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LETTER TO THE EDITOR

The Diagnostic Dilemma of Epithelial Marker Expression in Glioblastoma

George Stoyanov[1,2] · Martina Kitanova[3] · Deyan Dzhenkov[3] · Peter Ghenev[3]

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To the Editor,

Glioblastoma Multiforme (GBM) is a hot topic for research as the intimacies of this type of malignancy seem to be a long way from being truly understood. Diagnostically however, despite decades of research and many attempts at standardizing the histopathological diagnostic process, GBM remains an entry to be diagnosed by experienced neuropathologists.

A key point in the pathological diagnostic process is the immunohistochemical (IHC) phenotypisation of tumor samples. While some glial specific IHC markers such as glial fibrillary acidic protein (GFAP) give a constant positive reaction, and are used as a diagnostic medium in GBM, there is a wide panel of IHC markers that give positive IHC reactions with GBM tissue samples. Some of these such as Vimentin are very unspecific and are mainly used as a positive control for IHC reactions, but can also be used in some instances to distinguish between epithelial and non-epithelial tumors.

Some IHC markers, such as cytokeratin (CK) AE1/AE3 and epithelial membrane antigen (EMA) are highly specific to epithelial cells, but can very often give positive IHC reaction with GBM tumor tissue, producing a diagnostic dilemma (Figs. 1 and 2) [1–5]. Terada (2015) reported positive IHC expression of several types of keratin antibodies, especially for the CK AE1/AE3 antibody, confirming the findings reported by other similar studies [1–3]. Terada also stated that this positivity is due to the production of keratin proteins from GBM cells, but this statement is not supported by anything more than IHC investigations [1].

However, IHC is not the most specific immunology based test and a phenotypically positive tissue sample on IHC may not truly express the antigens tested due to conformational mimicry between the antibody and a similar epitope in another antigen. Such is the case with keratins and perhaps also with other epithelial markers, such as EMA, in GBM [2–5].

Whilst many authors and practicing pathologists believe that IHC is a full proof testing method and that a high number of GBM cases express some type of keratin molecules, especially the epitheloid and giant-cell GBM subtypes. This is not entirely true, as demonstrated by Kriho et al. in 1997 in a comparative study of keratin expression in GBM [2]. She concluded that the AE3 fraction of the CK AE1/AE3 antibody cocktail is the one that reacts with an antigen in GBM cells, however in immunoblot and electrophoresis test a protein with the characteristics of keratin filaments was not detected [2]. Therefore, Kriho suggested that these IHC false positive results are caused by a three-dimensional conformational mimicry with another intermediate cytoskeletal protein such as the dysmorphic GFAP produced by the neoplastic astrocytes [2].

Although the result of Kriho et al. have not been recreated since, the specifics of a Western immunoblot test highly outweigh those of IHC and are used in explaining the GBM-CK AE1/AE3 phenomena by a number of authors [2–4]. Some

✉ George Stoyanov
georgi.geesh@gmail.com

[1] Department of Anatomy and Cell Biology, Faculty of Medicine, Medical University - Varna "Prof. Dr. Paraskev Stoyanov", Varna, Bulgaria

[2] Department of Physiology and Pathophysiology, Faculty of Medicine, Medical University - Varna "Prof. Dr. Paraskev Stoyanov", Varna, Bulgaria

[3] Department of General and Clinical Pathology, Forensic Medicine and Deontology, Faculty of Medicine, Medical University - Varna "Prof. Dr. Paraskev Stoyanov", Varna, Bulgaria

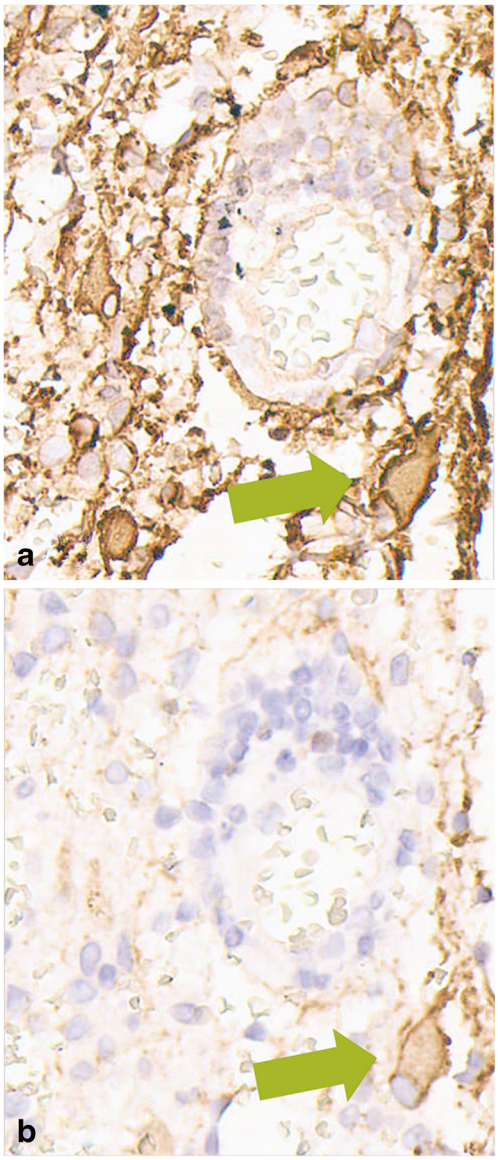

Fig. 1 GFAP (**a**) and CK AE1/AE3 (**b**) co-positivity in the same cell on consecutive IHC GBM slides (arrow). Original magnification 400×

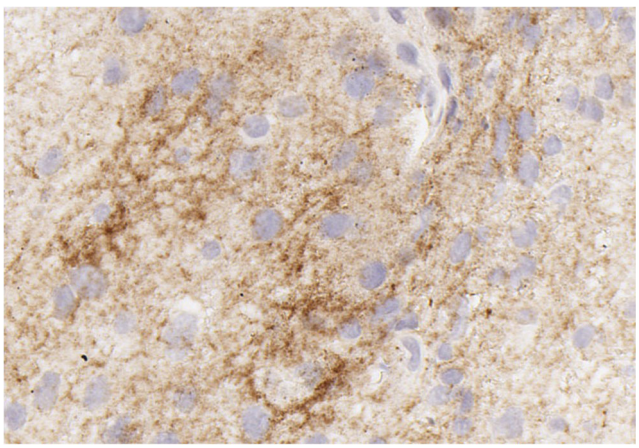

Fig. 2 EMA positive GBM. Original magnification 400×

authors such as Oh et al., who obtain similar IHC results and base a discussion and support Kriho's statements, without completely ruling out the possibility of some GBM actually producing keratin molecules, but stating it as highly unlikely based on the findings of IHC only [3].

Although not yet fully established and tested with means other than IHC, the positive reactions with EMA are another novel candidate for such false positive results, based again on the cellular specifics of the target antigen and the weak, mostly cytoplasmic IHC reaction with the EMA antibody, compared to the physiological membrane placement of EMA (Fig. 2) [5].

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