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Commentary: Evaluating potential glioma serum biomarkers, with future applications

Michael Goutnik, Brandon Lucke-Wold

Abstract

Systemic inflammation within malignant glioma is a topic of ongoing significance. In this commentary, we highlight recent findings from Gandhi *et al* and discuss alternative approaches. We present a counter argument with findings that IL-6 markers are controversial. We highlight the potential benefit of looking at microRNAs and other biomarkers. Finally, we present ideas for future application involving differentiation between radiation necrosis and recurrence. The commentary is intended to serve as a catalyst for further scientific discovery.

TO THE EDITOR

The paper titled “Novel molecular panel for evaluating systemic inflammation and survival in therapy naïve glioma patients” by Gandhi *et al* highlights the use of a non-invasive panel consisting of four inflammatory markers to distinguish between histological grades of glioma and IDH-mutant/wildtype glioma, as well as predicting overall survival [1]. The premise behind the potential effectiveness of such a panel is the chronic inflammatory state that results from various stimuli like tumor antigens and oncogenes that promote abnormal growth and leakage of markers into the peripheral circulation. The inflammatory environment of gliomas is not a new finding, as Morimura *et al* previously found [2]. 20-30% of cells in glioma samples were recognizable by various macrophage/microglia markers and that tumor proliferation

correlates with macrophage infiltration [2]. Parney *et al* similarly demonstrated the infiltration of gliomas by macrophages [3]. However, there is conflicting evidence as to whether these infiltrating macrophages are capable of secreting cytokines and promoting an effective immune response [4, 5].

Nonetheless, other studies have found similar results with respect to the markers that Gandhi *et al* focused upon within their paper. For example, Adams *et al* found the kynurenine pathway to be significantly activated in plasma samples from glioblastoma (GBM) patients, an effect that is hypothesized to inhibit anti-tumor immunity by depleting tryptophan from the tumor microenvironment and thus suppressing T-cell proliferation [6]. Du *et al* also demonstrated that the serum Kyn/Trp ratio in patients with high grade gliomas was significantly higher than in those with lower grade gliomas [7]. Similarly, Juhász *et al* used dynamic PET imaging of patients with gliomas to demonstrate shunting of tryptophan (Trp) toward kynurenine (Kyn) metabolism [8]. Mitsuka *et al* evaluated the expression of indoleamine 2,3-dioxygenase (IDO), an important enzyme in tryptophan metabolism that yields catabolites including kynurenine, in 75 surgical specimens including diffuse astrocytomas, anaplastic astrocytomas, and GBMs [9]. The authors found IDO expression correlated with glioma grade, expression increased in secondary glioblastoma relative to the initial lower-grade glioma, and stronger expression was associated with worse survival in GBM patients [9]. Zhai *et al* also found GBM patients with high kynurenine/tryptophan ratios to have worse survival compared to those with lower values [10]. However, no other studies were found that replicated Gandhi *et al*'s findings of tryptophan metabolites distinguishing between IDH-wildtype and mutant gliomas.

The neutrophil-lymphocyte ratio was another significant marker in Gandhi *et al*'s study, which has been shown to be effective in distinguishing between different grades of glioma and predicting overall survival and progression-free survival in a variety of gliomas [11-19]. Concurrent with Gandhi *et al*'s results, NLR has also been shown to

distinguish between IDH-mutant and wildtype gliomas, with mutant IDH1 gliomas featuring lower levels of NLR [17]. Furthermore, telomerase activity has also been associated with glioma grade and overall survival, which Gandhi *et al* also demonstrated [20-22]. However, IDH mutant cell lines appear to indirectly reactivate hTERT, which contrasts with Gandhi *et al*'s finding of higher hTERT in IDH-wildtype tumors [23].

Gandhi *et al* highlighted positive correlations between median marker values and tumor grade, as well as significantly higher molecular marker values for IDH-wildtype compared to IDH-mutant gliomas [1]. Furthermore, they found that IL-6 had a strong correlation with tumor grade, which has been replicated by immunohistochemistry, gene expression studies and CSF and serum analysis [24, 25]. Some of these findings have been challenged in the literature, however. Cytokines interact with receptors, antibodies, binding proteins, and also often have short half-lives, so total concentrations may not reflect production and/or secretion levels [26]. Samaras *et al* thus used the ELISPOT method (a cell-based cytokine measuring system) to demonstrate greater IL-6 secretion from peripheral monocytes and greater IL-10 secretion from peripheral mononuclear and tumor cells in glioma patients compared to controls [26]. However, there was only a marginal increase in significance in median IL-6 secretion between glioma grades, but this may be due to small sample size [26]. Holst *et al* studied 158 patients and found no difference in serum IL-6 between GBM and lower grade gliomas once age was accounted for, and that IL-6 was significant for worse survival only in univariate analysis [27]. However, Holst *et al* and Jiang *et al* did find *IL6* RNA expression to differ between IDH-mutant and wild type gliomas, which parallels the finding of Gandhi *et al* [27, 28]. Other studies have not found a relationship between IL-6 Levels and survival in GBM [29, 30]. In one study involving 38 glioma patients, serum IL-6 decreased in glioma patients and inversely correlated with grade, while serum IL-17A was specific to gliomas (compared to meningiomas and schwannomas) and

positively correlated with grade [31]. However, serum IL-6 has been associated with a negative prognosis in other cancers [32].

Divergent results regarding IL-6 may reflect confounding bias and/or differential treatment, as corticosteroid treatment may decrease plasma IL-6 [27, 33]. Similarly, brain surgery may increase serum inflammatory markers, suggesting that these proteins reflect brain injury and disruption of the blood-brain barrier rather than tumor burden [34]. There may also be false positives in patients with other inflammatory or malignant processes [12]. Furthermore, there are a variety of other circulating biomarkers that may influence survival, such as circulating tumor cells and microRNAs [35, 36]. In addition, other non-serum based noninvasive biomarkers like urinary 2-hydroxyglutarate (2-HG), a product of mutant IDH acting on α -ketoglutarate, may distinguish between IDH-mutant and IDH-wild type glioma [37, 38]. This metabolite may also be detected by magnetic resonance spectroscopy, and correlates with IDH mutation status [39]. Nonetheless, Gandhi *et al*'s panel is promising with a 94.4% sensitivity and 96.7% specificity, suggesting potential therapeutic targets. More prospective work with larger cohorts is needed to evaluate the efficacy of Gandhi *et al*'s proposed immune marker panel in predicting tumor grade and survival, and whether adding, removing, and/or combining other circulating and non-circulating biomarkers may be more effective in terms of accuracy and cost.

An interesting application of Gandhi *et al*'s work would involve testing the ability of their panel to differentiate tumor progression from radiation necrosis [40]. Inflammation, including the pro-inflammatory IL-6 cytokine, likely contributes to the pathophysiology of radiation necrosis [41, 42]. It is feasible that a different set of thresholds for the four molecular markers, or the inclusion of other markers like miR-21 [43], predicts radiation necrosis compared to tumor progression. Furthermore, a different choice of patient controls could be useful in further evaluating the panel's specificity. Instead of forty-five healthy controls without a history of inflammation or autoimmune

disease, patients with non-glial brain tumors and/or other inflammatory conditions may serve as controls.

Further testing of the panel may include other potentially important molecules like IL-33. IL-33 has been shown to induce a pro-inflammatory environment within gliomas and inversely correlates with survival ^[44-46]. De Boeck *et al* also demonstrated IL-33 induced upregulation of inflammatory gene expression, including IL-6, and proposed that IL-33 secretion from glioma cells recruits monocytic cells from the circulation ^[47]. Thus, IL-33 may be more specific to glioma than Gandhi *et al*'s markers, and may also be sufficient alone as a marker. Differentiating the markers that distinguish high grade verse low grade gliomas early will be valuable and can be validated in preclinical studies.

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