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IMMUNOLOGICAL ASPECT OF INF-γ, TNF-α AND ICAM-4 LEVELS IN A GROUP OF PATIENTS WITH GIT TUMOR IN BABYLON PROVENCE

Dr. Raheem Tuama Obayes Al –Mammori[1], Dr. Marwan Hamid Al- Alwany[2], Dr. Ammar Malik Dokhin[3]

[1]Ph. D. Clinical Immunology, PCR and Immunology unit, Babylon GIT Center, Iraq
[2,3]Subspecialty in GIT and liver diseases, Endoscopy Unit, Babylon GIT center, Iraq
Email: rheemalmamory@gmail.com

Abstract

The study was planned to assessment the mean factors and risk population in which that exposure to infected with different GIT tumors, and determined the mean of population related to malignant GIT tumor than other tumor types. Measurement of certain immunological parameters are done to assessment it activity on such conditions. Serum samples were taken from 88 person they choose to evaluating the level of different studied parameters and grouped as (Malignant GIT tumor (42) , Benign GIT tumor (29) , Irritable bowel disease as a positive control (10) and Health individual as a negative control (7) in related age group. All patients admitted in GIT and level center of Babylon in Marjan Medical city at April up to December - 2020. The ICAM-4, INF-γ and TNF-a level were measured by using ELISA manual procedure of Elabscience company, Statistical analysis were done by using SPSS program.

The result show younger male is more infected with malignant GIT tumor, than Benign GIT tumor as well as IBD and healthy individuals, and there is an increased in ICAM-4 level , IFN- γ, in comparison with decreased of TNF-α levels. In the correlation study of parameters revealed that the , level gradually decreased with age prognosis, increased ICAM-4 lead to decreased in IFN- γ and TNF- α level among patients infected with GIT tumor . While increased interferon might be lead to increase in ICAM-4 level.

In Conclusions : The early age male infected with malignant GIT tumor in Iraqi population. Serum ICAM-4 levels were higher in malignant patients compared to healthy controls and benign GIT tumors. Also, serum IFN-γ and TNF- α levels in malignant patients were higher than in benign GIT tumors. Specific more studies with large number of patients should be recommended to exclude the factors in which that lead to such conditions.

Introduction

The immune response to cancer consists of innate and adaptive elements with the collective aim of eradicating malignant cells. Tumour cells come to the attention of the innate immune system when neo-antigens, the result of genomic mutations and instability, are recognized, captured and processed by antigen presenting cells (APCs), most commonly dendritic cells (DCs).(Andre et al., 2021). The innate cytokines are released driving activation and recruitment of other innate immune cells including natural killer (NK) cells, macrophages and neutrophils to the site of inflammation, where they may assist the anti-tumour response (Demaria et al., 2019).

T helper type 1 (Th1) cells, a $CD4^+$ T cell subset also primed by DCs, play a key role in

facilitating $CD8^+$ T cell function; conversely, T helper type 2 (Th2) cells are more traditionally considered as 'pro-tumour' in action and are linked with inhibition of cell-mediated immunity (Rodvold et al., 2012). It is typical to observe marked increases in interleukin (IL)− 1β, IL-6, tumor necrosis factor α (TNF-α), sTNFR1, IL-1 receptor antagonist (IL-1Ra) and transforming growth factor β (TGF-β). Platelets can impair immune mediated cytotoxicity and IFN-γ production by NK cells through conferring 'normal' MHC-class I molecules onto the surface of neoplastic cells (Comber and Philip, 2014).

Tumor necrosis factor-alpha (TNF-α), a pro-inflammatory mediator, regulates cellular communication within the tumor microenvironment and is associated with the progression of the metastatic phenotype. TNF-α, at concentrations reported to be present in serum and tumor tissue from colorectal cancer patients (Ferlay et al., 2020).The role of TNF-α in the development of cancer and the associated elevated miR-21 expression has prompted us to investigate potential mechanisms whereby these mediators influence the progression of the metastatic phenotype in colorectal cancer epithelial cells. (Aminah et al., 2023)

Metastatic transformation of cells is commonly associated with the presence of inflammatory mediators, such as TNF-α, the relationship between TNF-α and the metastatic transformation of cells is not yet clear. Metastatic transformation is a multifactorial process and the mechanisms involved in TNF-α-mediated phenotypic changes are complex (Dekker et al., 2019)**.** Tumour necrosis factor (TNF)-α plays an important role in inflammatory, infectious, and tumor processes, and it is closely related to the early stages of gastric cancer. It is a pro-inflammatory cytokine, produced not only by macrophages and monocytes but also by the lymphocytes, mast cells, neutrophils, keratinocytes, smooth muscle cells, and some tumor cell lines. (Zhu et al., 2016) TNF alpha protein specifically binds to cell-surface nucleolin and then enters the gastric cancer cells, Nucleolin localizes on the surface of gastric cancer cells, and interaction between TNF alpha and cell-surface nucleolin causes a cancer-oriented microenvironment that increases the risk of gastric cancer (Mihai et al., 202). Tumor necrosis factor alpha (TNF-α) was initially recognized as a factor that causes the necrosis of tumors, but it has been recently identified to have additional important functions as a pathological component of autoimmune diseases. TNF-α binds to two different receptors, which initiate signal transduction pathways. The inappropriate or excessive activation of TNF-α signaling is associated with chronic inflammation and can eventually lead to the development of pathological complications such as autoimmune diseases. Understanding of the TNF-α signaling mechanism has been expanded and applied for the treatment of immune diseases, which has resulted in the development of effective therapeutic tools, including TNF-α inhibitors. Clinically approved TNF-α inhibitors have shown noticeable potency in a variety of autoimmune diseases, and novel TNF-α signaling inhibitors are being clinically evaluated (Dan-in et al., 2021). Intracellular adhesion molecule-4 (ICAM-4) is an ICAM family member that is expressed in erythroid cells. The interaction of ICAM-1 with integrin CD18 could promote carcinoma cell dispersion (Bai et al., 2015). Cancer cells linked to macrophages enable transcoelomic metastasis via ICAM-1 adhesion (Yin et al., 2016). Prostate

and breast cancer risk may be influenced by ICAM-4, ICAM-1, and ICAM-5. Furthermore, ICAM is linked to two prevalent cancers. The first is lymphoma, which is a tumor originating from lymphatic tissues (Al-Mahdi Ghazi et al., 2020), which is linked to ICAM-1. The second example is breast cancer, a prevalent location of malignant disease in which ICAM-1 downregulation lowers the metastatic ability of breast carcinoma cell lines (Liu et al., 2020).

Materials and Methods

From the different areas of Babylon province 88 person were taken to evaluating the level of different studied parameters and grouped as (Malignant GIT tumor (42), Benign GIT tumor (29), Irritable bowel disease as a positive control (10) and Health individual as a negative control (7) in related age group. Serum samples were collected from all patients and controls after confirm diagnosis by GIT specialist doctors through endoscopy and biopsy sections. All patients admitted in GIT and liver center of Babylon in Marjan Medical city at April up to December - 2023. The ICAM-4, INF-g and TNF-a level were measured by using ELISA manual procedure of Bio-Assay company. SPSS used in statistical analysis of descriptive statistic and LSD value.

Results

By using ELISA technique different parameters were chose to study and revealed the following result as listed in the following figures and tables.

The result of ICAM-4 level show that increased level in patients with malignant GIT tumor in comparison with Benign GIT tumor as well as positive control (IBD) and negative or healthy control, at Mean ±SD (28.6±8.19, 24.9±5.80, 25.8±4.77, 25.57±5.04) respectively, the LSD value (2.64). The figure (1) show the result of ICAM-4 level.

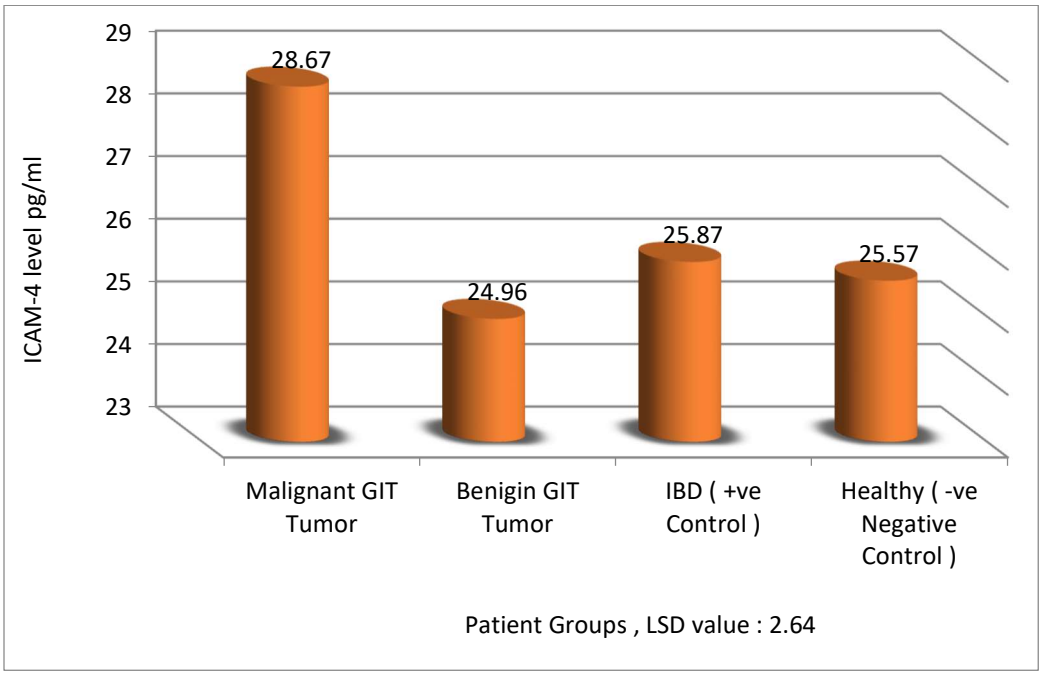

Figure (1) The ICAM-4 level among GIT tumor patients in comparison with Controls .

The male patients revealed higher level of ICAM-4 than female in comparison with male and female control Mean ± SD (27.4 ± 6.6, 26.2 ± 7.3, 25.0 ± 5.4 , 26.2 ± 4.77) in respective manner at LSD vale (1.67) as listed in Table (1)

Table (1) The Gender distribution of ICAM-4 level

ICAM 4 Level/ Sex		N	Mean ± SD	LSD value
Patients	Male	42	27.40± 6.61	1.67
	Female	29	26.28± 7.36	
Control	Male	10	25.07± 5.41	
	Female	7	26.29± 4.77	
Total		88	26.68±6.58	

The result of INF-γ level show that increased level in patients with malignant GIT tumor in comparison with Benign GIT tumor and lower than positive control (IBD) and negative or healthy control, at Mean ± SD (46.8 ± 33.5, 39.6± 18.1, 48.3 ± 18.6, 55.3± 15.1) respectively, the LSD value (3.45). The figure (2) show the result of INF-γ level.

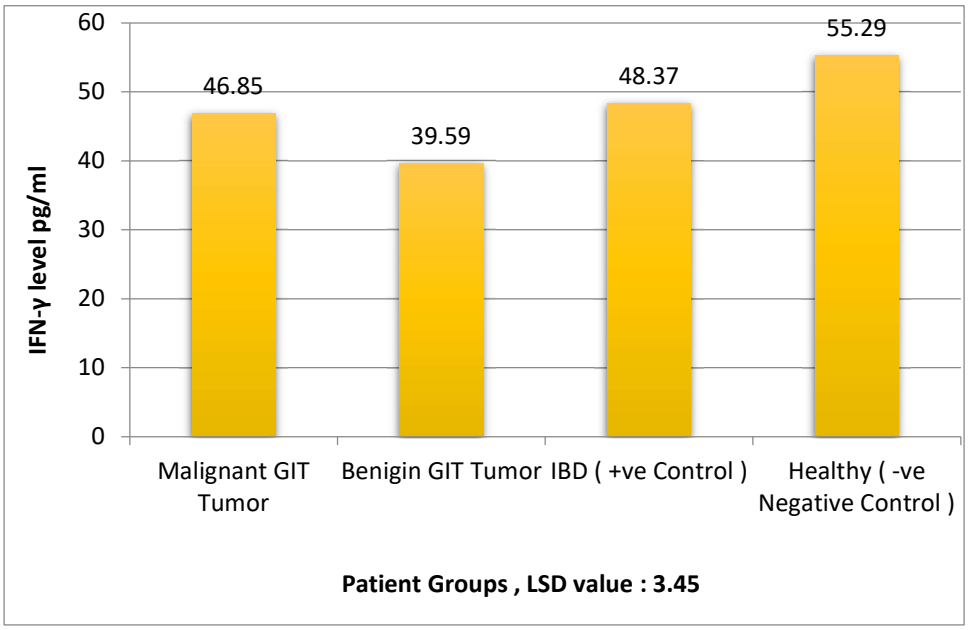

Figure (2) The INF-γ level among GIT tumor patients in comparison with Controls

The male and female patients revealed lower level of INF-g than male and female control at Mean ± SD (45.4 ± 26.1, 45.4± 27.3, 57.8 ± 19.3, 51.5 ± 4.4) in respective manner at LSD vale (6.13) as listed in Table (2).

Table (2) The Gender distribution of INF-γ level

INF-g Level/ Sex		N	Mean ± SD	LSD value
Patients	Male	42	45.44± 6.13	6.13
	Female	29	45.44± 7.39	
Control	Male	10	57.89± 9.32	
	Female	7	51.57± 4.45	
Total		88	47.34± 4.91	

The result of TNF-α level show that increased level in patients with malignant GIT tumor in comparison with Benign GIT tumor, lower than positive control (IBD) and negative or healthy control, at Mean ± SD (23.71 ± 7.6 , 20.44 ± 4.8 , 18.95 ± 4.9, 18. 15 ± 3.8) respectively, the LSD value (2.54). The figure (2) show the result of INF-γ level.

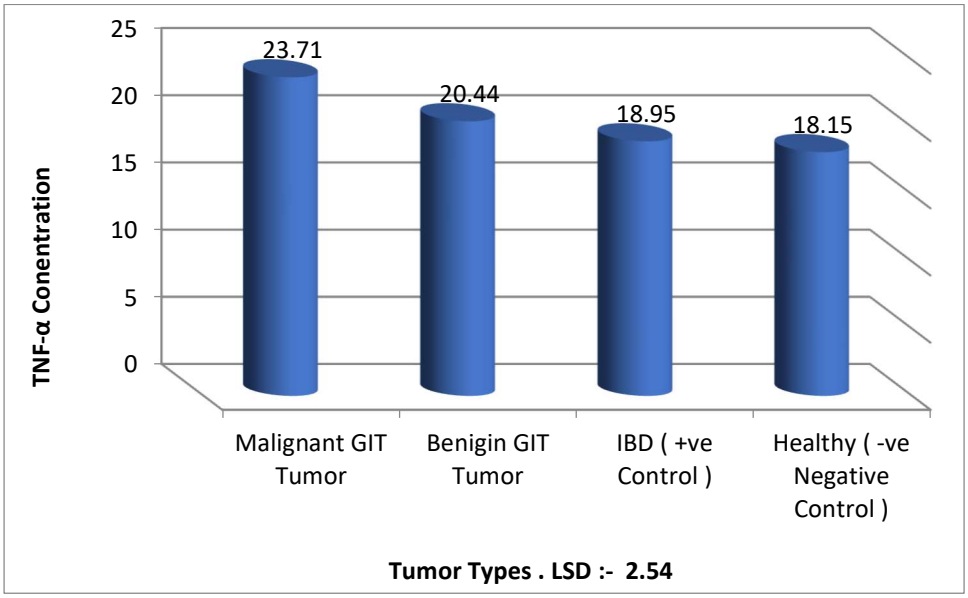

Figure (2) The result of TNF- α level of patients and control

The male and female patients revealed lower level of TNF- α than male as well as negative control at Mean ± SD (22.84 ±9.0, 20.64 ±2.5, 17.57 ±2.9,18.98 ±2.4) in respective manner at LSD vale (2.25) as listed in Table (3).

Table (3) Result of TNF- α concentration of patients and control

TNF- α Level/ Sex		N	Mean ± SD	LSD value
Patients	Male	42	20.64 ±2.5	2.25

	Female	29	22.84 ±9.0	
Control	Male	10	17.57 ±2.9	
	Female	7	18.98 ±2.4	
Total		88	20.88±5.7	

In the result of correlation between studied parameters , there is a direct correlation between ICAM-4 level , TNF- α and INF- γ , this result might be increased ICAM-4 lead to increased TNF-α and INF-g level among patients infected with GIT tumor . The results are mentioned in table (4).

Table (4) Result of correlation between studied parameters

Correlations		**ICAM 4 Level**	**TNF - α level**	**IFN- γ Level**
ICAM 4 Level	Pearson Correlation	1		
	Sig. (2-tailed)			
TNF- α level	Pearson Correlation	.245*	1	
	Sig. (2-tailed)	.021		
IFN- γ Level	Pearson Correlation	.252*	.123	1
	Sig. (2-tailed)	.018	.253	
****. Correlation is significant at the 0.01 level (2-tailed).**				
***. Correlation is significant at the 0.05 level (2-tailed).**				

Discussion

The increase in ICAM-4, and IFN-γ, levels compared to healthy individuals, Increasing the probability of infection with GIT tumor. ICAM-4 levels may grow and increase as interferon levels rise. The younger males are more prone to malignant GIT and the serum levels of ICAM-4, and IFN-γ are high in malignant patients compared with benign GIT tumors and lower than the healthy control (Ali et al., 2023).

A multifaceted molecule known as interferon-gamma (IFN-γ) is connected to anti-proliferative, pro-apoptotic, and antitumor processes the production of IFN-γ by NK cells is an independent predictive factor for survival in advanced GISTs. However, few studies have been conducted on ICAM-4, especially in GISTs (Castro et al., 2018).

The linearity of IFN-γ, ICAM-4, TNF-α concentrations, as well as optical density, were only investigated. Cell surface glycoprotein receptors known as ICAMs are involved in cell-matrix and cell-cell adhesive contacts (Harjunpää et al., 2019). According to recent findings from the "Dutch GIST-Registry," younger males are more prone to malignant GIT tumors in their fifth decades of life than benign tumors or healthy individuals. In oncology research, the youthful population has gained prominence as a group with unique psychosocial requirements and bimolecular

characteristics (de Rojas et al., 2020).

Previous findings reveal that ICAM-1 and ICAM-4 are both required for eliciting an immunological response (Bui et al., 2020). In comparison to the benign and control groups, the current study results demonstrated a high level of ICAM-4 in patients with GIT tumors. ICAM-4, which work with the granulocyte/monocyte-enriched 2 integrin CD11b/CD18 (Mac-1, M2), and may play a similar role to ICAM-1 in the growth and spread of GIT cancers (Ihanus et al., 2007). The fundamental structural similarities and molecules that interact with both ICAM-1 and ICAM-4 may explain the elevated levels of both in GIT malignancies (Harjunpää et al., 2019).

A positive correlation between ICAM-4 and IFN-γ as well as TNF- α observed in present study, has not been previously reported in other studies. IFN-γ enhances the expression of ICAMs, the production of inflammatory cytokines, and the antitumor activity of monocyte-macrophage cells. The activation of cellular lipopolysaccharide responses via IFN-γ is referred to as the "priming effect". (Kurihara and Furue, 2013). Cancer immuno-modulation is a process in which both innate and adaptive immune systems, as well as cytokines such as ICAMs, IFN-γ, TNF- α , and others, work together to suppress and/or control tumor growth (Burhan et al., 2020).

Conclusion

According to the findings of present study, younger males are more susceptible to malignant GIT tumors in their fifth decades of life as compared to benign tumors and healthy individuals. Serum ICAM-4 levels were higher in malignant patients compared to healthy controls and benign GIT tumors. Also, serum IFN-γ and TNF- α levels in malignant patients were higher than in benign GIT tumors

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