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Evaluation of Transforming Growth Factor-Beta 1 (TGFβ1) Levels in Cases with Multiple Myeloma: Case-Control Study among Iraqis

Ghazi Mohamad Ramadan[1], Hayder Abdul-Amir Makki Al-Hindy[2*], Mazin Jaafar Mousa[3], Hafidh I. Al-Sadi[4]

1,4 Ahlulbayt University College, Karbala, Iraq.
2Ph.D., (Physiology), College of Pharmacy, University of Babylon, Iraq.
3F.I.B.M.S, (Histopathologist), College of Pharmacy, University of Babylon, Iraq.

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Abstract

Background: The expansion of Multiple myeloma cells (MM) is regulated by cellular cytokines, including TGFβ1, which is suggested recently as the main growth factor. It was the purpose of this study to determine serum TGFβ1 levels in MM patients and to seek a correlation with tumor stages.

Materials and Methods: This comparative case-control study involved 55 MM patients, which were diagnosed by specialist hematologists. The treated group included (26 stages II and 16 stages III), and the newly diagnosed MM group included (6 stages II and 7 stages III), as well as 25 healthy individuals as controls. The measurements of TGFβ1 were done by a specific ELISA kit. SPSS was the software applied for statistical analysis. ROC curve was tested to predict MM patients from the healthy subjects, and stage II from stage III, with a p-value < 0.05% as significant.

Results: The mean ages of the total included subjects were 60.1±0.7 years (range 45-80 years). The mean serum TGFβ1 levels were 409.9±63 (range 13.5-4497.3). The gender revealed non-significant variations in the distribution of all the study variables. The levels of TGFβ1 were significantly higher in control subjects compared to the MM patients (p-0.001). There was a better ability of lower TGFβ1 levels to differentiate between stage 3 from stage 2 MM patients by the ROC curve analyses: AUC0.723, 95%CI 0.587–0.859, sensitivity 0.784, specificity 0.662, and p-0.005.

Conclusion: The MM patients exhibited significantly lower values of TGFβ1 compared to healthy controls (p-0.001), and a better ability of lower TGFβ1 levels to differentiate between stage 3 from stage 2 MM patients.

Keywords: TGFβ1, Multiple myeloma, plasma cells, neoplasm, bone marrow

1. INTRODUCTION

Multiple myeloma (MM) is bone marrow neoplasia characterized by unbalanced proliferating plasma cells and signifies the2nd most common malignancy after non-Hodgkin lymphomas[1, 2]. MM resulted from an irregular bone remodeling that increases osteoblastic activity and decreases osteoblastic activity[1]. M-protein in plasma and/or urine is usually associated with MM.MM is an incurable tumor, although prognostically it has improved evidently during the past two decades owing to the introduction of new therapies[2-4].

Plasma cell neoplasm has an unclear etiology, however, it generally arises among certain employments. Several researchers proposed that many etiological elements may have contributed to MM etiology including autoimmune illnesses, viral infections, inflammatory diseases, allergic disorders, and familial tendencies[2, 3].

Different cellular cytokines have been often linked with pathogenesis and progression of myeloproliferative neoplasms including platelets-derived growth factor (PDGF) and transforming growth factor-β (TGFβ), and others [5]. PDGF is a cytokine that was refined from extracts of platelets and has mitogenic activities [5-7]. Revisions

concentrating on PDGF expression in myeloproliferative neoplasms patients have initiated in the 1980s [5], despite their debatable outcomes [8, 9].Along similar channels, TGFβ is another multifaceted cytokine regulating different cell activities like migration, multiplication, and differentiation, besides survival[10-14]. It influences various living processes such as normal development, carcinogenesis, fibrosis, atherosclerosis, bronchial asthma, and even mental activity [5, 12, 15-17]. In patients MM, higher levels of TGFβ1 are secreted by neoplastic plasma cells and marrow cells. TGFβ1release increases with a differentiation stage of B cells (Figure-1) [18]. Several lines of evidence give reason to believe that TGFβ1has a dual function in the bone marrow. In the course of hemopoiesis, the TGFβ1signaling path is a strong adverse regulator for proliferation, whereas activating differentiation and apoptosis when suitable[19].

This study aims to evaluate the levels of TGFβ1 cytokine in patients with multiple myeloma compared to healthy controls among Iraqis.

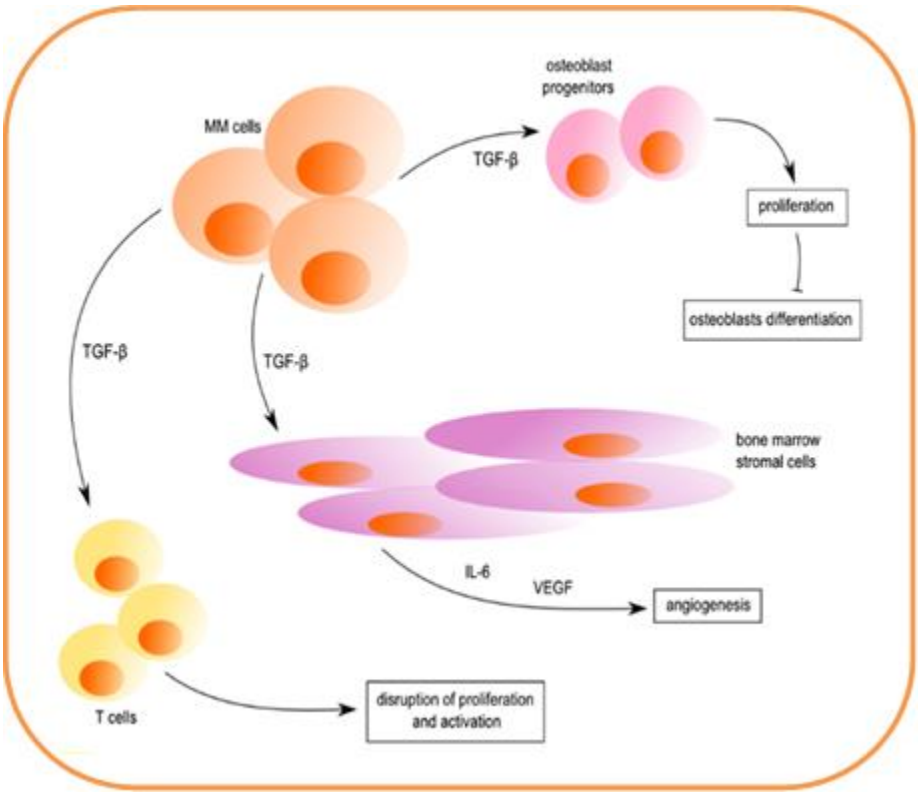

Figure-1: The signaling of TGFβ in the bone marrow of MM patients. The cancerous cells can produce TGFβ, which affects cells of the marrow including osteoblast progenitors and stromal cells. Furthermore, it interrupts T-cell activation and proliferation [18].

2. MATERIALS AND METHODS

Study population and design

This case-control work was run through the period from March to September 2021 in Merjan Medical City (oncology unit) in Babylon, Iraq. The study's 80 applicants comprised 55 multiple myeloma patients, and 25 healthy controls, with an age range of 40-80 years. The diagnosis of MM has been confirmed by professional hematologists, based on"EHA-ESMO Clinical Practice Guidelines for diagnosis of MM"[20].The MM patients were on first-line therapy"bortezomib or lenalidomide chemotherapy"divided into four treatment groups. Group I comprised 26 stages II patients, and group II had 16 stages III patients. As well, the newly diagnosed 13 patients formed the third group of stage II 6 patients and stage III 7 patients.

Those with type 1 DM, hepatitis, and renal impairment were excluded from this study.As well,patients under the therapy of other lines and those submitted to autologous marrow transplants were excepted.

Ethical issue

All participants of this study passed a written agreement before being involved in the study. The entire study protocol was approved and permitted by the local hospital and institutional health authorities of Babylon health directorate and was following Helsinki Declaration.

Data acquisition, TGFβ1 assessment

The demographic data, basal characteristics, some of the blood and biochemical indices of the studied patients, as well as the staging, were taken from the hospital patients' archives. The measurements of TGFβ1 were done by the authors and completed in the laboratories of the College of Pharmacy, University of Babylon after 2ml of centrifuged blood samples were collected from all the applicants. The evaluation procedure was according to the manufacturing instruction of "Elabscience® ELISA kit for human TGFβ1 kit".

Statistical investigations

The study variables were composed and organized in a Microsoft Excel sheet, then processed and studied by the "SPSS/V24-IBM". The variables were described and appeared in the results according to their (continuous or categorical) characteristics, whether as mean (SE) or No (%). ROC curve analyses were also applied to assess the predictive ability of TGFβ1 to differentiate between MM patients from healthy controls and to distinguish between those in stage II and stage III of the disease.

3. RESULTS

The main descriptive frequencies of the studied participants were shown in table-1. The mean ages of the total included subjects were 60.1±0.7years (range 45-80 years). The mean serum TGFβ1 levels were 409.9±63 (range 13.5-4497.3). The mean levels of urea and creatinine were moderately within average values (48.4±3.4, 1.3±0.3), respectively. The mean erythrocyte and leukocyte counts were within normal ranges (3.4±0.1 $x10^6$, 5.4±0.3 $x10^3$), respectively.

Table 1: The main descriptive frequencies of the studied participants (N-80)

Study variables	Minimum	Maximum	Mean	Std. Error
Age	45	80	60.1	0.7
TGFβ1 (pg/ml)	13.5	4497.3	409.9	63.4
Creatinine	0.45	1.9	1.3	0.3
Urea	28.9	45.0	48.4	3.4
RBCs	1.6	6.4	3.4	0.1
WBCs	2.6	10.5	5.4	0.3

The differences in the baseline characteristics of the study variables among the two study groups were shown in table-2. There were no significant differences between the MM patients and the control group in all of the study variables apart from the number of WBCs and the levels of serum TGFβ1. The levels of TGFβ1 were significantly higher in control subjects compared to the MM patients (p-0.001).

Table 2: Baseline characteristics of the study variables among the two groups

Characteristics		Total (N-80)	Multiple myeloma patients (N-55)	Healthy controls (N-25)	P- value
Age/years*		60.1±0.7	58.8±0.9	62.1±1.1	> 0.05
Sex N (%)	Males	55 (61.1)	33 (60)	22 (62.9)	>0.05
	Females	35(38.9)	22 (40)	13 (37.1)	
RBCs*		3.4±0.1	3.1±0.1	3.8±0.2	>0.05
WBCs*		5.4±0.3	5.2±0.3	5.6±0.5	0.001
Blood urea (mg/ml)*		48.4±3.4	46.8±4.6	37.1±5.1	> 0.05
Serum creatinine (mg/ml)*		1.3±0.3	1.7±0.2	0.4±0.1	>0.05
Serum TGFβ1 (pg/ml)*		409.9±63.3	335.4±38.9	573.8±182.2	0.001
*mean± SE					

In this study, the distribution of the study variables according to the treatment groups and stages of MM revealed no significant differences in most of the variables apart from the number of RBCs (table-3).

Table 3: Distribution of the study variables according to the treatment groups and stages of multiple myeloma

Characteristics		Treatment Groups				P-value
		Treated patients		Newly diagnosed		
		Stage-II (n-26)	Stage-III (n-16)	Stage-II (n-6)	Stage-III (n-7)	
Age/years*		59.6±1.3	56.3±1.5	56.7±2.8	63.9±2.1	> 0.05
Sex	Males	17 (51.5%)	9(27.3%)	3 (9.1%)	4 (12.1%)	>0.05
	Females	9 (41%)	7 (31.8%)	3 (13.6%)	3 (13.6%)	
RBCs*		2.6±0.3	4.2±0.3	2.9±0.1	2.9±0.1	0.03
WBCs*		3.7±0.2	8.6±0.5	3.9±0.3	3.9±0.2	> 0.05
Blood urea*		45.1±9.1	32.1±0.9	36.7±2.1	39.9±2.6	> 0.05
Serum creatinine*		1.1±0.2	1.3±0.1	1.1±0.2	1.3±0.2	> 0.05
Serum TGFβ1 (pg/ml)*		418.1±59.4	111.4±28.1	497.8±134.7	401.1±84.7	> 0.05
*mean± SE						

The gender revealed non-significant variations in the distribution of all the study variables (table-4).

Table 4: Gender distribution of the study variables among the included participants

Variables	Sex	Mean	SD. Error	P-value
Age	M	59.9	1.2	> 0.05
	F	57.2	1.2	
Creatinine	M	1.1	0.5	> 0.05
	F	1.4	0.1	

Urea	M	47.3	3.6	> 0.05
	F	49.8	6.3	
RBCs	M	3.6	0.1	> 0.05
	F	3.2	0.2	
WBCs	M	5.1	0.4	> 0.05
	F	5.7	0.4	
TGFβ1	M	314.1	48.9	> 0.05
	F	367.4	64.7	

To evaluate the predictive ability of lower TGFβ1 serum levels to differentiate between healthy and MM patients, a ROC curve was performed that resulted in a non-significant (p> 0.05) AUC measure of 0.424, 95% CI (0.292-0.556), and low sensitivity (0.40), although the specificity was good (0.74). However, there was a better ability of lower TGFβ1 levels to differentiate between stage 3 from stage 2 MM patients (table-5).

Table 5: ROC curve results of TGFβ1 to predict: A- MM patients from the healthy control subjects. B-Stage 3 from stage 2 MMpatients

The ability of TGβ1 to predict	AUC	Sensitivity	Specificity	P-value	95% CI
A: MM patients from the healthy subjects	0.424	0.40	0.74	0.278	0.292 – 0.556
B: Stage 3 from stage 2 MM patients	0.723	0.784	0.662	0.005	0.587 – 0.859

4. DISCUSSION

Multiple myelomarepresents around 1% of all malignancies and about 10% of overall hematologic cancers. Over 30,000 new annual cases are registered in the US and over 12,000 deaths.Whereas the prevalence rate of MM amongthe Iraqipopulation may reach 1.08 % [4].

The main outcomes of this study were the MM patients exhibited significantly lower values of TGFβ1 compared to healthy controls (p-0.001), and a better ability of lower TGFβ1 levels to differentiate between stage 3 from stage 2 MM patients, which is in line with previous studies [19, 21-23].

The TGFβ1 cytokine signaling is one such mechanism that has a distinct (although controversial) role in the regulation of normal hemopoiesis and is often disruptedin hematologic cancers[19]. In MM, the precise immune pathway of monoclonal gammopathy is not well understood[24]. The growth of MM cells is regulated by a variety of cytokines[19]. In recent times, it has been advocated that serum TGFβ1, a pleiotropic cytokine secreted by different cells, may play a role in MM [21].Inhematologic cancers, like lymphomas, leukemia,myeloproliferative disorders, and MM, struggle with these normal homeostatic properties of TGFβ1can be developed. This mechanistic struggle comprises gene deletionor mutation of family members of the TGFβ1intracellular signaling processes and disordered pathways by oncoproteins. These homeostatic shifts determine a tumor-suppressive role for the TGFβ1 signaling in hematologic tumors[19]. Thus this was the drive of this work to evaluate blood TGFβ1 levels in MM patients and also to observe a correlation with MMstages.

This is not all the story, high circulatory levels of TGFβ1 can enhance myelofibrosis and some other blood malignancies through their influences on the stromal cells and immune pathway. Improvements in the field of the TGFβ1 signaling pathway would empower the targeting of this mechanism for the treatment of some hematologic malignancies including MM [18, 19, 23].

The cells of MMhome to the bone marrow as soon as established, where many cellular cytokines, such as VEGF, IL-6, and TGFβ, regulate their migration and multiplying.TGFβ is a powerful inhibitor of immunoglobulin

production and B cell proliferation[25]. In MM, TGFβ is released at increased levels from both neoplasm and marrow stromal cells[26]. Consequently, TGFβ1exhibits paradoxical effects in terms of a tumor suppressor and tumor promoter.

A closer look at the outcomes of this study revealed that the age of the patients was parallel to the ages of the MM patients reported by other studies [22]. A preceding survey on the incidence of MMamong Iraqi people reported ages ranging from 41-72 years[24]. Another Iraqi survey last year revealed a comparable giving age to the ages of patients in this study and the neighboring countries however less than western nations [4].

The effect of gender on outcomes in MM is indefinite. However, the male sex was significantly predominant in the current study, consistent with the study from the USA that included 78,351 MM patients [27], and another trial that included newly diagnosed 2268 MM patients [28]. Given that males are more expected to develop MM compared to females, a study of all malignancies using the "National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program" proposed potentially worse MM survival for males[29].

The advances in the field of molecular biotechnologycanfurther interpret the oncogenic activities of TGFβ and result in a robust background to target TGFβ signaling pathway in MM therapy. Nevertheless, the precise mechanisms intricate in the malignant change of TGFβ necessitate more clarification, which could be the horizon of further studies.

5. CONCLUSION

The main conclusions of this study were the MM patients exhibited significantly lower values of TGFβ1 compared to healthy controls (p-0.001), and a better ability of lower TGFβ1 levels to differentiate between stage 3 from stage 2 MM patients.

6. LIMITATIONS

The lower number of study participants can be considered at the top of the limitations of this study. Added, other recently argued cytokines included in the progression of hematological malignancies (like VEGF, IL-6, PDGF) were more informative and conclusive. Their assessment in further studies would further support our outcomes.

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