Chorioretinal Dysplasia in Sprague-Dawley Rats: Ophthalmologic and Histopathologic Characterization

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ABSTRACT

Introduction: Sprague-Dawley (SD) rats are frequently used for toxicology testing. Ophthalmology examination is a common endpoint to monitor for potential lesion development in safety toxicology studies. An ophthalmoscopic finding of focal linear increased scleral reflectivity, almost invariably presenting unilaterally, and described as "chorioretinal hypoplasia" is seen with a prevalence of 0.41% in the MPI Research SD colony. The aims of this study were to: 1) generate a detailed histopathological characterization of lesions associated with the ophthalmoscopic findings, and 2) harmonize clinical and histopathological language.

Methods: On pre-study indirect ophthalmoscopy exams, a board-certified ophthalmologist identified multiple SD rats (11 males, 10 females) with lesions of chorioretinal hypoplasia, and wide-field fundus imaging was performed. Serial H&E-stained microscopic sections of these eyes were examined by a board certified pathologist; ophthalmoscopic and histopathologic findings were compared.

Results: SD rats with ophthalmoscopic lesions had histopathologic findings of choroidal absence with or without accompanying absence of one or more retinal layers in an outer-to-inner progression. We propose using harmonized call language of chorioretinal dysplasia for this finding, differentiating it from other rat retinal atrophies. Conclusion: Chorioretinal dysplasia in the SD rat is characterized by ophthalmoscopic findings of focal linear increased scleral reflectivity, and histopathologic findings of retinal and choroidal thinning to absence.

Impact Statement: This study describes a previously unreported ophthalmologic finding in the Sprague-Dawley rat and provides a descriptive pathologic classification of the lesion. Recognition of this background finding is important, as it could be misinterpreted as an adverse, compound-related lesion.

INTRODUCTION

Sprague-Dawley (SD) rats are used extensively in toxicology studies, with both ophthalmological and histopathological ocular assessment. One important aspect of many of these studies is the characterization of congenital and spontaneous ocular lesions, facilitating differentiation from toxicologically relevant findings. Ophthalmologists at MPI Research currently routinely visualize a lesion initially designated as chorioretinal hypoplasia. It is described as marked, focal scleral hyper-reflectivity, and is typically unilateral, linear, and sharply demarcated. Animals manifesting this finding at pre-initiation screening are not used on study, resulting in a historic lack of histopathological characterization of these findings. When it has been explored in other studies, the ophthalmoscopic lesion is almost unanimously described microscopically as thinning or absence of the outer nuclear layer, and discontinuity in the retinal pigment epithelium and choroid. Several manuscripts have documented this finding histopathologically in SD rats, but with variable terminology, including focal chorioretinal atrophy, linear focal retinopathy, linear retinochoroidal dystrophy, retinal dysplasia, and choroidal defect.[1,3,4] The purpose of this study was to identify affected SD rats at MPI Research with ophthalmology pretesting, and compare ophthalmoscopic findings to histopathologic findings to better classify the lesion in this species.

METHODOLOGY

Routine pre-study ophthalmology examinations identified 21 SD rats with linear retinal hyper-reflectivity. Rats were evenly divided between mature males and females. Twenty of these animals were removed from the study control population and humanely euthanized. At necropsy, eyes were removed and fixed in modified Davidson's solution. Eyes were vertically sectioned from the nasal to temporal side at 250 micron intervals and stained with hematoxylin and eosin. Slides were assessed by a board-certified veterinary pathologist and morphologic diagnoses were compared to the ante mortem lesion. Full characterization of each lesion was made using both ante mortem and histopathologic findings. Four animals did not have images available for retrospective analysis of ophthalmologic findings and two of these had no histopathological findings.

RESULTS

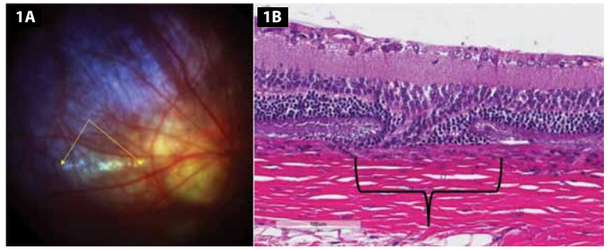

Figure 1: A. Small area of linear scleral hyper-reflectivity temporal to optic nerve. **B.** Histopathology of same eye, showing abrupt discontinuity of choroid and disorganization of the nuclear layers (H&E 200x).

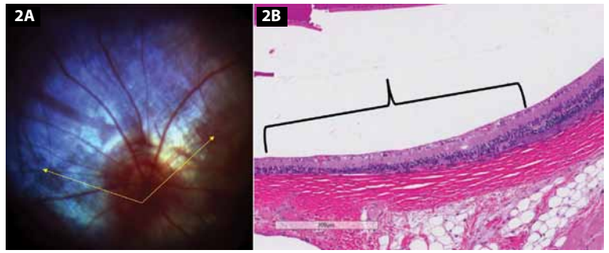

Figure 2: A. Large area of scleral hyper-reflectivity in the superior nasal to temporal aspect of the eye. **B.** Histopathology of same eye, showing an area of complete absence of outer nuclear layer, retinal pigmented epithelium, and choroid (H&E 80x).

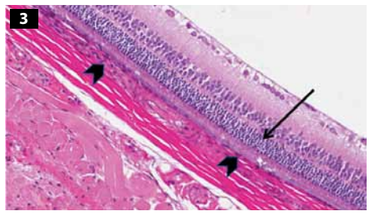

Figure 3: Normal retina with outer nuclear layer (black arrow) and choroid (arrowheads) (H&E 200X).

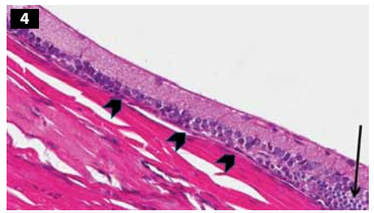

Figure 4: Affected retina and choroid. Note the progressive loss of choroid (arrowheads) and outer nuclear layer (black arrow) (H&E 200X).

- All animals had only unilateral findings, with the majority of findings in the right eye (14/20).
- Of the 20 animals with ophthalmic findings, 17 (85%) had correlated histopathological findings.
- There was variation in areas affected. Most were in the nasal half of the eye (13/17), with fewer in temporal regions (7/17), with findings less commonly seen in both regions (5/17).
- The number of affected sections varied between 3/19 (17%) and 19/19 (100%), with an average of 59% of sections examined being affected in those animals with histopathological findings, and 50% overall, including animals with no histopathological findings (n=3).
- The smallest lesion that was detected both ophthalmoscopically and microscopically was seen across 3 sections and measured approximately 720 microns in length by 100 microns in width.
- The largest lesions spanned the entire range of sectioning (19/19) and measured approximately 4.56 mm in length by 4 mm in width.
- The prevalence of this ophthalmological finding in the MPI Research SD colony is 0.41%, with affected rats removed from the study population.

RESULTS CONTINUED

Ophthalmic findings: Unilateral, focal, linear to regional, scleral hyper-reflectivity.

Microscopic findings: Chorioretinal lesions correlating to the focal scleral hyper-reflectivity consisted of thinning to complete absence of the outer retinal nuclear layer, retinal pigmented epithelium, and choroid. The inner retinal nuclear layer in these regions was also decreased in thickness.

Morphologic diagnosis: Chorioretinal dysplasia

CONCLUSIONS

- The ophthalmoscopic and microscopic characteristics are similar to previous descriptions.
  - Tanaka et al. (1993) found similar incidence of the lesion (0.5%) and called it focal chorioretinal atrophy. They considered it to be secondary to choroidal capillary damage and hemorrhage, although we found no evidence of hemorrhage.
  - Hubert et al. (1994) called the lesion linear focal retinopathy and described it as loss of the outer nuclear layer with no disruption of the choroid. This contrasts with the clear disruption and absence of the choroid seen in these rats.
  - Others did not specifically address this finding, but may have included it under retinal atrophy or degeneration.[2,4,5]
- Chorioretinal dysplasia was considered to be the most appropriate term for this finding.
  - The segmental loss of the choroid, retinal pigment epithelium, and the outer nuclear layers support the presumptive failure of normal choroid formation and the term dysplasia.
  - This lesion should be distinct from atrophy and degeneration.
    - Atrophy as a morphologic diagnosis does not distinguish between developmental, environmental, or hereditary causes. We have no evidence that the choroid and retina were initially normal and progressed to what we are seeing. However, this has not been fully investigated and will be the aim of a subsequent study.
    - We did not find any supporting evidence of cellular degeneration, merely a loss of choroidal and retinal structure and cells.
    - This is seen in young animals, suggesting it is not typical age related or chronic light exposure-induced degeneration.
- Ophthalmoscopic pre-study examinations can pick up small lesions that may not be identifiable histologically, particularly on single section examination of the eye.
- To date, we have not tracked the progression of these findings, although this is planned for further characterization of the finding.
- Further investigation of these retinal findings may allow the improved understanding and elimination of this background finding, or even utilization of as a model system.

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Special thanks to the ACVP for the ACVP Student Externship Scholarship, the Society of Toxicologic Pathology for the STP Student Travel Award, the MPI Research Pathology Externship Program for supporting Leah Stein, and Brian Samek for his embedding and histology efforts on this project.

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