUN Working Group.[12] Improvement was described as a two-step decrease in the level of inflammation or a decrease to grade zero. A diagnosis of presumed TB-uveitis was made when (1) a TB screening test was positive; (2) other diagnoses were excluded; and (3) a response to therapy was seen. A suspicious chest radiograph was considered helpful but not necessary.

We used the methods and assumptions of sensitivity and specificity previously described,[7] and Bayes' theorem to calculate post-test probability.[13] Post-test probability (or PV Pos)=(pretest probability × sensitivity)/{(pretest probability × sensitivity)+[(1−pretest probability)(1−specificity)]}, where the pretest probability is equal to the prevalence of TB-uveitis in a given population. The negative predictive value (PV Neg) was calculated as described by Vecchio.[14] The prevalence of TB-related uveitis was determined overall and for foreign-born patients.

Statistical analysis was performed using SAS, V.9.2, for Windows (SAS Institute, Inc, Cary, North Carolina, USA). Descriptive statistics were used to compare demographics. To examine the significance of the association (contingency) between the two test groups, Fisher exact test was used for categorical data that resulted from binary classification. χ^2 Test was used to evaluate statistical significance of categorical variables for which there were large samples. Statistical significance was defined as $p \leq 0.05$; p values were not corrected for multiplicity.

RESULTS

Of the 142 patients included, 66 (46.5%) were US-born. The foreign country with highest representation was Mexico with 58 (40.8%).

A total of 130 patients (91.5%) received PPD; of these, 23 (16.2% of total 142) were positive (table 1); two were diagnosed with presumed TB-related uveitis, one with TB scleritis based on PCR of biopsy specimen, and one with presumed TB panuveitis in the setting of presumed systemic TB. Among the 107 patients (75.4%) with negative PPD, one patient had positive IGRA with uveitis that responded to ATT, giving that patient a final diagnosis of presumed TB panuveitis. PPD was deferred in 12 patients (8.5%), of whom five had a recent history of positive PPD. Three of these patients had positive IGRA, two were treated with ATT, and one responded to treatment and was diagnosed with presumed TB panuveitis. In total, six patients (4.2%) were diagnosed with TB-related uveitis.

Overall, 30 patients (21.1%) had a positive PPD and/or IGRA. Among these patients, 1 (3.3%) had definite TB-uveitis (by PCR) in a setting of systemic TB, 4 (13.3%) had presumed

Table 1 Patients who received intradermal PPD skin test

		IGRA performed?	IGRA result	Chest x-ray result	Anti-TB treatment or prophylaxis?	Treatment response?	Final diagnosis
130 PPD placed	23 PPD-positive	Yes	Positive	Normal	No	NA	Idiopathic anterior uveitis (AC PCR-negative)
		No	NA	Normal	No	NA	Ocular toxoplasmosis
		No	NA	Normal	No	NA	Lupus/antiphospholipid +
		Yes	Positive	Normal	INH×3 months	No	Ocular toxoplasmosis
		No	NA	Normal	INH×3 months	No	AZOOR
		No	NA	Normal	INH×9 months	Unknown*	VKH
		Yes	Positive	Normal	INH×9 months	No	HLA B27
		Yes	Positive	Normal	INH×9 months†	Unknown*	Panuveitis NOS
		No	NA	Nodule at lung base	INH×9 months	No	RA scleritis
		No	NA	Normal	INH×3 months	No	HLA B27
		No	NA	Normal	INH×9 months	No	VKH
		No	NA	Normal	INH×5 months	No	HLA B27
		No	NA	Normal	INH×9 months	No	ACIOL-induced uveitis
		No	NA	Normal	INH×5 months	Unknown*	VKH
		No	NA	Normal	RIPE×3 months‡	No	VKH
		Yes	Positive	Normal	RIPE×9 months	Yes; at 3 months	**TB panuveitis (presumed)**
		Yes	Negative	Normal	RIPE×9 months	Yes; at 2 months	**TB anterior uveitis (presumed)**
		No	NA	Normal	RIPE×9 months	No	VKH
		Yes	Positive	Normal	RIPE×9 months	No	Uveitis NOS
		No	NA	RUL disease, nodules	RIPE×9 months	Yes; after steroid	**TB scleritis (PCR+)**
		No	NA	Normal	RIPE×9 months	No	Multifocal choroiditis NOS
		Yes	Positive	Normal	RIPE×9 months	No	VKH
		No	NA	Prominent right paratracheal region	RIPE×9 months	Yes; at 2 months	**TB panuveitis (presumed); systemic TB (presumed)**
	107 PPD-negative	Yes	Positive	Normal	RIPE×9 months	Yes; at 4 months	**TB panuveitis (presumed)**
		106 No	NA	106 No§	106 No	106 NA	106 Other

*Response to INH was unknown, primarily because it was given as prophylaxis but also because it was administered concomitantly with other agents, namely, prednisone.
†RIPE therapy was discontinued due to persistent nausea and vomiting.
‡RIPE therapy was discontinued due to persistent nausea and vomiting.
§Two patients with abnormal lung fields on chest x-ray: a PPD-negative patient whose final diagnosis was VKH had a left, lower lobe granuloma on chest radiograph. Another patient with final diagnosis of sarcoidosis-related uveitis had interstitial lung disease and prominent hilum.
AC PCR, anterior chamber PCR; ACIOL, anterior chamber intraocular lens; AZOOR, acute zonal occult outer retinopathy; HLA B27, human leukocyte antigen B27; IGRA, interferon γ release assay; INH, isoniazid or isonicotinylhydrazine; NA, not applicable; NOS, not otherwise specified; PPD, purified protein derivative; RA, rheumatoid arthritis; RIPE, rifampicin, isoniazid, pyrazinamide and ethambutol; RUL, right upper lung; TB, tuberculosis; VKH, Vogt–Koyanagi–Harada disease.

TB-uveitis (by response to ATT) and 1 (3.3%) had presumed systemic TB with presumed TB-uveitis. Of the TB screening positive cases, 20.0% were presumed or definite TB-uveitis, of whom all were foreign-born.

As summarised in table 2, the only significant risk factor was being foreign-born. Being born in Mexico yielded an OR of 2.26 (95% CI 1.01 to 5.13; p<0.01), and being born in a foreign country other than Mexico yielded an OR of 4.90 (95% CI 1.74 to 13.83; p<0.01). Chest x-ray abnormalities were not significant.

Considering a 75% sensitivity and 85% specificity for a positive PPD,[8] the PV Pos was 17.2% in our total uveitis-clinic population and 30% in foreign-born patients; the corresponding PV Neg values were 98.8% and 97.5%, respectively. No value could be calculated for US-born patients because none of our US-born, TB screening-positive patients had a final diagnosis of TB-uveitis.

The brief clinical summaries of TB-uveitis patients are presented in table 3.

COMMENT

Overall, at least 4% of the total and 8% of our foreign-born study population had a final diagnosis of intraocular TB. Bayesian analysis for the PV Pos of TB screening in a uveitis patient yielded a 17.2% (all patients) and 30.3% (foreign-born patients) chance of being associated with ocular TB.

In 1990, a study explored the utility of routine TB screening of patients with uveitis, using 10 mm of induration as the cut-off for PPD.[7] The study used a 75% sensitivity and 85% specificity, and an estimated prevalence 0.2%. A PV Pos of 1.0% and 99.94% PV Neg were derived. The study concluded that routine PPD testing of patients with uveitis is inappropriate because of the low predictive value and that in the theoretical case of 1% prevalence and 95% specificity, a 13% PV Pos may justify testing.

We show that positive TB screening in non-US-born patients is highly predictive of TB-uveitis and that PPD should be placed in higher-risk patients. Our results differed from the above-mentioned study, mostly because our population more closely approximates the multicultural community in many metropolitan US cities, which undergo constant migratory change.

In many developed countries, immigration sustains the TB rate,[1 15] making community hospitals in urban settings the intersection of the developed and developing worlds. This is highlighted by the CDC's data.[1] In 2011, California, Florida, New York and Texas combined accounted for 50.4% of TB cases. Among US-born persons the rate dropped 80.1% since 1993, and 49.0% among foreign-born; however, this rate is still 11.5 times the US-born population's.[1] Our results portray a similar picture: none of the six TB-uveitis patients were US-born, and among all US-born patients, only 4 (6.1% of 66) had positive PPD. Notably, all foreign-born patients with positive TB screening emigrated from TB-endemic regions and most were unaware of contact with TB-infected individuals. Two patients (Patients B and D) disclosed contact with known TB-infected individuals; no US-born patients gave such history.

The homeless and HIV-positive patients (of whom there were <5) were excluded due to highly erratic follow-up and poor compliance. The two incarcerated individuals, one from Mexico and one from USA, were both PPD-negative.

Our data show that over the course of 1 year at LAC+USC Medical Center, 4.2% of referrals made to the uveitis clinic had a diagnosis of TB-related uveitis. Other studies have wide-ranging results based on unique characteristics of each population. Wakabayashi *et al*[16] reported that among 189 patients at a Japanese tertiary referral centre, 6.9% had intraocular TB which responded to ATT, but no criteria were provided as to PPD or IGRA. Islam and Tabbara[17] reported that 10.5% of 200 uveitic

Table 2 Risk factors for positive tuberculosis screening

	Positive PPD or IGRA					
	TB-related uveitis	Not TB related	Total	Negative	OR	p Value
Variable	(n=6)	(n=24)	(n=30)	(n=112)	(95% CI)	
Age, mean (SD), years	49.7 (8.3)	41.9 (14.6)	43.4 (13.8)	42.0 (12.9)	x	x
Sex, no.						
Male	4	13	17	51	1.56 (0.65 to 3.81)	0.31
Female	2	11	13	61		
Country of birth						
USA	0	4	4	62	0.12 (0.04 to 0.38)	<0.01
Mexico	5	12	17	41	2.26 (1.01 to 5.13)	
Non-USA/Mexico*	1†	8	9	9	4.90 (1.74 to 13.83)	
Laterality						
Unilateral	2	12	14	48	1.17 (0.48 to 2.82)	0.84
Bilateral	4	12	16	64		
Major manifestation						
Panuveitis	4	10	14	53	0.87 (0.39 to 1.91)	0.87
Anterior	1	7	8	27	1.05 (0.42 to 2.61)	
Intermediate	0	1	1	5	0.69 (0.08 to 6.13)	
Posterior	0	6	6	22	0.94 (0.35 to 2.57)	
Scleritis	1	2	3	5	2.21 (0.50 to 9.81)	
Chest x-ray (lung fields)						
Normal	4	23	27	109	4.04 (0.77 to 21.12)	0.1
Abnormal	2	1	3	3		

*Non-USA/Mexico includes Armenia, Brazil, China, Egypt, El Salvador, Ethiopia, Guatemala, Iran, Peru, Puerto Rico, Taiwan, Thailand and Turkey.
†TB-related uveitis diagnosed in Patient F.
IGRA, interferon γ release assay; PPD, purified protein derivative; TB, tuberculosis; x, unable to calculate.

Table 3 Brief clinical summaries of TB-uveitis patients

Patient	Demographic	PMH	Initial eye exam	Treatment and response	Other findings and history
A	54 year F, from Mexico	IDDM, HTN, dyslipidaemia, renal insufficiency	Markedly asymmetric uveitis, OD >OS. Large KPs	RIPE, topical prednisolone acetate 1%, PO prednisone; complete resolution uveitis by 3-month visit, with no further recurrence after more than 9 months of follow-up, off topical and systemic steroids	Outside physician initially diagnosed patient with VKH. Despite history of untreated positive PPD, patient started mycophenolate mofetil, cyclosporine and prednisone, as well as topical prednisolone acetate, without clinical improvement and without development of a sunset glow fundus. Positive IGRA. Normal CXR
B	54 year M, from Mexico	IDDM, HTN, dyslipidaemia, CAD	OU: 2+ AC cell, 2+ anterior vitritis	RIPE, topical prednisolone acetate 1%; complete resolution of uveitis by 3.5-month visit, with no further recurrence after more than 8 months and is no longer taking topical steroids	Brother and nephew in Mexico diagnosed with pulmonary TB. Negative PPD. Positive IGRA. Normal CXR
C	48 year F, from Mexico	None	OU: stellate KPs, 1+ AC cell, retinal vasculitis and many grey chorioretinal scars; multifocal choroiditis	RIPE, topical prednisolone acetate 1%; complete resolution of uveitis by 3-month visit, with no further recurrence after more than 8 months and is no longer taking topical steroids	No close contact with TB-infected individuals. Positive PPD. Positive IGRA. Normal CXR
D	57 year M, from Mexico	None	OU: 3+ AC cell	RIPE, topical prednisolone acetate 1%; complete resolution of uveitis by 2-month visit, with no further recurrence after more than 7 months and is no longer taking topical steroids	History of recurrent uveitis over several years. Vague recollection that his neighbour in Mexico had been diagnosed with TB. Had been treated with topical steroids and PO prednisone > 1 year. Positive PPD. Negative IGRA. Normal CXR
E	34 year M, from Mexico	Chronic osteomyelitis	OS: granulomatous anterior uveitis and a non-tender, inflamed scleral nodule in the left eye	RIPE, PO prednisone (40 mg/day); the anterior chamber inflammation resolved after 4 months; however, the patient remained on prednisone for the duration of the scleral inflammation, which resolved over the course of the subsequent 4 months	During the course of treatment, patient was admitted for workup of pathological knee fracture, which showed TB osteomyelitis of the left femur. Positive PPD. Right upper lobe disease on CXR. PCR of scleral nodule positive for TB
F	51 year M, from China	None	OD: 2+ AC cell, 3+ anterior vitritis, vitritis overlying a slightly elevated, superonasal choroidal lesion; OS: 1+ AC cell	RIPE, PO prednisone (40 mg/day); intraocular inflammation subsided after 2 months of therapy without further recurrences 6 months after steroids have been tapered off. The skin lesions also resolved with minor scar formation	Referred by outside ophthalmologist for concern of acute retinal necrosis. Physical examination showed numerous lesions on the lower extremities, with biopsy specimens showing a reactive process and negative acid-fast stains. Positive PPD. CXR: fullness in right para-tracheal region

AC, anterior chamber; CAD, coronary artery disease; CXR, chest x-ray; HTN, hypertension; IDDM, insulin-dependent diabetes mellitus; IGRA, interferon γ release assay; KP, keratic precipitate; PMH, past medical history; PPD, purified protein derivative assay; RIPE, rifampicin, isoniazid, pyrazinamide and ethambutol; OD, right eye; OS, left eye; OU, both eyes; PO, by mouth; TB, tuberculosis; VKH, Vogt -Koyanagi -Harada disease.

patients seen in a Saudi Arabian centre were diagnosed with intraocular TB, with criteria of >20 mm induration by PPD and response to ATT.

We used a PPD cut-off value of 10 mm of induration, because the American Thoracic Society guidelines suggest this cut-off point for 'individuals with normal or mildly impaired immunity with high likelihood of being infected with TB'.[18] Although for low-risk individuals (eg, US-born), 15 mm is recommended, we selected the 10 mm cut-off to have a lower TB suspicion threshold. Despite this measure, no US-born patients proved to have a true-positive PPD.

Post-test probabilities could not be calculated for US-born patients because none of our US-born patients had a final diagnosis of TB-uveitis; however, assuming that one US-born patient had been diagnosed with intraocular TB (1.5%), we would have a PV Pos of 7.1% and a PV Neg of 99.6%.

Insofar as application of our findings, sensitivity and specificity data, although limited by lack of a gold standard, will not vary much. The most important variable is pretest probability. The PV Pos depends more on the specificity than on the sensitivity,[14] but at the prevalence values we have (0.04 and 0.08), even at very high sensitivity and specificity (both 99%), PV Pos reaches maximum values of 80.5% and 89.6%, respectively. Our PV Neg is 98.8% and 97.5% for prevalence of 0.04 and 0.08, respectively; but sensitivity and specificity values have little effect on this post-test parameter compared with PV Pos. Although higher prevalences are uncommon in the general US population (3.4 cases of TB per 100 000 persons in the USA),[1] when a group to be tested is preselected on the basis of history, clinical examination or another test, disease prevalence increases.

When examining risk factors for TB-screen positivity (table 2), being foreign-born was singly significant with OR 2.26 (95% CI 1.01 to 5.13; $p<0.01$) if born in Mexico and 4.90 (95% CI 1.74 to 13.83; $p<0.01$) if born in another foreign country versus 0.12 (95% CI 0.04 to 0.38; $p<0.01$) if US-born. Half of the ocular TB patients had posterior/panuveitis, as might be expected according to Yeh *et al*[19] but, as this type of inflammation is not exclusive to TB, the pattern of uveitis was not found to be significant. This is illustrated by the absence of classically TB-associated ocular findings in most of our patients. Although such exam findings would have guided testing and therapy, they were not considered necessary for ocular TB diagnosis. Furthermore, our patients highlight the fact that TB-uveitis may have varied presentations, including anterior uveitis, scleritis, chronic iritis and subretinal abscess.[5]

Abnormal chest x-ray failed to reach statistical significance ($p=0.1$). It has been shown that postinflammatory lesions are

not TB-specific,[20] and most cases of TB-uveitis show no lung involvement.[21] Some say that the majority of TB infections are clinically and radiographically unapparent, with positive PPD being the only indication of infection.[22] The diagnostic criteria for active systemic TB in the USA are clinical- and/or laboratory-based[23] and do not depend on chest x-ray. Because the diagnosis of intraocular TB is more complex, Gupta *et al*[5] proposed guidelines based on laboratory investigations and clinical parameters, follow-up examinations, and therapeutic response to ATT. To add to our understanding of the diagnosis of ocular TB, we present evidence that PPD and IGRA have considerable PV Pos for diagnosis of TB-related uveitis.

In select cases, both PPD and IGRA were performed at the treating physicians' discretion, when the risk for infection was increased or clinical suspicion existed and confirmation was desired.[24] Notably, four patients who were both PPD- and IGRA-positive did not receive RIPE therapy, either based on the TB control clinic's decision not to treat in light of alternative explanation of uveitis or the patient's refusal based on absent systemic symptoms. We acknowledge that the prevalence may be underestimated for this reason.

Although retrospective, this study's main strength is inclusion of a mixed population and observation of post-test probabilities. Routine TB screening has an important role in developed nations when diagnosing and treating uveitis, especially among its indigent patients and immigrants, as is the case with our study population. A positive PPD is clinically significant in predicting TB-related uveitis, especially in patients from TB-endemic regions. Meanwhile, we agree that TB screening might not be helpful in US-born patients. We excluded BCG vaccination status from our analysis because we cannot exclude a recall bias; and similar to the study by Manuel and colleagues,[11] almost half of our population came from countries where BCG is administered at birth.

Our TB-uveitis patients (table 3) all received topical prednisolone as frequently as every hour and some patients oral prednisone at doses up to 40 mg daily. However, it must be noted that the degree of inflammation by SUN criteria never fell more than one step at any given follow-up visit until there was an absence of inflammation between 2 and 4 months after RIPE therapy initiation. Also, TB-uveitis patients are typically treated with combination of systemic corticosteroids and ATT to avoid paradoxical reaction.[25] In all patients, absence of inflammation continued beyond 6 months of follow-up despite discontinuing all steroids. Of note, patients who were started on RIPE therapy by the TB control clinic were generally maintained on it for 9 months to preclude genesis of resistant strains, and uveitic response to RIPE were independent of decision to treat systemically.

In conclusion, PPD and IGRA provide supportive evidence in intraocular TB diagnosis, especially in patients from TB-endemic countries. Clinicians must be mindful of the quickening pace of globalisation and use this knowledge in making informed decisions regarding pretest probability. Prudent use of TB tests is essential as false positives in a population with low pretest probability will confuse the clinical picture and may commit a patient to a course of TB drugs with a significant side-effect profile. Meanwhile, we do recommend the continued use of PPD in the diagnosis of ocular TB in at-risk populations.

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