Cancer precursor project - characteristics of premalignant precursors, part 2 (brain and eye tumors)

24 April 2024

NAT PERNICK
APR 24, 2024

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 (currently 1,232) and their premalignant precursors (currently 191). Note: these numbers change based on our research and feedback from pathologists and scientists worldwide.

In part 1 of this series, we noted that the percentage of identified precursors varies widely by pathology subspecialty (see table below) and discussed precursors for subspecialties with epithelial sites (breast, head & neck, gyn, GI / liver, GU / adrenal and thoracic). In this essay, we discuss actual and possible malignant precursors associated with neuropathology.

	Cancers	Precursors	%
Neuropathology	114	1	0.9%
Dermatopathology	79	6	7.6%
Bone, joints and soft tissue	143	11	7.7%
Hematopathology	207	19	9.2%
Breast	58	8	13.8%
Head & neck	128	19	14.8%
Gyn	96	20	20.8%
GI / liver	203	47	23.2%
GU / adrenal	141	34	24.1%
Thoracic	63	26	41.3%
Grand total	1232	191	15.5%

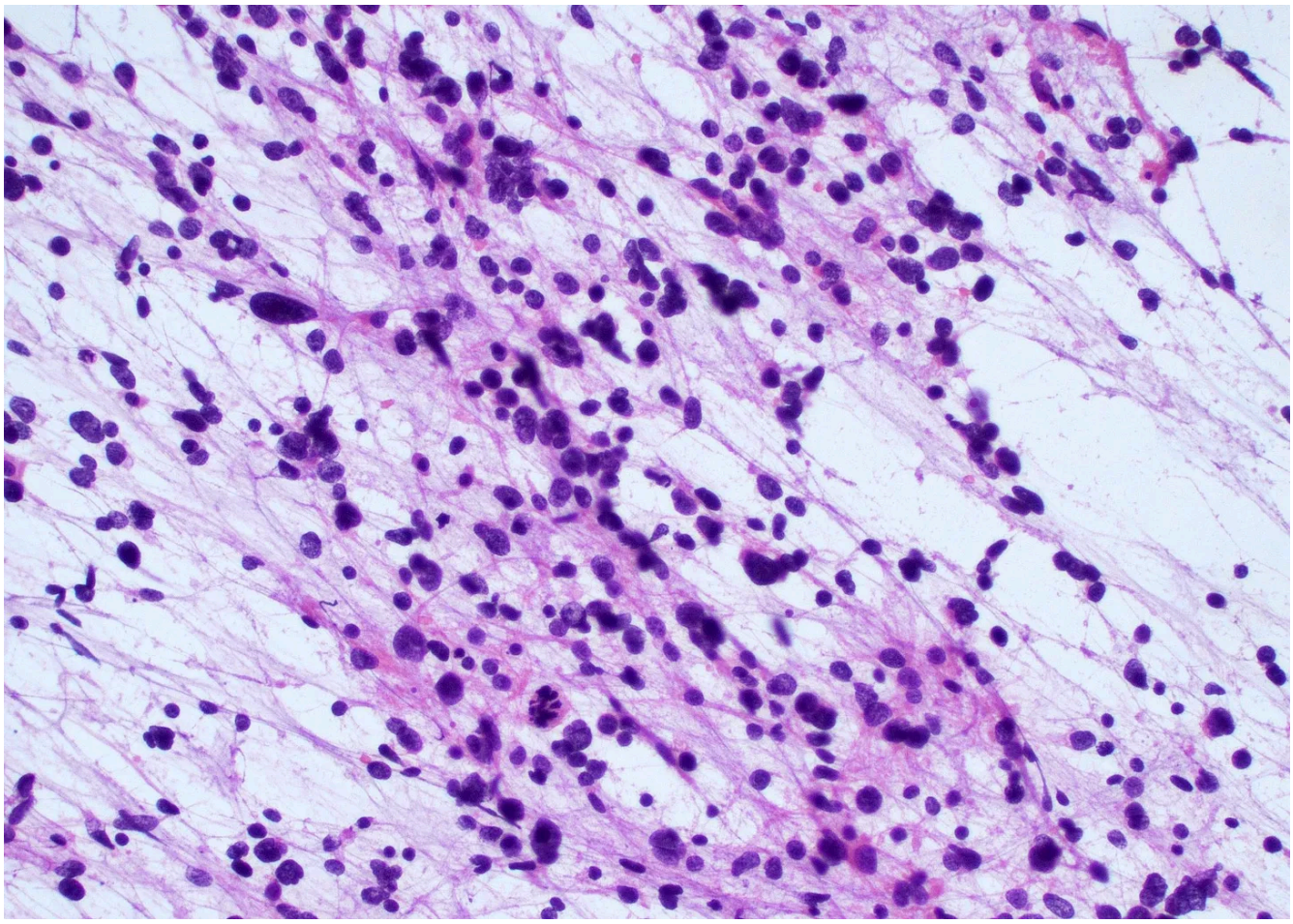
Premalignant precursors of distinct malignancies by subspecialty

In neuropathology, no precursor has been identified for any of the 100 CNS malignancies listed. How is this possible? It seems unlikely that pathologists and other scientists have overlooked them. Perhaps the traditional concept of precursor does not apply:

> Cancer precursors are the tissue antecedents of cancer. They are distinguished from biomarkers in that they reflect a morphologic as opposed to a merely biochemical or genetic association with a specific cancer. Precursors to cancers are **increasingly recognized as universal**, relevant to carcinogenesis, and providing a unique potential for primary and secondary prevention. As the molecular, imaging, and genomic tools to investigate them evolve, it is becoming increasingly evident that **virtually all malignancies are preceded** by these clinically silent states where the molecular lesions that characterize the specific cancer emerge. Caporaso 2013 [emphasis added]

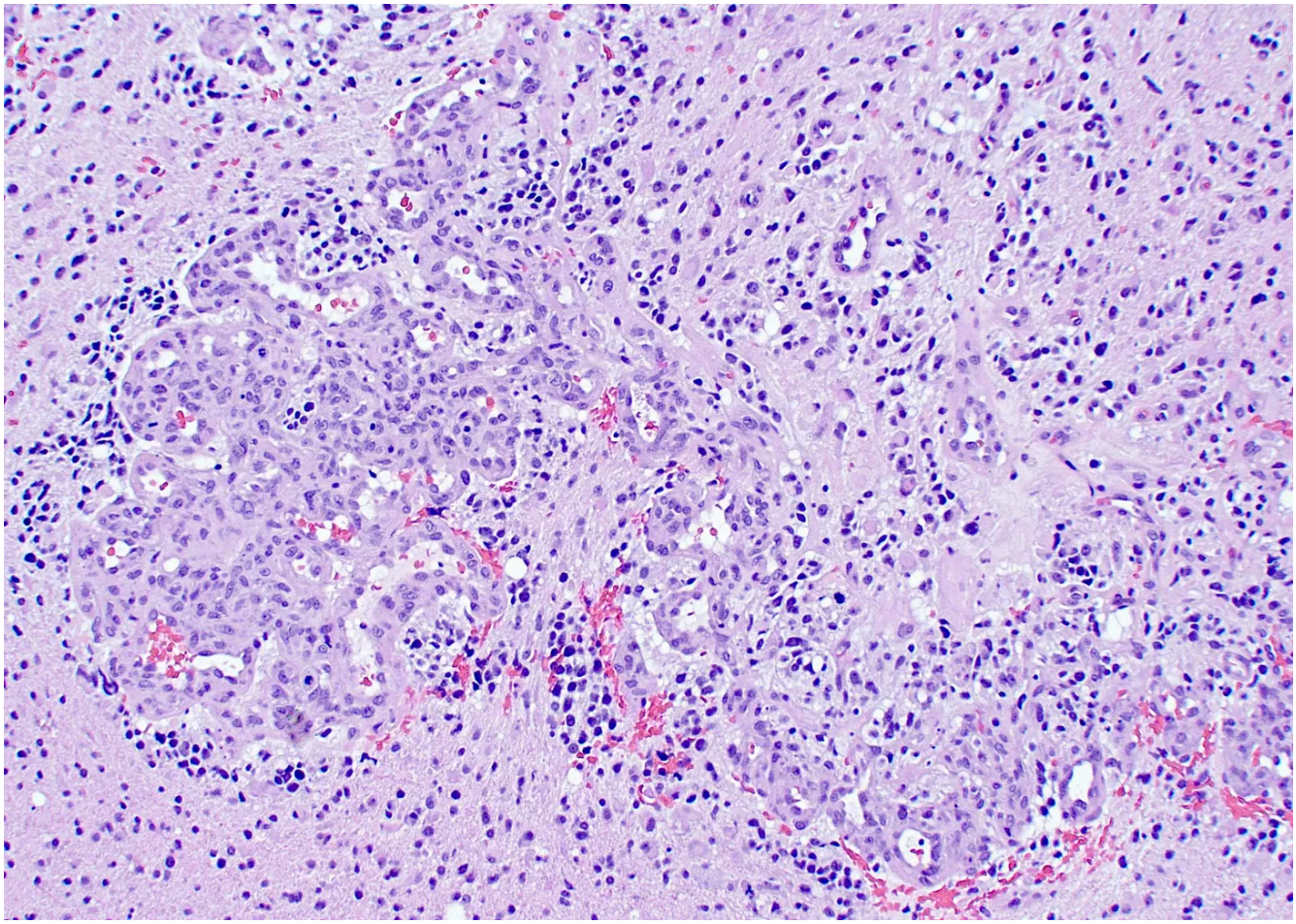
However, based on our work, it now appears that most CNS malignancies do NOT have a morphologic precursor. A CNS malignancy may be initiated by a defining mutation in a single stem or progenitor cell or small cluster of cells that multiplies and acquires additional malignant properties over time. Due to its small size, detection may not be possible, at least with current methods, until it is large enough to be clinically evident.

For glioblastoma, the most common brain malignancy in adults, we recently speculated that its premalignant precursor might consist of "milder" versions of its defining molecular or histologic changes in a nonmalignant context, although we now believe, based on further reflection, that there may be no detectable precursor to this and other CNS tumors.



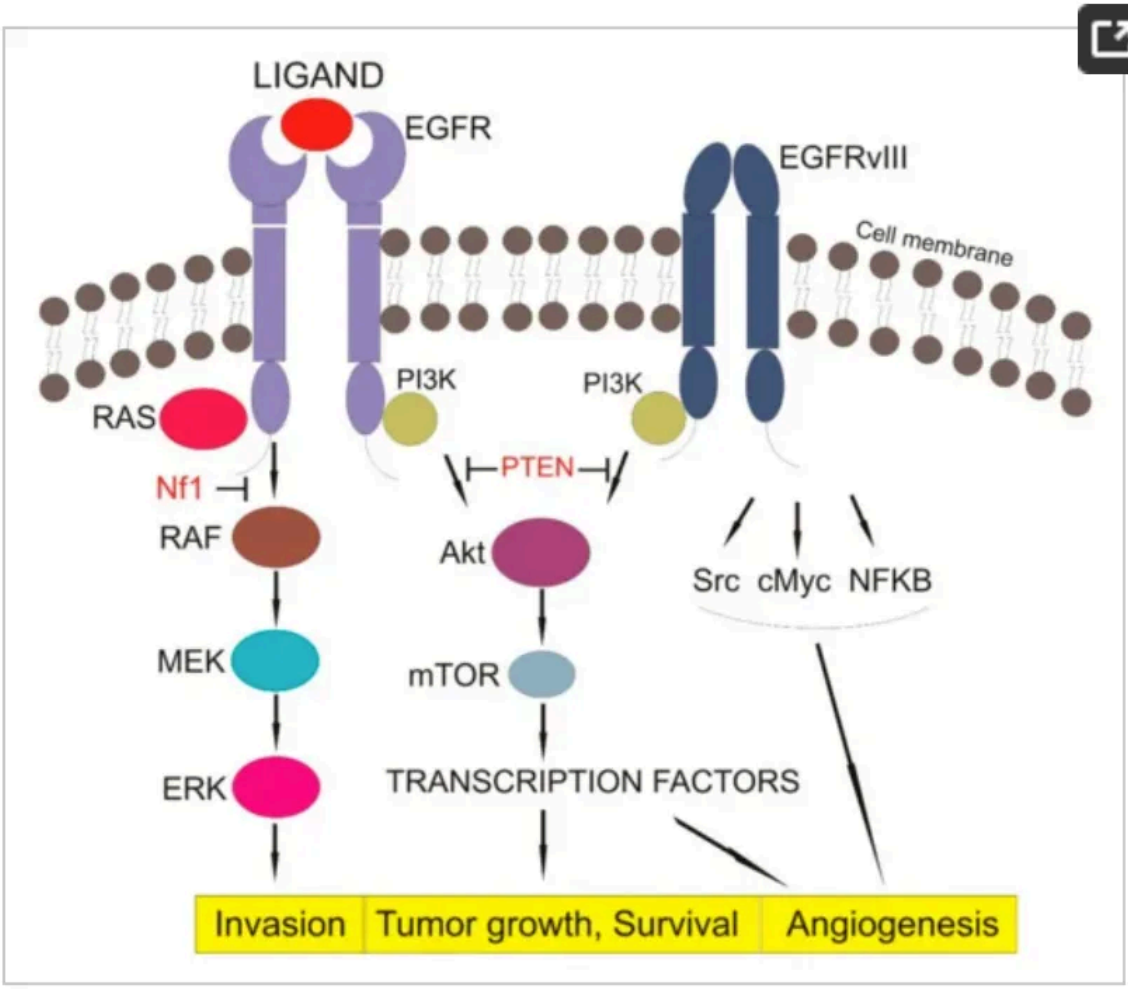
Glioblastoma: this intraoperative smear shows astrocytic cells with nuclear pleomorphism and fine glial processes (contributed by Bharat Ramlal, M.D.).

Small clusters of these cells may be the earliest identifiable indication of glioblastoma.



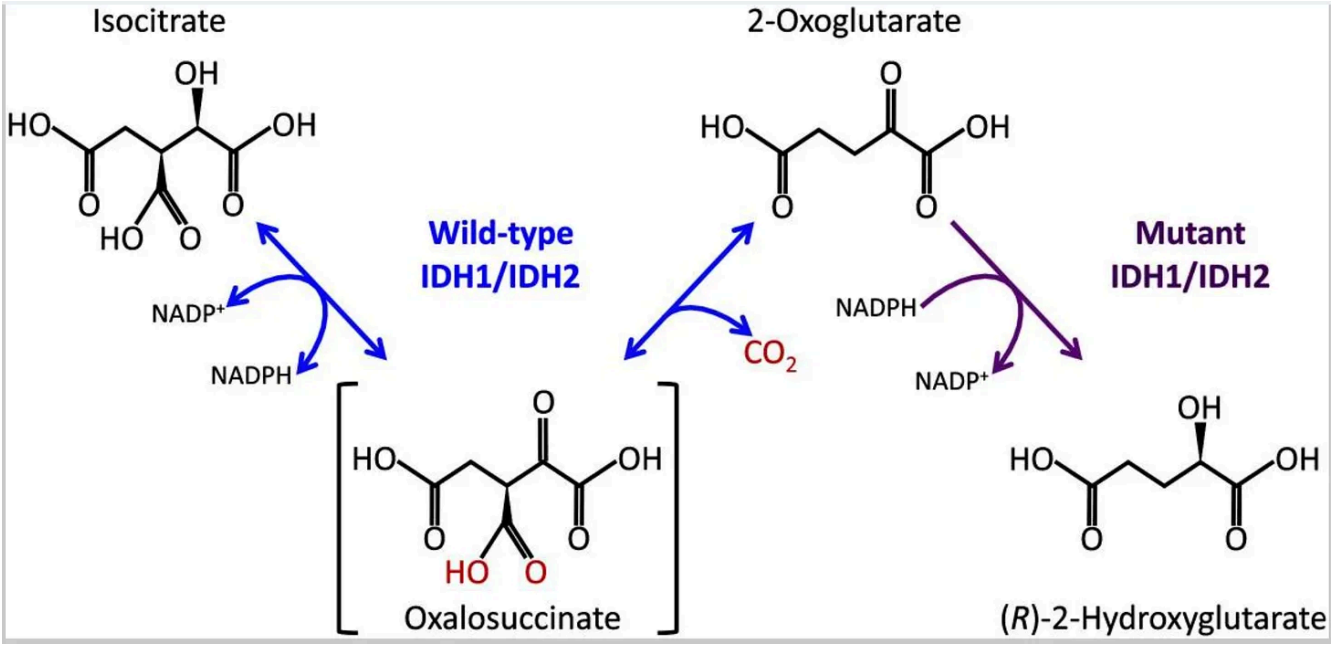
Glioblastoma: glomeruloid microvascular proliferation associated with *EGFR* amplification (contributed by Bharat Ramlal, M.D.).

Glioblastoma may begin with a stem or progenitor cell that contains the defining molecular changes of *EGFR* amplification, *TERT* mutations or copy number changes in the form of a combined gain of chromosome 7 and loss of chromosome 10. Alternatively, there may be molecular changes to other networks that initiate the defining histologic changes of brisk mitotic activity and microvascular proliferation or necrosis. These molecular changes may promote genomic instability so that dividing cells acquire additional molecular changes or mutations that further the malignant process until a clinically evident tumor is identified. For this scenario, none of these steps would be considered a morphologic precursor.

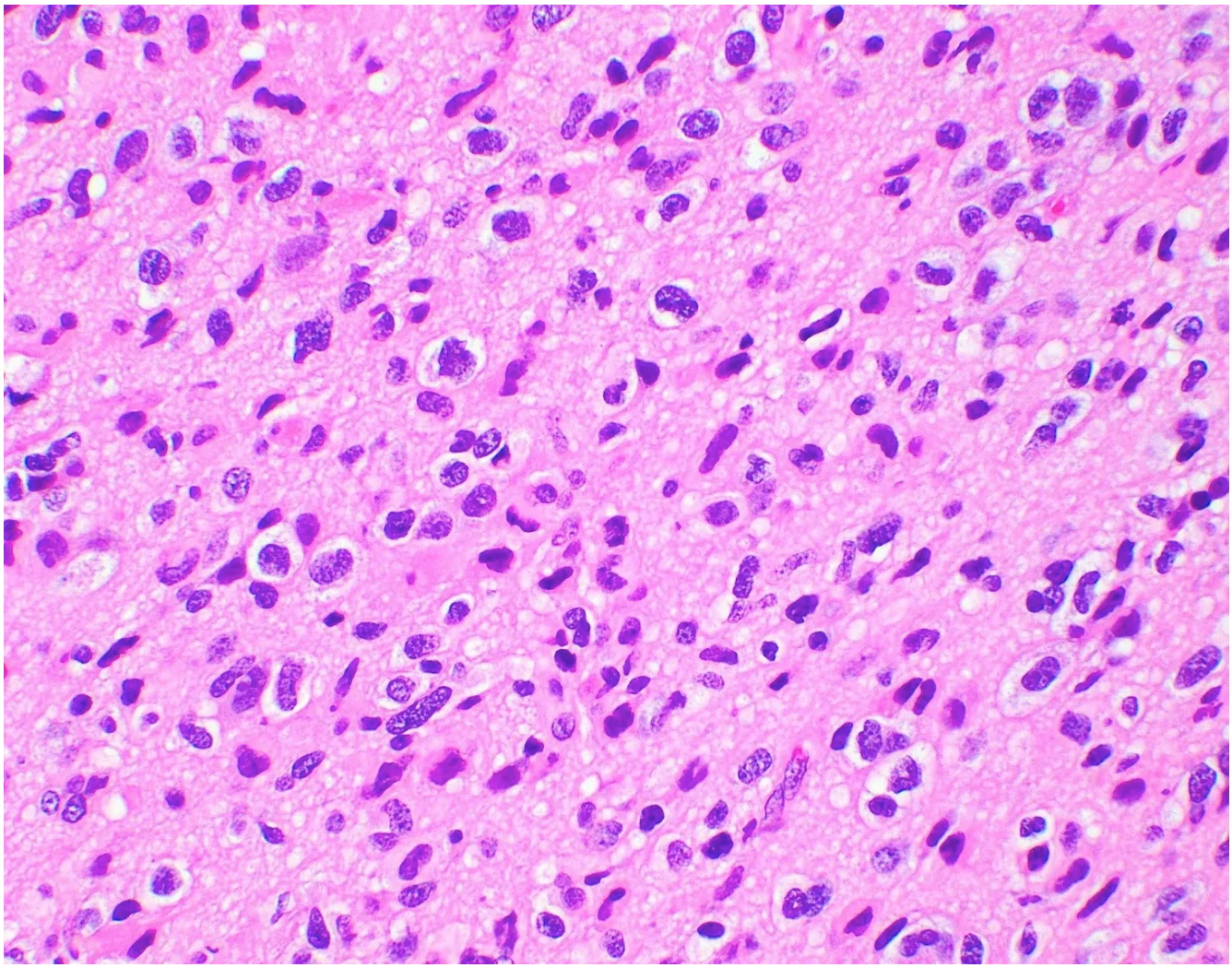


EGFR amplification and the *EGFRviii* mutation are common in glioblastoma and promote microvascular proliferation and other malignant properties (Oprita 2021).

Similarly, oligodendroglioma, a relatively uncommon brain tumor, has defining mutations in both *IDH1* or *IDH2* and 1p / 19q whole arm codeletions. These *IDH* mutations create an enzyme that generates a metabolite not normally detectable in the brain (Exner 2019). The metabolite disrupts the function of proteins involved in epigenetic modification and interrupts the differentiation process. The *IDH* mutation appears to be a gatekeeper that triggers uncontrolled proliferation, which renders cells vulnerable to additional mutations that further the malignant process until a clinically evident tumor is identified; however, as with glioblastoma, none of these steps would be considered a morphologic precursor.



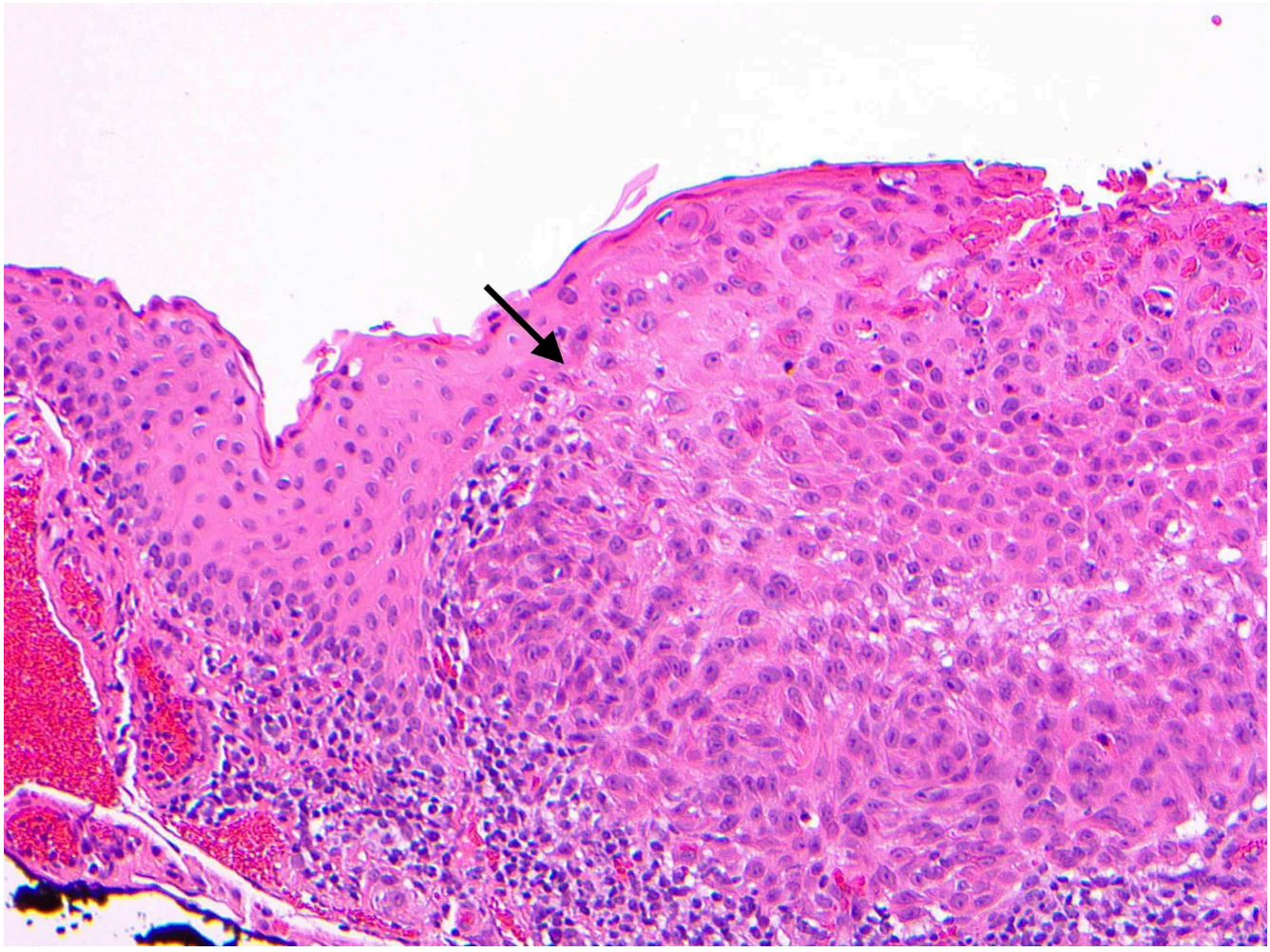
Mutations to *IDH1* or *IDH2* generate a unique enzyme (right side) that destabilizes brain cells and promotes malignancy (Losman 2013).



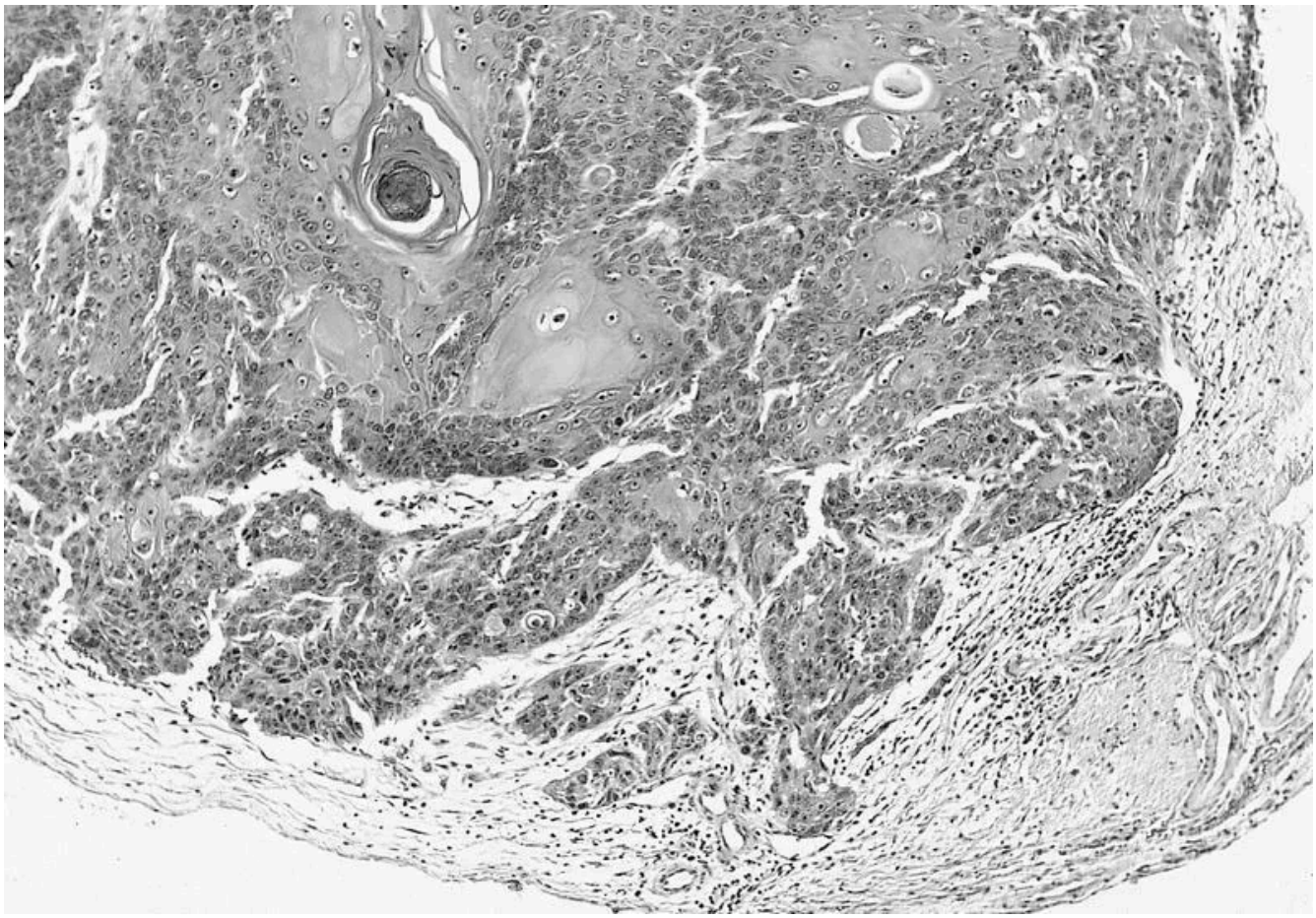
Oligodendroglioma: closely packed cells with small, round, monotonous nuclei and perinuclear clearing (fried egg appearance) (contributed by John DeWitt, M.D., Ph.D.). Small clusters of these cells may be the earliest identifiable indication of oligodendroglioma.

Pituitary hyperplasia, particularly in familial cases, may theoretically be a precursor to pituitary neuroendocrine tumors, analogous to how endocrine cell hyperplasia is a precursor to stomach neuroendocrine tumors, but adequate evidence is lacking.

In the eye, we have only identified one precursor: conjunctival intraepithelial neoplasia, which may lead to conjunctival squamous cell carcinoma and follows the classic intraepithelial neoplasia pathway described previously for carcinomas.



Conjunctival intraepithelial neoplasia (arrow) on the right side, compared to normal squamous epithelium on the left (contributed by Frederick A. Jakobiec, M.D., D.Sc.).



Conjunctival squamous cell carcinoma with deep invasion (contributed by AFIP).

Part 3 will discuss precursors associated with skin malignancies.

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