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So-called massive retinal gliosis: A critical review and reappraisal

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ABSTRACT

Massive retinal gliosis, a nonneoplastic retinal glial proliferation, was first described in detail over 25 years ago, before the era of immunohistochemistry, in a series of 38 cases—to which can be added 30 case reports or small series (no more than 3 cases) subsequently. We analyze a new series of 3 nontumoral intraretinal glioses and 15 cases of tumoral retinal gliosis, not all of which, strictly speaking, were massive. The data from this series are compared with the findings in previously published cases. Included are 2 cases of massive retinal gliosis diagnosed from evisceration specimens. In reviewing all published and current cases, we were able to establish 3 subgroups of retinal tumoral glioses rather than a single "massive" category: focal nodular gliosis, submassive gliosis, and massive gliosis. Among 43 reported cases, including the present series, but excluding the previous large series of 38 cases in which substantial clinical data were omitted, there were 19 men and 24 women. Their mean and median ages were 36.2 years and 36 years, respectively, with a range of 2 to 79 years. All lesions were composed of mitotically quiet, compact spindled fibrous astrocytes devoid of an Alcian blue-positive myxoid matrix. The most common associated ocular conditions were phthisis bulbi and congenital diseases or malformations. Histopathologically, all 3 tumoral categories were accompanied by progressively more extensive fibrous and osseous metaplasia of the pigment epithelium, the latter forming a clinically and diagnostically useful, almost continuous, outer rim of eggshell calcification in the submassive and massive categories that should be detectable with appropriate imaging studies. In decreasing order of frequency, microcysts and macrocysts, vascular sclerosis, exudates, calcospherites, and Rosenthal fibers were observed among the proliferating fibrous astrocytes. Immunohistochemistry was positive for glial fibrillary acidic protein in all cases and

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nestin in most (an intermediate cytoplasmic filament typically restricted to embryonic and reparative neural tissue). The nonneoplastic nature of all categories of gliosis was confirmed by absent *TP53* (tumor suppressor gene) dysregulation, Ki-67 negativity, and intact p16 expression (the protein product of the *p16* tumor suppressor gene) in the overwhelming majority of cases. These findings indicate an intrinsic attempt to regulate and maintain a low level of glial cell proliferation that becomes unsuccessful as the disease evolves. The categories of tumoral proliferation appeared to constitute a spectrum. We conclude that focal nodular tumors encompass lesions previously called retinal vasoproliferative lesions, which display the same histopathologic and immunohistochemical findings as 3 major categories of retinal gliosis characterized herein.

1. Introduction

Gliosis refers to the activation and subsequent nonneoplastic proliferation of glial cells in response to stimuli that disrupt neuroglial and neuronal function, structure, and homeostasis.[11] With regard to the mammalian retina, Müller cells and fibrous astrocytes constitute the 2 major types of glial cells.[9,24,30] The term *massive retinal gliosis* (MRG) has been used to describe a pseudoneoplastic proliferation of retinal glial cells that may occur in association with phthisis bulbi, congenital ocular malformations,[38] trauma, and retinal detachment, among other disorders.[75] MRG as an entity was originally described by von Hippel in 1905.[28] Friedenwald in 1926[21] and Ryan in 1954[57] later invoked the term and elucidated the lesion's benign nature.[21] Yanoff and coworkers further enlarged our knowledge of the clinical and histopathologic features and some clinical correlations of this entity by describing an additional 38 cases before the era of immunohistochemistry.[75]

In this review, we have several objectives: (1) to present the results of a cohort of new cases of intraocular gliosis that we were able to assess first-hand; (2) to evaluate the immunohistochemical features of these lesions with a uniform and expanded panel of biomarkers; and (3) to compare our results with those already reported in the literature. Most of our cases were diagnosed from enucleated globes; 2, however, were diagnosed for the first time from evisceration specimens. Immunohistochemical testing on our new cohort of patients included nestin (an intermediate cytoplasmic filament found in neuronal tissue during embryogenesis that mostly disappears in adult tissue, but can reappear with reparative responses) and *p16* (a tumor suppressor and antiproliferation gene) heretofore generally neglected in ophthalmic pathology. Finally, our studies have led to the discovery that many lesions are not "massive," which prompted a new 3-part classification schema for tumoral lesions and furnished additional proof of their essentially reactive nature.

2. Report of a new series

2.1. Sources of the specimens

A new cohort of patients was studied with the approval and under the auspices of the Institutional Review Board of the Massachusetts Eye and Ear Infirmary (protocol number 782968-2), which served as the center for collating data from 3 institutions, the Massachusetts Eye and Ear Infirmary, the Emory University Eye Center, and Duke University. Eighteen specimens from 17 patients were identified for inclusion in this study after critical review of diagnostic files, clinical histories, and histopathologic features as revealed in hematoxylin and eosin stained paraffin sections. One case occurring in a patient with neurofibromatosis type-1 has been previously reported.[37] Osseous metaplasia of the pigment epithelium required light decalcification in many cases of phthisis bulbi. Persistent and intact antigenicity was confirmed with internal positive controls of normal immunoreactivity in unaffected tissues of the globes. Immunohistochemical results on globes undergoing decalcification compared with those that did not receive this treatment did not disclose any staining differences.

2.2. Clinical findings

There were 8 men and 6 women in our series of 15 tumoral glioses (Table 1, cases 4–17); 1 case of Norrie disease was bilateral. The patients' ages ranged from 6 to 72 years, with a mean of 30.1 years and a median of 22 years. Nine patients had phthisis bulbi. The patients' clinical histories were often sketchy, but when stated, 4 included an intraocular mass, 3 had had significant penetrating ocular trauma, 2 eyes (1 patient) were from a patient with Norrie disease,[7] and 1 patient each had congenital microphthalmia, neurofibromatosis,[37] Coats disease, retinopathy of prematurity, endophthalmitis, or chronic uveitis. Two of the cases were unusual in being examples of MRG diagnosed from evisceration specimens (Table 1, cases 15 and 16; Fig. 1A and 1B).

2.3. New histopathologic diagnostic categories

The salient microscopic features of 15 tumoral lesions and 3 flat intraretinal reparative glioses discovered in the pathologic specimens are summarized in Table 2. In surveying the various patterns of pseudoneoplastic masses, 3 categories emerged. Excluded from this tripartite classification were instances of nontumoral, localized or diffuse, reactive/reparative intraretinal gliosis (Figs. 1C–F and 2A and 2B). This gliotic pattern was apt to be seen after trauma, infection, laser therapy, failed retinal detachment surgery, or in Coats disease