

Serum immuno-biomarkers in gliomas

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Gliomas comprise the majority of malignant primary brain tumors in adults and remain a devastating diagnosis.^[1] Despite therapeutic advances, median survival in the radiation and temozolamide era for the most common and most aggressive tumor type, glioblastoma (GBM), is 14-20 months and tumor recurrence is universal.^[2] A promising new direction to combat GBM is immunotherapy, which emerged from intensive research revealing that although highly immunogenic, GBM actively suppresses the host anti-tumoral immune response throughout a variety of mechanisms (reviewed in^[3] and^[4]). Current therapies to abrogate tumor immunosuppression and unleash T-cell mediated killing of GBM include: inhibitors of immune-checkpoints that are exploited by GBM to enhance tumor survival (therapeutic antibodies against CTLA-4 and PD-1, which are overexpressed in tumor-infiltrating lymphocytes, and against PD-L1, which is overexpressed on GBM cells and tumor-infiltrating immune cells); vaccination strategies against single or multiple tumor-associated peptides; infusion of autologous adoptive CAR T-cells primed against GBM-specific antigens; and inhibition of the immunomodulatory indoleamine 2,3-dioxygenase (IDO) pathway, which is also overexpressed in GBM.^[3,5] Recent work by Alexiou *et al.*^[6,7] published in this journal contributes to the use of immune mediators as prognostic surrogates of GBM aggressiveness

and survival and may be clinical indicators of which patients are likely to benefit in current and future immunotherapeutic trials.

In the first article, a prospective, single-institution, observational study of GBM patients treated with tumor resection followed by chemotherapy and radiation (under the Stupp regimen^[8]) for up to 1 year, Alexiou *et al.*^[6] demonstrate a lower neutrophil-to-lymphocyte ratio (NLR) to be an independent prognostic predictor of survival. Using a cutoff value of $NLR < 4.7$, both overall survival (OS) and progression-free survival (PFS) were significantly longer. This study supports other work^[9] which also revealed NLR as an independent prognostic predictor using a cut-off value of 4, and is consistent with other studies demonstrating the prognostic value of NLR in other tumor types. Importantly, both studies examined the NLR prior to administration of corticosteroids as corticosteroid use is itself an independent negative prognostic indicator, regardless of other chemo- or radiotherapy given.^[10,11]

Extensive work has explored the role of tumor-infiltrating lymphocytes (TILs) in glioma, both as markers of tumor aggressiveness and with patient survival, namely that infiltration of cytotoxic CD8+ T lymphocytes are decreased and CD4+ and CD4+/CD25+/FoxP3+ (Treg) populations of T lymphocytes



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increased in higher grade tumors, with increased Treg infiltration indicating a worse prognosis.^[12] Furthermore, it has been shown that TILs are enriched in the mesenchymal molecular GBM subclass,^[13] which has also been correlated with improved response to immunotherapy.^[14] Han *et al.*^[15] describe a prospective, single-center series of GBM patients comparing intratumoral infiltration of macrophages and T cells and corroborating pre-treatment NLR (using a cut-off value of 4) with survival, establishing that serum neutrophil and lymphocytes levels (and thus the NLR) reflect the presence of TILs within the tumor milieu. In another study by Berghoff *et al.*^[16] a single-center retrospective analysis (“Vienna cohort”), improved survival was not associated with TIL density (or PD-L1 overexpression), in contrast the other studies. Routine analysis of TILs is difficult in clinical settings, so it is crucial that the study of Alexiou *et al.*^[6,7] mirrors the use of serum kynurenine and tryptophan levels as another biomarker of the immunosuppressive effect of IDO catabolism in gliomas, which demonstrated prognostic significance for OS in a prospective, multi-center observational trial of GBM patients.^[17] Taken together, the work of Alexiou *et al.*,^[6] Bambury *et al.*,^[9] and Han *et al.*^[15] elaborate upon the role of TILs in GBM via an easily obtainable, non-invasive, serum biomarker proxy. These papers reinforce and expand upon the paradigm that GBM is a lymphocyte-suppressing tumor as well as that lymphocyte down-regulation is itself a marker of an aggressive tumor pathology.

The second article by Alexiou *et al.*,^[7] also a prospective, single-institution observational study of patients undergoing surgery for intracranial tumors (not limited to GBM), revealed that lower serum IgE levels in the GBM patients were a prognostic marker associated with poorer survival and higher-grade in gliomas, although the result was of marginal significance statistically. IgE levels in gliomas and meningiomas were also significantly lower than in metastatic tumors. This supports prior work on IgE and allergies in the development of malignancies. For example, in a large, multi-center, case-controlled study of self-reported medically-diagnosed allergies, there was an inverse relationship between allergies and gliomas. Furthermore, this association was incidence responsive, the greater number of medically-diagnosed allergies the lower the glioma risk.^[18] A number of previous studies also suggest that a general atopy phenotype rather than a specific allergy type/allergen is correlated with decreased glioma risk,^[18,19] which is consistent with the total serum IgE results discussed here. Thus, it is not a limitation of Alexiou’s study that allergen-specific IgE antibodies were not elucidated.

GBM continues to be a catastrophic tumor, with eventual recurrence and poor survival, in no small part due to tumor-based immunosuppression. Immunotherapy is a promising addition to the current standard of care. The studies highlighted here by Alexiou *et al.*^[6,7] emphasize the growing role of immune cells and antibodies in the understanding of both gliomagenesis, glioma progression, and the development of aggressive and treatment-resistant tumor types. They do not identify a causal role for certain inflammatory mediators either as protective or tumor-suppressive, but rather begin to pinpoint immune phenotypes of GBM. Furthermore, they provide easily measurable biomarkers for immunosuppressive GBM phenotypes, which are prognostic for patient survival and are clearly applicable to clinical trials for novel immunotherapies. Subsequent work is needed to correlate these findings to other prognostic GBM markers or subtypes (e.g. MGMT promoter methylation, presence of IDH1 mutations, *etc.*) and imaging characteristics (e.g. pseudoprogression following both standard treatment and immunotherapy is thought to be an immune-mediated response^[20]). In fact, immunotherapy-induced changes on neuroimaging have been incorporated in to the newest response assessment guidelines (“iRANO”^[21]), but whether these serum biomarkers correlate remains unclear. It is equally important to identify any mechanistic role of IgE, and also CD4+ Th2 cells, CD4+/CD25+/FoxP3+ Treg cells, or the IgE-driving cytokines IL-4 and IL-13, in the glioma milieu and the promulgation of tumor immunosuppression. Of further value would also be to expand upon the prognostic findings described here to determine if the serum NLR or IgE levels are useful to assess treatment response.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

No patient involved.

Ethics approval

This article does not contain any studies with human participants or animals.

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