Urine 2-Hydroxyglutarate in Glioma

We congratulate Fathi et al. [1] for their effort to analyze the oncometabolite 2-hydroxyglutarate (2-HG). This is an interesting work evaluating 2-HG in serum, urine, and cerebrospinal fluid (CSF) from patients with isocitrate dehydrogenase (IDH) mutant and IDH wild-type (WT) glioma. The objective of this study was to use 2-HG as a surrogate biomarker for IDH mutation. Serum 2-HG was found to be a surrogate biomarker of IDH mutation status in other neoplastic diseases [2, 3].

Fathi et al. found that 2-HG levels in urine were significantly higher in mutated IDH patients, whereas the levels in serum and CSF were not significantly different. These results were in contrast with those of a similar study by Lombardi et al. [4]; indeed, these authors showed that 2-HG levels in urine were significantly lower in patients with mutated IDH. Therefore, we highlight some questionable characteristics regarding the Fathi et al. study.

Fathi et al. [1] analyzed 60 patients, of whom only 16 had IDH-WT and 44 harbored IDH-mutated glial tumors; thus, there is a large difference in patient number between the two groups, which may consequently have produced false results. Moreover, Fathi et al. analyzed patients with different types of IDH mutations. The presence of different IDH mutations could lead to a wide range of 2-HG concentrations. Indeed, serum 2-HG levels were significantly higher in patients with IDH1R132H mutant gliomas than in patients with other variants. On the contrary, in the Lombardi et al. study [4], all patients had the IDH1R132H mutation.

Another questionable characteristic is the time of sample collection; peripheral blood and urine samples were obtained at various stages of disease course (immediately postoperative, during temozolomide, etc.), and this can affect the average concentration of 2-HG; in fact, Fathi et al. found that urine 2-HG levels were higher in the group that received prior adjuvant treatment compared with no adjuvant therapy. On the contrary, Lombardi et al. excluded patients in whom chemotherapy had been performed within the previous 28 days from sample collection.

In both studies, serum 2-HG levels were not significantly different between patients with IDH mutant and WT gliomas. Thus, it appears difficult to understand why urine 2-HG levels may have been different between the two groups. In addition, the levels of urine 2-HG were found to be different between the two studies: Fathi et al. [1] found levels significantly higher among patients with IDH-mutant gliomas, whereas Lombardi et al. [4] showed higher values in patients with IDH WT. The reason for this discordance is not clear.

Because the intracellular accumulation of 2-HG results from a greater production of the D-enantiomer of 2-HG only and not of the L-isomer [5], it appears essential to analyze the D-enantiomer. However, neither of the two studies performed this analysis, although the two enantiomers could have different affinity with the transporters in the kidneys.

The use of urine 2-HG as a surrogate biomarker of IDH mutation status appears very interesting in patients with glioma, but it needs more accurate studies with well-defined inclusion and exclusion criteria and more homogenous patients. Analysis of D-enantiomer levels remains essential.

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Disclosures
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