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The Brain Adjacent to Tumor (BAT)

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1. Introduction

Gliomas represent the classical intra-axial tumors of the brain and glioblastoma multiforme (GBM) is the most frequent and malignant glioma. It is an extremely aggressive tumor with a high invasive potential. After treatments, it invariably resumes proliferation and its recurrences occur most often within 2 cm from the resection margins (Hochberg & Pruitt, 1980; Wallner et al., 1989; Oppitz et al., 1999). The dispersion of glioma cells in the surrounding normal brain puts them out of reach of surgery, radio- and chemotherapy, because outside of the limits of surgical resection and of the irradiated volume, established in order to avoid damages to the normal brain. The BAT, therefore, is the place where tumor cells migrate and invade and where a series of biological, pathological and molecular events occur as far as the interaction between host and tumor is concerned. Migrating cells from the tumor, reacting astroglia and microglial cells, elements of the immunological response or belonging to the monocytic phagocyting system reaching the tumor from the blood flow, and cells from gliogenetic zones of the brain make the BAT a melting pot of interactions among cells and factors. It has special importance also from the neuroimaging point of view for the recognition of the tumor limits and of peritumoral edema, which may have, at the same time, a prognostic significance (Ramakrishna et al., 2010). With MRI, beside the peripheral increase of T2 signal, uptake of gadolinium, hypodensities corresponding to vasogenic edema, necrotic cyst formation, other features can be shown by special technical procedures. The correlation, therefore, between neuroimaging and histopathology and molecular biology in the BAT is of the greatest interest.

2. Cell migration and invasion

The process of tumor cell invasion of the brain recognizes some fundamental steps (Nakada et al., 2007): cell detachment from the tumor mass; their attachment to the degraded extra-cellular matrix (ECM) and cell migration. Each of these steps is regulated by a series of molecular events with different gene expression profiles associated with motility, cytoskeleton modifications, transduction molecules, surface receptors and components of ECM (Table 1).

How GBM acquires an invasive phenotype is still discussed. It is known that carcinoma invasion is driven by an "epithelial to mesenchymal transition" (EMT) (Kalluri & Weinberg, 2009), which is activated by the helix-loop-helix protein TWIST1. Recently, a mesenchymal change in GBM has been recognized (Phillips et al., 2006; Tso et al., 2006; Carro et al., 2010),

associated with a more aggressive phenotype. TWIST1 is up-regulated in GBM cell lines *in vitro* (Elias et al., 2005) and it promotes cell invasion through mesenchymal molecular and cellular changes which can be demonstrated by Affymetrix gene expression array. It mediates cell-cell adhesion, the interaction with the substrate, migration and cytoskeleton modifications, activating specific gene expression profiles of invasion and without involving the cadherin switch (Mikheeva et al., 2010). In the rim of GBM, there is an increase of the Na^+/H^+ exchanger regulatory factor1 (NHERF-1), which sustains glioma invasion and migration and, if inhibited, migration ceases and apoptosis increases and cells become more sensitive to Temozolomide (Kislin et al., 2009). Genes for matrix degrading are up-regulated both *in vivo* and *in vitro* in cells with ΔEGFR (Lal et al., 2002). Also Neuropilin-1, a receptor for semaphorin3A, is required for GBM cell migration. GBM cells secrete Sema3A endogenously, and RNA interference mediated down-regulation of Sema3A inhibits migration and alters cell morphology that is dependent on Rac1 activity. Sema3A depletion also reduces cell dispersal, which is recovered by supplying Sema3A exogenously (Bagci et al., 2009). Migrating glioma cells show a downregulation of the major histocompatibility complex (MHC) (Zagzag et al., 2005).

Detachment from the original site	CD44, NCAM,α- and β-Catenin, F-Actin, N-Cadherin, Hyaluronic acid
Attachment to ECM	Tenascin-C, Integrins, FAK, ILK
Degradation of ECM	ADAM, MMP, uPA, β-Cathepsin
Migration	EGF - EGFR, c-met - HGF

Table 1. Invasion phases with some relevant molecular steps.

Motility of glioma cells has been demonstrated both *in vivo* and *in vitro* (Pilkington, 1994); it increases with malignancy (Chicoine & Silbergeld, 1995) and it is at the basis of glioma spreading. The growth of gliomas is generally attributed to cell proliferation which conditions invasiveness, but not enough attention has been paid to cell motility.

2.1 Mechanisms of migration and invasion

GBM cells have been demonstrated to migrate individually with a mesenchymal mode of motility (Friedl & Wolf, 2003; Caspani et al., 2006; Beadle et al., 2008): a polarized extension of leading edge membrane processes in the direction of migration takes place. A complex interaction with the environment is realized, as it will be said below, with the creation of a track by the leader cell, followed by other cells. The cells travel mainly along white matter tracts and blood vessels (Zhong et al., 2010). Neoplastic glial cell motility is dependent upon dynamic remodeling of the actin cytoskeleton and vimentin characterizes developing and poorly differentiated glial cells, as nestin is typical of developing neuroectodermal cells. Cytoskeleton remodeling implies redistribution of many components, polarization and extension of active membrane processes with lamellipodia and filipodia (Lefranc et al., 2005). Co-expression of nestin and vimentin serves as a marker of enhanced motility and invasion in gliomas and GFAP has the opposite meaning (Bolteus et al., 2001). The ECM components, i. e. laminin, fibronectin, collagen IV, Tenascin-C and vitronectin interact with invading glioma cells as permissive substrates (Tysnes & Mahesparan, 2001) and many of them are upregulated in high-grade gliomas (Gladson, 1999). On the subject, different experimental tumor models are available.

CD44, a transmembrane glycoprotein functioning as an adhesion molecule, plays a role in cell detachment from the tumor mass. It is the principal receptor of hyaluronan and inhibits adhesion of glioma cells to fibronectin, laminin, vitronectin and collagen I. It is present in glioblastomas (Fig. 1) and shows numerous isoforms derived from alternative splicing the functions of which are still unclear. Cleaved by ADAM (a disintegrin and a metalloproteinase) it promotes cell migration, but if it is blocked invasion is reduced (Bolteus et al., 2001). In the same fraction of the process, neural cell adhesion molecules (NCAM) can act as a paracrine inhibitor of glioma cell locomotion, whereas other molecules such as cadherins that are calcium-dependent transmembrane cell adhesion glycoproteins mediating cell-cell β-adhesion, play a role as well (Perego et al., 2002).

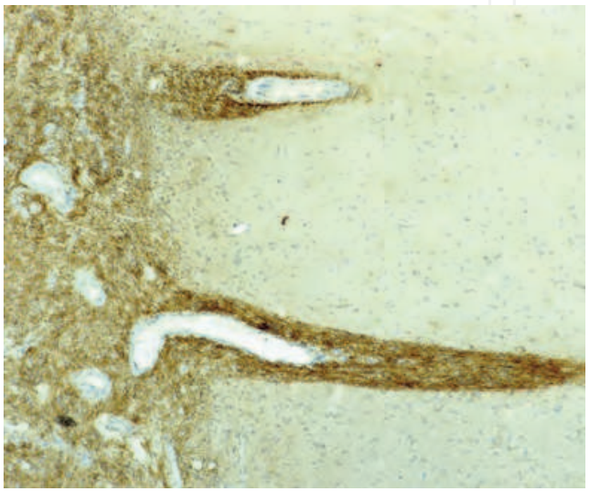

Fig. 1. CD44 positive invading cells, DAB, x100.

ECM proteins have a great importance in cell migration and ECM can be remodeled by glioma cells which produce their own matrix. Tenascin-C is highly concentrated around hyperplastic vessels in gliomas (Zagzag et al., 1995) and enhances migration of endothelial cells and phosphorylation of the focal adhesion kinase (FAK) that interacts with integrin-β1 mediating tenascin C signaling (Plopper et al., 1995). It is over-expressed in invasive gliomas (Mariani et al., 2001). The interest for tenascin recently increased, because specific anti-tenascin antibodies labeled with I^{131} have been used for therapy (Bigner et al., 1995; Goetz et al., 2003).

The proteins of the matrix must be disrupted by proteases or protease-activators such as the zinc-dependent enzymes metalloproteinases (MMPs), classified as collagenases, gelatinases and stromelysin and secreted as proenzymes, which are in balance with their inhibitors or tissue inhibitors of metalloproteinases (TIMPs). Several studies demonstrated the expression of these genes in brain tumors (Pagenstecher et al., 2001) and MMPs have been shown to potentiate tumor cells to migrate along white matter tracts (Belien et al., 1999) or activating other growth factors (McCawley & Matrisian, 2001a, 2001b) and to support gliomas to develop angiogenesis (Forsyth et al., 1999). GBM cell invasiveness and MMP2 expression are suppressed *in vitro* by PAX6 (Mayes et al., 2006). ADAM family has similar effects (Yong et al., 2001; Bauvois, 2004) and it seems to play a role in tumor invasion (Wildeboer et al., 2006).

Urokinase-type plasminogen activator (uPA) binds to its receptor converting plasminogen to plasmin that degrades fibrin, laminin, fibronectin amd proteoglycan. Among cysteine

proteinases, cathepsin B must be reminded. Cell adhesion to ECM is favored by integrins, composed by transmembrane glycoprotein units of which β1 is the critical one. Integrins variously occur on glioma cells both in cell lines and biopsies and can be considered as the rungs of a ladder on which cells attach (Tysnes & Mahesparan, 2001). Upregulation of many integrins has been found in glioma cells, compared with normal brain and astrocytes, with α3β1, αvβ1, αvβ3 and αvβ5 playing major roles in migration of tumor astrocytes (Rutka et al., 1999). The *avβ*3 complex can recognize several ligands, such as laminin, fibronectin, vitronectin and Tenascin-C and it can play a role in the angiogenesis activating VEGFR-2. A particular importance has been recently given to lectins, which are carbohydrate-binding proteins, and in particular to selectins and galectins (Lefranc et al., 2005).

Cell migration and invasion are regulated by many factors, first of all EGFR. *In vitro*, cells with strong expression of EGFR are more stimulated to migrate than those with lower expression (Tysnes et al., 1997). Cells with highly amplified EGFR are found at the invading edge of the tumor rather than at the solid tumor centres (Okada et al., 2003), Another very important factor in the regulation of tumor glial cell motility is PTEN: its phosphatase–independent domains reduce the invasive potential of glioma cells, distinctly of the PKB/Akt pathway (Maier et al., 1999). PTEN/Akt/PI3-K/mTOR pathway regulates also the switch between migration and apoptosis and in this context the role played by NF*k*B must not be forgotten. There is a complicated integrin-mediated signaling to which kinases such as FAK and ILK belong. FAK seems to be necessary for integrin-mediated motility (Sieg et al., 2000) and it is in the focus of a very complicated circuit (Günther et al., 2003). Integrins play also a role in cell growth and proliferation. Other factors involved in controlling cell motility are the scatter factor/hepatocyte growth factor (SF/HGF) (Lamszus et al., 1999) and TGF-β1 (Merzak et al., 1995). The regulation of the entire process of cell invasion is really not so simple (Demuth & Berens, 2004) and integrin receptors and focal adhesions, the FAK/Src signaling, the actin function and GTPase in mesenchymal migration have been the most studied steps (Zhong et al., 2010).

A series of novel molecules have been proposed influencing glioma invasion (Nakada et al., 2007). Among extracellular secreted proteins there are: IGFBP (insulin-like-growth-factor-binding protein), Cyr61 (cystein-rich 61/connective tissue growth factor), angiopoietin 2, YKI40, Autotaxin. Among membrane-type proteins Fn14/TWEAK, member of TNF super-family, EphB2/ephrin-B3, of the receptor protein tyrosine kinases, CD155, member of the immunoglobulin family of cell adhesion molecules, have been listed together with intracellular proteins (Nakada et al., 2007)

New synthetic low-molecular weight inhibitors are unceasingly investigated against specific molecular targets of glioma invasion, but one aspect of the process must be kept in mind. There is an inverse correlation between cell motility and cell proliferation (Dalrymple et al., 1994; Giese et al., 1996; Schiffer et al., 1997; Mariani et al., 2001). If migrating cells lower their proliferation rate, they become resistant to treatments and decrease their ability to undergo apoptosis, maybe through activation of PI3/Akt pathway (Joy et al., 2003). From the therapeutic point of view it is important that glioma invasion and angiogenesis share common mechanisms (Lakka et al., 2005).

3. Pathological findings

The study of glioma diffusion is very important from the diagnostic and therapeutic point of view and biomathematical models have been recently developed for a better understanding

(Swanson et al., 2003). It has been calculated that the velocity of tumor expansion is linear with time and varies from about 4 mm/year for low-grade gliomas to 3 mm /month for high grade gliomas. In tumor spheroids, tumor cells diffuse experimentally in the three dimensions following a mathematical model (Stein et al., 2007). Other models are useful in assessing different biological properties of GBM (Eikenberry et al., 2009).

After surgical resection of GBM, recurrence originates from residual invasive cells that in 96% of patients arise from the resection margin, 2-3 cm from the resection cavity (Burger et al., 1983), close to highly cellular tumor (Giese et al., 2003). It has been shown that patients with absence of tumor cells in the adjacent normal nervous tissue had better survival than those with tumor cells (Mangiola et al., 2008). A complete study has been carried out on residual tissue after removal of the tumor and it has been demonstrated that residual cells are distinct from the cells found in routinely resected GBM tissue. They vary in content of stem/progenitor cells, proliferative and invasive capacity, marker and molecular target profiles, and sensitivity to *in vitro* drug and irradiation challenges. Thus, one may speculate that residual cells represent distinct, malignant GBM subentities (Glas et al., 2010).

It is long debated whether infiltrated tissue can be recognized by MRI, not only when adjacent to tumor, but also at a distance. It has been observed that low grade gliomas, which locate preferentially in the insula and the supplementary motor area, spread along distinct sub-cortical fasciculi (Mandonnet et al., 2006). Analyzing different peri-tumor areas with different MRI methods, it has been shown that fractional anisotropy and not apparent diffusion coefficient can be used for evaluating glioma cell invasion. An attempt to classify different peritumoral tissues by a voxel-wise analytical solution using serial diffusion MRI has been made (Ellingson et al., 2011).

Neuropathology is long since discussing infiltrating and invading cells in the BAT and also at a distance from the tumor (Schiffer, 2006). The main problem is how to recognize them, being nuclear anomalies often not sufficient signs. Today, Nestin expression (Kitai et al., 2010) and mainly IDH1-2 mutations (Capper et al., 2010) are convincingly useful in this matter. Critical contributions during the last decades outlined how gliomas spread in the brain and a systematic study has been carried out in one hundred autopsy cases of glioblastomas and astrocytomas (Table 2) (Schiffer, 1986). The knowledge of the spreading modalities of gliomas is particularly useful when a tumor type must be recognized in small surgical samples by its spreading modalities, when these are the only tumor signs present in the sample. Even more difficult is to assess whether a tissue sample contains or not glioma cells.

Gliomas may spread in the homolateral hemisphere and/or to the contralateral hemisphere, mainly along the long axis of short and long fibre bundles. Typical is the diffusion to the contralateral hemisphere through corpus callosum and lamina terminalis. Fibre bundles may also represent an obstacle to diffusion, when they are reached by tumor cells along their short axis. Each tumor location has preferential pathways: fronto-parietal tumors may spare the temporal lobe and the opposite occurs with occipital tumors. Temporal tumors may spread toward hypothalamus and low midline structures or the temporal stem. Interestingly, glioblastomas with evident astrocytic areas, very likely remnants of a previous astrocytoma, spread more frequently to the same hemisphere, whereas glioblastomas, very likely of primary origin, spread through corpus callosum. The Table 2 shows the spreading modalities of a series of glioblastomas.

Anatomical structures	%	Tumor type
Homolateral diffusion	44	1 > 3 > 2
Contralateral diffusion	56	3 > 2 > 1
Sub-arachnoidal diffusion	25	2 > 3 > 1
Sub-pial diffusion	9	2 > 1 > 3
Corpus callosum	35	3 > 2 > 1
Septum pellucidum – fornix	18	3 > 2 > 1
Infiltration > 2 cm from tumor edge	22	2 > 3 > 1
Seeding on ventricular walls	6	3 > 2
Multicentric growth	8	2 > 3 > 1
Necrotic tumor with no regrowth	10	1 0 0

Table 2. Spreading modalities of glioblastoma. 1 = tumors with evident astrocytic character; 2 = tumors with diffuse anaplastic aspect; 3 = tumors with a mixed character.

The cerebral cortex may be invaded from tumors located in the white matter, either with or without a perineuronal satellitosis, or from the sub-pial infiltration of a tumor that has invaded from the opposite gyrus, or from cells coming down from sub-arachnoidal seedings along penetrating vessels. Basal ganglia are invaded by local tumors that invade also corpus callosum, or by adjacent tumors. Frequently they reach the temporal stem or the hypothalamus. Septum pellucidum is often passed through by tumor cells which establish a traffic between hypothalamus and basal cortical structures and corpus callosum.
Sub-arachnoidal seeding is frequent (Nishio et al., 1982; Rosenblum, 1995), sometimes as small clusters of tumor cells, visible at naked eyes. Anterior basal, posterior cerebellar and lateral cisterns are involved and even sagittal scissura can be involved when the gyrus cynguli is invaded. When tumor cells invade the underlying cortex, this shows a remarkably intense gliosis. Also spreading in the ventricular system is frequent: tumor cells collect on the ventricular surface and adhere to it where ependymal cells are lacking on an area of pilocytic gliosis.

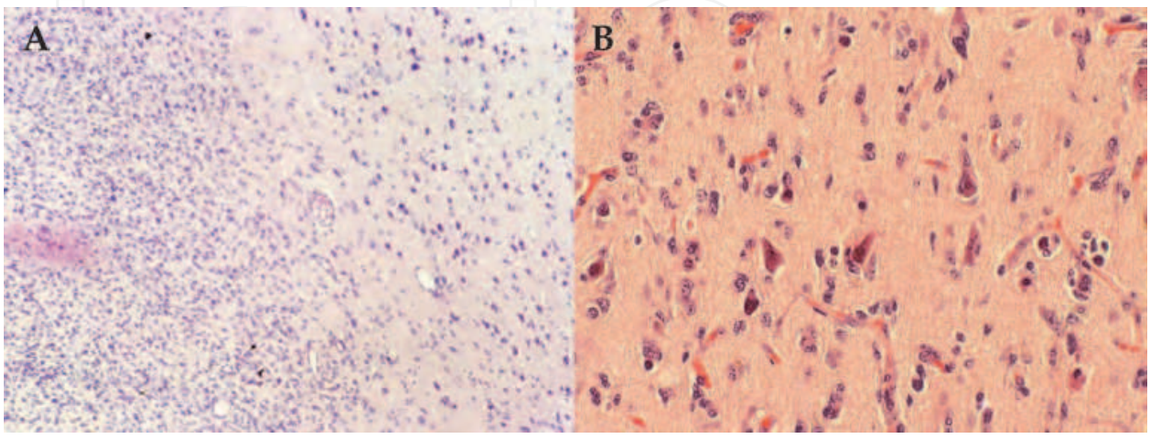

Fig. 2. A - Sharp edge toward normal brain, H&E, x 100; B - Infiltrated cortex with dying neurons, H&E, x 200.

The most important aspect of tumor spreading is the existence of a gradient of tumor cell density towards normal tissue and it could be really interesting to know how far from the tumor edge neoplastic cells can be found and recognized (Fig. 4A, B, C). This datum could be of paramount importance either during intervention, in the attempt of not leaving behind tumor cells, or for establishing post-surgical irradiation modalities: classically a 2 cm distance from the tumor edge is considered a limit of safety (Burger et al., 1988). Sometimes, an infiltrated cortex represents the whole sample removed at the intervention or the sample does not contain the typical signs of the maximum grade of malignancy: necroses, vascular proliferations or high cell proliferation. In these cases, one should be based on the knowledge of what kind of relationships exist among the different tumor features. For example, between cell invasion and cell proliferation. There are *in vitro* evidences suggesting that the two events may be antithetic (Pilkington, 1992; Merzak et al., 1995) and examples of infiltrating, but non-proliferating tumor cells are known (Dalrymple et al., 1994; Schiffer, 1997).

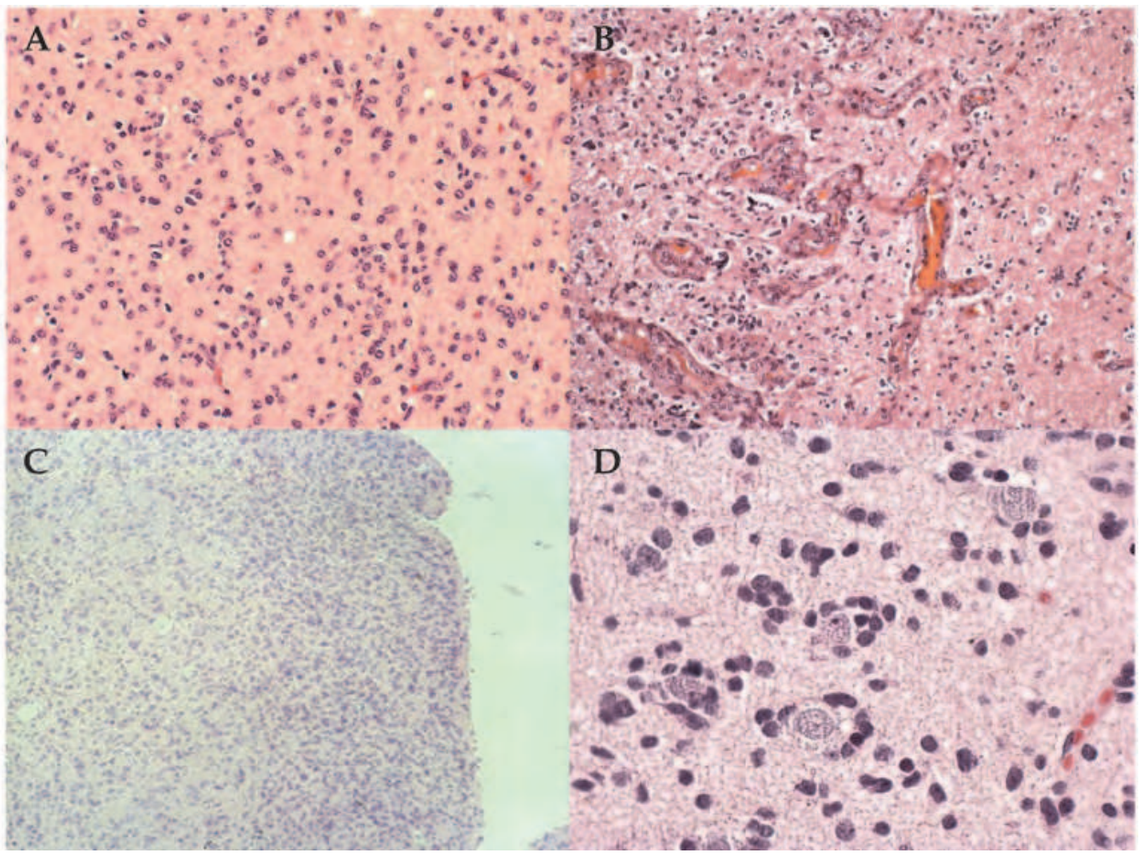

Fig. 3. A – Deeply infiltrated cortex, H&E, x 200; B - Neoformed vessels at the tumor edge, H&E, x 100; C – Invading cells accumulated in the molecular layer, H&E, x 100; D - Perineuronal satellitosis, H&E, x 200.

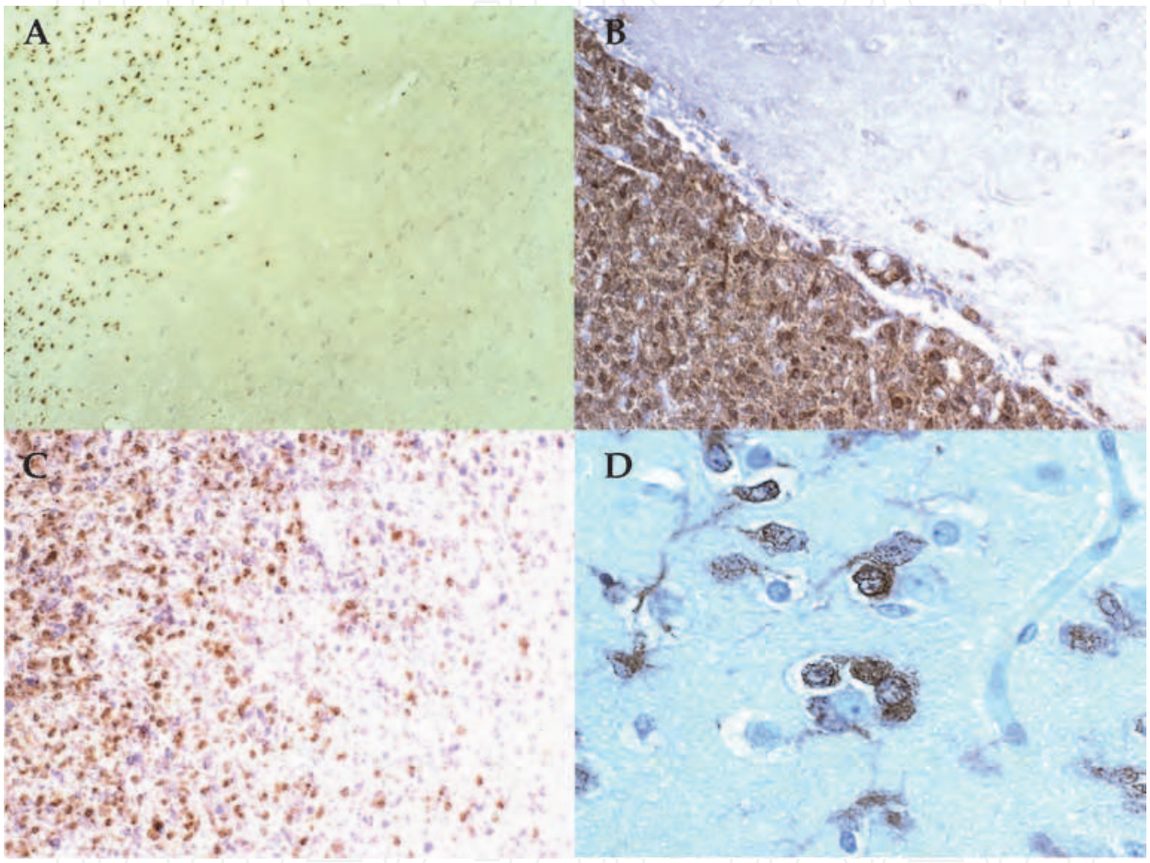

Fig. 4. A - The proliferation ceases at the sharp tumor edge, Ki.67/MIB.1, x 100; B - Sharp tumor edge, IDH1^{R132H} mutation, x 200; C – Gradient of proliferating cells, Ki.67/MIB.1, x 100; D - Positive perineuronal satellites, IDH1^{R132H} mutation, x 400.

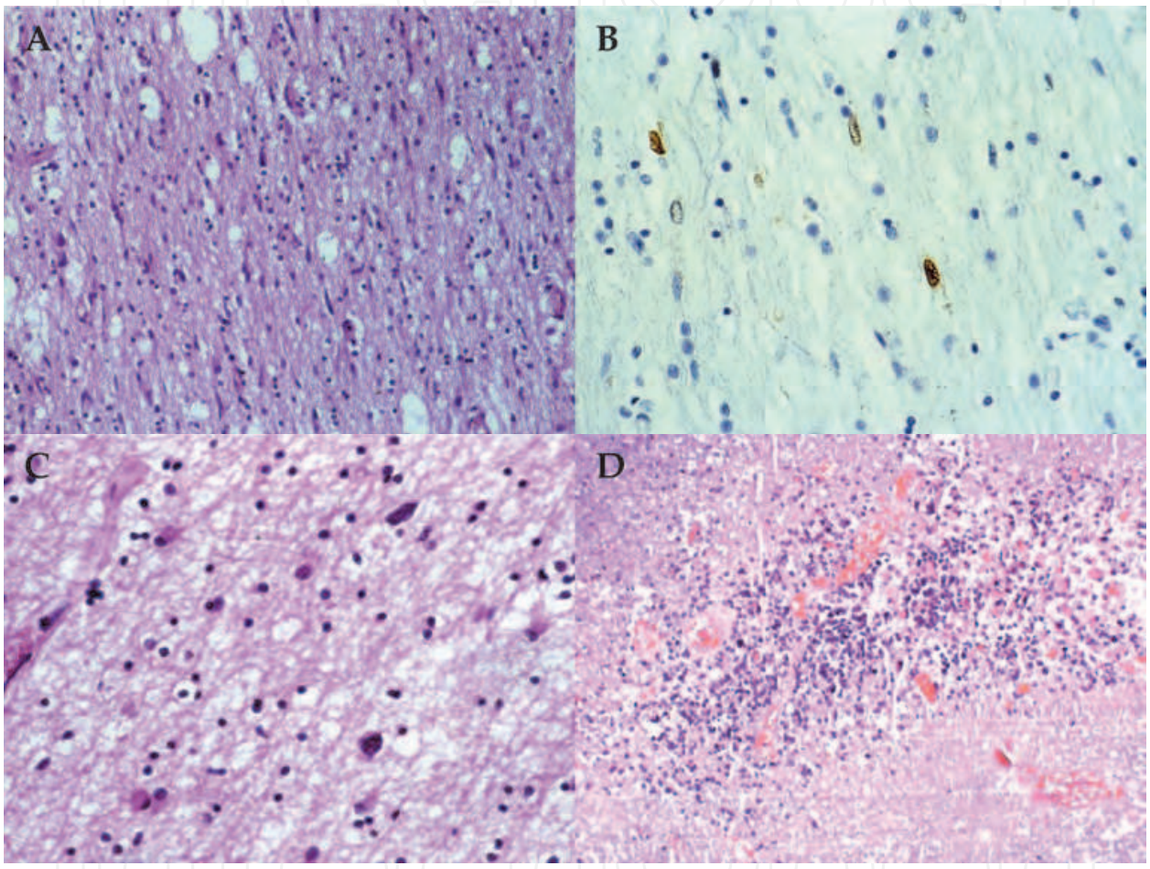

Fig. 5. A - Infiltrated white matter, H&E, x 200; B - PCNA-positive nuclei in the corpus callosum, H&E, x 200; C - Deformed nuclei in the BAT, H&E, x 200; D – Island of viable tumor cells in a radionecrosis, H&E, x 100.

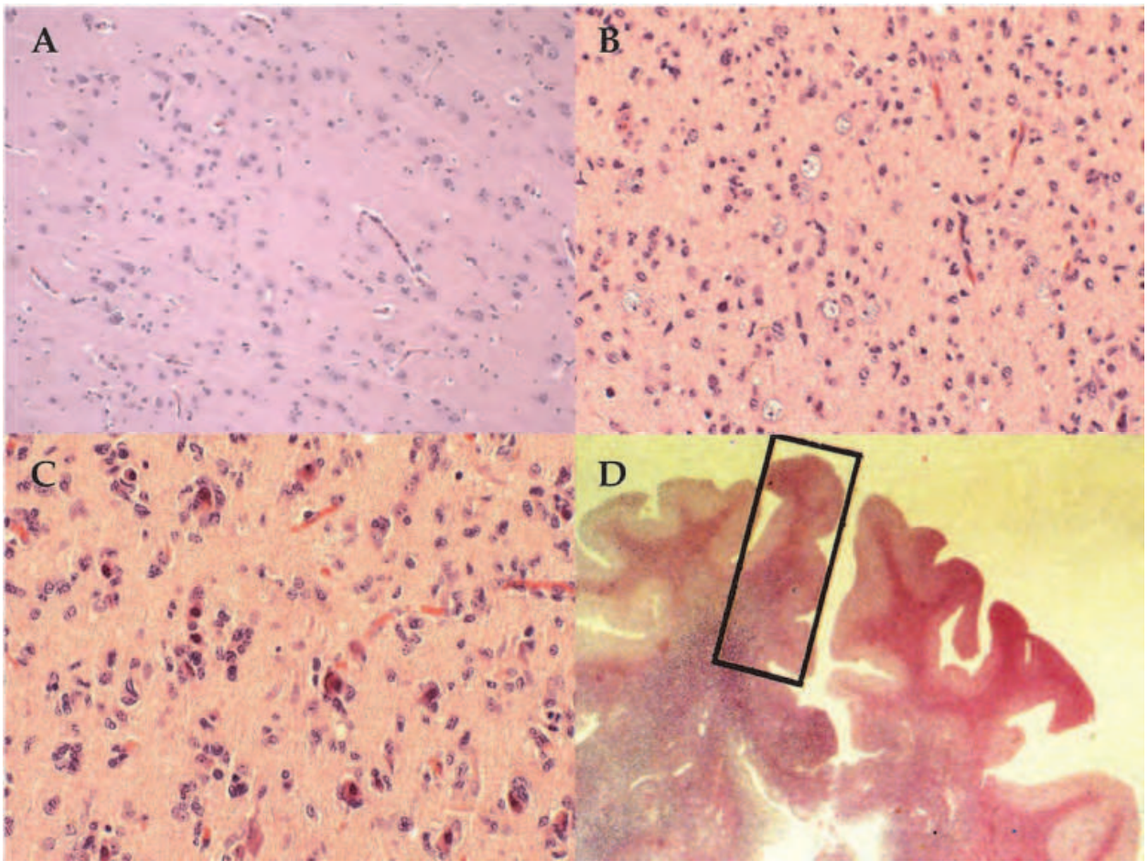

Fig. 6. A - Normal cortex, H&E, x 100; B - Invaded cortex, H&E, x 200; C – id. with sclerotic neurons, H&E, x 200; D – Gradient of tumor cells in a gyrus, H&E.

1.	Normal white matter	96±10
2.	Tumor peripheral area	213±36
3.	Infiltrated area	171±13
4.	Apparently normal area	148±8
5.	Edematous infiltrated area	55±8

Table 3. Cell Count in the gradient of Fig. 6D (mean number of nuclei per μm^2).

Between the solid tumor and the cortex there is a cell density gradient (Fig. 2A, 2B, 3A) more frequently than between solid tumor and the white matter where the border is usually sharp. There is also a gradient for mitoses and nuclei stained for proliferation markers, such as Ki.67/MIB.1 (Fig. 4A). Sharp borders (Fig. 4B) and cell gradient are, therefore, antithetic. It frequently happens to recognize in completely normal long fibre bundles tumor cells by Ki.67/MIB.1 or PCNA or IDH1-2 mutations (Fig. 5A, 5B). Perineuronal satellitosis is another invasion modality (Fig. 3D, 4D).

The occurrence of isolated tumor cells can be ascertained by these methods (Burger et al., 1986; Schiffer et al., 1997), or by stereotactic procedures (Kelly et al., 1987) or by systematic topographic studies (Burger et al., 1988; Burger & Kleihues, 1989). Tumor cell occurrence in

the final part of the cell gradient, where it is more difficult to recognize them, can also be deduced from cell counting showing a higher number of cells than normal (Fig. 6D, Table 3) (Schiffer et al., 1997). Not infrequently, the antitheticity between cell proliferation and migration can be verified in the infiltrated cortex where tumor cells migrating to the cortical surface show a very low MIB.1 LI (Labeling Index), whereas this increases again when the cells terminate migration and accumulate under the pia membrane in the outer cortical layer (Fig. 3C) (Schiffer et al., 1997). *In vitro*, the two properties may appear as mutually exclusive: cells expressing A2B5, i.e. gangliosides, which are highly expressed during development in migratory cells (Small et al., 1987), are not labeled by BrdU or PCNA (Pilkington, 1992, 1994). Isolated tumor cells and solid tumor cells seem to be under a different genetic control (Liotta & Stetler-Stevenson, 1991) and this is very important, because radiotherapy and certain forms of chemotherapy are likely to be scarcely effective on poorly proliferating cells. On the contrary, the proliferation rate of subarachnoidal seedings and of the cells invading the cortex is very high.

Interesting are the re-growth modalities of malignant gliomas after radio-therapy (Schiffer et al., 1982). They are not discussed in this chapter and radionecrosis is just mentioned, but the finding of abnormal, pleomorphic nuclei around the tumor after irradiation (Fig. 5C) or the occurrence of nests of viable tumor cells in a radionecrosis (Fig. 5D) around tumor must be reminded.

4. Migration of neural stem cells (NSCs) toward gliomas

Targeting brain tumor stem cells (BTSCs) for therapy is a new goal today and conversely it has been found that NSCs can target tumors (Shah et al., 2005). NSCs exhibit tumor-homing capability: immortalized murine NSCs, implanted into glioma-bearing rodents, distributed within and around tumors, even migrating to the contralateral hemisphere (Aboody et al., 2000). Genetically engineered NSCs with their tropism for gliomas may have an adverse effect on the latter (Ehtesham et al., 2002; Shah et al., 2003; Kim et al., 2005; Uhl et al., 2005), especially if they are also transduced with herpes simplex virus-thymidine kinase (*HSVtk*) gene and followed by the administration of systemic ganciclovir (Li et al., 2006; Rath et al., 2009; Tyler et al., 2009). Human NSCs implanted in rat brains containing a C6 glioma migrated in the direction of the expanding tumor (Jeon et al., 2008). The same properties are shown by mesenchymal stem cells, injected either into carotid arteries or intracerebrally (Nakamura et al., 2004; Nakamizo et al., 2005) and by hematopoietic progenitor cells (Tabatabai et al., 2005).

Endogeneous progenitor cells have been observed to migrate from the sub-ventricular zone (SVZ) toward a murine experimental glioblastoma (Glass et al., 2005). The migrated nestin-positive cells were positive for Ki-67/MIB.1 and 35% of them for musashi-1 (Pirzkall et al., 2002). Chemokines, angiogenic cytokines and glioma-produced ECM can play a role in the NSC tropism (Xu et al., 2007). It is possible to take advantage of the natural capacity of chemokines to initiate migratory responses, and to use this ability to enhance tumor-inhibitory neural progenitor cells to target an intracranially growing glioma (Honeth et al., 2006). The therapeutic possibilities offered by NSCs are continuously increasing. For example, they can be engineered as sources of secreted therapeutics, exploiting their mobility toward nervous system lesions. They could function as minipumps (Chen et al., 2007).

Rat embryonic progenitor cells transplanted at a distance from a glioma grown in the striatum migrate and co-localize with it. They modify their phenotype, express vimentin and reduce the volume of the tumor, demonstrating that a cross-talk exists between them and the tumor (Staflin et al., 2007). It has been shown that hypoxia is a key factor in determining NSC tropism to glioma and that this is mediated by stromal-derived factor.1 and its receptor (SDF-1/CXCR4), urokinase-type plasminogen activator and its receptor (uPA/uPAR) and VEGF/VEGFR2 (Zhao et al., 2008). It could be interesting to try to enhance motility of adult NSCs towards central nervous system injury or disease and to take into account that EGFR could play a role, because of its participation to malignant transformation (Ayuso-Sacido et al., 2006). It has also been recognized that a limitation exists to the possibility of migration of neural precursors from SVZ to an induced cortical glioblastoma in mice. The limitation is given by age and the proliferation potential of SVZ: adult mice supply fewer cells than younger mice, depending on the expression of D-type Cyclins as Cyclin D1 is lost during aging and only Cyclin D2 remains (Walzlein et al., 2008).
Recently, novel treatment strategies using NSCs have been proposed, for example the suicide gene therapy using converting enzyme (Barresi et al., 2003) and others and new ones will emerge from further studies of NSCs and BTSCs (Oh & Lim, 2009). Just a warning: is it possible that tumors grow from transplanted NSCs (Amariglio et al., 2009)?

5. Microglia/macrophages

It is a common knowledge that malignant gliomas are rich in microglia/macrophages. They are classified as ramified or resident microglia, ameboid or activated microglia, macrophages and perivascular microglia (Fig. 7A) (Graeber & Streit, 1990); therefore, they are both intrinsic to the CNS and blood-borne recently arrived, because of the local production of chemoattractans (Frei et al., 1992). They are increased either in the centre or in the periphery of the tumors (Roggendorf et al., 1996) and it has been calculated that up to one third of cells in glioma biopsies are represented by macrophages (Morimura et al., 1990; Roggendorf et al., 1996). Undoubtedly, they proliferate in response to tumor growth and have a cytotoxic defense function (Sutter et al., 1991), as well as the capacity for antigen presentation (Flugel et al., 2001), but they can also promote tumor infiltration and proliferation as well (Huettner et al., 1997; Graeber et al., 2002).
Macrophages (Fig. 7B) have long been recognized as critical components of immunity against tumors, because, when appropriately stimulated, they can attack tumor cells by contact interaction or secreting cytotoxic and cytostatic factors (Burke et al., 2002). However, they can also contribute to tumor development, secreting growth factors such as angiogenic factors, proteinases, which degrade the matrix, and immunosuppressor factors (Bingle et al., 2002). Their dual function is exerted mainly through TNF which demonstrates both an anti-cancer (Lejeune et al., 1998) and a pro-cancer activity (Orosz et al., 1993). However, it has also been shown that TNF can reduce glioma growth and prolong survival (Villeneuve et al., 2005).
Together with fibroblasts, pericytes, neutrophils, mastcells, lymphocytes, dendritic cells and endothelial cells, macrophages belong to the category of stromal cells which interact with the tumor, as said before, *via* cell-cell or by cytokine- or chemokine-mediated signaling. Tumor cells may influence stromal cells to produce growth factors such as VEGF, TNFα, TGFβ, IL1 or chemokines CCL2, CXCL8, CXCL12 that promote angiogenesis and tumor growth and, conversely, tumor cells are stimulated to produce chemokines influencing

angiogenesis and growth. There is an autocrine and a paracrine tumor growth stimulation (Somasundaram & Herlyn, 2009). The enrichment of stromal cells, especially microglia/macrophages, in the BAT strongly influences immunoregulation and tumor growth on the one side and represents a defense from the tumor on the other side. The observation that there is a positive relationship between microglia/macrophages and tumor initiating cells in the two opposite directions is relevant to the problem (Yi et al., 2011). The possibility to follow the concept that microglia can be exploited in tumor therapy remains today "in its infancy" (Graeber et al., 2002) and it must be interpreted also in a negative sense: the demonstration that microglia/macrophages promote glioma progression means that their inhibition can be a useful therapeutic tool (Zhai et al., 2011).

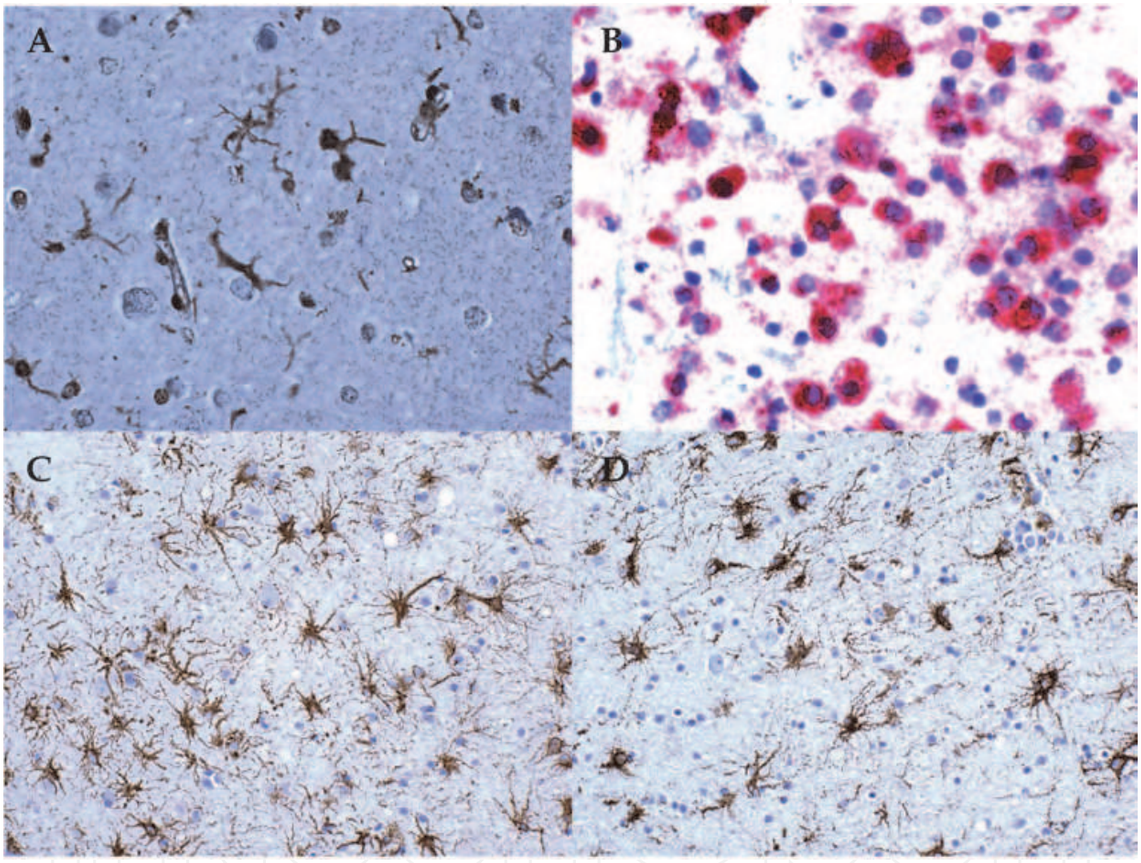

Fig. 7. A – Microglia cells in the cortex around the tumor, CD68, DAB, x 400; B – Macrophages in the BAT, CD68, DAB, x 400; C – Reactive astrocytes in the BAT, GFAP, DAB, x 400; D – Reactive astrocytes in a moderately infiltrated BAT, GFAP, DAB, x 400.

6. Reactive astrocytes

Astrocytes respond rapidly and dramatically to CNS injuries through hypertrophy and then hyperplasia. The first sign of a CNS injury is a progressive development of their cytoplasm to reach a gemistocytic aspect, followed by the production of processes which become in time longer and thicker to form isomorphic or anisomorphic gliosis. The best known hallmark of reactive astrocytes is up-regulation of intermediate filament (IF) proteins, in

particular GFAP, that is one among the 65 IF proteins identified in humans (Hermann & Aebi, 2004). In normal astrocytes, GFAP is the major IF protein, being the expression of Vimentin variable and low (Pixley & De Vellis, 1984). The cells show fine processes extending from the thicker ones. In reactive conditions, a hypertrophy of cellular processes with up-regulation of GFAP and Vimentin expression and re-expression of Nestin occur and a number of genes are involved with the cell functions (Hernandez et al., 2002). There are analogies between glial reaction and physiological maturation of astrocytes during embryogenesis. In initial phases, the fine processes originate directly from the cell soma and then from the thick and long processes (Bushong et al., 2004). Nestin and Vimentin would be the main IF of immature, whereas GFAP and Vimentin of the mature astrocytes (Clarke et al., 1994; Eliasson et al., 1999). In the post-natal brain, GFAP and Vimentin would replace Nestin (Wei et al., 2002). In normal rat brain, Nestin occurs in few astrocytes of the brain stem, whereas in reactive astrocytes it has been observed everywhere: in hippocampus by lesions with kainic acid (Clarke et al., 1994), in hemispheres in experimental ischemia (Duggal et al., 1997) and in trauma where Nestin expression increases in time with GFAP (Sahin Kaya et al., 1999). A complicated and not yet completely solved problem remains that of hyperplasia. It can be realized through an increased number of regional astroglia cells in response to a *noxa*, or by proliferation and migration of sub-ependymal cells (Takamiya et al., 1988; Schiffer et al., 1993; Frisén et al., 1995; Holmin et al., 1997). It was shown that subsets of reactive astrocytes can recapitulate stem cell/progenitor features after damage (Buffo et al., 2010), i.e. some astrocytes acquire stem cell properties after injury and hence may provide a promising cell type to initiate repair after brain injury (Buffo et al., 2008).
Peritumoral reactive gliosis (Fig. 7C, 7D) has a particular importance because of three main characteristics: reactive astrocytes divide by mitosis as tumor cells do; progressively they lose Nestin and increase GFAP expression, as during development and they may exert regionally a series of metabolic and molecular influences (Schiffer, 1997). The most important point is that reactive astrocytes may be included in the advancing tumor in which they become progressively no more recognizable from tumor cells. The question is whether they disappear suffocated by the high density of tumor cells, or if they remain, unrecognizable from tumor cells, contribute to the pleomorphic aspect of gliomas or they are transformed into tumor cells (Tamagno & Schiffer, 2006). The precise origin of reactive astrocytes is still a matter of debate, i.e. whether they are mostly migrated progenitor cells from the sub-ventricular zone (Clarke et al., 1994; Frisén et al., 1995; Lin et al., 1995; Sahin Kaya et al., 1999) or originating from regional astrocytes (Duggal et al., 1997; Li et al., 1999). There is no evidence that tumors can develop from the proliferating reactive glia; however, they might originate from radial glia, which has the capability to proliferate and into which differentiated astrocytes can regress under certain stimuli (Magavi et al., 2000).

7. Autocrine glutamate signalling

Glutamate can promote glioma cell invasion. Glioma cells lack functional EAAT transporters (Ye et al., 1999) and, therefore, glutamate is released rather than taken up (Ye et al., 1999). Glutamate promotes tumor growth, besides causing neuronal excitotoxicity on the neurons surrounding tumor and, therefore, being responsible for the epileptic seizures frequently associated in the symptomatology of gliomas (Sontheimer, 2003). Glutamate release is caused by the cellular cystine uptake *via* x_{C^-} which is a heterodimeric protein complex made by a catalytic light chain xCT and a regulatory heavy chain 4F2hc localizing

the transporter into the membrane (Sato et al., 1999). It imports cystine for the synthesis of glutathione with exchange of glutamate (McBean & Flynn, 2001). It has been demonstrated that glioma cells *in vitro* are stimulated to migrate in response to glutamate (Lyons et al., 2007). The role played by glutamate in the BAT is frequently emphasized, but it does not seem to be adequately considered.

8. Peritumoral edema and infiltration zone

The main problem for invasive gliomas is how far from the tumor border invasive cells can be found. Theoretically, as already said, a zone of two centimetres has been calculated as the limit of target volume for radiotherapy. Even though from the pathological point of view it is a common experience that cells can go farther, the limit expresses the maximum distance from the tumor border seen by MRI compatible with the preservation of the normal nervous tissue with radiotherapy and the minimum for including the most part of invasive cells in the radiation field. In this way the diffusion of tumor cells in the BAT overlaps with peritumoral edema, making it difficult for MRI to distinguish the invasive zone. In low grade gliomas and in secondary GBM such a distinction could be made, even not in the entire BAT, by detection of IDH1-2 mutations in the surgical samples, with the exception of primary GBM (Capper et al., 2010; Mellai et al., 2011).

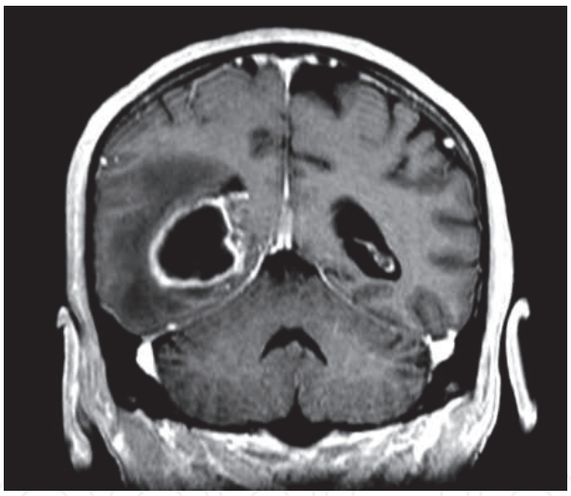

Fig. 8. MRI, T1, peritumoral edema (From the courtesy of Dr. Consuelo Valentini, Dept. Radiology, CTO Hospital, Turin).

For neuroimaging, the coexistence of invasive cells and edema in the BAT (Fig. 8) represents a real problem, because there is not a precise answer to the question whether conventional MRI can distinguish between edema due to reactively altered vital brain tissue from edema plus invasive cells. Using more sophisticated MRI with 1.5 Tesla, it seems that this can be possible. In experimental tumors transplanted into the mice, superimposing immunohistochemistry to MRI it has been observed that in edema districts around the tumor reactive astrocytes, activated microglia, increased expression of aquaporin-4 and invasive tumor cells can be found (Engelhorn et al., 2009). The working concept that brain blood barrier (BBB) is preserved in the BAT to the point that attempts have been made for crossing it to allow chemotherapeutics drugs to reach invasive cells (Madsen & Hirschberg,

2010), is not completely true. In some experiences, BBB after experiments with dexamethasone is considered in the BAT as partially disrupted (Straathof et al., 1998).
Very interesting are the observations on the expression of Aquaporin (AQP4) that is the highest in peritumoral tissue where it correlates with edema, whereas in the tumor it correlates with HIF.1α, VEGF and the grade of malignancy (Mou et al., 2010). In the daily experience of radiologists, radiotherapists and neurosurgeons, the border zone between tumor infiltration and normal brain tissue represents a crucial point, because it is difficult to define the margin for the purposes of treatment planning: to leave small areas of tumor infiltration out of the treatment volume or to include too much normal nervous tissue in it. That is to say to increase the risk of recurrence or that of nervous tissue toxicity (Pirzkall et al., 2004). It must not to be forgotten that volume is a factor of toxicity beside dose and time (Marks et al., 1981) and that small-volume radiotherapy decreases neuropsychological sequelae in comparison with large volume-radiotherapy (Hochberg & Pruitt, 1980; Maire et al., 1987).
It has been demonstrated that tumor cells can be revealed > 3 cm distant from the contrast-enhancing margin of the tumor (Matsukado et al., 1961; Burger et al., 1988) and relapses occur within 2 cm from the original tumor (Hochberg & Pruitt, 1980; Wallner et al., 1989; Oppitz et al., 1999). Therefore, tumor cell invasion is realized inside the area of edema.
With conventional MRI, the detection of tumor infiltration is even more difficult when this is very low and recently attempts are being made with more specific MRI procedures. Magnetic resonance spectroscopy imaging (MRSI), that so much information produced on glioma grading (Law et al., 2003; Nelson, 2003), demonstrated that infiltration could be detected along white matter fibre tracts (Pirzkall et al., 2001, 2002). It is known that with MRSI metabolic changes can be investigated in brain lesions. In gliomas, for example, there is an increase of choline-containing compounds and a decrease of N-acetyl-aspartate (NAA) signal (Pirzkall et al., 2001). Creatine is used to calculate the ratios. It has been demonstrated that MRSI is a valuable tool for assessing residual tumor after surgery (Pirzkall et al., 2004); however, tNAA seems to be more suitable to detect low tumor cell infiltration (Stadlbauer et al., 2007). The problem of detecting tumor cell infiltration in peritumoral edema started to be solved in neuroimaging, even though it cannot be said that it has been completely solved. It parallels that of distinguishing recurrent tumor from radiation injury that can be accomplished by multivoxel 3D Oritin MR spectroscopy (^{1}H-MRS) (Zeng et al., 2007).

9. Conclusions

Different cell types can be found in the BAT, but they do not exhaust all its phenotypic features. Other events may occur in the peritumoral tissue and one of them, calcifications, may have repercussions on neuroimaging of tumors. Calcifications may be found either at a distance from the tumor or in the infiltration zone, because reached by the advancing tumor with time. Another event is the occurrence of teleangectatic vessels just outside the zone of solid tumor or in the healthy tissue and successively included in the invading tumor.
The aspect of the greatest interest is that the existence itself of a BAT as before depicted and its thickness are not a constant finding around malignant gliomas. Sometime it happens that the tumor confines with the normal tissue in a sharp way and there is no tumor cell gradient. This is not infrequent when the tumor meets a white matter bundles perpendicularly. Conversely, when it proceeds from the deep white matter to the cortex along ascending and descending fibres the cell gradient can be very wide, to the point that it

can be difficult to establish, without an accurate cell count (Schiffer, 2006), where the tumor ends. This is a real challenge for neuroimaging, because theorethically tumor cells can be found at any distance from the tumor and the safety margins are more conventional than real. Just think to the passage through the corpus callosum, septum pellucidum, commissures, and seeding in the subarachnoidal spaces. The occurrence of tumor cells far from the tumor, can be a problem relevant to gliomagenesis and the relationship between brain and glioma origin (Schiffer et al., 2006, 2010), falling, therefore, outside the present chapter.

Another crucial point is that the cell composition of the BAT can be manifold with an inconstant proportion among them in the different zones of the front between tumor and the healthy tissue. For example, the quota of macrophages/microglia may greatly vary, as well as that of reactive astrocytes, depending also on the treatments received from the tumor. For example, in tumors after radiotherapy large areas of packed macrophages can be found around the tumor, not identifiable directly with radionecrosis (Schiffer et al., 1980). On the contribution of migrating stem cells from the SVZ there is no available information on human pathology. Their participation to the BAT is just deduced from experimental neuro-oncology and it is an hypothesis to be taken into account. That of BAT is a working concept that will be fruitful in the future, together with the advancement of neuroimaging.

10. References

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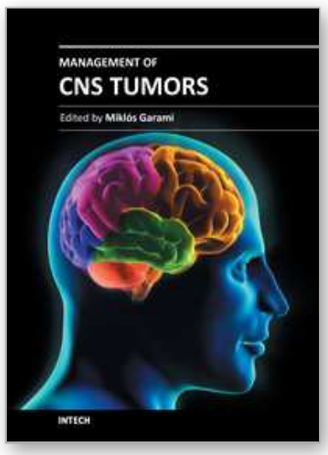

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