JOURNAL OF CLINICAL IMMUNOLOGY AND MICROBIOLOGY

E-ISSN: 3068-5168
Journal of Clinical Immunology & Microbiology

ATHENAEUM SCIENTIFIC PUBLISHERS

Research Article

The Systemic Cellular Immune Functions in Cardiomyopathy: Revisiting Approach

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Citation: Shnawa IMS, et al. The Systemic Cellular Immune Functions in Cardiomyopathy: Revisiting Approach. J Clin Immunol Microbiol. 2026;7(2):1-7.

https://doi.org/10.46889/JCIM.2026.7203

Received Date: 01-05-2026

Accepted Date: 17-05-2026

Published Date: 24-05-2026

Abstract

The cardiologist of the working team based onto clinical and laboratory evidences diagnose 23 cardiomyopathy cases at Mirgan Teaching Hospital-Babylon /Iraq. Whom complaining concurrent inflammatory infectious respiratory and/ or urinary disease in continuum with senescence. The objective of the present work was to investigate the systemic cellular immune functions in these cardiomyopathy patients. The test battery was including clinical tuberculin DTH skin test at strength of 2,5 and 20 IU20 tuberculin and Mcarophage inhibition factor cytokines against same tuberculin concentrations. Tuberculin responder patterns were as; non-responders, low, medium and high responders. Twelve out of the 23 were tuberculin allergic and eleven out of the 23 patients were skin tuberculin anergic. Five of the tuberculin anergic were boosted with BCG shot, one week latter, tuberculin ID injection have shown that no evidence for immune-conversion to tuberculin skin allergic state. MIF investigation has shown that both of the allergic and anergic patients presented nosignificant, boarderline and significant MIF cytokine percentages, a state indicating cellular immune divergence. The statistical correlation between tuberculin concentration and MIF % was of simple linear negative type as regression analysis indicated. Leukocyte irresponsiveness were traced to 2 IU tuberculin both in allergic and anergic patients. Taken together, cardiomyopathy patients were found tuberculin allergic and anergic. The anergic cases were non-convertible to allergic onto a week post to BCG booster shot. Both of the allergic and anergic cases showed divergent systemic cellular immune functions.

Keywords: Allergy; Energy; DTH; Divergence; Mycobacterium; Skin; Test

Introduction

The immune system plays a functional part in cardiac biology and plays a critical role in cardiac homeostasis and disease. As well as the outcomes of both natural innate immune and adaptive immune responses can be beneficial and/or detrimental in the pathogenesis of an array of cardiac diseases. Cardiomyopathies represent a broad group of heart disorders with hetero-genus causals that are characterized by cardiac dysfunction which are mainly induced by myocardial inflammation and ventricular remodeling. Cardiomyopathy is frequently observed in microbial and immune mediated diseases directly affecting the heart [1-4]. The objective of the present work was to map the systemic cellular immune functions in cardiomyopathy.

Materials and Methods

Based on the clinical examination ,electrocardiography and laboratory investigations the study patients attending Mergan teaching Hospital-Babylon /Iraq were diagnosed by the team cardiologist as;ischemic heart disease 2/23(13.0%), acute myocardial infarction, 9/23(39.13%), heart failure 2/23(8.6%), old myocardial infarction 3/23(13%), cardiovascular atherosclerosis with heart failure 1/23(4.4%) and heart failure with pneumonia (3/23 %). Among these patient there were 3/23(13%) with chronic active pulmonary tuberculosis. Five normal adulthood and five aged normal subjects were the test and control groups. *M. tuberculosis* purified protein derivative PPD, the tuberculin as 2IU, 5IU and 20IU (Vaccine and Serum Institute, Baghdad/Iraq.) were used as sensitizer for ID skin test and sensitin for the *in-vitro* Macrophage Inhibitory Factor MIF test. The score of clinical tuberculin reactions were as induration and redness at 48 hrs. post injection [5]. The MIF was performed by labori- fuged heparinized blood capillary loaded facing tuberlin sensitins in an agar well as in the method of Soberg [6]. The MIF was calculated as;

$$MIF = \frac{\text{Distance with sensitin}}{\text{Distance without sensitin}} \times 100$$

The significance limits were from 30 up to 68% inhibition, 70 is boarder-line results. Means, analysis of variance and regression were done as in [7].

Results

Inflammation Versus Infection

The diagnosed 23 cardiomyopathy patients were found inflamed, concurrently counteracting respiratory and or urinary tract infections in continuum with senescence and non-anemic (Table 1).

Analytical Features	Positive/total	Percentages
Aging	23/23	100%
Concurrent respiratory infections	14/16	87.5%
Concurrent urinary infections	2/16	12.5%
Hb% 11-18	18/19	94.7%
Elevated ESR	12/19	63.2%
Leukocytosis	10/19	52.63%

Table 1: Laboratory biology of the test patients.

Clinical Allergy Versus Anergy

The intradermal tuberculin skin DTH test with 2,5,20 IU strenght have shown 12/23(52.17%) were clinically allergic tuberculin positive patients and 11/23(47.82%) were clinically anergic tuberculin negative patients. Five out of the eleven anergic cases were boosted with BCG vaccine left one week then retested with tuberculin, they were still anergic failing to immune converted to tuberculin positive.

Cellular Immune Function

Both tuberculin allergenic and anergic patients heparinized blood samples were tested with 2, 5 and 20 IU strength tuberculin using capillary MIF test to trace the cell mediated immune functions. The tuberculin positive patients have shown 6/11 (54.54%) were significant MIF% and 5/11(45.45%) were of boarder line significance at 2IU. While at 5IU 5/11(45.45%) were with Significant MIF and 6/11(54.54%) were with boarder line significance. At 20IU,10/23, (90.90%) were significant MIF and 1/11(9.09%) was boarder line significance (Table 2).

Gross Tuberculin Results/Mm	2IU/MIF%	5IU MIF%	20IU/MIF%
10	80	26.6	26.6
10	80	26.6	26.6
20	86	70	56
20	86.6	70	56.6

15	96.6	73.3	46.4
20	72.6	66.5	46.5
15	80	46.6	11.1
10	60	33.3	20
25	20	11.1	6.6
15	76	73.3	46.4
10	31.3	76.6	71

Table 2: Clinical tuberculin allergic and MIF cellular reactions among patients.

For tuberculin anergic patients the MIF cytokine have shown that at 2IU tuberculin 5/11(45.45%) were significant and 6/11(54.54%) were non-significant. While at tuberculin 5IU, 10/11(90.90%) were significant and 1/11(9.09%) was non-significant. At tuberculin 20IU, all of the test cases showed significant MIF% (Table 3).

Clinical Tuberculin Anergic	2IU MIF%	5IUMIF%	20IU MIF%
-	66.6	40	26.6
-	60	40	40
-	93	60	26.6
-	100	56.6	26.6
-	80	73.3	26.66
-	50	6.6	3.3
-	23.3	23.3	23.3
-	80	46.6	40
-	83.3	10	6.6
-	40	30	26.6
-	79.5	46.6	40

Table 3: Clinical Tuberculin anergic and cellular immune function MIF percentages among patients.

Normal adulthood and normal senescence controls were showing significant MIF cytokine percentages (Table 4).

Tuberculin Strength/Concentration IU	*Mean Normal Aged MIF%	*Mean Normal Adulthood MIF %
2	65	6.25
5	60	31.3
20	35	25
*Mean of five readings		

Table 4: Normal cellular immune functions among aged and adulthood controls.

Biometry

The correlation between tuberculin strength/concentration and MIF cytokine % results using regression analysis were found to be simple linear type both in anergic and allergic cases. The regression equations proved that the correlation was of simple linear negative type. The correlation coefficients were ranging from 0.6-0.9,0 (Table 5).

Observations	X1tub.con	Y1 MIF 1	X2 tub.con	Y2 MIF2	X3 tub.con	Y3 MIF3
	2	74.8	2	72	2	60.8
	5	46.1	5	56.7	5	31.3
	20	36.1	20	34	20	27.3
Statistical Features						
	N	3		3		3
	X	9		9		9
	Y	52.3		54.2		39.8
	A	67.33		42.5		51.5

	Bxy	-1.67		-1.3		-1.3
	Yhat	67.33-1.67x		42.5-1.3x		51.5-1.3x
	Y4 3IU	47.3		38.6		47.6
	Y5 15IU	27.25		23.0		32.0
	100r	0.642		0.43		0.469
	R	0.801		0.655		0.685
	F	1.194		0.755		0.884

Table 5: Tuberculin-MIF % statistical analysis for patients.

Normal controls have shown simple negative correlation between (Table 6).

Observations	X1	Y1	X2	Y2
	2	65	2	6.25
	5	60	5	31.3
	20	35	20	25
Statistical Features	N	3		3
	Y	50		39.6
	By	-1.18		-1.55
	A	60.65		53.55
	Yhat	60.65-1.18x		53.55-1.55x
	Y3	57.11		66.0
	Y15	42.95		37.4
	100r	0.0731		0.554
	R	0.2704		0.744
	MSR	259		446.4
	MSC	3281		360.1
	F	0.0789		1.2396

Table 6: Biometry of Normal controls tuberculin concentration and MIF%.

Discussion

The patients diagnosis have been following standard protocols [8,9]. The chronic inflammatory responses as indicated by elevated ESR and leukocytosis have associated with cardiomyopathy [10]. Inflammatory cardiomyopathies are associated with distinct functions of MIF [1]. The systemic immune system and cardiovascular system are closely interconnected with systemic immune cells. Such, immune cells are taking part as an essential player in maintaining cardiac health and affecting disease progression [3,11,12]. Systemic immune mediated responses associated with dilated cardiomyopathy [2]. Aging of cardiac micro-vasculature do affect immune cell trafficking and inflammatory disease [13]. Ageing have been shown to present a case of immune-senescence which starts as an acute low grade inflammation, chronic low grade inflammation, inflammageing inlfamma-immuno-ageing then immune-senescence [14]. The plan of the present work was to typify systemic cellular immunity functions by clinical DTH tuberculin test, BCG boosting and at the cellular levels the capillary MIF test. The theme for such typifying was based upon memory immune cell function on recall induction both at clinical and cellular levels. Such immune memory gained from pre-immunity and /or environmental exposure [15]. Those three cases with chronic active pulmonary tuberculosis, recent efforts of the workers on the tuberculosis-cardiovascular disease, rise their believe that there is a causal correlation between the tuberculosis systemic cellular immunity and the evolution of cardiovascular diseases [16-18]. Hence our cardiomyopathy patients systemic cellular immunity stems from past-vaccination and infection. The authors hold the believe that 20/23(86.95%) of the patient systemic cellular immunity stem from memory T cell originated from past BCG vaccination and the remaining 3/23(13.04%) stem their cellular immune reaction from infection induced memory T cell subsets.

Tuberculin skin DTH test performed for patients and controls .Patients have shown clinical allergy, clinical anergy. Anergic patients on boosting BCG vaccine, a week later on failed to be immune converted to tuberculin allergic state. This can be due to existence of true anergy case or clinically anergic but at cellular levels are reactive allergic [19]. Both of anergic and allergic patients have shown significant and non-significant MIF cytokines, Tables 3 and 4. A finding indicating dissociation of clinical and cellular immune functions and/or to a state of cellular immune divergence as that reported in scar and non-scar bearing childhood BCG vaccine .The patterns of patients leukocyte responses to tuberculin within MIF test were showing non-responder, low responder, medium responders and high responders [20]. The statistical correlations between tuberculin concentrations and MIF functions done via simple regression analysis have shown simple linear negative type, Table 6,7. The biometric analysis revealed non-significant determination and correlation coefficients. Such findings can be explained on the basis of; presence of cell mediator other than the test allergen may play in inhibition or to extract purity of the allergenic sensitizer as well as the affinity of cell receptors, presence of suppressive factors or blocking factors [21,22,29]. The clinical tuberculin anergy among cardiomyopathy patients may be due to the suboptimal immune reactions mediated by an exhausted special T cell subsets [23].

Immune Features of Cardiomyopathy

Associated with notable Immune ageing. Exhibit marked clinical tuberculin allergy and anergy. Together with the low dose cellular anergy. BCG boost fails to restore clinical tuberculin allergy in anergic patients. MIF both for allergic and anergic cases showed marked immune divergence.

Revisiting Map

Through mapping literature concerning the systemic immunity of cardiomyopathy patients were depicted in Table 7.

Achievements	References
Antitroponin autoantibodies	[24]
Anti-DNA and IgM anti IgG auto antibodies in angina pectoris patients	[4]
Serum anti-laminin, anti HSP27 and anti-actin autoantibodies in cardiovascular diseases	[25]
IgG3 subclclass autoantibodies implicate as a possible cause cardiomyopathies	[26]
Systemic immune cells control the cardiac microenvironment and orchestrate inflammatory responses that facilitate myocardial repair following ischemic heart changes	[11]
Anti-endothelial and anti-myocardial autoantibodies leads to myocarditis	[27]
Activation of the cell mediated process towards recognition of myocardium as non-self , leading to auto-immune cardiomyopathy	[28]
Active tuberculosis induce immune mediated necrotizing myopathy	[17]
M.tuberculosis specific systemic macrophage, lymphocyte and their cytokines act as main derivers of atherogenesis suggesting potential role in evolution of cardiovascular disease	[18] [16]
Systemic immunity inflammation index II as; Platelet count x neutrophil count/lymphocyte count associate with heart failure	[10]
Macrophage Inhibitory Factor MIF is involved in the pathogenesis of cardiomyopathy	[1]
Tuberculin clinical allergy/Anergy versus systemic cellular allergy/anergy showed patterns of tuberculin-MIF immune divergence.	This Study

Table 7: Systemic immunity concerning cardiomyopathy patients, current literature map.

Conclusion

The findings encompassing this work are still standing in between the update as a novel conclusion concerning the systemic cellular immune cellular immune functions. Systemic memory immune cells were forming the main base for tackling systemic cellular immune functions with characteristic cellular immune divergence in cardiomyopathy patients. Immuno-senescence appeared to be of marginal role in anergy state since both controls showed clinical skin allergy tests.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding Statement
This research did not receive any specific grant from funding agencies in the public, commercial or non-profit sectors.

Acknowledgement
The authors have no acknowledgments to declare.

Data Availability Statement
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement
The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement
Informed consent was obtained from all participants included in the study.

Authors' Contributions
All authors contributed equally to this paper.

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