Original Article

Iranian Journal of Immunology

March 2024; 21(1):65-73.

Serum Interleukin-38 and Tumor-Infiltrating Lymphocytes in Primary Brain Tumors

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ABSTRACT

Background: Tumor-infiltrating lymphocytes (TILs) and brain stromal cells produce immunosuppressive cytokines, contributing to an immunosuppressive tumor microenvironment (TME). Interleukin-38 (IL-38) is a novel anti-inflammatory cytokine and a natural modulator of the innate and adaptive immune system. However, its biological roles in brain tumors are not well defined.

Objective: To assess the serum levels of IL-38 and the percentages of TILs in the tumor tissues of patients with primary brain tumors and to determine their associations with the pathological features of the disease.

Methods: IL-38 was evaluated in sera using the enzyme-linked immunosorbent assay (ELISA). Hematoxylin and eosin (H&E)-stained sections were scored to determine the percentages of TILs in four different areas: the invasive margin, central tumor, perivascular and perinecrotic areas.

Results: IL-38 serum levels were significantly higher in low-and high-grade tumors than in healthy individuals, meanwhile, its levels remained consistent between these two grades. Although no significant difference was found in IL-38 serum levels between different histological subtypes of brain tumors, its levels were significantly higher in intra-axial brain tumors than in extra-axial ones. Additionally, a significant positive correlation was observed between serum levels of IL-38 and tumor size in patients with low-grade tumors. TILs were detected in at least one of the four examined areas; however, no statistically significant correlation was found between IL-38 levels and TILs.

Conclusion: Our data may suggest a connection between IL-38 and immune suppression and tumor progression in primary brain tumors. Further investigation is needed to uncover the role of IL-38 in the brain tumor microenvironment.

Keywords: Brain Tumors, Interleukin-38, Tumor-Infiltrating Lymphocytes

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Cite this article as:
Haghshenas MR, Khademolhosseini A, Dehghanian AR, Ghanipour F, Ghaderi H, Khansalar S, Sotoodeh Jahromi A. Serum Interleukin-38 and Tumor-Infiltrating Lymphocytes in Primary Brain Tumors. *Iran J Immunol.* 2024; 21(1):65-73, doi: 10.22034/iji.2024.100597.2697.

Received: 2023-10-24
Revised: 2024-01-21
Accepted: 2024-01-23

INTRODUCTION

Primary brain tumors refer to tumors that originate from the brain tissue or its surrounding structures. Although rare, they are responsible for a significant burden of morbidity and mortality worldwide (1). Primary brain tumors represent a highly diverse group of malignancies, characterized by significant heterogeneity in histology, epidemiology, clinical characteristics, treatment, and survival (2). Glioblastoma and meningioma are the most commonly diagnosed malignant and non-malignant brain tumors, accounting for 49.1% and 54% of malignant cases. Pituitary adenoma is also a common subtype (3). While the central nervous system (CNS) was traditionally viewed as immunologically isolated, brain tumors are not confined by the blood-brain barrier. Like other types of tumors, innate and adaptive immune responses play a role in the prevention, development, and defense against brain tumors (4, 5). Different types of immune cells including T, B, NK and regulatory T cells, myeloid-derived suppressor cells (MDSCs) and macrophages were found within the brain tumor microenvironment (TME) (6, 7). As a result, the interplay of cytokines and immune infiltration within the tumor microenvironment is intricately linked to the progression of the tumor (8). Tumor-infiltrating lymphocytes (TILs) have exhibited association with survival in high-grade brain tumors (9). In addition to immune cells, cytokines participate in constructing the TME of brain tumors. Surprisingly, a range of pro-inflammatory and anti-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-8, transforming growth factor-β (TGF-β), and IL-10 have been observed to play distinct roles in brain tumor progression (10, 11). Additionally, it has been reported that dysregulation of the IL-1 pro-inflammatory cascade was associated with cancer initiation, progression, and invasiveness in human malignant gliomas, and it can be considered as a promising therapeutic target in clinical practice (12). IL-1 family is known as a key mediator of immunity and inflammation. These includes seven cytokines with receptor agonists properties (IL-1α/β, IL-18, IL-33, IL-36 α/β/γ) and four cytokines with anti-inflammatory or antagonistic properties (IL-1 receptor antagonist (Ra), IL-36Ra, IL-37, IL-38) (13). IL-38 is a newly-discovered member of the IL-1 cytokine family and shares strong sequence homology with receptor antagonists of IL-1 and IL-36 (IL-1Ra and IL-36Ra) (14). Interaction of IL-38 with its ligands (including IL-1R1, IL-36R and interleukin-1 receptor accessory protein-like 1 (IL-1RAPL1)) leads to anti-inflammatory responses (15). The anti-inflammatory mechanism of IL-38 is explained by its dual role in inducing regulatory T cells while concurrently inhibiting the pro-inflammatory activities of IL-36 (16). The existing body of evidence regarding the role of IL-38 in pathogenesis of cancer is limited and subject to significant controversy. In colorectal cancer, IL-38 expression was found to be significantly associated with more favorable outcomes, including smaller tumor size and higher survival rate (17). However, in lung adenocarcinoma, it was significantly associated with unfavorable clinicopathological characteristics, such as lower survival, and programmed death-ligand 1 (PD-L1) positivity (18). To the best of our knowledge, no prior studies have explored the role of IL-38 in the pathogenesis of brain tumors. Consequently, the primary objective of this study is to assess the IL-38 serum levels in patients with primary brain tumors and compare it with the healthy controls. We also aimed to investigate the potential correlation between IL-38 serum concentrations and the percentage of TILs infiltration in high-grade brain tumors.

MATERIALS AND METHODS

Study Population

In this case-control study, we enrolled 60

patients diagnosed with primary brain tumors and matched them with 60 healthy individuals. All the patients were recruited from Chamran Hospital, Shiraz University of Medical Sciences, Shiraz, Iran, and the primary brain tumors were histopathologically confirmed by the pathologist. The study group included 28 male (46.7%) and 32 (53.3%) female with the mean age of 46.51±13.04 years (mean±SD). The control group comprised 25 (41.7%) males and 35 (58.3%) females with an average age of 48.60±12.44 years. The mean age did not exhibit a significant difference between the patients and the control group (p=0.47). The brain tumors encompassed various histopathological types and grades. An overview of the patient's histopathological characteristics is provided in Table 1. Overall, 35 patients were diagnosed with low-grade tumors, while 25 patients presented with high-grade tumors. Brain tumors were composed of 8 different histological types including glioblastoma, NOS grade 4 (n=15), typical meningioma grade 1 (n=14), pituitary adenoma grade 1 (n=12), diffuse astrocytoma grade 2 (n=9), anaplastic meningioma grade 3 (n=5), anaplastic astrocytoma grade 3 (n=3), anaplastic ependymoma grade 3 (n=1), and medulloblastoma grade 4 (n=1). Inclusion criteria required clinical and pathological confirmation of the disease, while exclusion criteria involved the absence of any other malignancies or autoimmune diseases in the patients. Both the patients and the control groups had no prior history of infectious diseases or the use of anti-inflammatory drugs in the month preceding the study. Informed consent was obtained from every participant prior to involvement. The study was approved by the Jahrom University of Medical Sciences ethics committee (IR.JUMS.REC.1401.027).

Serum IL-38 Measurement

The blood samples were obtained from all the participants and centrifuged (Hettich, Germany) at 2500 ×g for 10 min at 4°C to collect the serum sample. The serum samples were kept at -80°C until further analysis. IL-38 serum levels were measured performing enzyme-linked immunosorbent assay (ELISA) with commercially available kit (ZellBio GmbH, Ulm, Germany). The assay range of kit and its sensitivity were 7.5 to 240 ng/L and 0.9 ng/L respectively.

Evaluation of Tumor-Infiltrating Lymphocytes (TILs)

The infiltration of lymphocytes was evaluated in 25 patients with high-grade brain tumors using H&E-stained sections according to recommendations of the International TILs Working Group 2014 (19). The percentage of TILs (TILs score) was assessed in the invasive margin, central tumor, perivascular and perinecrotic areas.

Statistical Analysis

Statistical analyses were conducted using SPSS 22. The Kolmogorov–Smirnov test was used for the verification of the normal

Table 1. Pathological and demographical characteristics of the patients with brain tumors

Grade	Intra-axial/Extra-axial	Histological type
Low-grade (n=35)	Extra-axial (n=26)	Typical meningioma grade 1, (n=14 (23.3%))
		Pituitary adenoma grade 1, (n=12 (20%))
	Intra-axial (n=9)	Diffuse astrocytoma grade 2, (n=9 (15%))
High-grade (n=25)	Extra-axial (n=5)	Anaplastic meningioma grade 3, (n=5 (8.3%))
	Intra-axial (n=20)	Glioblastoma, NOS grade 4 (n=15 (25%))
		Anaplastic astrocytoma grade 3 (n=3 (5%))
		Anaplastic ependymoma grade 3 (n=1 (1.7%))
		Meduloblastoma grade 4, (n=1 (1.7%))
Age (years)		46.51±13.04 (Mean±SD)
Sex		Male=28 (46.7%)
		Female 32 (53.3%)

distribution of the data. The non-parametric tests, such as Mann–Whitney U and Kruskal–Wallis H were used to compare the IL-38 serum levels between the patients and the control group and to evaluate their association with pathological features. The correlation of IL-38 serum levels with age, tumor size and TILs score in brain tumors was assessed using Spearman's correlation test. Statistical significance was considered as a *p*-value of less than 0.05.

RESULTS

IL-38 Serum Concentrations in Patients and Healthy Individuals

IL-38 serum levels exhibited a significant increase in the patients with primary brain tumors (39.88±0.68 ng/L), both high-grade and low-grade, when compared with the healthy individuals (33.69±2.76 ng/L, p=0.003), meanwhile, its levels remained consistent between the patients with low-grade (39.97±0.81 ng/L) and high-grade tumors (39.73±1.18 ng/L, p=0.580). The comparisons of IL-38 serum concentrations in the studied groups are illustrated in Fig. 1.

IL-38 Serum Levels Across Different Brain Tumor Histological Types and Locations

In the present study, IL-38 serum levels were also compared across different histological types of brain tumors. Adequate representation in each group was ensured for the assessed histological types, which encompassed glioblastoma (NOS grade 4), typical meningioma (grade 1), pituitary adenoma (grade 1), and diffuse astrocytoma (grade 2). As shown in Table 2, IL-38 serum levels exhibited a roughly similar pattern across various histological types of brain tumors, with no statistically significant differences discernible between these tumor types (p=0.26). However, diffuse astrocytoma grade 2 (42.10±2.19 ng/L) and pituitary adenoma grade 1 (38.46±0.88 ng/L) exhibited the highest and lowest IL-38 expression, respectively. In addition, IL-38 serum levels were compared between intra-axial brain tumors (including diffuse astrocytoma grade 2, glioblastoma, NOS grade 4, anaplastic astrocytoma grade 3, anaplastic ependymoma grade 3 and medulloblastoma grade 4) and extra-axial brain tumors (including typical meningioma grade 1, pituitary adenoma grade 1, and anaplastic meningioma grade 3). As shown in Fig. 1, IL-38 serum levels were significantly higher in the intra-axial brain tumors (40.70±1.2 ng/L) than in the extra-axial (39.10±0.69 ng/L) ones (p=0.042).

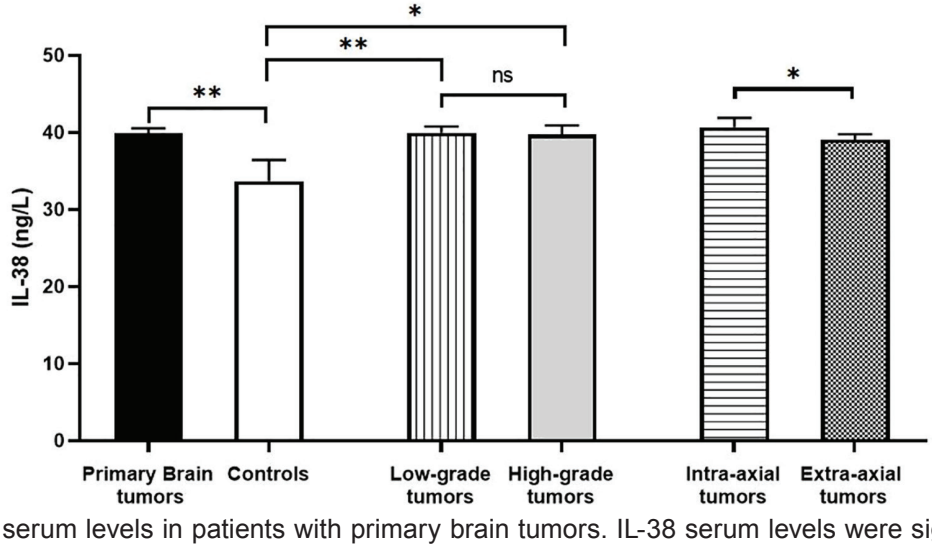

Fig. 1. IL-38 serum levels in patients with primary brain tumors. IL-38 serum levels were significantly higher in primary brain tumors, low grade tumors and high grade tumors than in the healthy individuals as the control group, meanwhile, its levels remained consistent between low and high-grades. Furthermore, IL-38 serum levels were significantly higher in intra-axial brain tumors than in extra-axial ones.

Table 2. Comparing IL-38 serum levels across primary brain tumors with different histological types and locations

Histological type	IL-38 serum concentration (ng/L)				*p*-value
	Mean±SEM	Median	Minimum	Maximum	
Glioblastoma, NOS grade 4	41.04±1.51	41.76	27.55	49.11	0.26
Typical meningioma grade 1	39.90±1.23	39.02	33.11	49.41	
Pituitary adenoma grade 1	38.46±0.88	38.38	33.61	45.03	
Diffuse astrocytoma grade 2	42.10±2.19	39.97	30.83	51.89	
Intra-axial tumors (n=29)	40.70±1.20	39.97	23.28	51.89	0.042
Extra-axial tumors (n=31)	39.10±0.69	38.78	33.11	49.41	

Table 3. Tumor-infiltrating lymphocyte (TILs) percentage in high-grade primary brain tumors

No	High grade tumors	TILs in invasive margin (%)	TILs in the central tumor (%)	TILs in perivascular areas (%)	TILs in perinecrotic area (%)
1	Glioblastoma NOS grade 4	0-5	0-5	0-5	-
2	Glioblastoma NOS grade 4	0-5	0-5	0-5	-
3	Glioblastoma NOS grade 4	5-10	0-5	0-5	15-20
4	Glioblastoma NOS grade 4	0-5	0-5	0-5	-
5	Glioblastoma NOS grade 4	5-10	0-5	0-5	-
6	Glioblastoma NOS grade 4	40-45	30-35	30-35	10-15
7	Glioblastoma NOS grade 4	40-45	40-45	30-35	20-25
8	Glioblastoma NOS grade 4	30-35	35-40	10-15	10-15
9	Glioblastoma NOS grade 4	0-5	5-10	5-10	10-15
10	Medulloblastoma grade 4	-	0-5	0-5	-
11	Anaplastic meningioma grade 3	5-10	0-5	0-5	5-10
12	Anaplastic meningioma grade 3	-	0-5	0-5	-
13	Anaplastic meningioma grade 3	5-10	0-5	0-5	-
14	Anaplastic astrocytoma grade 3	5-10	0-5	0-5	-
15	Anaplastic astrocytoma grade 3	40-45	40-45	30-35	20-25
16	Anaplastic ependymoma grade 3	0-5	0-5	0-5	5-10

The percentage (score) of tumor-infiltrating lymphocytes (TILs) was assessed in the invasive margin, central tumor, perivascular areas, and perinecrotic areas of high grade tumors by H&E-stained sections according to the recommendations of the International TILs Working Group 2014.

TILs Infiltration and Correlation between IL-38 Serum Concentrations and TILs Score in High-grade Brain Tumors

Due to negligible infiltration of TILs to the low-grade brain tumors, TILs were only evaluated in high-grade brain tumors. Among 25 evaluated high-grade brain tumor, 16 tumors displayed lymphocyte infiltration to at least one of four investigated areas. Overall, 14 patients had TILs in invasive margin of tumor, 16 patients in central tumor, 16 patients in perivascular areas, and 8 patients in perinecrotic areas. The frequency of TILs in different areas in each patient is demonstrated in Table 3. Spearman's correlation analysis did not show any significant correlation between IL-38 serum levels and TILs score in any of the four investigated areas in high-grade tumors.

IL-38 Correlation with Tumor Size and Age in Brain Tumors

No correlation was observed between IL-38 serum levels in either tumor size or patient age. However, in the patients with low-grade brain tumors, IL-38 levels showed a significant positive correlation with tumor size (n=35, r=0.34, p=0.04).

DISCUSSION

In the present study, we observed elevated serum levels of IL-38 in the patients with brain tumors, both low- and high-grade tumors, compared with the healthy individuals. However, IL-38 serum levels in the patients with high-grade tumors did not differ from low-grade ones. Recent studies propose a significant relationship between IL-38 and autoimmune disorders, however, the biological role of IL-38 in tumor growth has not been well elaborated (16). In agreement with elevated levels of IL-38 in sera of patients with brain tumors in our studies, the expression of IL-38 was found to be elevated in lung adenocarcinoma and stage I of cervical squamous cell carcinoma compared with the normal tissues (18, 20). Moreover, our results indicated a positive correlation between IL-38 serum levels and tumor size in low-grade brain tumors. In lung adenocarcinoma, IL-38 high mRNA expression showed a significant correlation with undesirable clinicopathological characteristics including higher grade, stage, T status, N status and the presence of pleural and vessel invasions as well as the expression of PD-L1 (18). IL-38 is able to suppress the inflammation and can modulate both innate and adaptive immune responses (21, 22). Elevated levels of IL-38 is reported to be associated with abrogation of an anti-tumor immune responses (20). The contribution of IL-38 in anti-tumor activity might be explained by the up-regulation of regulatory T cells function regarded as a major immune-suppressive factor (14, 23). Moreover, it has been reported that IL-38 can dampen anti-tumor immune responses through inhibiting the IL-36, a pro-inflammatory cytokine with anti-tumoral activity (16, 22). Due to the strong link between inflammation and cancer, the role of the IL-1 family of cytokines in the tumor pathogenesis has received increasing attention (24). IL-37 and IL-38 are the most recent member of Interleukin-1 superfamily acting as natural inflammatory suppressors, and they seem to play similar roles in cancer pathogenesis (25, 26). These cytokines might be associated with unfavorable features as reported in ovarian, bladder and lung cancers (18, 27, 28). Interestingly, our prior study demonstrated a significantly higher levels of IL-37 in sera of patients with brain tumors, in both low and high-grade tumors, in comparison with the healthy controls (29). Considering the increase in infiltration of regulatory T cells in brain tumors, especially in glioblastoma, it may be suggested that the elevation in IL-37 and IL-38 serum levels might contribute to the Tregs recruitment and that may play critical roles for cytokines-mediated immunosuppression in both low and high-grade brain tumors (30). Interestingly, it has been shown that blocking the IL-38 recovers immune infiltration and promotes anti-tumor immune responses by generating tumor-specific memory cells, a situation that was associated with inhibiting tumor growth (20). However, unlike tumors in which IL-37 and IL-38 had a pro-tumoral role, in colorectal cancer (CRC), these two cytokines exhibited similarities in the abrogation of tumor growth (31). Moreover, the higher expression of IL-38 was observed to be associated with smaller tumor size in CRC (17). The discrepancies could be due to the differences in the biology of various tumor types which requires more investigations. Moreover, we observed a difference in IL-38 serum levels between intra-axial and extra-axial tumors. In line with this, a previous study in brain tumors showed a difference in inflammatory marker (neutrophil-to-lymphocyte ratio) between the intra-axial and the extra-axial ones (32). Probably, due to their different locations, intra-axial and extra-axial brain tumors possess different biological behavior and immune responses (33). Moreover, we evaluated the infiltration of TILs in high-grade brain tumors and their correlation with IL-38 serum levels. Based on the frequency and the contexture of TIICs, anti-tumor responses is probably variable in gliomas and meningiomas as two most

common types of CNS tumors. In addition to their effect on anti-tumor responses, the contexture of infiltrated immune cells might be associated with biologic aggressiveness of tumors and/or patient outcome in different subtypes of cancers (34). In malignant brain tumors such as glioblastoma, TILs are important components of the tumor microenvironment and may influence the overall survival (9). Accordingly, the effector T cell infiltration improves the survival time in glioblastoma while tumor-derived TGF-β impairs it (35). Additionally, multiple studies in glioma have proven that indoleamine 2,3 dioxygenase (IDO) and MDSCs play critical role in recruitment of Tregs into brain tumor microenvironment, and contribute to the lack of effective immune activation. This process negatively impacts the survival (30, 36). Similarly, some evidences have shown the role of IL-38 in the pathogenesis of central nervous system diseases (37). As reported in sepsis, IL□38 may dramatically enhance the immunosuppressive activity of $CD4^+CD25^+$ Tregs, amplifying the immune responses through Th2 lymphocytes and reducing the proliferation of effector T cells (23). The studies have introduced IL-38 as an immunosuppressive cytokine that regulates both innate and adaptive immune responses and affects the tumor microenvironment components in cancer. It has been shown that the higher expression of IL-38 was associated with reduced infiltration but variable levels of multiple lineages of immune cells (e.g. T, B, NK and myeloid cells) in head and neck cancer, lung adenocarcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, esophageal cancer, and gastroesophageal squamous carcinoma (20). Additionally, it has been shown that elevated levels of IL-38 in lung tumor cells were inversely associated with CD8+ tumor-infiltrating lymphocytes (38). In our study, although the majority of high-grade brain tumors displayed lymphocyte infiltration to at least one of four investigated areas including invasive margin, central tumor, perivascular areas, and perinecrotic areas, we could not find any correlation between IL-38 levels and TILs. However, more studies are required to verify the role of IL-38 in immune cell infiltration in brain tumors.

In conclusion, our results indicate higher serum levels of IL-38 in the patients with brain tumor, both low- and high-grade cases compared with the healthy individuals and that there was a significant correlation between IL-38 levels and higher tumor size in low-grade tumors. Although further investigations are required to confirm our result, elevation in IL-38 levels and its positive correlation with tumor size might be associated with immune-suppressive activity and/or disease progression in brain tumors and may highlight its use in therapeutic strategies.

ACKNOWLEDGMENT

This project was a common project between Shiraz Institute for Cancer Research and Jahrom University of Medical Sciences, and conducted at Shiraz Institute for Cancer Research, Shiraz University of Medical Sciences, Shiraz, Iran. The project was approved by the ethics local committee (IR.JUMS.REC.1401.027), and financially supported by Jahrom University of Medical Sciences, Jahrom, Iran (Grant No: JUMS.401000015), as well as Shiraz Institute for Cancer Research, Shiraz University of Medical Sciences, Shiraz, Iran (Grant No: ICR-100-503).

AUTHORS' CONTRIBUTION

MH and ASJ contributed to the conceptualization and study design. MH and ASJ played a role in receiving academic grants. SK, AK, HG and MH contributed to the lab experiments, statistical analysis, and data interpretation. AD contributed to data gathering, pathological confirmation

of cancer, and TILs scoring. MH and ASJ supervised the project. AK, SK, and FG were involved in data gathering, drafting the proposal and manuscript, which was then revised by MH, ASJ and HG. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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