Science

Diagnosis of Tuberculous Meningitis Using a Combination of Peripheral Blood T-SPOT.TB and Cerebrospinal Fluid Interferon-γ Detection Methods

*Diya Lu, MD, Cheng Chen, MD, Shenglei Yu, MD, Shu Chen, MD**

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ABSTRACT

Objective: To evaluate the effectiveness of combined peripheral blood T-SPOT.TB and cerebrospinal fluid interferon-γ (cIFN-γ) detection methods in the diagnosis of tuberculous meningitis (TBM).

Methods: A total of 30 individuals with TBM and 39 control individuals without TBM participated in this study. IFN-γ–secreting T cells were detected by enzyme-linked immunospot (ELISPOT), and cIFN-γ was detected by enzyme-linked immunosorbent assay (ELISA). We collected cerebrospinal fluid from 10 patients in the TBM group on initial visit and at 4 weeks, to observe changes.

Results: The sensitivity and specificity of peripheral-blood T-SPOT.TB testing in the diagnosis of TBM were 70% and 87%, respectively. The area under the ROC curve of cIFN-γ for TBM diagnosis was 0.819, and the corresponding sensitivity and specificity were 83% and 85%, respectively. When T-SPOT.TB and cIFN-γ results were positive, the specificity and positive predictive value of TBM diagnosis reached 100%.

Conclusions: Combined use of T-SPOT.TB and cIFN-γ could improve the diagnosis efficiency of TBM. Dynamic observation of cIFN-γ is also important in monitoring TBM because the level of this analyte significantly decreases after treatment.

Keywords: tuberculous meningitis, T-SPOT.TB, interferon-γ, diagnosis, cerebrospinal fluid, combined detection

Tuberculous meningitis (TBM), the most severe form of tuberculosis (TB), accounts for 5% to 10% of extrapulmonary TB and 0.5% of systemic TB worldwide.[1] Those who have contracted this disease have a mortality rate of 20% to 41% in developed countries and 44% to 69%[2-4] in developing countries; 25% of the survivors of TBM sustain permanent neurological damage.[5]

At present, there is no established laboratory test to diagnose early TBM, to our knowledge. The sensitivity of the current method of acid-fast staining (AFS) cerebrospinal fluid (CSF) smears is less than 20%; also, the sensitivity of CSF culture varies between 25% and 70%, dropping to only 10% in developing countries.[6] In addition, it usually takes several weeks to obtain results with this method.[7] *Mycobacterium tuberculosis (M. tuberculosis)* DNA can be detected in CSF using polymerase chain reaction (PCR). However, due to a high rate of false-positive results and exacting experimental conditions, PCR is unlikely to be widely used in underdeveloped areas.

A newly developed ELISPOT-technique test, T-SPOT.TB (Oxford Immunotec International, Oxfordshire, England), provides a novel method for the diagnosis of TB. The high sensitivity and specificity of this technique have resulted in its becoming a prominently used technique in the diagnosis

Abbreviations:

TBM, tuberculous meningitis; TB, tuberculosis; AFS, acid-fast staining; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; IFN-γ, interferon-γ; CSF, cerebrospinal fluid; cIFN-γ, cerebrospinal fluid interferon-γ; ELISA, enzyme-linked immunosorbent assay; PBMC, peripheral-blood mononuclear cells; ESAT-6, 6-kilodilation early-secreted antigenic target; CFP-10, culture filtrate protein 10; PBS, phosphate-buffered solution; BCIP, nitro-blue tetrazolium chloride; NBTPLUS, 5-bromo-4-chloro-3′-indolyphosphate p-toluidine salt; SFCs, spot-forming cells; CI, confidence interval; ROC, receiver operating characteristic; TST, tuberculin skin test; BCG, Bacille Calmette-Guérin; TNF-α, tumor necrosis factor–α

Department of Infectious Diseases, Huashan Hospital, Fudan University, Shanghai, China

*To whom correspondence should be addressed.
hschenshu@163.com

of TB infection; it is most widely used for the diagnosis of latent TB infection in the United States. However, T-SPOT.TB is rarely used in the diagnosis of TBM because studies[8-10] have shown that the results of T-SPOT.TB in TBM patients are inconsistent, with sensitivity ranging between 62% to 91% and specificity between 57% and 100%. In recent years, several studies have evaluated the T-SPOT.TB test in CSF for diagnosis of TBM.[7-9] The method aims to detect T cells that secrete interferon-γ (IFN-γ) by measuring specific antigen stimulation in the CSF; however, the small volume of CSF that can be safely extracted per specimen and few cells limit the application of this method in clinical diagnosis. In contrast, ELISA, which requires less CSF to detect unstimulated IFN-γ, may serve as a more effective method for detecting TBM. The clinical significance and cut-off value of CSF IFN-γ (cIFN-γ) varies between reports.

In this study, we used TBM ELISPOT to detect TB-specific antigens in peripheral blood by stimulating the secretion of IFN-γ in T cells and analyzed changes in unstimulated cIFN-γ levels via enzyme-linked immunosorbent assay (ELISA). We compared the clinical significance of the 2 TBM diagnostic tests and determined the diagnostic value of the combined approaches.

Materials and Methods

Specimens

We carried out our research according to the principles of the Declaration of Helsinki and obtained informed consent from all patients. This study was approved by the Ethics Committee of the Huashan Hospital, Shanghai, China. All study participants were enrolled from March 1, 2011, through March 1, 2013. We defined suspected TBM cases among our cohort according to the latest clinical diagnostic criteria published in the journal *The Lancet Infectious Diseases* in 2010.[11]

A total of 30 patients were suspected of harboring TBM, of whom 6 were clinically diagnosed as having TBM and 24 as probably harboring the disease. These patients included 24 men and 6 women, aged between 18 and 79 years, with a mean age of 45 years. The diagnostic criteria for TBM were positive AFS results or positive CSF culture results for M. tuberculosis. Diagnostic criteria of probable cases of TBM were as follows: Clinical entry criteria plus a total diagnostic score of 10 or more points (when cerebral imaging is not available) or 12 or more points (when cerebral imaging is available) plus exclusion of alternative diagnoses. At least 2 points should either come from CSF or cerebral imaging criteria. We designated 39 individuals as belonging to the control group with no TBM, including 24 males and 15 females, aged between 14 and 64 years (mean age, 36 years). The control group included 12 patients with viral meningitis, 16 with purulent meningitis, and 11 with cryptococcal meningitis.

CSF and Peripheral Blood Collection

After the first admission of each study participant from the TBM and control patient to the hospital, we collected a 1-mL CSF specimen from each via lumbar puncture. Additional 1-mL CSF specimens were collected from 10 patients in the group with TBM after 4 weeks of treatment. Immediately after collection, we centrifuged CSF at 2500 g for 10 minutes at room temperature and stored the supernatant at −80°C. We collected 5 mL of fresh, anticoagulated peripheral blood within 2 days of patient admission to the hospital. After adding cell-culture medium and lymphocyte-separation medium, blood was centrifuged at 2500 g for 20 minutes, and peripheral blood mononuclear cells (PBMC) were extracted.

T-SPOT.TB Detection

According to the manufacturer instruction, 4-well microtiter plates coated with anti–IFN-γ antibody were used for the reaction. A total of 50ul of cell-culture medium was added to the first well as a negative control and 50 ul of lectin was added to the second well as a positive control. A total of 50 ul of *M. tuberculosis*–specific polypeptides mixture A and B, which contains ESAT-6 (6-kilodilation early-secreted antigenic target) or CFP-10 (culture filtrate protein 10), was added to the final 2 wells. PBMC was prepared as a cell suspension of 2.5×10^6 per mL and added to each well.

After incubation at 37°C in 5% CO_2 for 16 to 20 hours, we washed each plate with phosphate-buffered solution (PBS) 4 times, added alkaline phosphatase-labeled mouse anti–human INF-γ monoclonal antibody, and incubated each plate at 2°C to 8°C for 1 hour. Each plate was then washed with PBS 4 times, and the chromogenic substrate solution BCIP/

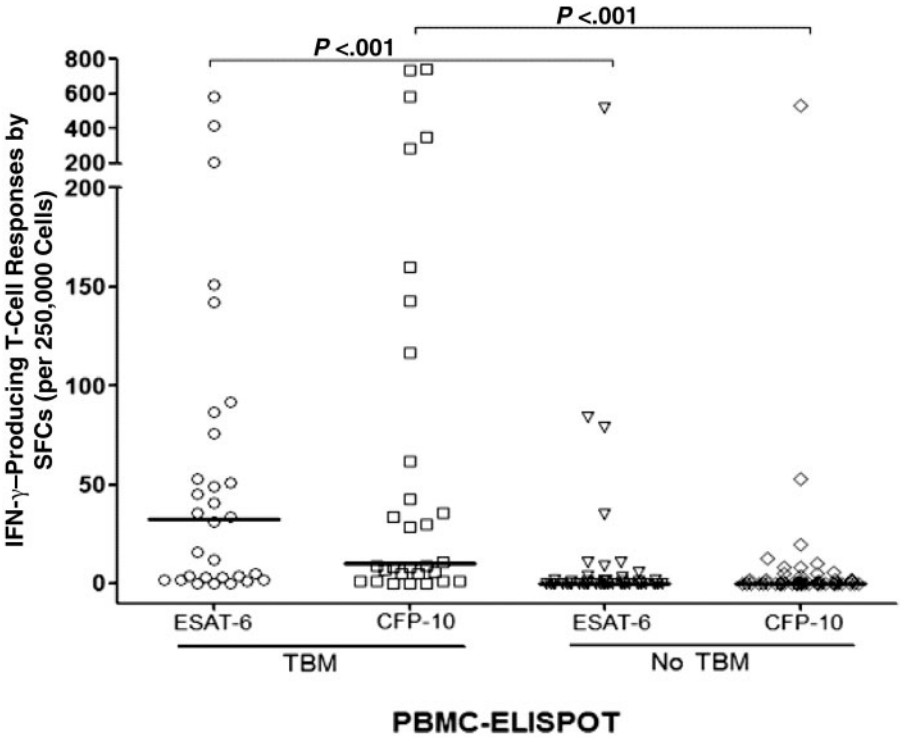

Figure 1

Scatterplot outlining the distribution of number of ESAT-6– (6-kilodilation early-secreted antigenic target) and CFP-10 (culture filtrate protein 10)–antigen spot-forming cells (SFCs) in cohort individuals with tuberculous meningitis (TBM) and control individuals without the condition. *The phrase No TBM indicates individuals without TBM; black line, the median of the formation of spot-forming cells in each group; IFN, interferon; PBMC, peripheral-blood mononuclear cells; ELISPOT, enzyme-linked immunospot.*

NBTPLUS (Bromo-4-chloro-3-indolyl phosphate [BCIP] and nitro blue tetrazolium [NBT]) was added. Then, each plate was left to stand for 7 minutes at room temperature for observation. The test was successful if we observed spots in positive- and negative-control wells. Test well contents were determined to have tested positive if the number of spots in the negative-control well was between 0 to 5 and the number of spots in the testing well minus the number of spots in the negative-control well was greater than 6; or if the number of spots in the negative-control wells was greater than 6 and the number of spots in the test wells was greater than twice that of the negative-control wells.

IFN-γ Detection

We used an ELISA to measure cIFN-γ levels in the specimens we collected. A standard curve was plotted to calculate IFN-γ levels. The CSF-culture and smear results from TBM cases and controls were also recorded and analyzed.

Statistical Analysis

We used SPSS statistical software, version 17.0 (SPSS Inc., Chicago, IL), for data analysis. A *t*-test was used for comparison of 2 independent specimens with continuous variables and normal distribution, whereas the nonparametric Wilcoxon test was used for skewed-distribution specimens. The χ^2 test was used to compare response rates between the 2 groups. A *P* value of less than .05 (2-sided) was considered statistically significant. We used GraphPad Prism 5 software to draw scatterplots.

Results

Our comparison of clinical data between individuals with TBM and controls showed no statistical difference in age, male/female ratio, duration, or clinical manifestations of the disease. A significant difference was observed for positive rate of T-SPOT.TB between the TBM group (21 of 30 [70%]) and the control group (5 of 39 [13%]). The medians of the ESAT-6– and CFP-10–antigen spot-forming cells (SFCs), respectively, in the TBM group were significantly higher than in control group (**Figure 1**). The sensitivity of T-SPOT.TB in diagnosis of TBM was 70% (95% confidence interval [CI], 54% to 86%) and the specificity was 87% (95% CI, 73% to 96%).

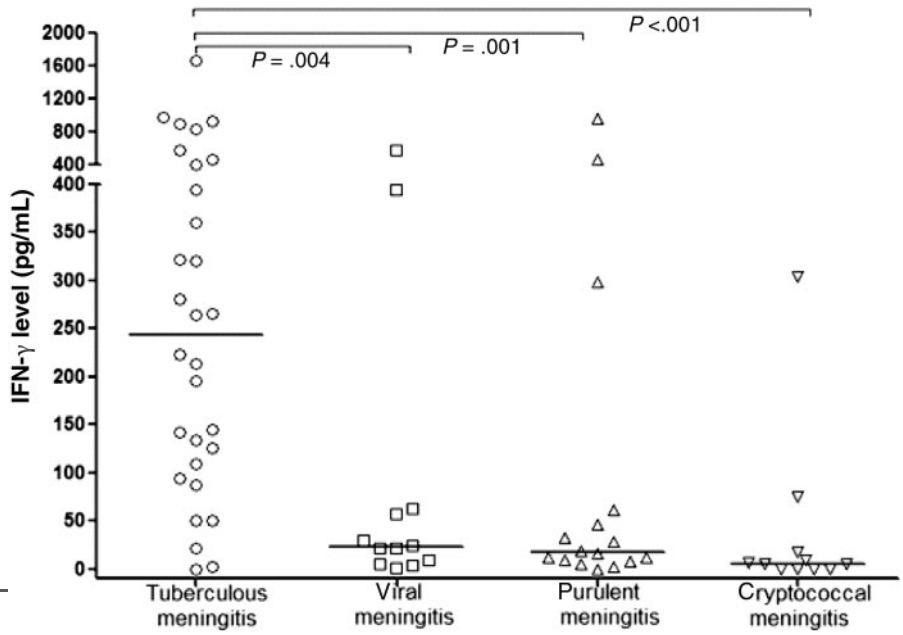

Figure 2

Scatterplot outlining the distribution of cerebrospinal fluid IFN-γ levels (pg/mL) in the group with tuberculosis meningitis, and the control group with viral meningitis, purulent meningitis, or cryptococcal meningitis. The black line represents the median value of cerebrospinal fluid interferon-γ detected in each group.

The average levels of cIFN-γ measured via the first lumbar-puncture specimen showed a significant difference (P = .001) between the TBM group (mean [SD], 350.97 [372.94]) and control group (92.46 [31.71] pg/mL). The cIFN-γ level of the TBM group was significantly higher than that of the other groups (**Figure 2**). We observed a significant difference in the mean (SD) levels of cIFN-γ in 10 patients with TBM before treatment (500.48 [504.86] pg/mL) and after treatment (103.62 [92.57 pg/mL]) with a P value of .04. **Figure 3** showed the receiver operator characteristic (ROC) curve of cIFN-γ in the diagnosis of TBM; the area under the curve is 0.819, with a 95% CI of 0.710 to 0.928. The strongest diagnostic cut-off point is 81.36 pg per mL, and the corresponding sensitivity is 83% (95% CI, 65% to 94%), with specificity of 85% (95% CI, 69% to 93%).

As shown in **Table 1**, the sensitivity of *M. tuberculosis* culture was 20%, significantly lower than the sensitivity of the T-SPOT.TB (70%) and IFN-γ (83%) tests. We observed no statistical difference in the sensitivity and specificity of CSF and IFN-γ in peripheral-blood T-SPOT.TB testing. If peripheral T-SPOT.TB and cIFN-γ testing yielded at least 1 positive result, the sensitivity of TBM diagnosis increased to 90%, with a negative predictive value of 90%; if results for both tests were positive, the specificity for TBM diagnosis was 100%, with a positive predictive value of 100%. In the TBM group, poor consistency was observed between the

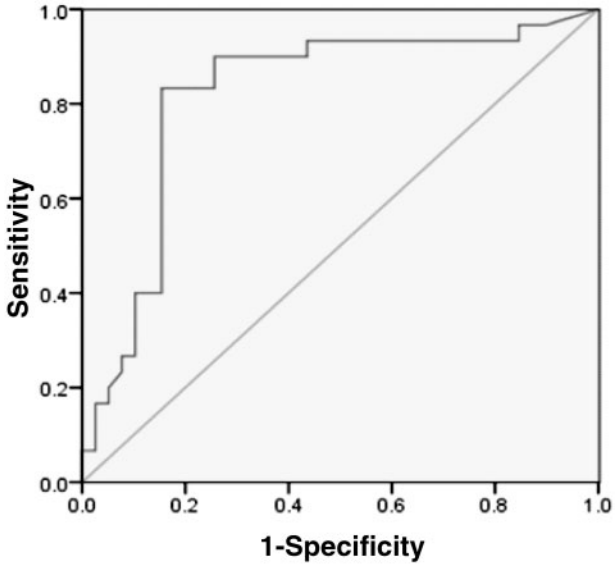

Figure 3

The receiver operating characteristic (ROC) curve of cerebrospinal fluid interferon-γ (IFN-γ) in diagnosis of tuberculous meningitis (TBM). The ROC curve was calculated by the sensitive and 1-specificity of cINF-γ in the diagnosis of TBM, using SPSS statistical software, version 17.0 (SPSS Inc, Chicago, IL). The area under the curve is 0.819, with 95% CI of 0.710 to 0.928. The optimal cut-off point is 81.36 pg/mL; the corresponding sensitivity is 83% (95% confidence interval [CI], 65% to 94%) and specificity is 85% (95% CI, 69% to 93%).

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Table 1. Comparison Between T-SPOT.TB and IFN-γ Testing Methods and the Combination of Those Methods in Diagnosing TBM

Diagnostic Tool	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value
CSF culture	20%	100%	68%	100%
T-SPOT.TB[a]	70%	87%	79%	81%
IFN-γ[b]	83%	85%	87%	81%
T-SPOT.TB and/or IFN-γ[b]	90%	72%	90%	71%
T-SPOT.TB and IFN-γ[b]	63%	100%	78%	100%

IFN, interferon; TBM, tuberculous meningitis; CSF, cerebrospinal fluid.
[a]Manufactured by Oxford Immunotec International, Oxfordshire, England.
[b]>81.36 pg/mL.

peripheral-blood T-SPOT.TB and cIFN-γ approaches (κ = 0.27; consistency rate, 73% [95% CI, 53% to 89%]).

Early diagnosis is crucial to the prognosis and treatment of TBM. Currently, the criterion standard for TBM diagnosis is etiological. However, microbiological examination has poor sensitivity because phagocytosis by monocytes in the spinal cord results in low levels of TB in the CSF. Additionally, culturing *M. tuberculosis* is time consuming and delays diagnosis and treatment of TBM. In this study, testing of 6 of 30 case individuals yielded a positive result for TBM via CSF culture, with a sensitivity of only 20%. Specimens from none of these individuals showed a positive AFS result. Novel laboratory diagnostic methods with higher sensitivity and higher specificity are urgently needed to improve the early diagnosis rate of TBM.

As a novel ELISPOT technique, T-SPOT.TB provides a new method for the diagnosis of TB. The principle of this T-cell immune-spot test relies on the presence of TB-specific activation of T lymphocytes in peripheral-blood mononuclear cells of *M. tuberculosis*–infected patients. These lymphocytes secrete IFN-γ after stimulation with *M.* tuberculosis–specific antigen material (ESAT-6 or CFP-10). According to a review by Lalvani,[12] the sensitivity of T-SPOT.TB in TB diagnosis was 83% to 97%. The sensitivity in tuberculin skin test (TST)–positive household contacts who have been exposed to TB is increased to 85% and the specificity is 100%.[13] China has a high incidence of TB and Bacille Calmette-Guérin (BCG) vaccination; thus, T-SPOT.TB detection is particularly important in Chinese patients. T-SPOT.TB detection has been widely used in the diagnosis of TB in China and worldwide; this is less the case in TBM.

We performed the T-SPOT.TB test to diagnose TBM. Our results showed that the positive-result rate for T-SPOT.TB was 70% in the TBM group and 13% in the control group; a significant difference was observed between the 2 groups. The median number of ESAT-6– and CFP-10–forming spots in the TBM group is significantly higher than those values in the control group; this suggests that the T-SPOT.TB test, which is based on the detection of levels of 2 antigenic peptides, can clearly distinguish TBM and the absence of this disease. Reports[14,15] have shown that with the extension of anti-TB treatment time, T-SPOT.TB positivity was significantly decreased. False-positive results of T-SPOT.TB testing may occur in patients with latent TB and active extracranial TB. In this study, the active or longtime TB harbored by some patients caused false-positive test results. This suggests that TBM and TB are closely related; as a result, this limits the use of the T-SPOT.TB assay system in individuals previously exposed to TB.

Cellular immunity plays a key role after TBM infection and involves a number of cytokines, such as INF-γ and tumor necrosis factor–alpha (TNF-α). After infection with *M. tuberculosis*, INF-γ is the most important cytokine for immune response because it yields anti-infective, antitumor activity and immunomodulatory effects in the resistance of the body to infection.[16] Therefore, determination of CSF INF-γ levels may reflect the condition of the immune response of the body to MTB infection; because of this, it is valuable in the clinical diagnosis of TBM.

This study detected CSF levels of INF-γ via ELISA, using the ROC curve to determine the diagnosis of TBM; the optimal cut-off point was 81.36 pg per mL the corresponding sensitivity is 83% and the specificity is 85%. A previous study[17] reported that cINF-γ was susceptible to TB treatment; in this study, test results from patients who had not received anti-TB treatment had sensitivity of 89% and negative predictive value of 92%.[17] Another study reported that herpes virus and cerebrospinal meningitis caused by *Streptococcus pneumoniae* are typically present in patients who also have high levels of IFN-γ; the presence of the former 2 disease entities can lead to false-positive results.[18] In this study, cIFN-γ levels in the TBM group were significantly higher than in the control group; 10 patients with TBM who received anti-TB treatment experienced improved health after 4 weeks, and cIFN-γ levels in those individuals were significantly lower. Studies by Kashyap et al[17] and Donald et al[19] reported similar findings, namely, that IFN-γ plays an important role in anti-TB immunity. cIFN-γ levels in

individuals with TBM were significantly higher than levels of viral meningitis, purulent meningitis, cryptococcal meningitis, and meningoencephalitis. This suggests that INF-γ plays a role in the pathogenesis of TBM.

We observed no significant difference in the sensitivity and specificity of cIFN-γ and T-SPOT.TB in peripheral blood, which may be due to the low number of individuals in our cohort and control groups. If the peripheral-blood T-SPOT.TB or cIFN-γ result were positive, the sensitivity of the diagnosis of TBM would increase to as high as 90% and the negative predictive value to 90%. In contrast, if both of these tests were positive, the specificity for the diagnosis of TBM would be as high as 100% and positive predictive value as high as 100%. This would indicate that TBM could be ruled out when detection results via peripheral-blood T-SPOT.TB and cIFN-γ were both negative, whereas TBM could be confirmed when the 2 methods yield positive results.

The consistency is poor between peripheral-blood T-SPOT.TB and cIFN-methods ($\kappa = 0.27$; consistent rate, 73% [95% CI, 53% to 89%]), probably due to the factors that could result in false-negative and false-positive results. However, this finding may partially confirm that the combination of 2 approaches can improve the efficiency of diagnosis of TBM.

Discussion

Because TBM is relatively rare, the number of patients in our cohort is relatively small. Moreover, differences among patients in disease severity, disease progression, and the time at which specimens were collected cannot be strictly controlled in such a way that specimens are harvested at the same serological milestone in the progression of the disease. This factor could possibly affect the accuracy of the results, which suggests that further study, with a larger number of specimens, is needed to further validate our results. T-SPOT.TB is an expensive test that cannot distinguish between active TB and latent TB infection.[20] Owing to widespread vaccination with BCG and the high incidence of TB in China, validating the diagnostic value of T-SPOT.TB on a large scale, via comprehensive and integrated clinical evaluations, is still required. Likewise, peripheral blood T-SPOT.TB and cIFN-γ detection in the diagnosis of TBM merit further study.

In conclusion, cIFN-γ testing is a rapid, economical, and highly sensitive approach to the diagnosis of TBM. Dynamic observation of cIFN-γ is important for monitoring patients with TBM, a condition that responds well to treatment. Peripheral blood T-SPOT.TB testing for TBM diagnosis is also important. The combination of peripheral blood T-SPOT.TB and cIFN-γ detection can improve overall sensitivity and specificity in the diagnosis of TBM.

Acknowledgments

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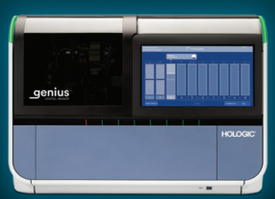

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