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Research Article

Nevus Cells Associated with Primary Posterior Uveal Melanomas. A Real-World Study

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Abstract

Background/Objective: Two independent reports of systematic histopathological review of primary posterior uveal malignant melanomas published more than 50 years ago indicated that nevus cells were associated with the uveal melanoma in approximately 75% of cases. The purpose of this study was to determine the frequency of identification of uveal nevus cells associated with primary posterior uveal melanomas in official ophthalmic pathology reports not generated as part of a systematic pathologic study. **Methods:** Retrospective review of official ophthalmic pathology reports on 132 primary posterior uveal melanomas generated over a 40-year interval by 8 different ophthalmic pathologists. The numbers of reports that contained specific mention of nevus cells or spindle A melanocytic uveal cells or a description of cells consistent with uveal nevus cells or spindle A cells were determined. **Results:** Only approximately 25% of official ophthalmic pathology reports reviewed for this study contained any mention of uveal nevus cells or spindle A melanocytic uveal cells or any description of unnamed cells consistent with uveal nevus cells or spindle A cells. **Conclusions:** Uveal nevus cells do not appear to be a prominent feature of most primary posterior uveal melanomas.

Introduction

Independent reports of systematic histopathological review of hematoxylin & eosin stained microsections of primary uveal malignant melanomas by 2 different groups of ophthalmic pathologists [1, 2] published more than 50 years ago indicated that nevus cells were associated with the uveal melanoma in approximately 75% of cases. The objective of the study reported in this article was to determine the frequency with which nevus cells associated with primary posterior uveal melanomas were mentioned in official ophthalmic pathology reports generated as part of standard histopathologic study of primarily enucleated eyes over a 40-year interval.

Materials and Methods

The author generated a date-of-treatment ordered list of cases of patients with primary posterior uveal melanoma treated by primary enucleation during the interval January 1979 through December 2018. The source of this list was a comprehensive inventory of all cases encountered by the author in his clinical ocular oncology practice during this 40-year interval. Using a random number method, the author selected (without knowledge of the size of the primary intraocular tumor, the tumor's officially-assigned uveal melanoma cell type, the patient's outcome with regard to metastasis, or the identity of the ophthalmic pathologist who generated the official ophthalmic pathology report) from this list 33 cases from each of four sequential 10-year intervals (i.e., interval 1 = 1979-1988; interval 2 = 1989-1998; interval 3 = 1999-2008; interval 4 = 2009-2018) for a total of 132 cases. The author reviewed the official ophthalmic pathology report of each of these cases and determined whether the report specifically mentioned uveal nevus cells [3] associated with the primary posterior uveal melanoma. The author also determined how many of these reports specifically mentioned spindle A-type uveal melanocytes, a type of atypical uveal melanocytic cells originally categorized as a malignant uveal melanoma subtype [4] but subsequently recategorized as a specific type of benign uveal nevus cells [5], or described without naming uveal melanocytic cells consistent with nevus cells [6] within or contiguous with the primary posterior uveal melanoma. Reports that identified or described a posterior

uveal nevus somewhere in the eye that was not contiguous with the primary posterior uveal melanoma were not counted as instances of associated uveal nevus cells.

Results

The 132 posterior uveal melanocytic tumors described in the official ophthalmic pathology reports included 85 exclusively choroidal tumors (64.4%), 44 ciliochoroidal tumors (33.3%), and 3 iridociliochoroidal tumors (2.3%). The tumors ranged in size from 4 to 23 mm in largest basal diameter (mean 13.3 mm, std. dev. 3.9 mm), from 3.6 to 19 mm in smallest basal diameter (mean 11.8 mm, std. dev. 3.6 mm), and from 1.3 to 18 mm in maximal thickness (mean 7.8 mm, std. dev. 3.7 mm). Based on the reported tumor measurements, 20 tumors (15.2%) would have been categorized as T1 clinical tumor size according to the American Joint Commission on Cancer's Tumor Node Metastasis (TNM) classification system [7] while 36 (27.3%) would have been categorized as T2, 55 (41.7%) as T3, and 21 (15.9%) as T4. Forty-two of the tumors (31.8%) were categorized by the pathologist as purely spindle cell melanomas, 70 (53.0%) as mixed cell type melanomas, 17 (12.9%) as epithelioid cell melanomas, and 3 (2.3%) as necrotic melanomas.

Eight different ophthalmic pathologists had generated the official ophthalmic pathology reports of these cases. All of these pathologists had trained at least in part at the Armed Forces Institute of Pathology (AFIP) under the late Dr. Lorenz E. Zimmerman or had received at least part of their ophthalmic pathology training supervised by an individual who had trained at the AFIP. The number of reports generated by each of these eight pathologists ranged from a maximum of 43 to a minimum of 1 (see Table 1).

Pathologist	Number of reports generated by pathologist	Number of reports containing specific mention of nevus cells	Number of reports containing specific mention of spindle A cells	Number of reports containing description of cells consistent with nevus cells	Number of reports containing description of cells consistent with spindle A cells
1	43	0	8	5	1
2	30	0	0	2	0
3	28	0	5	3	
4	12	1	1	2	1
5	9	1	1	0	0
6	8	1	2	0	0
7	1	0	0	0	0
8	1	0	0	1	0
Totals	132	3 (2.3%)	17(12.9%)	13(9.8%)	2(1.5%)
2 reports (1 by pathologist 1 & 1 by pathologist 3) mentioned spindle A cells specifically and described balloon cells consistent with nevus cells. 1 report (by pathologist 6) mentioned both spindle A cells and nevus cells specifically.					

Table 1: Numbers of official ophthalmic pathology reports that mentioned or described nevus cells and/or spindle A cells associated with primary posterior uveal malignant melanoma.

Only 3 of the 132 reports (2.3%) specifically mentioned uveal nevus cells associated with the primary posterior uveal melanoma. Seventeen of the reports (12.9%) specifically mentioned spindle A cells associated with the posterior uveal melanoma. Only 1 report specifically mentioned both uveal nevus cells and spindle A cells associated with the posterior uveal melanoma. Thirteen reports (9.8%) described cells consistent with nevus cells without naming those cells specifically, and 2 reports (1.5%) described uveal melanocytic cells consistent with spindle A cells without naming them specifically. Two reports mentioned spindle A cells specifically and also mentioned balloon cells, a specific category of uveal nevus cells [6], associated with the malignant tumor. One hundred one reports (76.5%) did not mention or describe either nevus cells or spindle A cells associated with the posterior uveal melanoma. Only thirty one reports (23.5%) specifically mentioned nevus cells or spindle A cells or described melanocytic cells consistent with nevus cells or spindle A cells.

The uveal nevus cells that were mentioned and/or described in the reviewed reports were (1) admixed with the malignant cells of the tumor in 15 cases, (2) located at the periphery or margin of the malignant tumor in 12 cases, (3) located at the base of the tumor in 3 cases, and (4) located within a distinct lobule of the malignant tumor in 1 case. Two of the reports that mentioned or described such cells did not specify where those cells were located relative to the malignant portion of the tumor.

Discussion

In this study, uveal nevus cells and/or spindle A melanocytic uveal cells were identified and/or described in only 31 of 132 reviewed official ophthalmic pathology reports (23.5%). This percentage is markedly different than the 147 of 195 cases (75.4%) with associated uveal nevus cells reported in aggregate by Naumann, Yanoff & Zimmerman [1] and Arnesen & Nornes [2]. The difference between our study and the aggregated reports is strongly statistically significant (chi squared = 85.5, $P < 0.00001$).

How can one explain the difference in percentage of cases with uveal nevus cells associated with the primary uveal malignant melanoma between these studies? Possible explanations include the following:

1. The ophthalmic pathologists who generated the official ophthalmic pathology reports reviewed in the current study were incompetent (i.e., unable to recognize nevus cells associated with the malignant uveal melanoma when they were present) and therefore did not detect such cells in many cases that actually contained them. In my opinion, this potential explanation seems highly unlikely. Several of the ophthalmic pathologists who generated reports reviewed in this study are well-known experts in their field and authors of multiple peer reviewed articles on pathology of uveal melanoma.

2. The ophthalmic pathologists who generated the official ophthalmic pathology reports actually detected uveal nevus cells associated with many of the malignant melanomas they studied but failed to mention them in their official reports. While one cannot discount this potential explanation, this also seems unlikely. Ophthalmic pathologists as a group tend to be accustomed to identifying all relevant features of evaluated specimens in their reports and not just the most important features.

3. The cases evaluated in this study were somehow substantially different than those evaluated in the studies by Naumann, Yanoff & Zimmerman [1] and Arnesen & Nornes [2] and did not have uveal nevus cells associated with the primary uveal melanoma nearly as frequently as those evaluated by the prior investigators. This potential explanation also seems unlikely unless the cases reviewed by Yanoff & Zimmerman and Arnesen & Nornes were somehow remarkably similar just by chance alone.

4. Naumann, Yanoff & Zimmerman [1] and Arnesen & Nornes [2] both over-identified uveal nevus cells associated with the primary uveal melanomas in the cases they studied. However, the fact that both groups detected approximately the same proportion of cases having associated nevus cells suggests that this explanation is also unlikely.

5. Many of the cases reported by Naumann, Yanoff & Zimmerman and by Arnesen & Nornes may have had only a few nevus cells associated with the malignant melanoma. While such cases would have been counted as having associated nevus cells in those systematic studies, the nevus cells in such cases might well be overlooked in routine pathologic studies therefore not mentioned in most of the pathology reports reviewed in this study. In my opinion, this explanation seems most likely. The fact that such cells were not mentioned in most of the official ophthalmic pathology reports reviewed in this study suggests that nevus cells were not a prominent component of or association with most of those primary posterior uveal melanomas.

Conclusion

While nevus cells may be associated with over 70% of primary posterior uveal melanomas when studied systematically, this study suggests that such cells are likely to comprise an inconspicuous component of most such tumors.

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