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Oligoastrocytoma: Who's afraid of the ... *Liger?*

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Sir,

We thank Dr Bai and colleagues[1] for their comments concerning our paper regarding the diagnostic utility of ATRX/IDH1 immunohistochemisty in oligoastrocytomas[2].

We agree with the authors' attitude toward fostering the principle of *parsimony* (also known as Ockham's razor[3]) – whereby no unnecessary entities/labels should be posited whenever a phenomenon can be reduced to a set of less complex constituents. Nevertheless, we take issue with some of the shortcuts which we feel they engaged in along their line of reasoning.

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Foremost, it was neither our intention nor the actual message of our paper to – as Dr Bai and colleagues put it – "provide evidence for a biologic or genetic signature specific to [oligoastrocytoma]". Quite on the contrary, our study design was based on the explicit premise "that [oligoastrocytomas] actually should be considered as «morphologically ambiguous» rather than «mixed»".

A (hypothetical) analogy may help to clarify our point (Table 1). For the sake of argument, we assume that some individuals within the genus *Panthera* could not be classified unequivocally as either lion or tiger based on their morphological traits alone. Zoologists might have grown to apply the descriptive term *liger* to such ambiguous specimens. Furthermore, we assume there was a classical test that would react positive in almost all animals that looked like a typical tiger as well as in some *ligers*; conversely, it would react negative in almost all morphologically typical lions (and any other unrelated species). Subsequent research would have shown that almost all *ligers* are either lions or tigers biologically and that their true nature was closely correlated with the respective results of the above classical test.

This deliberately overdrawn paraphrase of our working paradigm may illustrate why, in our opinion, some of the statements by Dr Bai and colleagues' inadequately reflect the paper's content.

First, a purported caveat that *liger* – as counterpart of oligoastrocytoma – "frequently presents with heterogeneous morphology" is simply a tautology, because it was defined in the first place as not being clear cut. In terms of our thought experiment, if someone had demonstrated that animals classified as *ligers* had a higher chance of genetically being tigers if they *look more like* tigers, the objection that the "morphological score" adopted in that particular study "can be significantly biased by the interpretation preferences of three [*zoologists*] at a single institution and their tendency to agree with each other" would become moot. More generally, advice that "morphological scores should be based on the presence of certain […] features rather than the preferences of [*zoologists*] at a single institution" would miss the key point of the study, which rather than attempting to define a normative standard of practice, would have been to provide a proof of principle.

Second, we feel that one major argument in Dr Bai and colleagues' criticism of our approach is flawed semantically. "Subjectivity" – as used in the context by these authors – should not be equated to "arbitrariness". Some degree of subjectivity in pathological diagnosis is probably inevitable to compensate for the actual fuzziness of supposedly "objective" criteria. Lack of awareness of such dialectics is prone to end in diagnostically unproductive short circuits in the form of *misplaced concreteness*[4] – in the specific case of our subject matter: in mistaking diagnostic criteria of an entity for the entity itself. By such reasoning, an oligodendroglioma with neurocytic differentiation[5] (or a tiger without a tail) would not be recognized as oligodendroglioma (or tiger), because they deviated from previously established diagnostic criteria by a detail that has not been pre-specified.

The point we did try to make is: even in what is a morphological grey zone by definition, morphology is able to predict to some extent the underlying biological nature. In our perception, this emphasizes the value of careful morphological assessment (while we do acknowledge its limitations).

To make our analogy come full circle: in our thought experiment the question would not be if *liger* "should be a distinct entity", but rather if the term *liger* should be further applied to morphologically ambiguous animals. It might be considered perfectly acceptable to do so, as long as it were done on the understanding that almost all of these were biologically either lions or tigers, with *true ligers* (i.e., hybrids) being exceedingly rare.

Along the same line, one may well consider the term "oligoastrocytoma" acceptable, if it is implied to indicate a morphological grey zone in histopathological terms rather than a biologically distinct entity. Alternatively, one may prefer a non-committal terminology such as e.g. "diffuse glioma, IDH1-mutant, NOS, with morphological features intermediate between astrocytoma and oligodendroglioma, LOH testing pending".

This question, however, is one of terminology alone and independent of the scientific observation that true hybrid tumours are exceedingly rare.[6] Furthermore, we do not believe that any real-life diagnostic difficulties will be resolved just by eliminating the term "oligoastrocytoma".

Subject matter	IDH-mutant gliomas	Genus *Panthera*
Species #1	Oligodendroglioma	Tiger
Species #2	Astrocytoma	Lion
Traditional terminology for morphologically ambiguous cases	Oligoastrocytoma	(Hypothetical) Liger
Classical test	LOH 1p19q	Hypothetical classical test positive in tigers
Newer markers	IDH1/2, ATRX	Hypothetical newer markers
Possible non-committal terminology	Diffuse glioma, IDH1-mutant, NOS, with morphological features intermediate between astrocytoma and oligodendroglioma	Panthera, NOS, with morphological features intermediate between lion and tiger
Rare true hybrid	True oligoastrocytoma	True liger
Professionals	Pathologists	Zoologists

Table 1: Overview of the analogies used in the text to illustrate the conceptual difference between grey zone and hybrid.

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