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ORIGINAL ARTICLE

Study of Serum Total Immunoglobulin E in Egyptian Patients with Newly Diagnosed Colorectal Carcinoma

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ABSTRACT

Background: Total immunoglobulin E (IgE) has roles in allergy and anti-parasitic immunity. Recently IgE showed a major role in cancer immune surveillance; an increased risk of solid and blood malignancies has been associated with total IgE deficiency. This study aimed to determine the level of serum total IgE in colorectal carcinoma (CRC) patients and its association with CRC staging. **Methods**: This case-control study included 60 patients with newly diagnosed CRC and 60 healthy age and sex-matched controls. All participants were subjected to detailed medical history taking, physical examination, assessment of CRC stages, complete blood count and serum total IgE level.

Results: Regarding CRC patients, the mean (± SD) age was 53.18 ± 13.52 years, 34/60 patients were males, The median (IQR) total IgE level was 42.5 (22.5 - 77.5) IU\ml. Six CRC patients had a total IgE level ≤ 5 IU\ml, 43 patients had a total IgE level 6-100 IU\mL, and 11 patients with a total IgE level >100 IU\mL. Twenty CRC patients were stage II, 19 patients were stage III, and 21 were stage IV. 53/60 CRC patients were diagnosed with adenocarcinoma. 40/60 patients had colonic carcinoma and 18 patients had rectal carcinoma. There was statistical significance between cases and controls regarding the level of total IgE (p-value <0.05). There was no significant association between total IgE levels and CRC stages, histopathological findings, nor anatomical sites.

Conclusions: Total IgE levels may play a role in CRC, with statistical significance between CRC patients and controls but no correlation with CRC stages.

Keywords: Adenocarcinoma; Colorectal carcinoma; Total IgE

INTRODUCTION

Immunoglobulin E (IgE) is the most recently identified immunoglobulin family member [1]. It plays an important role in atopic illnesses and anti-helminthic immunity [2]. Early studies dating back to the 1960s found that lower cancer risk was related to allergy, indicating a link between IgE or IgE-mediated illnesses and malignancy [3]. IgE has a major role in cancer immune surveillance, resulting in anti-tumor antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cell-mediated phagocytosis (ADCP). Furthermore, anti-tumour cell responses are induced by IgE-mediated cross-presentation of various tumor cell antigens by dendritic cells [4]. In a therapeutic context, the very high affinity of IgE for its cognate Fcε receptors and the lack of inhibitory IgE Fc receptors suggest the potential

for long-lasting and efficient anti-neoplastic effector cell responses [5-7].

As a result of the loss of tumor immune-surveillance function, IgE deficiency is linked to an increased risk of solid and blood malignancies. Eventually, IgE-deficient individuals (IgE < 2.5 IU/L) had higher rates and risk of having a diagnosis of any malignancy compared with non-IgE deficient individuals (IgE ≥ 2.5 IU/L) [5].

When it comes to cancers that are protected by allergy/atopy or high serum IgE levels, several site-specific cancers stand out, such as lung cancer (in the absence of asthma), colorectal cancer (CRC), particularly rectal cancer, and pancreatic cancer [8]. Colorectal cancer is Egypt's seventh most prevalent cancer, accounting for 3.47 % of male and 3% of female cancers [9].

No data exist detecting the relationship between total IgE level and various tumors in Egypt, and few data exist worldwide reporting the relationship between CRC and total IgE. In this context, our study aimed to determine the level of serum total IgE in patients with CRC as an example of solid tumors and the relationship between serum total IgE level and colorectal carcinoma staging.

METHODS

Study population:

This case-control study included 60 adult patients with newly diagnosed CRC who attended an oncology outpatient clinic at Ain Shams University Hospitals for 6 months period, and 60 healthy gender and age-matched controls. Individuals with a low total leucocytic count were excluded from the study. Individuals with a known history of primary immunodeficiency diseases, who had been on cancer chemotherapy or an anti-CD 20 drug, immunosuppressive drugs, anti-IgE (Omalizumab), corticosteroids, anti-parasitic drugs for at least 6 months before the study, or who were taking any drug that caused B lymphocyte depletion or bone marrow suppression were also excluded.

The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. The current study protocol received ethical approval from the Ain Shams University Faculty of Medicine Research Ethics Committee (reference MS 274/2021). Informed written consent was obtained from each participant.

Clinical evaluation:

All participants were subjected to detailed medical history taking, smoking history and full clinical evaluation. Patients were assessed regarding the CRC stage, according to (NCCN guidelines Version 2.2021), which includes the site of the primary tumor (T), LN affection (N), distant metastasis (M), then the CRC stages were assigned into 4 stages 0,I,II,III, IV [10].

Laboratory investigations:

From each participant, 4 ml venous blood sample was obtained and divided into two vacutainer tubes: 1) a Potassium Ethylene Diamine Tetra Acetic acid (K-EDTA) tube for complete blood picture (CBC) with white blood cell differential count analysis by Sysmex XT-1800i autoanalyzer (Sysmex, Japan). Eosinophil normal reference range in blood is 0.0-0.5 x 10^9/L [11]. The absolute eosinophil count was calculated by multiplying the percentage of eosinophils by the total white blood cell count, and 2) a plain vacutainer tube with a clot activator for serum separation. Blood on the plain tubes was allowed to clot completely before separation by centrifugation at 2500×g for 15 minutes.

Separated sera were stored at -80◦C till further analysis of serum total IgE levels by enzyme-linked immunosorbent assay (ELISA) (PerkinElmer Health Sciences, INC., USA, cat no :10602) with a sensitivity of 5.0 IU /mL [12]. Participants were categorized according to their total IgE levels into four groups: (low) < 5 IU /mL, normal: 6-100 IU /mL, high: 100-1000 IU /mL, and very high: ≥1000 IU /mL [13].

Statistical Analysis:

The sample size was calculated using PASS11 program, setting power at 80, alpha error at 5 % and with reviewing results from previous relevant studies [5]. The collected data

was revised, coded, tabulated and introduced to a PC using Statistical Package for Social Science (SPSS 25) IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. For Descriptive statistics, Mean and standard deviation (± SD), and range were used for parametric numerical data, while Median and Interquartile range (IQR) for non-parametric numerical data. Mann Whitney test (U test) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups. Kruskal Wallis test was used for comparing two or more independent non-parametric samples of equal or different sample sizes. Shapiro test was used to determine the Gaussian distribution of data. *p*-value of ≤ 0.05 was considered statistically insignificant.

RESULTS

The patients' mean (±SD) age was 53.18 ± 13.52 years. 34 (56.7%) patients were males. The median (IQR) total IgE level was 42.5 (22.5 - 77.5) IU\ml. Six (10%) CRC patients had a total IgE level ≤ 5 (IU\ml), 43 patients had a total IgE level of 6-100 (IU\mL), and 11 patients with total IgE level>100 (IU\mL). Regarding CRC staging, Twenty CRC patients were stage II, 19 patients were stage III, and 21 patients were stage IV. Fifty-three patients were diagnosed with adenocarcinoma, two patients had mucinous adenocarcinoma, two patients had tubulovillous adenocarcinoma, two patients had villous adenocarcinoma, and one patient had squamous cell carcinoma (SCC). Regarding the anatomical site of the tumor, 18 patients had rectal carcinoma, 40 patients had colonic carcinoma, and only two patients had colorectal carcinoma (Table 1).

Regarding medical history, 15 patients had hypertension, 13 patients had D.M, three patients had positive HCV antibodies, and one patient had chronic kidney disease. Regarding smoking history, 19/60 patients were smokers, and 8/60 patients were ex-smokers (Table 2).

Comparing cases and controls, there was statistical significance between cases and controls regarding the level of total IgE with a p-value <0.05 (Figure 1).

There was no statistical significance between different total IgE levels and CRC staging, *p*-value = 0.408. There was no statistical significance between different total IgE levels and CRC histopathological findings, *p*-value = 0.536. There was no statistical significance between different total IgE levels and CRC anatomical site, *p*-value= 0.922. There was no statistical significance between different total IgE levels and medical history or smoking history (Table 3).

We tried to detect the best cut-off value of total IgE to differentiate between CRC cases and healthy controls, and it was > 42.50 IU\mL, with sensitivity=50% and specificity=85% (Figure 2).

Table 1: Demographic data, IgE distribution and Histo-pathological data of study population

		Min.	Max.	Mean	SD	
Age		21	78	53.18	13.52	
		N		%		
Sex	Male	34		56.7%		
	Female	26		43.3%		
		Min.	Max.	Median	Q1	Q2
Total IgE level		5.00	700.00	42.50	22.50	77.50
		No of cases		%		
IgE (IU/mL)	≤ 5	6		10.0%		
	6-100	43		71.6%		
	>100	11		18.3%		

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		Min.	Max.	Mean	SD
				N	%
Stage	II			20	33.3%
	III			19	31.7%
	IV			21	35.0%
Pathology	Adenocarcinoma			53	88.3 %
	Mucinous adenocarcinoma			2	3.3%
	Tubulovillous adenocarcinoma			2	3.3%
	Villous adenocarcinoma			2	3.3 %
	SCC			1	1.7%
Tumor site	Rectum			18	30.0%
	Colon			40	66.7%
	Both			2	3.3%

Data presented as number, percentage, median; Q: Quartile; SCC: squamous cell carcinoma

Table 2: Smoking and Medical history of study population:

Medical history		N	%
Hypertension	Positive	15	25 %
	Negative	45	65 %
Diabetes	Positive	13	21.7 %
	Negative	47	78.3%
HCV Abs	Positive	3	5 %
	Negative	57	95 %
CKD	Positive	1	1.7 %
	Negative	59	98.3 %
Smoking	Smoker	19	31.7%
	ex-smoker	8	13.3%
	Non smoker	33	55%

Data presented as number and percentage; HCV Abs, Hepatitis C antibodies; CKD, chronic kidney disease

Table 3: Relation between IgE level and tumor criteria and medical history of study population.

		IgE level (IU\mL)						P value
		≤ 5		>10-100		>100		
		N	%	N	%	N	%	
Stage	II	1	5%	13	65%	6	30%	0.408 NS
	III	3	15.8 %	13	68.4%	3	15.8%	
	IV	2	9.5%	17	81.%	2	9.5%	
Pathology	Adenocarcinoma	6	11.3%	38	71.7%	9	17%	0.536 NS
	other types	0	0.0%	5	71.4%	2	28.6%	
Tumor site	Rectum	2	11.1%	13	72.2%	3	16.7%	0.922 NS
	Colon	4	10%	28	70%	8	20.0%	

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		IgE level (IU\mL) ≤ 5		>10-100		>100		P value
		N	%	N	%	N	%	
	Both	0	0.0%	2	100.0%	0	0.0%	
Hypertension	Positive	1	6.7%	9	60%	5	33.3%	0.217 NS
	Negative	5	11.8%	34	75.6%	6	13.3%	
DM	Positive	1	7.7%	8	61.5%	4	30.8%	0.422 NS
	Negative	5	10.6%	35	74.5%	7	14.9%	
HCV	Positive	0	0%	2	66.7%	1	33.3%	0.700 NS
	Negative	6	10.5%	41	71.9%	10	17.5%	
CKD	Positive	0	0%	0	0%	1	100%	0.104 NS
	Negative	6	10.2%	43	72.9%	10	16.9%	
Smoking	Smoker	3	15.8%	11	57.9%	5	26.3%	0.145 NS
	ex- smoker	1	12.5%	4	50%	3	37.5%	
	Non smoker	2	6.1%	28	84.8%	3	9.1%	

Data presented as number and percentage; significant p value < 0.05; HCV Abs, Hepatitis C antibodies; CKD, chronic kidney disease

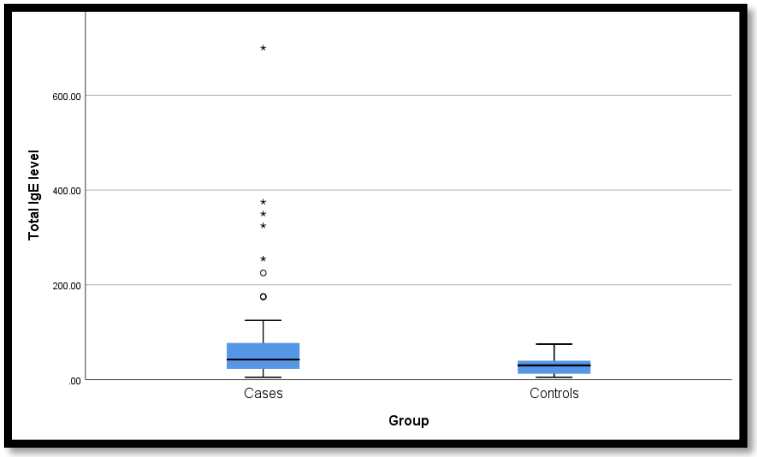

Figure 1: Comparison between cases and controls regarding IgE level.

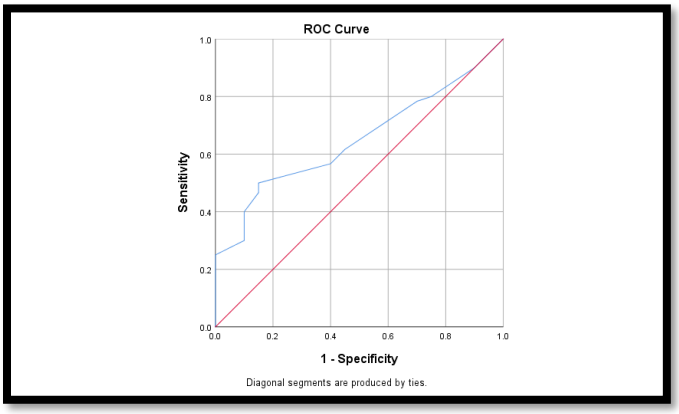

Figure 2: ROC curve analysis for ability of IgE level to differentiate between cases and controls:

DISCUSSION

CRC is the third most common cancer diagnosed in both males and females in the US [12] and the 7th commonest cancer in Egypt, representing 3.47% of male cancers and 3% of female cancers [9]. Links between IgE or IgE-mediated diseases and malignancy have been reported. Early studies reported decreased cancer risk associated with allergy and decreased prevalence of atopy in cancer patients [3].

Our study aimed to assess the level of serum total IgE in patients with CRC as an example of a solid tumor and its association with the staging of CRC. The study included 60 adult patients with newly diagnosed CRC attending the oncology outpatient clinic at Ain Shams University hospitals over 6 months and 60 healthy controls matched to age and sex.

34 (56.7%) patients were males. Their mean ± SD age was 53.18 ± 13.52 years. The median (IQR) of the total IgE level was 42.5 (22.5 - 77.5) IU\ml. Six (10%) CRC patients had total IgE level ≤ 5 (IU\ml), 43 patients had total IgE level 6-100 (IU\mL), 11 patients with total IgE level >100 (IU\mL).

This is similar to what had earlier been reported in many pieces of literature [14-15], which stated that males were more susceptible to colorectal cancer than females, where socio-cultural barriers for females delayed screening and diagnosis. On the other hand, a study performed by ***Kim et al.*** detected a higher risk of developing right-sided (proximal) colon cancer among females than males.[17]

Regarding the histopathological analysis of the patients' biopsies, our study stated that Most CRC patients had adenocarcinomas (90%). In comparison, the other 10% had other types which are not frequently seen (mucinous adenocarcinoma, tubulovillous adenocarcinoma, villous adenocarcinoma, squamous cell carcinoma); this comes in line with the study done by ***Recio-Boiles & Cagir,*** who reported that more than 90% of colorectal carcinomas were adenocarcinomas [18].

In the current study, we reported that the most common anatomical site of colorectal carcinoma was the colon (66.7%), including caecum, ascending colon, descending colon, hepatic and splenic flexures; it was similar to a previous study which included 1,759 colorectal patients among which 1,345 had colonic carcinoma, and only 380 patients had rectal cancer [19].

In the current study, there was a statistical significance regarding the level of total IgE between CRC cases and controls (*p*-value < 0.05).

In agreement with our findings, a study conducted by **Helby *et al.*** reported an association between higher IgE levels and a higher risk of carcinoma of the oral cavity, pharynx, esophagus and lung (*p*-value 0.03, 0.05), respectively, in contrast to hematological malignancies where high levels of IgE were associated with low risk of cancer developments such as in chronic lymphocytic leukemia (CLL), lymphoma and myeloma [20]. Another study conducted by **Fu *et al.*** showed a statistical significance between higher levels of total IgE and pancreatic tumors; they explained their last interesting findings that they also detected tumor specific IgE, which had an anti-tumor cytotoxic function against tumor cells [21]. Another two studies previously detected anti-tumor IgE antibodies among gastrointestinal tumors, especially in CRC cases [22, 23].

We obtained Contradictory results from different studies evaluating the role of total IgE and atopy among cancer patients, whether they are solid or hematological tumors; for instance, a study performed by **Ma *et al.*** demonstrated that increased serum total IgE was negatively related to the development of meningioma, suggesting a protective role of IgE and atopic status in meningioma risk [24]. Another study reported an association between high-level IgE and low risk of melanoma, breast and other gynecological cancers in women [25]; regarding hematological malignancies, a study performed by **Nieters *et al.*** showed that high levels of total IgE were inversely correlated with the risk of

lymphoma subtypes, especially CLL and myeloma. Moreover, they found that low levels of IgE preceded the clinical diagnosis of CLL by five years, explaining that a mild relative degree of immunodeficiency state might encourage CLL development [26].

On the other hand, several studies demonstrated that allergic diseases such as asthma and atopic dermatitis were associated with higher levels of cancer lung and non-melanoma skin cancer due to the chronic state of inflammation [27, 28]; also, some studies reported a decreased level of glioma development with antihistamines usage in allergic patients assuming that skewing the immune response from T-helper2 (Th2) toward Th1 response had a protective role against tumors. Bringing all data together, the authors suggested that the risk of tumor development and allergic conditions was related to sites with direct contact with inflammatory mediators [29].

Our study revealed no statistical significance between different total IgE levels and CRC staging, histopathological type and anatomical site of CRC, p-value =0.408, 0.536, and 0.922, respectively. Similar to our results, a study on pancreatic tumor patients reported no significance between total IgE level and tumor stages [21]. But, in contrast to our results **Wrensch *et al.*** showed that higher total IgE level was associated with higher survival and prognosis in patients with glioma.[30]

Our study is one of few studies investigating the role of total IgE among CRC patients. Future wider scales studies detecting tumor specific IgE may be needed to understand IgE's anti-tumor role better. In conclusion, total IgE has a potential role in cancer colon patients being significantly higher among Egyptian patients with CRC.

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