Retinal Reactive Astrocytic Tumor (Focal Nodular Gliosis): The Entity Also Known as Vasoproliferative Tumor

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Ascribing the best name to a biologic process not only allows for accurate determination of its pathogenesis, but also enables discovery and application of appropriate treatment. This is particularly true in the age of molecular medicine. These iterative name changes often coincide with histopathologic and molecular diagnostic interpretations of clinically described entities. As has occurred many times in the past, such as for the retinal tumors retinoblastoma and hemangioblastoma, a name change is currently underway for the retinal tumor reactive retinal astrocytic tumor (focal nodular gliosis), formerly known as vasoproliferative tumor [1–3].

This entity was described by Henkind and Morgan [4] as “peripheral retinal angioma” [5]. It was subsequently termed “angioma-like mass” [6], “retinal angiomatous mass” [7], “neovascular fundus abnormalities” [8], “peripheral nodular retinal telangiectasis” [9], and “angiomatoma-like lesion” [10] occurring after numerous con-

ditions including retinopathy of prematurity, retinal detachment surgery, uveitis, sickle cell disease, and others. Shields and co-workers [11] described this condition as “presumed acquired retinal hemangioma” and finally as “vasoproliferative tumor” [12], a name that persists in the current literature and clinical practice. Recent histopathologic analyses have shown that the vascular component of the tumor is minor and the glial/astrocytic component predominates, even in early lesions [1, 2, 13–16]. These findings and their interpretations [17, 18] have led to some controversy centering in the desire to preserve the use of clinical appearances as the best way to define the lesion. There is a concomitant resistance to more refined cytometabolic [13] molecular genetic characterization [1] – ideally correlated with clinical data.

Based on histologic, immunohistochemical, and molecular diagnostic findings, this tumor was called “reactive retinal astrocytic tumor” [1]. In fact, when experienced neuropathologists reviewed the histopathology of this tumor, none thought that it was vascular in nature; all interpreted these to be primary glial/astrocytic tumors and wondered if they could even be low-grade malignant astrocytomas. Studies of this tumor included a lack of BRAF-KIAA gene rearrangement and IDH1-R132H mu-

tation, which were associated with central nervous system astrocytomas (especially pilocytic examples). Therefore, the notion of pilocytic astrocytoma was excluded [1, 19]. Furthermore, pilocytic astrocytoma, the preeminent benign tumor of the optic nerve frequently seen in neurofibromatosis type I [20], has never been convincingly reported as a primary lesion of the retina in contradistinction to submassive and massive gliosis. Subsequent gene expression profiling studies showed that this tumor exhibits genes upregulated in reactive astrocytes and not vascular endothelium, thus supporting the primary astrocytic nature of this tumor [13]. Jakobiec and co-workers [2] analyzed 15 cases of retinal tumoral astrocytic proliferations and reviewed the literature. That study showed a spectrum of retinal reactive astrocytic proliferations, including reactive gliosis, focal nodular gliosis (occupying <25% of the posterior compartment), submassive gliosis (25–50% of the posterior compartment), and massive gliosis (>50% of the posterior compartment). They suggested that these lesions are all interrelated and exist on a continuous spectrum [2]. Hudson and co-workers [3] published the “missing link” case, in which a patient first clinically diagnosed with a “retinal angioma” (focal nodular gliosis) was followed over a period of years during which the tumor slowly progressed; the eye was subsequently enucleated and it was shown to contain massive gliosis. Taken together, it is now clear that retinal reactive astrocytic tumor (focal nodular gliosis) is the preferred name for this entity.

Changing the name of a clinically described retinal tumor based on the pathology of the tumor is not without precedent. The story of retinoblastoma is several centuries old, as it was first recognized in a young child’s autopsy report from 1597 [21]. Between the 16th and 19th centuries, the tumor carried several names, mostly describing its gross appearance including “soft cancer” and “fungus haematodes” [22]. Microscopic techniques in the 19th century allowed for the discovery of glioma-like features in some cases, thus inspiring Virchow [23] to coin the term “glioma of the retina.” In the later part of the century, Flexner [24] and Wintersteiner [25] separately observed that photoreceptor-like rosettes were frequently present in tumor sections, and re-named the tumor “neuroepithelioma.” Given the coexistence of glial and neuronal cell types from a common retinal precursor, Verhoeff and Jackson [26] suggested that the term “retinoblastoma” be used, and this name was officially adopted at the 1926 American Ophthalmological Society meeting. Later techniques, including electron microscopy and immunohistochemistry, have given further credence to the name

“retinoblastoma” by confirming that the tumor is of retinal precursor cell origin, and has the potential to remain in an undifferentiated state or to differentiate into photoreceptor-like cells [27–34].

The story of retinal hemangioblastoma dates back to 1904, when von Hippel [35] described a “very rare disease of the retina” which he named “angiomatosis retinae.” The name “retinal angioma” was used for nearly a century, due to the striking vascular appearance of the tumor, occurring as a solitary retinal finding in von Hippel disease or in a systemic context with other tumors in von Hippel-Lindau syndrome [36]. Conventional staining methods of fixed sections allowed for initial tumor descriptions, including the finding of vacuolated foamy stromal cells among vessels [37, 38]. More recently, laser capture microdissection, in conjunction with polymerase chain reaction of DNA from tumor cells, allowed for the discovery that the loss of heterozygosity of the VHL gene was in fact in stromal cells, and not in the vascular component of these tumors [39]. Furthermore, it was by immunohistochemical staining and Western blot analysis that VHL tumor cells were shown to be developmentally arrested hemangioblasts; they expressed fetal hemoglobin, indicative of primitive hematopoiesis, and they co-expressed Epo and EpoR, suggestive of arrested vascular development [40, 41]. As a result, over the later part of the 20th century, the names “retinal angioma” and “retinal capillary hemangioma” have been dropped in favor of the more accurate “retinal hemangioblastoma,” which highlights that these tumors are not of a purely mature vascular origin, but rather, of a more primitive cellular origin, and thus may give rise to the stromal cells or endothelial cells seen within the tumor.

Histopathologic and molecular diagnostic studies of a clinical entity trump its clinical descriptive terminology, albeit a change in engrained habits may be difficult. It is important to embrace these changes, as appropriately naming an entity and understanding its basic biology are relevant to progress in treating the entity. We now add to the list of “retinoblastoma” as the preferred name for “glioma” and “hemangioblastoma” as the preferred name for “angioma” that “reactive retinal astrocytic tumor” or “focal nodular gliosis” should replace the name “vasoproliferative tumor.”

Disclosure Statement

The authors declare no conflicts of interest.

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