Neurosurg Rev (2017) 40:357–358
DOI 10.1007/s10143-017-0818-z

LETTER TO THE EDITOR

Atypical pituitary adenomas: clinical characteristics and role of Ki-67 and p53 in prognostic and therapeutic evaluation. A series of 50 patients

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Received: 9 January 2017 / Accepted: 18 January 2017 / Published online: 22 January 2017

I would like to congratulate with Dr. Del Basso De Caro and colleagues for the interesting article [1] on the clinical characteristics and role of Ki-67 and p53 in prognostic and therapeutic evaluation of atypical pituitary adenomas (PA). According to the 2004 WHO classification [2], atypical PA are defined by an invasive growth, Ki-67/MIB-1 proliferative index greater than 3%, high p53 immunoreactivity, and increased mitotic activity.

A little bit less than 20 years ago, we reported our experience on more than 100 anterior PA analyzing their invasiveness in relation to their Ki-67 labeling index (LI), detected with the MIB-1 monoclonal antibody [3]: the overall mean Ki-67 LI was 2.64 ± 3.69% (median 1.5). Our data confirmed that Ki-67 LI can be considered a useful marker in the determination of the invasive behavior of anterior PA. In particular, the mean index was 3.08 ± 4.59% in functioning and 1.97 ± 1.78% in nonfunctioning tumors and 5.47 ± 9.52% in ACTH adenomas and 2.33 ± 2.42% in others ($p = 0.01$). It was 3.71 ± 5.17% in invasive and 2.01 ± 2.45% in noninvasive PA ($p = 0.027$), and 5.58 ± 7.24% in CS-infiltrating versus 2.10 ± 2.39% in CS-noninfiltrating adenomas ($p = 0.0005$). In order to identify a value of Ki-67 LI beyond which PA should be considered invasive and another one beyond which a CS infiltration should be suspected, normality Q-Q plots have been obtained: a threshold LI of 3.5% for invasive adenomas and of 5% for CS-infiltrating adenomas was defined, with statistically significant differences ($p = 0.02$ and $p = 0.004$, respectively).

Analyzing in detail the behavior of adrenocorticotropic hormone-secreting PA [4], our data showed that ACTH-secreting adenomas have a higher growth fraction than other PA, especially in older patients; presumably this observation can explain the higher incidence of relapse of these tumors also after macroscopically total removal. In particular, the mean Ki-67 LI was 5.88 ± 9.13% versus 2.33 ± 2.40% in non-ACTH PA ($p = 0.0025$). It was 13.27 ± 15.42% in invasive and 3.11 ± 4.37% in noninvasive ACTH adenomas, and 18.40 ± 17.82% in patients over 50 years versus 3.10 ± 4.09% in younger subjects ($p = 0.02$).

This last result was also analyzed in detail [5], and our results showed that PA in patients aged more than 65 years seem to be more often nonfunctioning, occuring frequently with visual disturbances. As regard the Ki-67 LI, older patients had a higher growth fraction than youngers: the overall mean index was 4.06 ± 6.73 versus 2.35 ± 2.54%, respectively ($p = 0.04$).

In another study [6], we observed that there was not a strict correlation between Ki-67 labeling index and volume of anterior PA. In detail, the mean Ki-67 LI was 2.59 ± 1.81 in microadenomas, 2.63 ± 3.45 in intrasellar macroadenomas, 1.91 ± 2.11 in intra-suprasellar macroadenomas, and 3.29 ± 5.45 in intra-supra-parasellar macroadenomas ($p = 0.27$). Once again, the index was 3.73 ± 5.13% in invasive and 2.03 ± 2.41% in noninvasive PA ($p = 0.02$), and 5.61 ± 7.19% in CS-infiltrating versus 2.09 ± 2.37% in CS-noninfiltrating ($p = 0.0005$).

In order to better understand the cellular growth rate and to correlate it with surgical evidences of invasiveness, we decided to perform the analysis of DNA with static cytometric quantitation on fresh surgical specimens, using a computer-assisted image processor [7]. The DNA index and the percentage of cells in S-phase (%SPh) were obtained in 61 patients. In relation to surgically verified infiltration of dura and bone, we identified 39 noninvasive and 22 invasive PA. The cavernous sinus (CS) was infiltrated in 13 cases. On the basis of immunohistochemical staining and of endocrine activity, we recognized 27 nonsecreting and 34 secreting adenomas. The DNA

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content was aneuploid in 33 cases (11 nonfunctioning, 22 functioning: $p = 0.05$), without correlation with invasive behavior of adenoma. The DNA index ranged between 0.93 and 2.50 (median 1.13); the range of %SPh was 0–12.00% (median 2.54%). In invasive adenomas, the mean DNA index was 1.33 (p not significant) and the mean %SPh was 4.03% ($p = 0.05$). In CS-infiltrating pituitary adenomas, the mean DNA index was 1.44 ($p = 0.04$) and the mean %SPh was 4.52% ($p = 0.05$). In relation to these preliminary results, it seems to exist a correlation between DNA index, %SPh, and invasive behavior of pituitary adenomas, encouraging the use of DNA analysis in the prognostic evaluation of these tumors.

In conclusion, we thank Dr. Del Basso De Caro and colleagues for their reappraisal of a very interesting and still actual topic and for the opportunity they gave to every scientist interested in PA biology and surgery to study them in detail.

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