The Importance of Peripheral Diabetic Retinopathy
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When I was first learning about diabetic retinopathy 40 years ago, I was fortunate to be personally tutored by Drs. Lloyd M. Aiello, Matthew Davis, and Arnall Patz. They all stressed the importance of lesions in the retinal periphery. Of course, they emphasized that this was a frequent site of neovascularization, but they also taught us to focus on other major lesions of nonproliferative diabetic retinopathy. In particular, they emphasized both extensive hemorrhages/microaneurysms and “featureless retina” as indications of peripheral nonperfusion. These peripheral lesions were elegantly and laboriously imaged in that era by Dr. Koichi Shimizu using fluorescein angiography. These angiograms, which were so painstaking to do at that time, are now elegantly simplified with ultra-widefield imaging. If the importance of these peripheral lesions has been known for decades, what is the relevance of the article by Silva et al (see page 949) in this issue of *Ophthalmology*?

Assessment of the severity of diabetic retinopathy and the risks of progression are largely based on the Modified Airlie House Classification system that was first proposed at the Airlie House Symposium on the Treatment of Diabetic Retinopathy in 1968, and modified for use in the Diabetic Retinopathy Study, and further modified on the basis of the accumulating results for the Early Treatment Diabetic Retinopathy Study. This system was based on reading center grading of the posterior pole of the fundus, using 7 standard 30-degree overlapping stereo photographic fields. As these protocols for assessing the severity of diabetic retinopathy developed, there was considerable discussion on how to include the peripheral fundus. Two major features limited how much of the periphery could be reproducibly assessed using the photographic methods available at the time. First, obtaining high-quality stereo 30-degree photographs in the periphery was technically difficult. Second, even if technically feasible, the burden on the patient of obtaining the additional stereo pairs necessary to cover the midperiphery was problematic. The compromise that evolved was to photograph only those peripheral fields outside the posterior 7 fields where neovascularization was observed or suspected. Because much of the literature associating lesions of diabetic retinopathy with the risk of retinopathy progression or vision loss is based on the assessment using the modified Airlie House grading system, the effect of lesions in the retinal periphery, although known to be important, has not been well documented and is not part of current grading systems for the severity of diabetic retinopathy.

The relative ease that new imaging techniques provide for obtaining photographs of the peripheral retina affords new opportunities to assess how important the peripheral lesions of diabetic retinopathy might be. The study by Silva et al in this issue addresses this question by dividing the population into 2 groups at baseline. They assessed the severity of diabetic retinopathy in the fundus covered by the traditional 7 stereo photographic fields and separately assessed the severity of diabetic retinopathy lesions in the peripheral retina, outside the 7 fields, using just ultra-widefield imaging without angiography. In the first group, the lesions used to assess retinopathy severity were equally or more prevalent in the 7 fields than in the periphery. In the second group, the lesions were more prevalent in the periphery and the group was identified as “predominantly peripheral lesions” (PPLs).

By dividing the population in this way, the authors were able to show that eyes with PPL were at considerably higher risk of progression of retinopathy compared with eyes without PPL. Of course, there is an inevitable bias in this analysis that favors progression in the PPL group. Because the assessment of severity is based on the level in the 7 fields, and because the PPL group is composed only of eyes with additional risk factors, it is highly unlikely that the group with more risk factors would be associated with slower or even the same rate of retinopathy progression. It is a comparison of eyes with equivalent or less retinopathy in the periphery with eyes with more severe retinopathy in the periphery. This is particularly obvious for the eyes with no retinopathy in the 7 fields. It is logical that the eyes with no retinopathy at all will be less likely to progress than eyes with retinopathy in the periphery. If one somehow reversed the analysis and based the severity of retinopathy on the lesions in the periphery and then created a subgroup with more severe retinopathy in the posterior pole, it is inevitable that one would find that the lesions in the posterior pole added to the risk estimate. There is no easy way to eliminate this bias. However, although the bias ensures the direction of the association, it is the magnitude of the association that is important in this case. These analyses demonstrate that there is considerable extra risk for eyes with lesions more prevalent in the peripheral retina. However, one cannot conclude that the lesions in the periphery are more important than posterior lesions, only that they add significantly to the risk assessment.

I suppose it is gratifying to prove that those who developed the grading systems years ago were correct when they...
emphasized the importance of peripheral lesions, but that is not the important result of this research. The important result is how it will change our clinical practice and future research. For clinical practice, it reinforces the need to assess the periphery when assessing the risk of progression for individual patients. The overall severity of retinopathy will help in determining how frequently patients need to be followed and when it is appropriate to intervene with treatment. It will also add to our ability to use telemedicine more accurately. For research, it suggests that we may need to further modify the “modified Airlie House grading system” because we can now reliably image the periphery. Including these peripheral lesions in a new grading system should provide better estimates of the overall risk of progression of diabetic retinopathy. This will be important in developing eligibility criteria for clinical trials designed to test interventions developed to slow the progression of retinopathy. It will also provide us with new guidelines for assessing the risks of retinopathy progression that we can use to discuss future risks and treatment options with our patients. There is no doubt that the new imaging tools that have evolved over the last decade dramatically improve our abilities to detect disease and thus provide better patient care.

References

Pictures & Perspectives

**Juvenile Xanthogranuloma**

Juvenile Xanthogranuloma (JXG) in 1-year-old boy who presented with a history of single left medial canthal lesion—smooth, raised, and orange—that was present for 10 months (Fig 1). Histopathology revealed diffuse granulomatous inflammation (Fig 2) with histiocytes and Touton giant cells (arrow).

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