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DIAGNOSTIC VALUES OF INTERLEUKINS 27, 35 AND ADA FOR TUBERCULOSIS PLEURAL EFFUSION: A REVIEW STUDY

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Abstract:

Aim of review*: This review sum up the current data regarding the accuracy of pleural fluid tests (ADA, IL27 and IL 35) in making the diagnosis of tuberculosis pleural effusion.*

Recent findings: *No pleural fluid test reliably rules-in TPE in settings with low TPE prevalence. ADA can reliably rule-out TPE in prevalences of less than 40% although in higher prevalences the product of interleukin-27 and ADA is the most accurate rule-out test.*

Summary: *The definite diagnosis of TPE requires the isolation of Mycobacterium tuberculosis from pleural fluid or biopsies. The concept of a pleural fluid test that accurately due to the low sensitivity of pleural fluid cultures and the invasiveness of pleural biopsy techniques .Many pleural fluid diagnostic tests have been evaluated and the most widely accepted one test for this purpose is ADA. During the last years, it has been demonstrated that the ability of ADA to rule-in or rule-out TPE is affected by the prevalence of TPE in the setting where the test is used. The complementary use of interferon-g or interleukin-27 increases the ability of ADA to rule-in or rule-out the disease, respectively.*

Keywords *adenosine deaminase, IL-35, interleukin-27, tuberculosis pleural effusion*

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INCIDENCE:

Approximated estimation that between 2 and 3 billion people are infected with Mycobacterium tuberculosis (MT) worldwide, of whom 5–15% will develop the tuberculosis (TB) disease during their lifetime [(1).] In 2014, 12% were human immunodeficiency virus (HIV)-positive, there were 9.6 million new TB cases [(1).] Disease burden was particularly high in South-East Asia and the Western Pacific regions (58% of all cases) [(1)]. World widely, an estimated 3.3% of new cases and 20% of previously treated ones are multidrug-resistant. China is one of the high Tuberculosis (TB) burden countries, ranked 2nd in terms of the absolute number of incident cases even at present. However, over the past 2 decades, China has made tremendous efforts in TB control and prevention: by 2004, the Government had implemented the DOTs strategy along with the built of world's largest internet-based communicable-disease reporting system; by 2010, China has reduced TB prevalence and mortality rate by half, which is 5 years ahead of the target year of the Millennium Development Goals (MDGs) set by United Nation [2]. A study done in china given the incidence ratio of TB, cumulative incidence of 848/100,000 over 5 years.[3] However, the rate of TB pleuritis has steadily declined in the region over the years and, in 2015, only 7 (1.9%) of 352 new pleural effusions were caused by it (unpublished observation). geographical areas where incidence of TB is high, it is believed that TB pleural effusions commonly develop from a primary infection, whereas in countries with lower TB incidence they more likely consequence of from a recurrent activation of a latent infection. one of the greatest risk factors for developing pleural TB prior to the routine use of effective antiretroviral therapies is HIV in past, patients under the newer regimens have less active TB.

Pathogenesis

Pleural TB effusion is thought to occur when a lesion of sub pleural parenchymal occurs and it rupture causes to release a small number of tuberculous bacilli into the pleural space, which in turn triggers a local immunological response. Monocyte migration and a strong T-helper type 1 lymphocyte reaction was followed by neutrophilic influx [(4)]. The presence of mycobacteria in the pleural space activates CD4 T lymphocytes, triggering a delayed hypersensitivity reaction [20]. This immune response is mediated by cytokines, such as interferon gamma (IFN-γ), with feedback mechanism involving other interleukins and cytokines.

Patients with pleural TB are commonly young males (70%) who present with an acute or subacute syndrome characterized by fever (>80%), cough (75%), pleuritic chest pain (70%) and other potential symptoms (e.g., dyspnea, constitutional symptoms) [(4, 5)].

Clinical presentation

The clinical presentation of TPT can be acute or sub-acute, with cough, chest pain, and fever (~70% of patients), malaise, fatigue, anorexia, weight loss, night sweats and different intensity of dyspnea. The pleural effusion is usually unilateral (95%), small to moderate in size, although it is sometimes bulky (12 to 18%) or loculated (30%) on chest x-ray.

Diagnosis

The peripheral leukocyte count is usually normal. Effusions are unilateral in 95% of the cases, occupy half or more of the hemithorax in nearly 50% [(5),] and coexist with ipsilateral lung parenchymal involvement in 15–27% on the radiographs of chest [(5,6)] and computed tomography scans (mainly micro nodules and interlobular septal thickening) up to 85%[(7).] Approximately 30–40% of cases was negative on skin tuberculin test [(8-10).] Provided that more than a minimal amount of fluid exists, chemistry analysis should be done on the suspected TB effusion sample. According to Light's criteria, pleural fluid is always exudative [(5).] About 90% of cases A lymphocytic predominance (>50% of the total leukocyte count) is seen, neutrophilic fluids being more characteristic early in the disease course.[(5] pleural protein concentrations greater than 5 g/dL, in about two third of patients.

Adenosine deaminase

Adenosine deaminase (ADA) is an enzyme that catalyzes the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively [11]. Its significance in host's immune response lies in maintaining low adenosine and deoxyadenosine levels, which is critical for the proper function of immune cells and especially lymphocytes [12]. ADA has two isoenzymes, namely ADA1 and ADA2 [13]. Although ADA1 is a ubiquitous enzyme found in most immune cells (i.e. neutrophils, lymphocytes, macrophages, monocytes), ADA2 is present only in macrophages and monocytes and its levels rise after infection by intracellular organisms, such as the M. tuberculosis. Pleural fluid ADA levels represent the sum of ADA1 and ADA2, reflect the activity of immune cells in the pleural cavity and seem to be correlated with the burden of mycobacterial antigens in the pleural space [14].

Pleural fluid ADA was first described as an adjunct to TBP diagnosis in 1978 by Piras et al. [15] and since then, numerous studies and five meta-analyses (Table 1) have been consistently demonstrating the high accuracy of ADA in the diagnostic approach to tuberculous pleural effusions, with pooled sensitivities and specificities of 88– 92% [16–20]. The maximum joint sensitivity and specificity (Q-point) in four of the five metaanalyses was higher than 90%. Although various methods (i.e. Giusti, Blake-Berman, Maruho, Toyobo, Constine, Boehringer, Ellis) were used for ADA measurement, the most common one in all meta-analyses was the colorimetric method of Giusti . The most accurate cutoff for the discrimination of tuberculous from nontuberculous effusions varied widely (range: 10–71 U/l) among studies with a trend for slightly higher values in those using the Giusti method (39–45 versus 33– 36 U/l for non-Giusti methods). However, the median cutoff in all meta-analyses irrespectively of the measurement method was at the level of 40 U/l, which has become the most widely accepted cutoff for this purpose. Pleural fluid ADA may also be found elevated in parapneumonic, rheumatoid, lymphomatous and malignant effusions. To increase the specificity of ADA for TBP diagnosis, its combination with other parameters (i.e. clinical characteristics or biomarkers) or the determination of ADA isoenzymes have been proposed.

In this context, high ADA levels in patients with lymphocytic pleural effusions or pleural fluid lymphocyte/neutrophil ratio more than 0.75 or in young (37.7) and low (94%) specificity, a recent study of 88 lymphocyte-predominant pleural exudates reported little (AUC 0.893 versus 0.875) additive value of ADA2 to the diagnostic accuracy of ADA. In any case, the use of ADA2 in routine clinical practice is limited because of the high cost and limited availability of the measurement. The combination of ADA with IL 27 is discussed below.

Table 1. Meta-analyses assessing the performance of ADA

Biomarker	Authors	Patients (n)	Studies (n)	Method	Sen %	Spe %	Acu	Cutoff	DOR	PLR	NLR
ADA	Greco et al. 2003	5485	31	Giust	92	89	NR	40 U/L	NR	8.36	0.09
	Goto et al. 2003	4738	40	Giust	92	90	NR	40 U/L	NR	11.5	0.09
	Liang et al. 2008	8093	63	Giust	92	90	0.96	40 U/L	NR	9.03	0.10
	Morisson et al. 2008	1674	9	Giust	92	88	0.97	NR	NR	NR	NR
	Gui et al. 2014	2244	12	Giust	88	88	0.93	37.5 U/L	NR	6.32	0.15
	Aggarwal et al. 2016	3524	40	Giust	95	89	0.96	40 U/L	119.85	6.80	0.06
	Palma et al. 2018	4147	60	Giust	93	92	0.93	42 U/L	NR	12	0.08

Interleukin-27

Interleukin-27 is a heterodimer cytokine included into the interleukin-12 cytokine family [21]. It consists of two subunits, namely EBI-3 (Epstein-Barr Virus-Induced-3) and p28 that are related to the p40 and p35 subunit of interleukin-12 respectively [22]]. Interleukin-27 is produced by antigen-presenting cells under the stimulation of pathogen associated molecular patterns binding to Toll-like receptors of their cell membrane and acts as initiator of Th1-type immune response by inducing differentiation of naive CD4þ T-cells into Th-1 cells[23]. Interleukin-27 can be measured in the pleural fluid with the use of ELISA. The results of four recent studies (Table 2) suggest that pleural fluid interleukin-27 may be a helpful diagnostic biomarker for TBP.

Yang et al. first reported that pleural fluid interleukin-27 levels in tuberculous pleural effusions are significantly higher than those in effusions of other causes. In their study, which included 154 (68 with TBP) patients with pleural effusions of various etiologies, pleural fluid interleukin-27 levels could diagnose TBP with a sensitivity and specificity of 93% and 99%, respectively. Pleural fluid-to-serum interleukin-27 gradient was more accurate (AUC: 0.996 versus 0.993) with a sensitivity and specificity of 97% and 99%, respectively. With the use of flow cytometry it was found that all cells (i.e. CD4þ/CD8þ T-cells, natural killer T-cells, B-cells, monocytes, macrophages and mesothelial cells) in the pleural cavity overexpress interleukin-27 and thus could be the source of increased production of the cytokine in TBP. In a subsequent study of 81 pleural effusions with 49% TBP prevalence, Wu et al. found interleukin-27 more accurate (AUC: 0.982 versus 0.849 versus 0.971) than either ADA or IFN-g for the detection of TBP. The reported sensitivity and specificity for this purpose at the cutoff of 900.8 ng/l were 95% and 97.6% respectively while both the

positive predictive value (PPV) and negative predictive value (NPV) were at the level of 95%.

The combination of positive interleukin-27 with positive ADA or IFN-g presented 100% specificity for TBP with a sensitivity of 82–85%. Two recent studies by Valdes et al. and by our group assessed the usefulness of interleukin27 for the diagnosis of TBP in a population of 431 and 121 patients with pleural effusions of various causes and a TBP prevalence of 30% and 8%, respectively.

Although interleukin-27 was found inferior to ADA in the first and superior to ADA in the second study, both studies agreed in that the product of interleukin-27 and ADA (i.e. interleukin27 value multiplied by ADA value) had significantly improved diagnostic accuracy compared with each biomarker alone by increasing their sensitivity to 100% and decreasing their negative likelihood ratio to zero, which means that no patient with TBP tests negative.

Table 2: Studies assessing the accuracy of interleukin-27 with or without comparison to other biomarkers for the diagnosis of tuberculosis pleuritis.

		Skouras et al.	Yang et al.	Wu et al.	Valdes et al.
	TBP prevalence (%)	8	39	49	16
Interleukin-27	Cutoff (ng/l)	391	1007	900.8	550
	Sensitivity (%)	80	92.7	95	91.4
	Specificity (%)	91	99.1	97.6	85.1
	LRþ	8.9	98	39	6.1
	LR	0.22	0.07	0.05	0.10
	AUC	0.93	0.99	0.98	0.94
ADA	Cutoff (IU/l)	31	–	24.5	56
	Sensitivity (%)	89	–	87.5	98.6
	Specificity (%)	80	–	85.4	93.4
	LRþ	4.5	–	6.1	15
	LR	0.14	–	0.15	0.01
	AUC	0.90	–	0.85	0.96
IL-27*ADA	Cutoff (IU ng/l^2)	6917	–	–	27 600
	Sensitivity (%)	100	–	–	100
	Specificity (%)	85	–	–	93.4
	LRþ	6.7	–	–	15
	LR	0	–	–	0
	AUC	0.96	–	–	0.99

Interleukin-35

Dong X et al, IL-35 is a novel anti-inflammatory and immunosuppressive cytokine primarily produced by Treg cells, and is involved in inflammatory diseases and autoimmune diseases. However, its roles in tuberculosis pleural effusion (TPE) remain unknown. We aimed to investigate the potential involvement of IL-35 in TPE.

Thirty TPE patients and 20 lung cancer patients with malignant pleural effusion (MPE) were recruited. After traditional pleurocentesis samples of pleural effusion (100 mL) were collected. Blood was sampled from TPE patients. Mononuclear cells were isolated by Ficoll-Hypaque gradient. Proportions of Th1, Th17, and IL-35-producing cells were analyzed by flow cytometry. IL-35 was assessed by real-time RT-PCR, ELISA, and immunofluorescence. To assess the effect of IL-35 on pleural effusion mononuclear cells (PEMCs) an ELISPOT assay was used.

Proportions of IL-35-producing cells were higher in TPE compared with MPE (49.4±6.0 vs. 15.8±5.4%, $P<0.001$) and blood from TPE patients (49.4±6.0% vs. 16.6±3.1, $P<0.001$). IL-35, IL-17 and IFN-γ were elevated in TPE compared with MPE (all $P<0.01$). ELISPOT assay showed that IL-35 reduced the proportion of IFN-γ-producing CD4+ T cells in TPE.

IL-35 mRNA expression was higher in TPE compared with MPE (P<0.001). Immunofluorescence showed that IL-35-positive cells were present in pleural tissues from TPE patients. Results suggest that there is an imbalance in IL-35 metabolism in TPE. However, further studies are required to assess the exact relationship with the immune system response to tuberculosis. IL-35 might play a role in

Effects of tuberculosis pleural effusion prevalence on the accuracy of diagnostic tests

Several researchers investigated the impact of TBP prevalence in the diagnostic accuracy of ADA and demonstrated that it's FPR in low (58%) and decreases with increasing prevalence to never reach levels of less than 11%, unless the prevalence of the disease exceeds 70% (Table 4). In contrast, its FNR is maintained sufficiently low to rule-out the disease in prevalence of 1–40% and increases to more than 10% thereafter. Table 3

We suggest that the preferred tests for ruling-in or ruling-out TBP in various levels of TBP prevalence might be as shown in Fig. 1

Table 3. Rate of adenosine deaminase false-positives and false-negatives in various prevalences

Study	Cutoff (U/l)	Prevalence		False-positives	False-negatives
		Actual[a]	Hypothetical		
Skouras et al.			1–10	80 10[b]	1 1[b]
	31	10	11–40	41 12[b]	5 2[b]
			41–70	16 5[b]	15 5[b]
Greco et al.			5	59	0.4
	47	34	25	19	2.4
			85	1	24
Porcel et al.	35	14	1	92.8	0.1
			14	44.5	0.8
Garcia-Zamalloa et al. (unselected effusions)		7.4		58.1	0.6
		11.8		31.8	2.3
	40		–		
		31.3		9.8	4.4
Garcia-Zamalloa et al.(lymphocytic effusions)		7.4		33.3	1.2
		11.8		6.2	2.2
	40		–		
		31.3		0	5.3

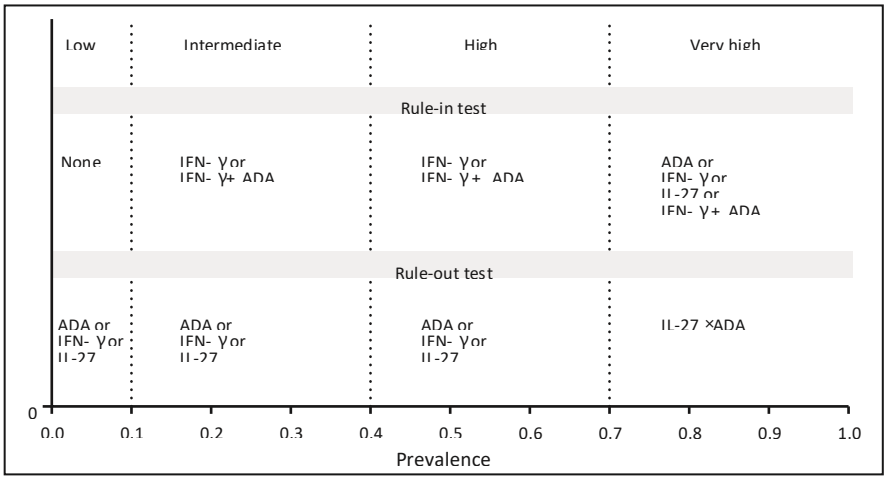

FIG 1:Suggested biomarkers for establishing or excluding the diagnosis of tuberculous pleuritis based on their rates of false results in settings with low (0–10%), intermediate (11–40%), high (41–70%) and very high (>70%) prevalence of the disease. ADA, adenosine deaminase; IFN-g, interferon-gamma; IL-27, interleukin-27

CONCLUSION:

ADA alone can establish the diagnosis only in very high (>70%) prevalence settings. However, ADA presents sufficient NPVs that allow its use as a rule-out test in low and intermediate prevalence settings while this can be achieved only with IL-27ADA in higher prevalences. IL 35 have been tested for their usefulness in the diagnostic approach to TBP, none has yet been proven more accurate than ADA for this purpose.

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