Vitreoretinal lymphomas (VRL) are rare diseases. They comprise about 1% to 3% of intraocular tumors and the incidence varies between 0.02 to 0.05 of 100 000 people in the North American population.\(^1\)

In almost 90% of cases, VRLs are diffuse large B cell lymphomas (DLBCLs) and are considered to be a subtype of the primary DLBCLs of the central nervous system (CNS). Sixteen percent to 34% of patients with VRL have CNS involvement at the time of diagnosis and 35% to 90% will develop CNS lymphoma during the course of their disease. Conversely, 15% to 25% of patients with CNS lymphoma develop VRL.\(^2,3\)

Optical coherence tomography (OCT) is an important non-invasive diagnostic tool in diagnosing and managing retinal diseases. In VRL, most of the morphologic features that are seen on OCT are nonspecific.\(^4-6\) The aim of this study was to describe an OCT feature in patients with confirmed VRL.

**Methods**

We conducted a retrospective medical record review of patients who received a diagnosis of VRL at the Department of Ophthalmology at Northwestern University. The protocol was approved by the institutional ethics committee, who waived patient consent, and adhered to the Declaration of Helsinki. Patients who had a diagnosis of intraocular lymphoma who were seen by 2 senior attending physicians (D.A.G. and L.M.J.) between July 2014 and January 2016 were identified using a search of electronic medical records. Patient records and all imaging modalities that were carried out at the initial visit and subsequent visits were collected and reviewed for completeness and consistency. The exclusion criteria were an uncertain diagnosis and inadequate OCT image quality. Optical co-
Vertical hyperreflective lesions on Optical Coherence Tomography in Vitreoretinal Lymphoma

Results

We identified 12 eyes of 7 patients (4 women [57.1%] and 3 men [42.9%]) with VRL. The mean (range) age at initial presentation was 62.4 (45-75) years. The Table shows the baseline characteristics of the patients. Five patients (71.4%) had primary VRL and 2 patients (28.6%) had secondary VRL. One of the patients with secondary VRL received a diagnosis of systemic DLBCL 3 years before developing intraocular lymphoma that involved the retina and vitreous. The other patient received a diagnosis of testicular lymphoma with brain and intraocular involvement that was confirmed by chorioretinal biopsy results. In both of these cases, the ocular lymphoma involved the vitreous, neuroretina, and the subretinal pigment epithelial space (sub-RPE) but stayed above the Bruch membrane and as such was classified as secondary VRL. All of the remaining patients with primary VRL received a diagnosis of DLBCL based on either vitreous biopsy results (2 patients [40%]) or brain biopsy results (3 patients [60%]).

In 7 eyes (58.3%) of 5 patients, we identified vertical hyperreflective columns that varied in width but extended from the inner retina (ganglion cell layer [GCL] or retinal nerve fiber layer [RNFL]) to the outermost part of the neuroretina and the retinal pigment epithelium (RPE). We describe these findings as vertical hyperreflective lesions (VHRLs) (Figure 1). The intensity of VHRLs showed great variability, ranging from a hyperreflectivity similar to the RPE to a much more subtle midreflectivity similar to the GCL, but they were always more hyperreflective than the surrounding retinal tissue. Vertical hyperreflective lesions were most commonly located along the major vessel arcsades or temporal to the fovea and were only rarely visible on OCT scans centered on the fovea. We found that VHRLs were often but not always adjacent to retinal vessels (Figure 1, Figure 2, and Figure 3; eFigure in the Supplement). None of the VHRLs were detectable on color fundus photography or on the infrared images even after magnification and appropriate brightness, contrast, and gamma adjustments (Figure 1). On fundus autofluorescence images that were of gradable quality, VHRLs colocalized with sub-RPE deposits were usually hyperautofluorescent, but VHRLs without sub-RPE deposits were undetectable. The eFigure in the Supplement describes a collection of representative VHRLs in the cohort.

On follow-up examination, in some cases VHRLs resolved as quickly as 2 weeks after intravitreal or systemic immunotherapy or chemotherapy. In other patients, VHRLs persisted for up to 4 to 8 weeks. After resolution of the lesions there were no apparent signs of atrophy in the inner retina. In 2 patients (28.6%) in whom VHRLs were located on sub-RPE deposits we observed small RPE defects. After the resolution of the lesions, a small patch of RPE and inner segment/outer segment layer atrophy developed (eFigure in the Supplement; Figure 2). In the 2 patients for whom there were follow-up examination results before any therapy we observed a spontaneous resolution of VHRLs and an appearance of new lesions elsewhere. In several cases, sub-RPE deposits colocalized with VHRLs and in some instances sub-RPE deposits appeared subsequent to the development of VHRLs at the same location (Figure 2 and 3). These sub-RPE deposits had medium reflectivity, were either solitary or confluent “drusen like,” and were clearly located above the Bruch membrane in all cases. Choroidal lesions (under the Bruch membrane) were not observed in any of the patients.

Discussion

There remains uncertainty about the pathophysiology of VRL. Our understanding of VRLs is increasing, but because of the rarity of the disease and the difficulty in obtaining substantial tissue specimens, most of our knowledge is derived from studies done on primary CNS lymphomas. To our knowledge it is still not completely clear where the abnormal lymphocytes originate and how and why they target the specific tissues where they finally manifest. It is still debated whether lymphoma cells infiltrate the retina from the retinal vessels, from the optic nerve, or from the choroid through the Bruch membrane and the RPE.

Vertical hyperreflective lesions are located between the inner layers of the retina (GCL and RNFL) and the RPE. They are not stationary but seem to be constantly evolving and resolving; while they disappeared in one place, new ones appear elsewhere. We have also observed—as shown in Figure 2 and Figure 3—the appearance of sub-RPE infiltrates in the same locations where VHRLs were seen previously, although we could not associate every sub-RPE infiltrate with prior VHRLs. We also found that most of the VHRLs...
were around retinal vessels and some appeared to connect retinal vessels with sub-RPE deposits.

Our hypothesis is that VHRLs represent early microinfiltrates that are not visible on fundus examination, infrared imaging, and fundus autofluorescence. They may originate from second-order and third-order retinal vessels and capillaries. They infiltrate the retina and subsequently the sub-RPE space. As such, they follow the fluid flow that is seen in diseases with blood-retina barrier breakdown in which fluid originating from the retinal blood vessels penetrates through the retina and is pumped to the choroid by the RPE. However, because we could not identify VHRLs before the appearance of every sub-RPE deposits we cannot rule out that sub-RPE deposits might occur without VHRLs. A histologic examination of retinal tissue would be needed to confirm this hypothesis.

Vitreoretinal lymphoma has various findings on OCT. Saito et al described “focal round lesions in the neural retinal layer.” On their article’s figures, some of these lesions are larger, funduscopically visible retinal infiltrates while others seem to be similar microinfiltrates to the VHRL that we describe, although they do not describe the characteristic features of VHRL. In their series “focal round lesions” were present in 5 of 26 eyes. In their methods, they describe that horizontal and vertical OCTs were done at the macular level and through lesions identified on fundus photographs.

Table. Patient Demographics

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Diagnosis</th>
<th>Involved Eye</th>
<th>Biopsy Site</th>
<th>VHRL Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/mid 70s</td>
<td>SVRL</td>
<td>Right</td>
<td>Cecum</td>
<td>Right</td>
</tr>
<tr>
<td>2/F/mid 50s</td>
<td>PVRL</td>
<td>Both</td>
<td>Vitreous</td>
<td>Both</td>
</tr>
<tr>
<td>3/F/early 70s</td>
<td>PVRL</td>
<td>Both</td>
<td>CNS</td>
<td>None</td>
</tr>
<tr>
<td>4/M/mid 40s</td>
<td>PVRL</td>
<td>Both</td>
<td>Vitreous</td>
<td>None</td>
</tr>
<tr>
<td>5/M/late 40s</td>
<td>SVRL</td>
<td>Right</td>
<td>Chorioretinal</td>
<td>Right</td>
</tr>
<tr>
<td>6/M/early 70s</td>
<td>PVRL</td>
<td>Both</td>
<td>CNS</td>
<td>Left</td>
</tr>
<tr>
<td>7/F/late 60s</td>
<td>PVRL</td>
<td>Both</td>
<td>CNS</td>
<td>Both</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; F, female; M, male; PVRL, primary vitreoretinal lymphoma; SVRL, secondary vitreoretinal lymphoma; VHRL, vertical hyperreflective lesion.
We found that VHRLs are much more common (we found them in 7 of 12 eyes [58.3%]), are usually outside of the macular area, and are not visible on fundus photography, so the imaging done by Saito et al\(^6\) may have missed some lesions. In our cohort, the 2 patients in whom VHRLs were not found only had macular scans as baseline and during follow-up, so we may have missed the lesions as well in these cases.

In a recent publication, Barry et al\(^11\) describe OCT changes seen in primary VRL in a cohort of 22 patients. They note hyperreflective infiltrates in the inner layers of the retina in 18.8% of eyes, discrete nodules of hyperreflective foci in the subretinal space in 21.9%, and confluent bands of hyperreflective foci in the subretinal space in 31.3%, and suggest that the latter was highly suggestive of vitreoretinal lymphoma. In our series, we only saw 1 patient with a similar confluent band of hyperreflectivity, but we found VHRLs in 7 affected eyes (58.3%). We also observed that some of the VHRLs were oblique to the cut of the OCT scan and on dense scans lesions appearing in the inner retina were traceable to the RPE on subsequent B-scan slices. We suggest that some of the inner or outer retinal infiltrates seen by Barry et al\(^11\) may have been VHRLs that were only partially imaged. Furthermore, some of the figures in their article show completely imaged VHRLs, but they are unrecognized as such. While other diseases, such as multiple evanescent white dot syndrome, may have hyperreflective material extending toward the outer nuclear layer, in these diseases the material has not been found to extend to the GCL/RNFL\(^12\).

The high variability of changes seen on OCT in VRL has made OCT a less reliable surrogate than in other retinal diseases as similar morphologic findings can be seen in various types of posterior uveitis, age-related macular degeneration, or diabetic retinopathy. Optical coherence tomography features that are highly suggestive of VRLs, such as the one proposed by Barry et al\(^11\), can help in the diagnostic process.

**Limitations**

A limitation of our study is its retrospective nature and the limited number of imaging studies that were performed. In 3 patients (42.9%), only OCT scans centered on the fovea were performed but no peripheral scans. Of these 6 eyes we found infiltrates...
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Conclusions

We believe that VHRL is a sign that may suggest the diagnosis of VRL and provide clues as to its pathogenesis. Performing OCT scans outside of the central macular area in patients in whom VRL is suspected might reveal the presence of VHRLs. Performing dense scan patterns helps in the detection as it enables the tracing of obliquely oriented VHRLs. If further confirmation is noted, the finding of VHRLs on OCT might justify adding VRL to the differential diagnosis in patients with otherwise undiagnosed retinal diseases.

REFERENCES


