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Role and value of inflammatory markers in brain tumors: A case controlled study

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ABSTRACT

Introduction: Brain tumor is one of the most devastating diseases in the world. The Pathogenesis is vary in multiple aspect of mechanism. The tumor microenvironment contains many different noncancerous cell types in addition to cancer cells. Inflammation is thought to be one of the factors that influence the oncogenesis process in brain tumors.

Methods: This study is a case controlled analytical study that analyzes the relationship between levels of inflammatory markers with the type of brain tumor. Samples of 35 people were then categorized according to the variables above and analyzing to measure its significance.

Results: Based on demografic study, most sample was male with age was 41–50 years It was found that high levels of procalcitonin were found in the case of glioma brain tumors. Procalcitonin level was considered a significant marker in predicting the severity of a brain tumor ($p < 0.005$). There was no significant value between the C-Reactive Protein and Neutrophyl-Lymphocyte ratio values for brain tumors.

Discussion: Abnormal inflammation is a characteristic of malignant cancers and malignant transformation of low-grade gliomas and other brain tumor. Inflammation-induced activation of transcription factors contributes to the survival and rapid growth of glioma cells.

Conclusion: As in other malignant cancers, inflammation may contribute to tumor progression. Biomarkers based on inflammation, such as the classical example of Procalcitonin and C-reactive protein, have been used to assess prognosis of glioma patients. These results should be validated and extended in larger clinical studies.

1. Introduction

Brain tumor is one of the most devastating diseases in the world. The Pathogenesis is vary in multiple aspect of risk and mechanism. The tumor microenvironment (TME) contains many different noncancerous cell types in addition to cancer cells, including endothelial cells, pericytes, fibroblasts, and immune cells[1] While several of these cell types are also prevalent in brain tumors, there are some important features that distinguish the normal brain from other tissues; the composition of the extracellular matrix (ECM) is distinctive, there are unique tissue-resident cell types including microglia, astrocytes and neurons, and it is physically protected from inflammation by the blood-brain barrier (BBB). Indeed, the normal brain was long considered to be one of the ''immune privileged'' organs in the body that must be sheltered from immune cell entry and/or attack for a number of reasons. For instance, activated immune cells produce inflammatory factors that can be cytotoxic and cause neurodegeneration. In addition, the skull provides a physical barrier to the swelling that often coincides with inflammatory reactions, and thus interactions with the immune system need to be exquisitely regulated within the brain [2].

Inflammation, plays an important role in occurrence of secondary injury. Inflammation cascade starts with the release of inflammatory mediators, such as microglia releasing cytokines (IL6, IL1, and TNF). Cytokines are mediators that trigger the release of PCT into plasma. High concentration of PCT in the blood has been used as a predictor of the occurrence of SIRS, sepsis and MODS. The immune system produces cytokines which is a polypeptide consisting of a mediator, such as interferon, interleukin (IL), tumor necrosis factor (TNF), with their respective roles. Systemic Inflammatory Response Syndrome (SIRS) is a systemic inflammation response caused by severe inflammation response [3,4].

Procalcitonin (PCT) is a peptide composed formed 116 amino acid

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that undergoes post translational proteolysisto become the hormone calcitonin. In the blood plasma of normal people, PCT is not present, or within 2 ng/ml, shown septic conditions. High PCT serum is usually found in patients with bacterial or fungal infection, but can also be found in acute phase of the trauma. High level of PCT in day one can be used as SIRS, Septic, and MODS predictor. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been recognized as inflammatory markers and used as prognostic makers in various cancers. The present study sought to investigate the prognostic role of NLR and PLR in patients with glioma [5,6].

Chronic inflammation occurring within the microenvironment of tumor lesions is now thought to either drive the first malignant-conferring genetic mutations and/or induce them as a result of oncogene expression. The present study sought to investigate whether Procalcitonin, C-Reactive Protein and NLR are significantly associated with patients with brain tumor. These results may help provide an evidence-based approach to stratifying patients by poor survival risk, thereby guiding the tailoring of treatment.

2. Methods

This study is a case controlled analytical study to find the relationship between levels of inflammatory markers in patients with brain tumors. Samples were collected from patients at Haji Adam Malik General Hospital in Medan, Indonesia. The patient's blood serum was taken to be checked for these variables. Sample collection began in March–September 2020. The sample obtained was 35 people who met the inclusion and exclusion criteria.

2.1. Inclusion criteria

1. Willing to be a sample
2. Complete medical records
3. Head scan and head contrast MRI have been performed to confirm the patient's diagnosis with a brain tumor.

2.2. Exclusion criteria

1. The patient's age is over 70 years
2. Patients with high comorbidities such as kidney failure, heart disease, diabetes, and others
3. Patients with a history of brain tumor surgery or previous brain tumor treatment

Samples were categorized based on demographic data (age and gender), then the samples were categorized based on the type of brain tumor suffered. Once categorized, the levels of inflammatory markers was examined. Specimens were taken from the patient's peripheral blood examination and analyzed in laboratorium. The results of these examinations are grouped on a nominal scale, and analyzed statistically.

Based on this analysis, it will be determined whether there is a significant relationship between levels of inflammatory markers in the incidence of brain tumors.

3. Results

In the demographic results, it was found that the most sample was male as many as 20 people (57%) and the most age was 41–50 years as many as 15 people (43%). This data can be seen in Table 1.

Types of tumors are divided into 3 broad categories, namely, Meningioma, Glioma and Brain metastases based on Head CT scan images, head MRI with contrast and histopathology. The most common type of tumor was meningioma as many as 15 people (44%). The data is attached in Table 2.

The sample obtained was then carried out an assessment of the degree of consciousness based on GCS and the value of performance status based on the KPS score (Table 3).

Table 1
Sample demografic.

No	Description	Parameter	Number of Samples	Percentage
1	Gender	Man	20	57%
		Woman	15	43%
		Total	35	100%
2	Age (year)	<20	3	9%
		21–30	3	9%
		31–40	5	14%
		41–50	15	43%
		51–60	5	14%
		61–70	4	11%
		Total	35	100%

Table 2
Brain tumor type.

Description	Classification	Number of Samples	Percentage
Brain Tumor Type	Meningioma	15	44%
	Glioma	10	28%
	Brain Metastasis	10	28%
	Total	35	100%

Based on the results of the examination of serum Procalcitonin levels, serum C-Reactive Protein levels and levels of Neutrophyl-Lymphocyte Ratio, an increase in procalcitonin levels> 2 μg/L (High level) in glioma and metastatic tumors (Table 4).

There is an increase in CRP level (Fig. 1), Procalcitonin level (Fig. 2), and NLR level (Fig. 3). C reactive protein level and NLR were not significant in every type of brain tumor ($p>0.005$), this can be seen in Table 5 and Table 6. Procalcitonin, CRP and NLR numbers tended to have lower levels in menigioma. There was an increase in the value of CRP and NLR in meningioma, glioma and brain metastatic tumors, but the increase was not significant. This may be because CRP and NLR are also influenced by other extracranial factors such as the presence of inflammation in other organs or patients with chronic disease who did not cause symptoms at the time of examination.

The markers of inflammation in brain tumor damage can be assessed based on the level of several inflammatory factors. At least, there are three important cytokines produced by microglia and astrocytes after injury, namely interleukin-1β (IL-1β), tumor necrosis factor α (TNFα), and interleukin-6 (IL-6) IL-6 which is produced to stimulate hepatocytes to increase the production of acute phase proteins such as C-reactive protein. This protein will reflect the inflammatory process so that there is an increase from normal levels. This inflammatory process also causes an increase in NLR and procalcitonin levels [5].

Table 3
GCS and KPS.

No	Description	Classification	Number of Samples
1	*Glassgow coma Scale* (GCS)	3–8	0
		9–12	2
		13–15	33
2	*Karnofsky Perfomance Score* (KPS)	100	33
		90	2
		80	0
		70	0
		60	0
		50	0
		40	0
		30	0
		20	0
		10	0
		0	0
		Total	35

Table 4
Serum procalcitonin level.

Procalcitonin (ug/L)	Brain Tumor Type			Mean ($\bar{x}$)	p Values
	Meningioma	Glioma	Brain Metastasis		
Low (<0,5)	6	0	2	0.32	0.112
Moderate (0,5–2)	7	3	3	1,4	0.213
High (>2)	2	7	5	3,1	0.002
Total	15	10	10		

*($\bar{x}$) = Mean, SD 95%.

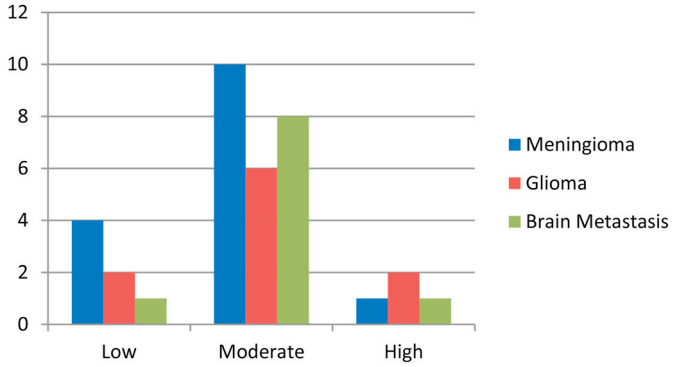

Fig. 1. C-Reactive Protein Level based on Brain Tumor Type.

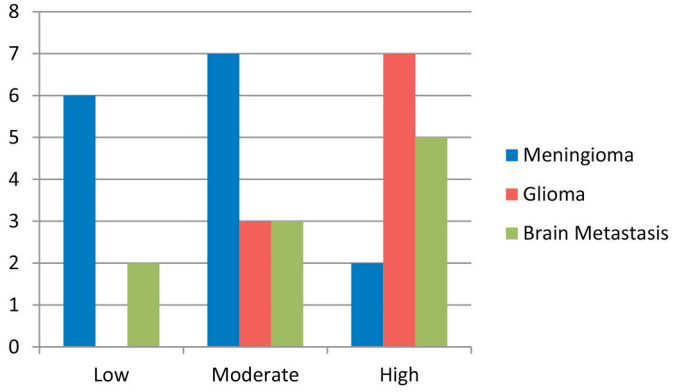

Fig. 2. Procalcitonin Level based on Brain Tumor Type.

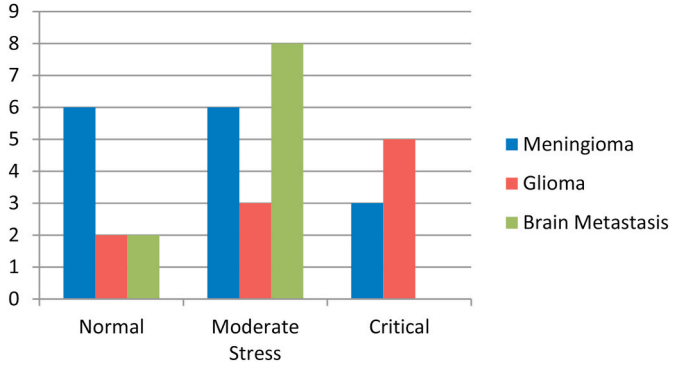

Fig. 3. NLR based on Brain Tumor Type.

Table 5
Serum C-Reactive protein level.

C-Reactive Protein (mg/dl)	Brain Tumor Type			Mean ($\bar{x}$)	p Values
	Meningioma	Glioma	Brain Metastasis		
Low (<5)	4	2	1	3.2	0.211
Moderate (5–10)	10	6	8	7.5	0.06
High (>10)	1	2	1	10.2	0.124
Total	15	10	10		

*($\bar{x}$) = Mean, SD 95%.

Table 6
Neutrophyl-lymphocyte ratio serum level.

Neutrophyl-Lymphocyte Ratio (NLR)	Brain Tumor Type			Mean ($\bar{x}$)	p Values
	Meningioma	Glioma	Brain Metastasis		
Normal (1–4)	6	2	2	3.8	0.411
Moderate Stress (5–9)	6	3	8	8.8	0.08
Critical (>10)	3	5	0	14.2	0.12
Total	15	10	10		

*($\bar{x}$) = Mean, SD 95%.

4. Discussion

Abnormal inflammation is a characteristic of malignant cancers and a driver of malignant transformation of low-grade gliomas. Inflammation-induced activation of transcription factors contributes to the survival and rapid growth of glioma cells. SIRS is defined as the systemic inflammatory syndrome due to an inflammatory response. SIRS can be the result of trauma, hemorrhagic shock, or caused by other ischemia, pancreatitis or immunological injury [7,8].

Excessive production of IL1, JL6, and TNFα in inflammation process hence will produce excessive cytokines. Cytokines will enter the circulation increasing the possibility of SIRS occurrence. IL6 and TNF are the mediators that triggers the release of PCT into the blood plasma. On the other hand, this complex cascade of neuroinflamation can also cause an opposite reaction, by inducing the production of protective and reparative factors [8].

Inflammation is the first line of defense in response to tissue injury and/or infection. Pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, Interleukin (IL)-1β, and IL-6 are synthesized to initiate the inflammatory cascade. IL-1 has been shown to be a key mediator in the proliferation of "reactive astrocytes". Next, either of two types of inflammatory processes may be activated depending on the stimulus. In the presence of microbial infection or necrotic cell death classical "type 1" inflammation ensues, characterized by the appearance of activated T helper (Th) 1 lymphocytes. Th2 inflammation is closely related to wound repair [9].

The initiation of the classical inflammatory response is marked by the localization and subsequent activation of blood circulating monocytes into M1 macrophage. The M1 macrophage are activated by cytokines produced by Th1 cells, like interferon-γ (IFN-γ), TNF-α, or after recognition of pathogen-associated molecular pattern molecules, through toll-like receptors (TLRs) or C-type lectin receptors. Upon activation, the M1 macrophage promote a proinflammatory environment by releasing cytokines such as TNF-α, IL-1, IL-6, IL-12, IFN-γ, and IL-23. IL-12 stimulates IFN-γ production in T lymphocytes and natural killer (NK) cells. Phenotypically, the M1 phenotype is associated with cell mediated cytotoxicity, tissue injury and destruction. Thus, the presence of the M1 macrophage is counter-productive once the invading threat is neutralized and tissue repair is in order. The resolution of the inflammatory response and transition into wound repair is facilitated by the M2 macrophage. One of the key events leading to

immunosuppression and activation of "type 2" inflammation is apoptotic cell death of recruited neutrophils. The apoptotic neutrophils signal to close classical inflammation and thus modulate immunosuppression after their engulfment by macrophages. In response, the macrophage upregulate expression of the Th2 anti-inflammatory cytokine IL-10, while significantly downregulating the pro-inflammatory cytokines TNF-α, IL-1β, and IL-12 [10,11].

Chronic inflammation can influence a wide range of ailments including heart disease, stroke, Crohn's disease, rheumatoid arthritis, multiple sclerosis, asthma, Alzheimer's, depression, fatigue, neuropathic pain, and - relevant to our discussion - cancer. Indeed, it is thought that around 15% of all cancer-related deaths are in some form linked with inflammation as a result of bacterial or viral infections. Further, chronic inflammation occurring within the microenvironment of tumor lesions is now thought to either drive the first malignant-conferring genetic mutations and/or induce them as a result of oncogene expression [12,13].

As in other malignant cancers, inflammation may contribute to glioma progression. Biomarkers based on inflammation, such as the classical example of Procalcitonin and C-reactive protein, have been used to assess prognosis of glioma patients [7,9]. Neutrophil-tolymphocyte ratio (NLR), a novel marker in many systemic inflammatory disorders, reflects immune response arising from various stress stimuli. It has shown prognostic potential in several cancers, including lung, breast, and kidney cancer. Another inflammation biomarker, the platelet-to-lymphocyte ratio (PLR), has shown prognostic potential for patients with solid tumors [14,15].

This systemic inflammation leads to a simultaneous increase in neutrophil count and decrease in lymphocyte count, which may reflect increased lymphocyte margination and apoptosis. The net result is inhibition of the cytolytic activity of immune cells and immunosuppression. Increased NLR has been described as a novel inflammation biomarker with prognostic potential in several cancers. Consistent with this, NLR in our patients increased with WHO grade, suggesting that preoperative NLR may be useful for predicting glial tumor grade [15,16].

Another study found that NLR correlates with glial brain tumor grade, and that NLR $>$ 2.579 may be a discriminative parameter for predicting glioma grade [17]. These results are similar to our study that found NLR $>$ 5 were mostly found in patient with glioma and brain metastasis.

In this study there was an increase in the value of CRP and NLR in meningioma, glioma and brain metastatic tumors, but the increase was not significant. This may be because CRP and NLR are also influenced by other extracranial factors such as the presence of inflammation in other organs or patients with chronic disease who did not cause symptoms at the time of examination. Level of procalcitonin are increasing significantly in patient with glioma and brain metastasis tumor, Therefore, procalcitonin can be said to be an inflammatory factor that affects the incidence of glioma type tumors and brain metastases.

5. Conclusion

Brain tumor is one of the most devastating diseases in the world. The Pathogenesis is vary in multiple aspect of risk and mechanism. The tumor microenvironment (TME) contains many different noncancerous cell types in addition to cancer cells, including endothelial cells, pericytes, fibroblasts, and immune cells. Chronic inflammation occurring within the microenvironment of tumor lesions is now thought to either drive the first malignant-conferring genetic mutations and/or induce them as a result of oncogene expression.

As in other malignant cancers, inflammation may contribute to glioma progression. Biomarkers based on inflammation, such as the classical example of Procalcitonin and C-reactive protein, have been used to assess prognosis of glioma patients.

The neutrophil-to-lymphocyte ratio (NLR) have been recognized as inflammatory markers and used as prognostic makers in various cancers. Increased NLR and are associated with worse tumor type, and NLR may be an independent risk factor to identify glioma patients with poor prognosis. These results should be validated and extended in larger clinical studies. Based on this study procalcitonin can be said to be an inflammatory factor that affects the incidence of glioma type tumors and brain metastases. It is hoped that in the future further research can be carried out on the effects of procalcitonin on the biomolecular pathway for brain tumor development.

5.1. The limitations of this study

1. The number of samples is still limited, it is hoped that with more samples, more representative results will be obtained.
2. Assessment of inflammatory factors is still using the commonly used markers
3. Limitations in assessing the biomolecular association of each inflammatory marker in each type of brain tumor.

Ethical approval

Health Research Ethical Committee Medical Faculty of Universitas Sumatera Utara No: 254/TGL/KEPK FK USU-RSUP HAM/2020.

Author contribution

Ridha Dharmajaya Author
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Registration of research studies

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Disclosure statement

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Provenance and peer review

Not commissioned, externally peer reviewed.

Declaration of competing interest

There is no conflict of interest in this study.

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References

[1] D. Quail, J. Joyce, Microenvironmental regulation of tumor progression and metastasis, Nat. Med. 19 (2013) 1423–1437.

[2] B. Engelhardt, P. Vajkoczy, R. Weller, The movers and shapers in immune privilege of the CNS, Nat. Immunol. 18 (2017) 123–131.

[3] C.S. Deutschman, Acute-phase responses and SIRS/MODS: the good, the bad, and the nebulous, Crit. Care Med. 26 (2000) 1630–1631.

[4] Suspected sepsis: a comparison with CReactive protein and neutrophil count, Pediatr. Crit. Care Med. 4 (2003) 190–195.

[5] R.M. Bambury, M.Y. Teo, D.G. Power, A. Yusuf, S. Murray, J.E. Battley, et al., The association of pre-treatment neutrophil to lymphocyte ratio with overall survival in patients with glioblastoma multiforme, J. Neuro Oncol. 114 (2013) 149–154.

[6] M. Hatherill, S.M. Tibby, K. Sykes, et al., Diagnostic marker of infection: comparison of procalcitonin with C-reaktive protein and leucocyte count, Arch. Dis. Child. 81 (1999) 417–421.

[7] N. Michelson, J. Rincon-Torroella, A. Quiñones-Hinojosa, J.P. Greenfield, Exploring the role of inflammation in the malignant transformation of low-grade gliomas, J. Neuroimmunol. 297 (2016) 132–140.

[8] E. Sen, Targeting inflammation-induced transcription factor activation: an open frontier for glioma therapy, Drug Discov. Today 16 (2011) 1044–1051.

[9] K.J. Tracey, A. Cerami, Tumor necrosis factor, other cytokines and disease, Annu. Rev. Cell Biol. 9 (1993) 317–343.

[10] A. D'Andrea, M. Rengaraju, N.M. Valiante, J. Chehimi, M. Kubin, M. Aste, S. H. Chan, M. Kobayashi, D. Young, E. Nickbarg, Production of natural killer cell stimulatory factor (interleukin 12) by peripheral blood mononuclear cells, J. Exp. Med. 176 (1992) 1387–1398.

[11] R.E. Voll, M. Herrmann, E.A. Roth, C. Stach, J.R. Kalden, I. Girkontaite, Immunosuppressive effects of apoptotic cells, Nature 390 (1997) 350–351.

[12] F. Balkwill, A. Mantovani, Inflammation and cancer: back to Virchow? Lancet 357 (2001) 539–545.

[13] A. Mantovani, P. Allavena, A. Sica, F. Balkwill, Cancer-related inflammation, Nature 454 (2008) 436–444.

[14] A. Conti, C. Gulì, D. La Torre, C. Tomasello, F.F. Angileri, M. Aguennouz, Role of inflammation and oxidative stress mediators in gliomas, Cancers 2 (2010) 693–712.

[15] S.S. Faria, P.C. Fernandes Jr., M.J. Silva, V.C. Lima, W. Fontes, R. Freitas-Junior, et al., The neutrophil-to-lymphocyte ratio: a narrative review, Ecancermedicalscience 10 (2016) 702.

[16] A.J. Templeton, O. Ace, M.G. McNamara, M. Al-Mubarak, F.E. Vera-Badillo, T. Hermanns, et al., Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis, Cancer Epidemiol. Biomark. Prev. 23 (2014) 1204–1212.

[17] P. Zadora, W. Dabrowski, K. Czarko, A. Smolen, E. Kotlinska-Hasiec, K. Wiorkowski, et al., Preoperative neutrophil-lymphocyte count ratio helps predict the grade of glial tumor - a pilot study, Neurol. Neurochir. Pol. 49 (2015) 41–44.