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Serum biomarkers for glioblastoma multiforme

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Abstract

A number of different serum biomarkers are currently being evaluated for their potential use as diagnostic and prognostic biomarkers in Glioblastoma Multiforme. Amongst these, a vast number of different microRNAs have been studied, that are up-regulated or down-regulated in relation to Glioblastoma Multiforme. Different studies have found numerous associations of these different microRNAs with recurrence, Karnofsky Performance Score, Progression Free Survival and Overall Survival. Other than microRNAs, serum Glial Fibrillary Acid Protein, cytokines and YLK-40, as well as a number of other candidate serum biomarkers are being studied.More studies, with larger sample sizes are required before these serum biomarkers can be routinely, and reliably used in clinical practice. Use of serum biomarkers can provide a non-invasive means for diagnosing and monitoring disease.

Keywords: Glioblastoma multiforme, Serum biomarkers, microrna, GFAP, YLK-40.

Introduction

The diagnosis of brain tumours including Glioblastoma Multiforme (GBM), their progression, as well as recurrence are presently monitored through imaging modalities. The gold standard for diagnosis is histopathology, which is performed on a tissue sample acquired through invasive neurosurgery. A non-invasive method to diagnose and monitor disease progression can be the use of serum biomarkers, on the same lines as most systemic infections and even some malignancies (Prostate Specific Antigen for prostate). A multitude of molecules are currently being evaluated for potential use as serum biomarkers for diagnosis and disease progression of GBM, and even though some of these biomarkers have shown reasonable sensitivity and specificity, none of these are used routinely in clinical practice as yet. We present a review of the ongoing research on potential serum biomarkers for their use in screening and prognosis of GBM.

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Review of Evidence

MicroRNAs are small non coding RNA molecules. Several studies have looked at an array of different microRNAs (miRNA) and their potential use as biomarkers of GBM.[1-4] Lan et al.[1] reported, serum exosomal miR-301a to be significantly up-regulated in high grade gliomas. The authors also observed association of miR-301a with lower

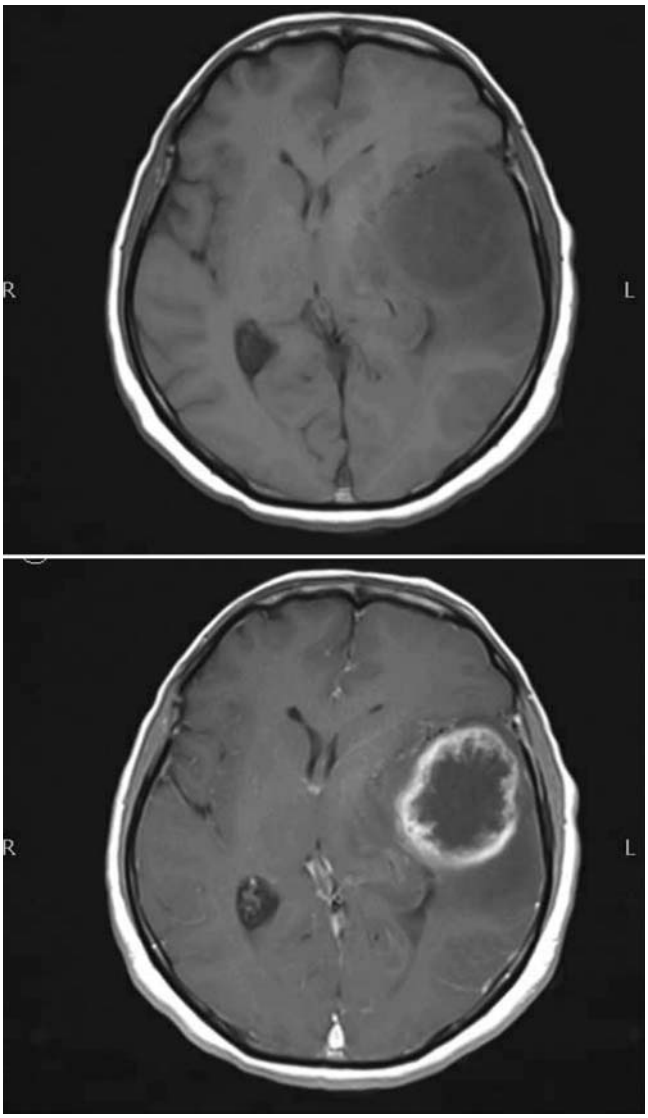

Figure (a & b): MRI axial sections T1WI plain and with contrast, showing typical features of a left temporal lobe glioblastoma multiforme.

Karnofsky Performance Score (KPS). Resection of the tumour resulted in decreased levels of miR-301a, whereas tumour recurrence resulted in increased levels.[1] Yue and colleagues, analyzed the expression of a different microRNA, miR205 and found serum levels of miR205 to be significantly lower in patients with GBM when compared with controls.[2] After tumour resection miR205 was increased, and it decreased with recurrence. Another significant correlation observed in this study was of low miR205 with increasing pathological grade, and lower KPS score. Longer Overall Survival (OS) was seen in patients with elevated serum miR205 compared to patients with lower levels of serum miR205.[2] MGMT methylation status has been linked with prognosis in GBM.[3] Wang et al.,[4] observed a correlation of elevated serum levels of miR-451a with positive MGMT expression. They also observed that low serum level of another microRNA, miR-485-3p, was associated with poor PFS and OS.[4] In a recent meta-analysis of 16 studies regarding different circulating miRNAs (from either serum or plasma) in glioma, it was suggested that circulating miRNAs can potentially be used as a means of early diagnosis. All the studies in this meta-analysis used qRT-PCR for detecting circulating miRNAs. Different miRNAs were observed to be either up-regulated or down-regulated in relation to GBM diagnosis, recurrence, and OS in all the studies included.[5]

Some other biomarkers that have been analyzed other than microRNAs include Glial Fibrillary Acid Protein (GFAP), YKL-40, cytokines and other serum proteins. Serum GFAP has been considered as a potential diagnostic biomarker for GBM, however it could not be established as a reliable indicator of tumour recurrence.[6-8] Nijaguna et al., in a study of 194 patients identified an 18 serum cytokine signature for GBM. Fifteen of these were increased and 3 were decreased in the serum of GBM patients. These cytokines were also analyzed from tumour samples and 13 of these showed similar regulation at transcript level in the GBM tissue.[9] Elstner et al., analyzed serum proteins and identified BMP2 (cell proliferation), CXCL10 (cell motility) and HSP70 (anti-apoptotic) as potential serum biomarkers for GBM diagnosis.[10] YKL 40 is an extracellular matrix glycoprotein that has also been studied as a serum biomarker of GBM. In several studies it has also shown potential as a prognostic biomarker.[11,12]

Conclusion

Several different serum biomarkers have shown promising results for diagnosing, predicting severity and recurrence as well as OS in GBM. However, before these biomarkers can be routinely used in clinical practice, studies with larger sample sizes, done in different populations of GBM patients would be required. As there is a multitude of serum biomarkers that all show some association with GBM prognosis, combining them in a panel or algorithm through more extensive translational research for clinical use would be pragmatic.

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