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Letter to the Editor

Mitotic index, microvascular proliferation, and necrosis define 3 pathological subgroups of prognostic relevance among 1p/19q co-deleted anaplastic oligodendrogliomas

Keywords: anaplastic oligodendrogliomas, 1p/19q co-deletion, mitoses, microvascular proliferation, necrosis.

Anaplastic oligodendrogliomas (AOs) are diffuse infiltrative gliomas occurring mainly in adults and classified as grade III in the current World Health Organization (WHO) classification.[1] In 2008, a dedicated program was set up in France to homogenize the management of de novo adult AOs (POLA network–Prise en charge des Oligodendrogliomes Anaplasiques), with the aim, inter alia, to provide a centralized pathological review of the cases and centralized molecular analysis.

In a previous paper,[2] we reported the histomolecular features of a series of 203 AOs with classic histopathological features and showed that despite careful pathological criteria, 1p/19q co-deletion (which remains a major prognostic factor) was recorded in 80% of these tumors. Following the Haarlem meeting,[3] it was therefore decided to establish the entity "oligodendroglioma (and anaplastic oligodendroglioma) *IDH*-mutant and 1p/19q co-deleted" in the future WHO classification.

In our previous paper,[2] we classified 1p/19q co-deleted AO into 3 pathological subgroups: group 1 (>5 mitoses per 10-high-power fields [HPF] but no microvascular proliferation [MVP] and no necrosis), group 2 (MVP and no necrosis), and group 3 (MVP and necrosis). The threshold value for mitotic index was previously set up by Giannini and coworkers.[4] At the time of publication, the short clinical follow-up of the cohort did not allow drawing definitive and robust conclusions in terms of prognostic value of these 3 pathological subgroups. Here, thanks to patient monitoring conducted within the POLA network, we could narrow down our results.

Briefly, 157 *IDH*-mutated, 1p/19q co-deleted patients were included in the present study. 1p/19q co-deletion was assessed by genomic-array analysis and *IDH* status by $IDH1^{R132H}$ immunohistochemistry and by *IDH1* and *IDH2* direct sequencing for cases lacking $IDH1^{R132H}$ immunostaining. Clinical characteristics of this cohort, as well as postoperative treatment, have been described in our previous study.[2] The following variables were searched for prognostic significance: age at diagnosis, sex, extent of surgical resection (biopsy and partial resection vs total and subtotal resection), preoperative KPS, pathological subgroups, MVP, necrosis, number of mitoses, Ki67 labelling index, and postoperative treatment (radiotherapy only, chemotherapy only, adjuvant Procarbazine, CCNU, and Vincristine (PCV) radiochemotherapy, or temoradiation and adjuvant temozolomide). Age at diagnosis, and pathological subgroup were used to build the multivariate Cox proportional hazards backward models. All statistical tests were 2-sided, and the threshold for statistical significance was $P = .05$. Analyses were conducted using PASW Statistics version 17.02 (IBM SPSS Inc.).

Median follow-up was 48.7 months (range: 2.8–77 mo), but median overall survival (OS) and progression-free survival (PFS) were not reached. The 5-year OS and PFS rates were 82% (SE = 4.3%) and 42% (SE = 8.7%), respectively. Among the clinical variables analyzed with univariate analysis (Fig 1A), age at diagnosis >50 years was a negative prognostic factor ($P = .30$ for OS and $P = .031$ for PFS), and preoperative KPS ≥ 80 was predictive of a longer PFS ($P = .013$). Postoperative treatment was predictive of PFS ($P = .008$) but was not predictive of OS. The worst prognosis was observed for patients treated with adjuvant temozolomide radiochemotherapy, as previously described.[2] Pathological subgroups were predictive of OS ($P = .025$, Fig 1B) and PFS ($P = .025$, Fig 1C), with the better prognosis being observed in group 1 patients.

On multivariate analysis, pathological subgroups adjusted by age at diagnosis remained of prognostic significance regarding OS and PFS, with patients belonging to group 1 having a lower tendency to recur (PFS: $P = .014$, HR = 1.87; 95%CI[1.14–3.09]) and patients belonging to group 3 displaying the worst prognosis (OS: $P = .032$, HR = 2.46; 95%CI[1.08–5.61]).

In AO, postoperative treatment has been shown to be associated with survival, as recently demonstrated by 2 phase 3 clinical trials.[5,6] However, these 2 clinical trials have also shown that impact of treatments in this tumor group need a median follow-up > 60 months to draw reliable conclusions.[7,8] Indeed, the major finding that 1p/19q co-deleted AOs benefit from early chemotherapy (reported in the 2013 paper) contradicted the 2006 reports (a feature linked to follow-up that was two short in the early papers). Since the median follow-up in our series is even shorter (48.7 mo), it appears premature to analyze these data at this stage. However, our results emphasized the usefulness of mitotic index, MVP, and necrosis to predict prognosis of "anaplastic oligodendroglioma *IDH*-mutant and 1p/19q co-deleted." Whatever the occurrence of MVP or necrosis, AO remains grade III. This is in contrast with the criteria of grading used for astrocytomas.[1] In a previous study, we reported that the prognostic impact of necrosis in high-grade diffuse gliomas was radically different according to molecular

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	1p/19q co-deleted patients (N = 157)	
	OS	PFS
Age at diagnosis	0.030	0.031
Sex	0.647	0.548
Preoperative Karnofsky performance status	0.234	0.013
Extent of surgery	0.515	0.633
Postoperative treatment	0.147	0.008
Pathological subgroups	0.025	0.025
Microvascular proliferation	0.025	0.079
Necrosis	0.035	0.013
Number of mitoses	0.024	0.036
KI67 expression	0.002	0.079

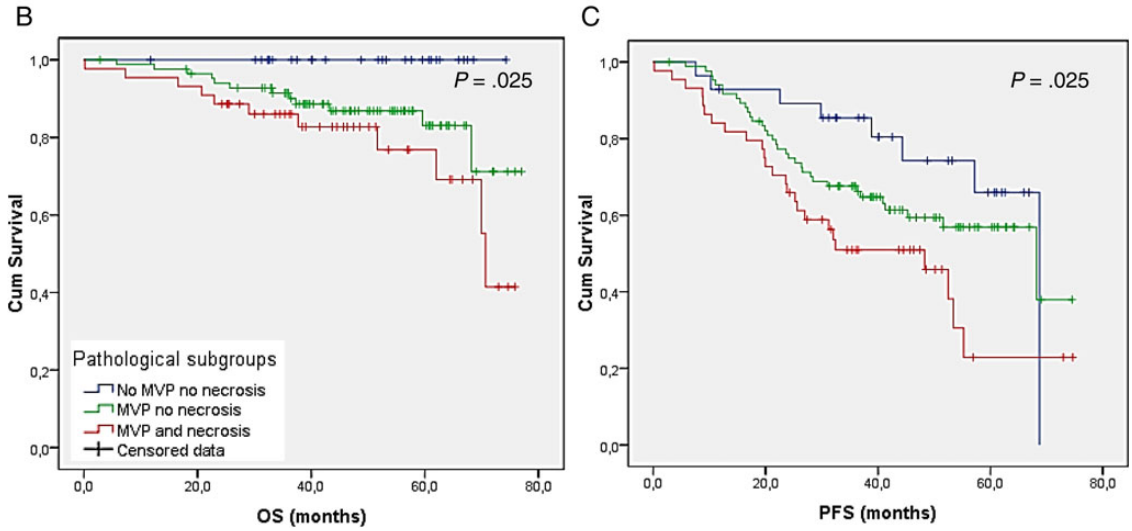

Fig. 1. Results of univariate analysis for the 157 1p/19q co-deleted AO. (**A**). The 3 pathological subgroups (group 1 (>5 mitoses per 10-HPF but no MVP and no necrosis), group 2 (MVP and no necrosis) and group 3 (MVP and necrosis)) are predictive of OS (**B**) and PFS (**C**). Abbreviations: AO, anaplastic oligodendroglioma; MVP, microvascular proliferation; OS, overall survival; PFS, progression-free survival.

subgroups,[9] with the best prognosis being observed in *IDH*-mutated 1p/19q co-deleted gliomas, the worst prognosis arising in *IDH*-wild-type gliomas, and *IDH*-mutated 1p/19q non–co-deleted gliomas being of intermediate prognosis. This favors keeping grade III for AOs even if they display necrosis. However, we learned from the present study that OS of patients with AO lacking MVP was excellent, although these tumors have a significant tendency to recur. This raises the question of assessing grade III in tumor samples showing strong mitotic activity but lacking MVP; to address this question, large cohorts of patients in randomized assays and long follow-up are mandatory.

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Dominique Figarella-Branger, Karima Mokhtari, Caroline Dehais, Catherine Carpentier, Carole Colin, Anne Jouvet, Emmanuelle Uro-Coste, Fabien Forest, Claude-Alain Maurage, Jean-Michel Vignaud, Marc Polivka, Emmanuèle Lechapt-Zalcman, Sandrine Eimer, Gabriel Viennet, Isabelle Quintin-Roué, Marie-Hélène Aubriot-Lorton, Marie-Danièle Diebold, Delphine Loussouarn, Catherine Lacroix, Valérie Rigau, Annie Laquerrière, Fanny Vandenbos, Sophie Michalak, Henri Sevestre, Michel Peoch, François Labrousse, Christo Christov, Jean-Louis Kemeny, Marie-Pierre Chenard, Danchristian Chiforeanu, François Ducray, Ahmed Idbaih, and Jean-Yves Delattre, POLA Network

APHM, Hôpital de la Timone, Service d'Anatomie Pathologique et de Neuropathologie, Marseille, France (D.F.B.); Aix-Marseille

Université, Inserm, CRO2 UMR_S 911, Marseille, France (D.F.B., C.C.); AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Service de Neuropathologie Raymond Escourolle, Paris, France (K.M.); Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, UPMCUniv Paris 06 UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, F-75013, Paris, France (K.M., C.D., C.C., A.I., J.-Y.D.); AP-HP, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, Service de Neurologie 2-Mazarin, F75013, Paris, France (K.M., C.D., C.C., A.I., J.-Y.D.); Centre de Pathologie et de Neuropathologie Est, Bron, France (A.J.); CHU Toulouse, Hôpital Rangueil, Service d'Anatomie Pathologique et Histologie-Cytologie, Toulouse, France (E.U.-C.); Inserm U1037, Centre de Recherche en Cancérologie de Toulouse, Université de Toulouse, France (E.U.-C.); CHU Saint-Etienne, Hôpital Nord, Service d'Anatomie et Cytologie Pathologiques, Saint-Etienne, France (F.F., M.P.); CHU Lille, Pôle Pathologie Biologique, Service Anatomie Pathologique, Lille, France (C.-A.M.); CHU Nancy, Hôpital Central, Laboratoire d'Anatomie Pathologique, Nancy, France (J.-M.V.); APHP, Hôpital Lariboisière, Service d'Anatomie et Cytologie Pathologique, Paris, France (M.P.); CHU Caen, Hôpital de la Côte de Nacre, Service d'anatomie Pathologique, Caen, France (E.L.-Z.); CNRS, UMR 6301 ISTCT, CERVOxy, GIP CYCERON, Caen, France (E.L.-Z.); CHU Bordeaux, Hôpital Pellegrin, Service de Pathologie – Neuropathologie, Bordeaux, France (S.E.); EA2406, Histologie et pathologie moléculaire des tumeurs, Université Bordeaux Segalen, Bordeaux, France (S.E.); CHU Besançon, Hôpital Jean Minjoz, Service Anatomie et Cytologie Pathologiques, Besançon, France (G.V.); CHU Brest, Hôpital de la Cavale Blanche, Service Anatomie Pathologique, Brest, France (I.Q.-R.); CHU Dijon, Plateau technique de biologie G. Mack, Service Anatomie et Cytologie Pathologiques, Dijon, France (M.-H.A.-L); CHU Reims, Hôpital Robert Debré, Laboratoire d'Anatomie et Cytologie Pathologiques, Reims, France (M.-D.D.); CHU Nantes, Hôpital Laennec, Service d'Anatomie Pathologique B, Nantes, France (D.L.); AP-HP, Hôpital Bicêtre, Service Anatomie et Cytologie Pathologiques, Kremlin-Bicêtre, France (C.L.); CHU Montpellier, Hôpital Gui de Chaulliac, Laboratoire d'Anatomie et Cytologie Pathologiques, Montpellier, France (V.R.); CHU Rouen, Hôpital Charles Nicolle, Laboratoire de Pathologie, Rouen, France (A.L.); CHU Nice, Hôpital Pasteur, Laboratoire d'Anatomie et Cytologie Pathologiques, Nice, France (F.V.); CHU Angers, Département Pathologie Cellulaire et Tissulaire, Angers, France (S.M.); CHU Amiens, Hôpital Nord, Service d'Anatomie et Cytologie Pathologiques, Amiens, France (H.S.); CHU Limoges, Hôpital Dupuytren, Service Anatomie Pathologique, Limoges, France (F.L.); AP-HP, Hôpital Henri Mondor, Service histologie-Embryologie, Creteil, France (C.C.); CHU Clermont-Ferrand, Hôpital Gabriel Montpied, Service d'Anatomie et Cytologie Pathologiques, Clermont-Ferrand, France (J.-L.K.); CHU Strasbourg, Hôpital Hautepierre, Service d'Anatomie Pathologique, Strasbourg, France (M.-P.C.); CHU Rennes, Hôpital Pontchaillou, Service d'Anatomie et Cytologie Pathologiques, Rennes, France (D.C.); Hospices Civils de Lyon, Hôpital Pierre Wertheimer, Service de Neuro-oncologie, Bron, France (F.D.); Department of Cancer Cell Plasticity, Cancer Research Centre of Lyon, INSERM U1052, CNRS UMR5286, Lyon, France (F.D.)

Corresponding Author: Dominique Figarella-Branger, MD, PhD, Aix-Marseille Université, Inserm, CRO2 UMR_S 911, Marseille, France (dominique.figarella-branger@univ-amu.fr).

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