Cancer precursor project - Premalignant precursors for glioblastoma

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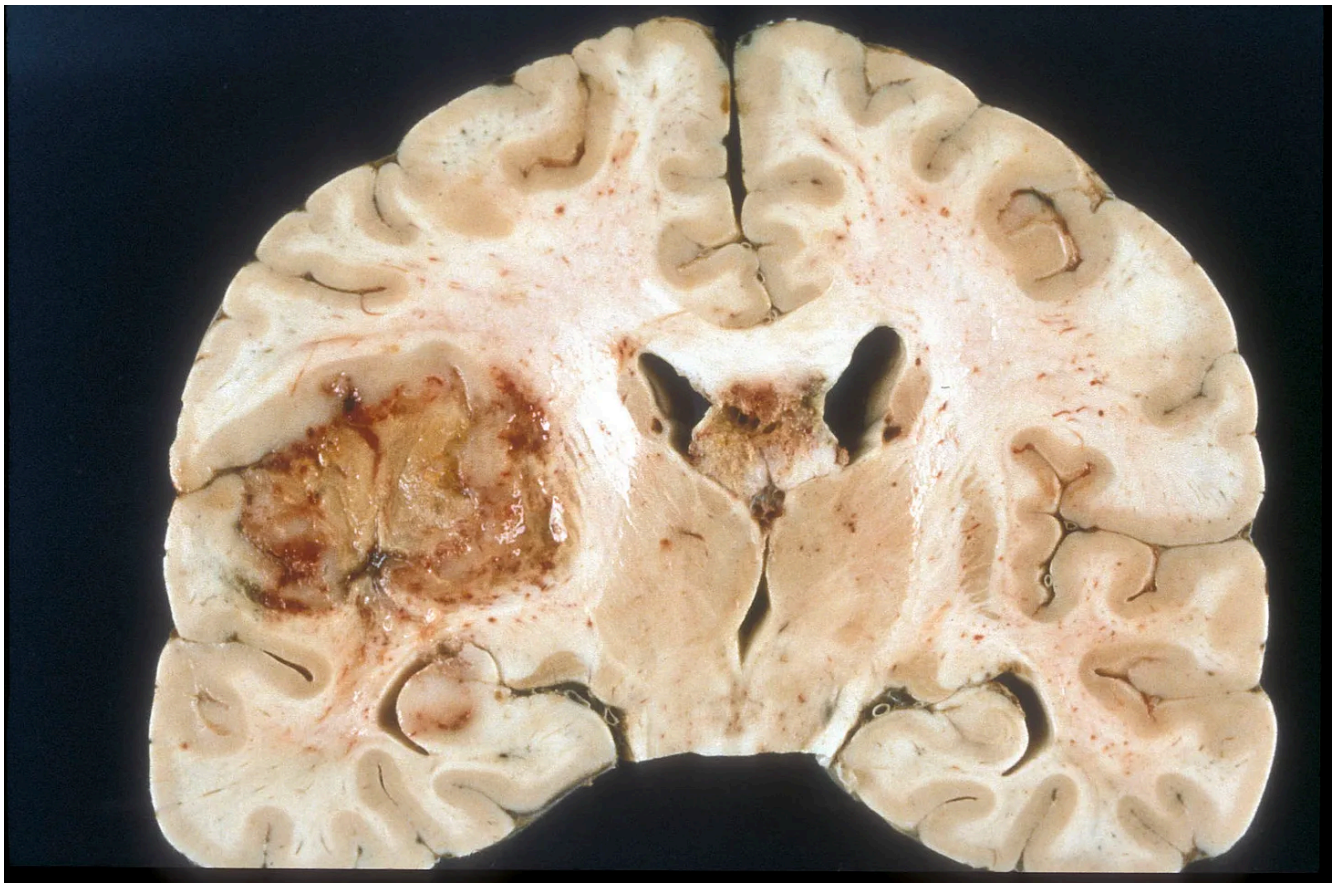


Glioblastoma (2007), but no molecular testing was done, source Wikipedia

The goal of our cancer precursor project is to better understand how cancer arises by compiling a regularly updated spreadsheet of all distinct human cancers (now ~1230) and their premalignant precursors (now ~190).

Malignant change is due to self-organized criticality, which describes catastrophic events such as earthquakes, stock market crashes and malignant transformation. It is nature's way of making large changes based on individual factors often thought too trivial to consider (Bak 1999). For example, in the punctuated equilibrium of species, one sees prolonged periods of apparent stasis (i.e. no new species), followed by bursts of new species (Eldredge & Gould 1972). During the "quiet" periods, minor changes are accumulating that may not be noticed. Similarly, under the influence of cancer risk factors or random events, human biological networks may have prolonged periods of minor changes with no apparent clinical or microscopic changes, followed by bursts of activity leading to premalignant precursors or frank malignancy (Cross 2016, Pernick 2023).

We propose that the premalignant precursors may be relatively stable based on the attractor concept and have distinctive molecular patterns that may or may not be identifiable histologically (Pernick 2018).

Glioblastoma, *IDH* wild type is the most common primary brain tumor in adults ("primary" in this context means not representing metastatic disease). It accounts for 14% of all primary central nervous system (CNS) tumors and 49% of all malignant CNS tumors in adults (Ostrom 2021). Most glioblastomas are designated as primary glioblastomas ("primary" in this context means no evidence of a prior malignant lesion, Ohgaki 2013). They are high grade tumors (i.e. aggressive) that typically occur in elderly patients with rapid development of symptoms. Secondary glioblastomas are glioblastomas that arise from prior CNS tumors that are typically low grade, diffuse or anaplastic astrocytomas (see Hardian 2019 for an example). Secondary glioblastomas have different clinical and molecular features than primary glioblastomas: they occur in younger patients, occur more often in the frontal lobe, have a significantly better prognosis and have *IDH1* mutations (Ohgaki 2013).

The 2021 World Health Organization (WHO) classification redefined glioblastoma as an adult grade 4 (i.e. aggressive) diffuse astrocytic glioma that is *IDH* wildtype and *H3*-wildtype (i.e. no mutations in these genes) and has either: (a) microvascular proliferation or necrosis or (b) a *TERT* promoter mutation, *EGFR* gene amplification or +7/-10

chromosome copy number changes. The term glioblastoma multiforme is no longer used and the term glioblastoma is no longer applied to pediatric tumors.

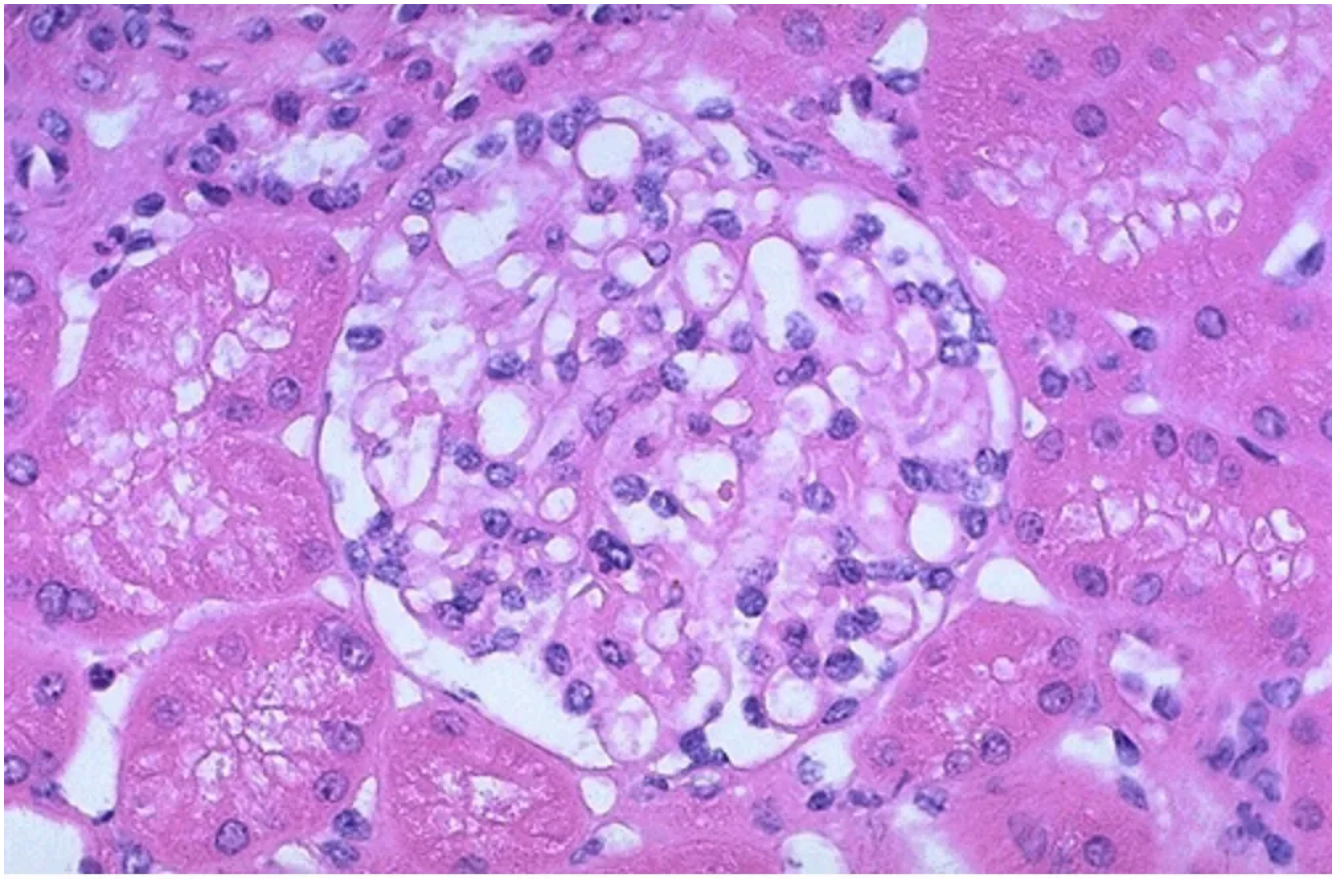
Although we believe that most malignancies have a premalignant precursor lesion, to our knowledge, none has been identified for primary glioblastoma or any primary CNS tumor.

Glioblastoma has three molecular subtypes based on gene expression profiling signatures: proneural, classical, and mesenchymal, although this does not impact clinical practice, possibly due to marked intratumoral heterogeneity (i.e. tumor cells differ from each other) and the differentiation plasticity of glioblastoma (i.e. subtypes can change over time and through therapy, Ah-Pine 2023, Neftel 2019). Each molecular subtype may have a different precursor lesion.

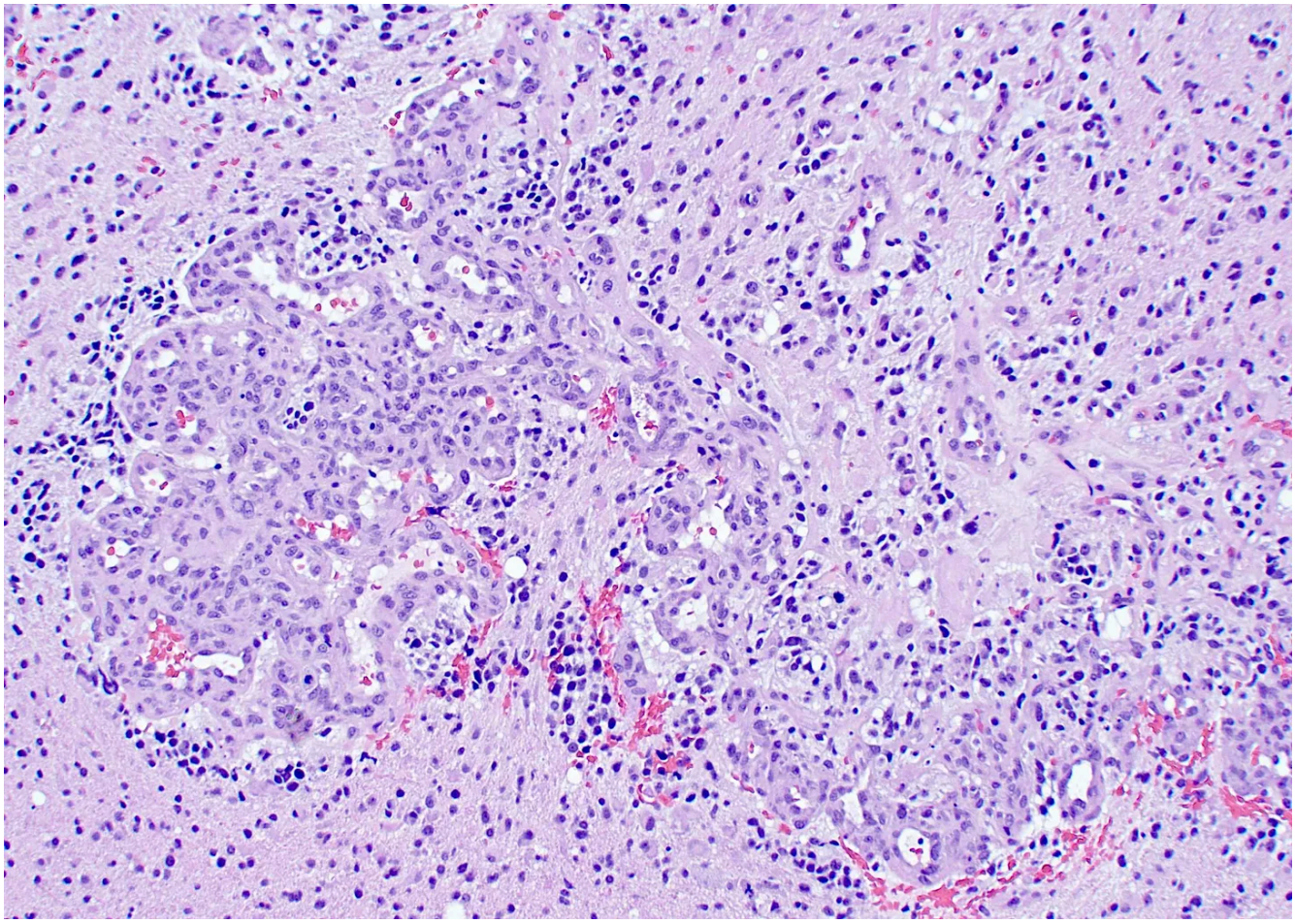
Glioblastoma may arise from neural stem cells or glial precursor cells by activating oncogenic pathways (Ah-Pine 2023). They may also originate from perivascular mesenchymal stromal cells which derive from the neural crest (Ah-Pine 2023).

What might a glioblastoma premalignant precursor look like? We suggest it may have "milder" features of glioblastoma but in a nonmalignant context.

First, it may have some type of microvascular proliferation, which consists of multilayered, small caliber vessels lined by endothelial cells and hyperplastic vascular smooth muscle cells creating a glomeruloid appearance (Haddad 1992). A normal glomerulus in the kidney is shown below for reference followed by a glomeruloid microvascular proliferation in glioblastoma.



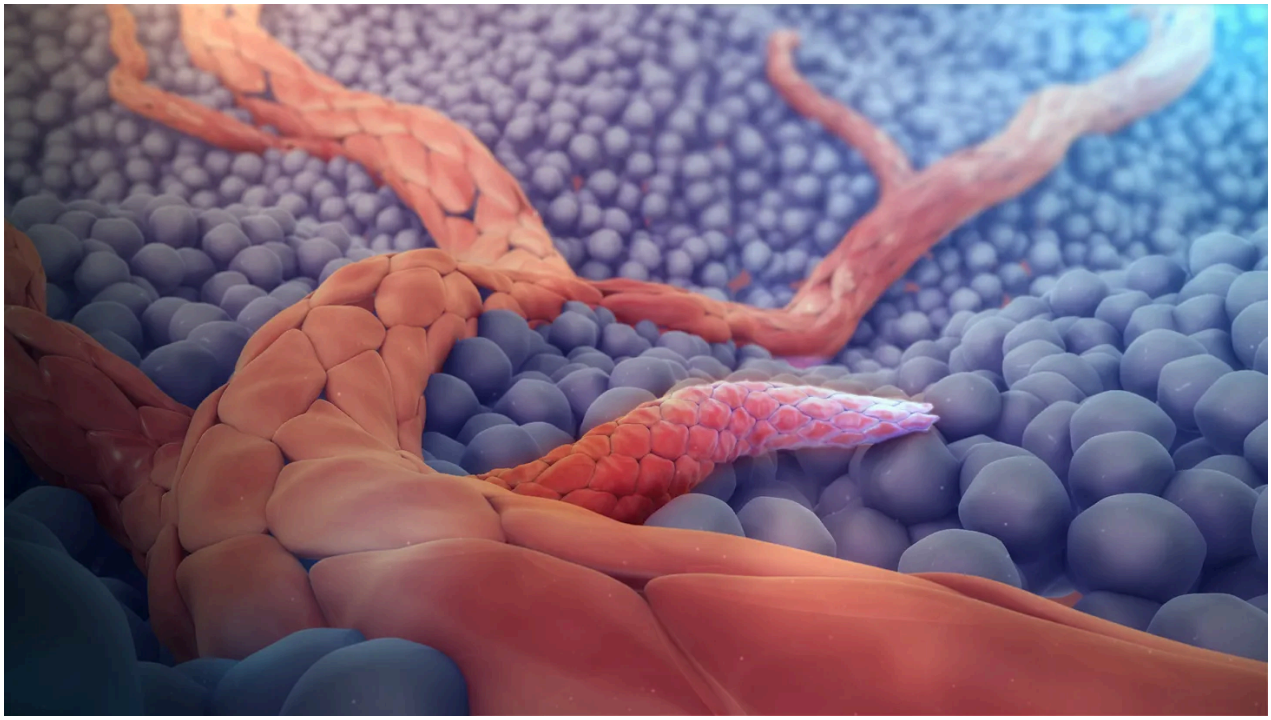
Normal kidney glomerulus, source Webpath



Glomeruloid microvascular proliferation, contributed by Bharat Ramlal, M.D., source PathologyOutlines.com

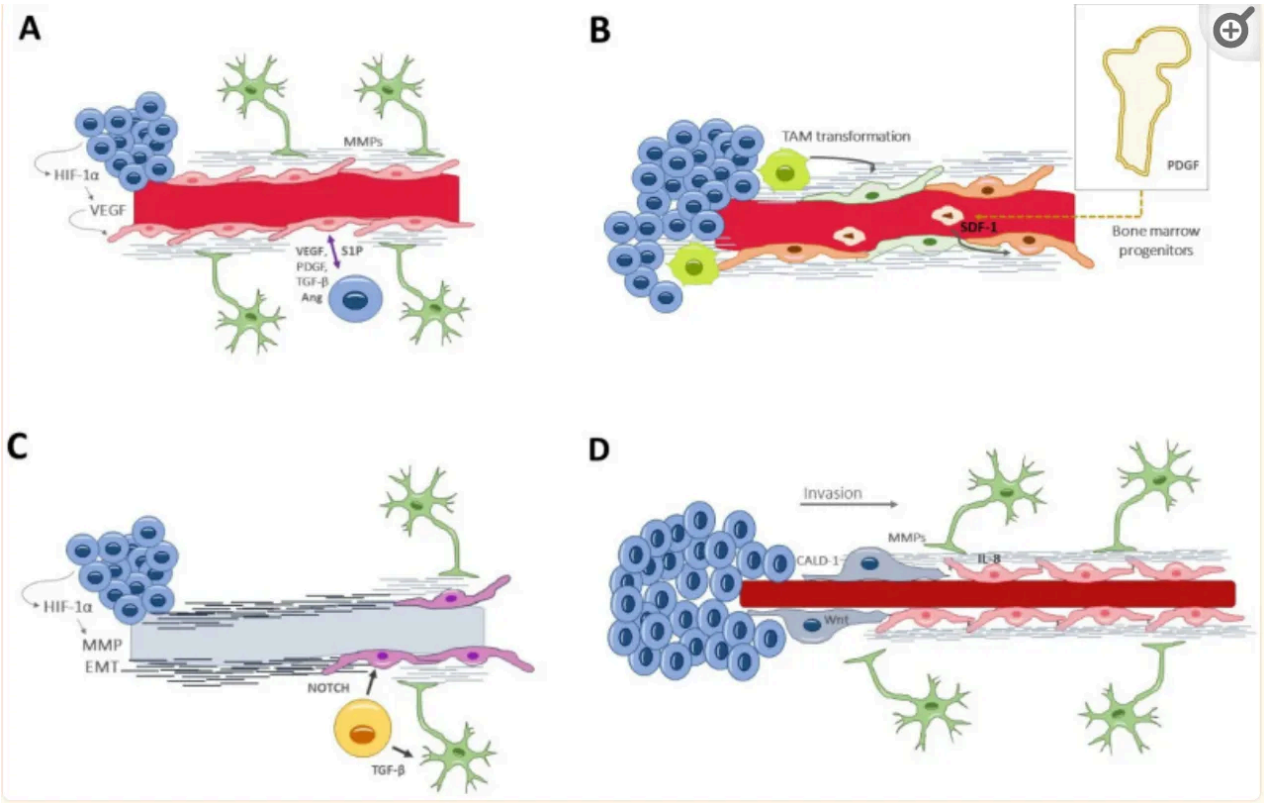
Since the prominent vasculature is an important component of glioblastoma, we propose that it may be part of its premalignant precursor. This vasculature is an intricate multifaceted phenomenon in glioblastoma that promotes tumor growth and spread by the following mechanisms (Mosteiro 2022):

- Angiogenesis (the formation of new blood vessels from existing vessels via sprouting): this promotes tumor growth because tumor cells need oxygen and other nutrients supplied by blood.



3D medical animation still showing angiogenesis, source Wikipedia

- Vasculogenesis (forming new blood vessels from precursor cells): endothelial cell progenitors are recruited from the bone marrow to assemble new blood vessels.
- Transdifferentiation: glioblastoma stem cells differentiate into endothelial cells.
- Vascular mimicry: glioblastoma stem cells differentiate into vascular smooth muscle cells or pericytes, which are components of blood vessels.
- Vessel co-option: tumor cells migrate along existing blood vessels enabling invasion throughout the brain, beyond surgical and even radiological detection of the tumor (Seano 2020).



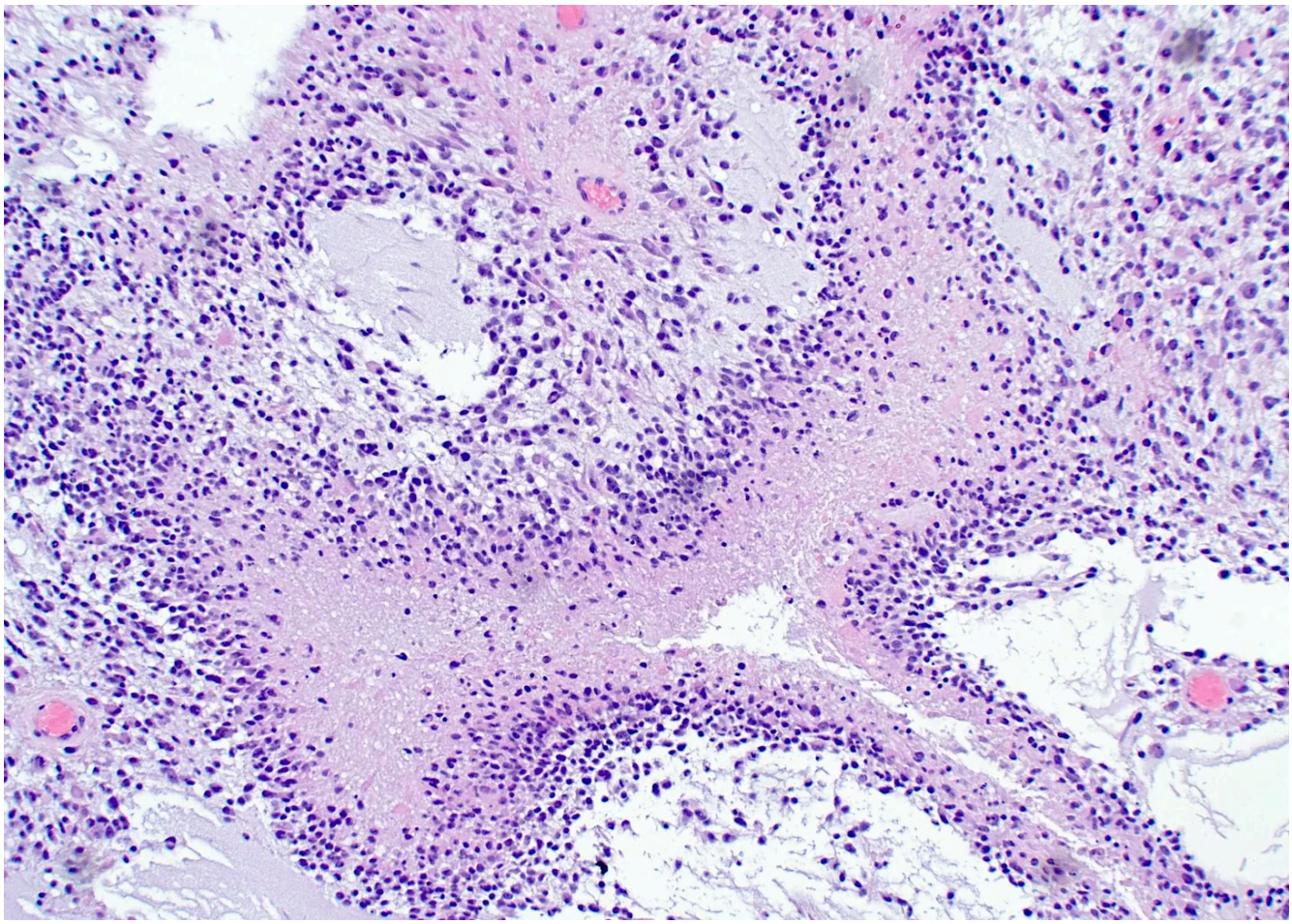
Vascular generation and related processes: (A) angiogenesis, (B) vasculogenesis, (C) vascular mimicry, (D) vascular co-option. Source Mosteiro 2022, figure 2

Microvascular proliferation in glioblastoma, particularly thick, branching and glomeruloid vessels, is also found in brain metastases (Gi 2017). Although glioblastomas only rarely metastasize (Lun 2011), microvascular proliferation may promote the malignant progression of glial cells in an unknown manner and may be an important feature of a premalignant precursor.

Second, a premalignant precursor to glioblastoma may have similar features to a low grade glioma, which is itself a precursor for secondary glioblastomas (Ohgaki 2013). Glioma stem cells can generate vascular pericytes that surround blood vessels within glioblastoma, so a premalignant glioblastoma precursor may also have prominent pericytes with this capability (Das 2013, Cheng 2013).

Third, a premalignant precursor to glioblastoma may have some type of necrotic niche, where hypoxia and lack of nutrients drive the formation of new vessels by diverse

processes (Mosteiro 2022). Histologically, this may appear as focal areas of necrosis that are not associated with identifiable tumor cells.



Necrosis in glioblastoma, contributed by Bharat Ramlal, M.D, source PahtologyOutlines.com. Its precursors may have a "milder" variant of this feature.

Finally, a glioblastoma precursor may resemble embryonic or juvenile cells of the cerebrum. Mouse models have shown that glioblastoma cells resemble these cells, suggesting either the persistence of these early lineages following oncogene activation or their reactivation during malignant transformation (Hamed 2022).

Autopsy studies

We suggest that premalignant precursor lesions be investigated using autopsy studies of glioblastoma patients (Griffin 2021), examining nontumor tissue for either the histologic changes noted above (microvascular proliferation, prominent perivascular pericytes,

focal necrosis or embryonic differentiation) or for one of the defining molecular changes of glioblastoma in nontumor tissue (*TERT* promoter mutation, *EGFR* gene amplification or combined whole chromosome 7 gain and whole chromosome 10 loss) or to detect the overexpression of vascular endothelial growth factor (*VEGF*), an important mediator of angiogenesis in glioblastoma (Weathers 2015). Other possible common alterations of interest include those of the *RTK* genes, *PI3K* pathway genes and *PTEN*, present in up to 90% of glioblastomas (Brennan 2013).

The identification of premalignant precursors of glioblastoma may provide a better understanding and ultimately more effective treatment.

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