SD-OCT and autofluorescence characteristics of autoimmune retinopathy

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INTRODUCTION

Autoimmune retinopathy (AIR) is a broad term that encompasses a set of rare but visually devastating immune mediated retinal degeneration syndromes that are characterised by acute or subacute vision loss, abnormal electroretinograms (ERGs) and serum antibodies directed against retinal antigens.1–4 This term includes the paraneoplastic syndromes of cancer associated retinopathy (CAR), melanoma associated retinopathy, and non-paraneoplastic associated retinopathy.2 Patients classically present with acute to subacute vision loss, nystagmus and photopsias. The physical exam is generally unremarkable, but findings may include optic nerve pallor, retinal pigment epithelial (RPE) changes, vitreous cell and most commonly vascular attenuation.5 Kinetic visual field testing can be used to detect peripheral field constriction. ERG testing will invariably be abnormal often with extinguished rod and cone responses.6 Circulating antibodies directed against retinal antigens can also be detected in patient serum by western blot (WB) or immunohistochemistry (IHC).

The paraneoplastic syndrome of CAR is the best studied and most widely recognised form of AIR. Two autoantibodies generally accepted as part of the CAR syndrome are the 23 kDa antirecoverin antibody and the 46 kDa anti-enolase antibody, although others have been described.7–9 There is data to support the role of the antirecoverin antibody in photoreceptor cell death but the role of other antibodies and whether they function in the pathogenesis of disease or represent a secondary response to the underlying retinal degeneration remains less clear. A complicating factor in understanding the role of antiretinal antibodies in disease pathogenesis is the finding that these antibodies are not specific to patients with AIR as serum from patients with diabetes, retinitis pigmentosa (RP) and normal controls can also show antiretinal antibodies.10–13 Ultimately, there is no one test that can diagnose an AIR, and it remains a clinical diagnosis that is often controversial.14,15

Imaging technologies such as fundus autofluorescence (FAF) and spectral domain optical coherence tomography (SD-OCT) can provide additional diagnostic information in conditions in which the conventional exam is unremarkable.16,17 A recent publication of four patients with AIR described a ring of hyper-AF on FAF that corresponded with a loss of the photoreceptor layer on SD-OCT.18 Here we report on an additional series of seven patients diagnosed with AIR at a tertiary referral centre, who underwent FAF and SD-OCT imaging. In the majority of patients, abnormalities with one or both imaging modalities were identified. In contrast to previous reports of a ring of hyper-AF, we identified significant variety in the appearance of the FAF, particularly in acute cases. In addition, we show follow-up imaging on one case of CAR that suggests that the hyper-AF ring may be a manifestation of a subacute or chronic disease.

PATIENTS AND METHODS

The Duke University Institutional Review Board approved this study. All of the patients were evaluated at the Duke University Eye Center in Durham, North Carolina. All patients underwent a complete ophthalmic examination including determination of best corrected visual acuity as measured on an Early Treatment Diabetic Retinopathy visual acuity chart, slit lamp and fundus assessment, serum autoantibody testing performed at Oregon Health and Science University, kinetic visual field testing, ERG testing, colour fundus photographs, FAF images and SD-OCT images obtained on a Heidelberg Spectralis (Heidelberg Engineering, Heidelberg Germany). Patients were identified in a retrospective manner based on a diagnosis of AIR as determined by authors PM and GJJ. Patients were first assigned a tentative diagnosis of AIR based on the
clinical presentation. The diagnosis was considered confirmed by the addition of positive autoantibody and ERG testing to the appropriate clinical presentation. The tentative diagnosis was assigned for the presence of a suggestive history including acute to subacute vision loss, nystagmus and a history of cancer in combination with objective findings of profound visual field loss documented by Goldman visual field (GVF) testing. Additionally, exam findings such as optic nerve pallor and vascular attenuation were considered suggestive. If evidence of other retinal conditions that could explain the visual field loss were identified the tentative diagnosis of an AIR was discarded.

RESULTS

Four women and three men with AIR were identified; average age was 53±19 years. Records were reviewed, and pertinent demographic, historical, exam and diagnostic study data were recorded (table 1).

No patient had a family history suggestive of a hereditary retinal degeneration or other inflammatory retinal disease. Six (86%) had a history of cancer including small cell lung, bronchogenic lung, metastatic melanoma, breast, acute myelogenous leukaemia (AML) and cervical neuroendocrine.

On exam, central Early Treatment Diabetic Retinopathy visual acuity was decreased to worse than 20/40 in 3 (21%) of 14 eyes. On ophthalmoscopic examination, vascular attenuation was the most common finding, noted in both eyes of six (86%) patients. Additional isolated findings on physical exam included epiretinal membrane and macular hole in the right eye of patient 2, bilateral diffuse RPE atrophy in patient 3, bilateral 1+ vitreous opacity and epiretinal membrane in patient 4 and bilateral bull’s eye maculopathy in patient 5.

All the patients tested had abnormal GVs (table 1). Visual field testing was not performed for patient 6 due to poor central vision. Full field ERGs were abnormal in six patients. Three patients (1–3) had significantly diminished rod and cone responses. Patient 4 had undetectable rod and cone responses. Patient 5 had significantly diminished rod responses and moderate cone dysfunction. Patient 7 had an undetectable rod and delayed cone response. An ERG was not performed on patient 6. All patients had at least one antiretinal autoantibody identified by western blot. The average number of autoantibodies detected per patient was 2.9±1.4 (range 1–5). The 40 kDa and 46 kDa antiendoenolase autoantibodies were the most prevalent, found in three patients. The 23 kDa antirecoverin antibody was found in two patients. Immunohistochemistry of patient serum against human retinal sections was performed in addition to WB for four patients (2, 5, 6 and 7). Staining was detected to cone and bipolar cells for patient 5, photoreceptors for patient 6 and cells in the outer plexiform (OPL) layer and bipolar cells for patient 7. No retinal staining was seen for patient 2.

Figure 1 shows the FAF and SD-OCT of both eyes of patient 1, a 54-year-old man who presented for evaluation of a 2-month history of decreased peripheral vision and photosopias. One month prior to presentation, he was diagnosed with small cell lung cancer. On ocular examination, the best corrected visual acuity was 20/20 in both eyes. On ophthalmoscopic examination, the retinal vessels were attenuated in both eyes, but the retina and optic nerve otherwise appeared normal. Kinetic visual field testing revealed constriction to within 60° of fixation in both eyes. An ERG was abnormal with a non-detectable rod response and significantly reduced cone responses in both eyes. The serum was positive for antiretinal antibodies directed against antigens with molecular weights 23 (recoverin), 42, 46 (α-ENase), 50 and 67 kDa. FAF imaging was remarkable for a striking pattern of oblong and variegated hyper-AF surrounding the normal central FAF. By SD-OCT, there was an intact external limiting membrane (ELM) and inner segment/outer segment (IS/OS) junction in the region of normal FAF, and loss of the outer retinal complex (IS/OS junction, ELM, outer nuclear layer (ONL)) in the areas of hyper-AF (figure 1 double arrows). He received two rounds of intravenous immunoglobulin therapy with subjective inferior visual fields improvement. However at the 8-month follow-up visit, visual field loss had progressed to a central island of less than 15° (figure 2). AF imaging shows a central region of normal FAF surrounded by a double ring of hyper-AF. The first ring is bound by the bars in figure 2. The area of normal FAF corresponded to the region of relatively preserved retinal structure on SD-OCT, however there was disorganisation or loss of the IS/OS junction except in the subfoveal area. The inner border of the first hyper-AF ring corresponded to the area where there is thinning of the ONL and loss of the ELM. The outer ring of hyper-AF was mottled in appearance and corresponded to the area beyond which the ONL is absent.

Figure 3 shows the left eyes of three patients with CAR. The right eyes had similar findings (data not shown). Patient 2 is a 73-year-old woman with a history of breast cancer. FAF reveals a ring of hyper-AF with an indistinct boundary around the normal FAF. SD-OCT imaging shows loss of outer retinal layers in the area of hyper-AF. The inner boundary of the hyper-AF begins at the peripheral border of the retained IS/OS junction. The ELM and ONL extend into the area of hyper-AF briefly before disappearing.

Patient 3 is a 24-year-old woman with a history of AML. She was seen as a second opinion 2 years after initial loss of vision. Generalised RPE atrophy with an area of retained subfoveal RPE is seen in the colour fundus photo (figure 2 arrow). A ring of hypo-AF surrounds the fovea. Beyond this ring, mottled hypo-AF extends into the vascular arcades. By SD-OCT, there is almost complete loss of outer layers, and marked disorganisation of the remaining inner retinal layers beyond the fovea. The inner border of the hypo-AF ring (dotted lines) corresponds to the peripheral edge of the retained outer retinal complex. In the area of the hypo-AF ring an irregular hyper reflective region is present that could represent abnormal RPE or outer retinal structures. The diffuse loss of the RPE is reflected in the increased choroidal penetration of the SD-OCT signal.

Patient 4 is a 31-year-old woman with a recently diagnosed small cell neuroendocrine carcinoma of the cervix. Vitritis is seen on colour fundus imaging. By SD-OCT, loss of the ONL and ELM occur in the peripapillary macula (figure 3 arrowhead). Diffuse thinning of the ONL is seen throughout the macula, and loss of the IS/OS junction is prominent between the arrowhead and the fovea. In the perifoveal region, discreet round hyper-reflective bodies are seen adjacent to the inner plexiform layer. The presence or absence of a hyper-AF ring in the area of outer photoreceptor layer loss is unable to be determined due to vitritis. Intraretinal inflammation is not common in patients with CAR, but low levels of iritis and vitritis have been described previously. In the case of this patient, who had very rapid vision loss as well as a profound and early involvement of her central vision, we hypothesise that the vitritis is a reflection of the fulminating nature of her course.

Figure 4 shows the right eye of a patient with α-ENase associated AIR (patient 5), with CAR and bronchogenic lung cancer (patient 6) and with melanoma associated retinopathy (patient 7). Patient 5 is a 63-year-old woman with no history of cancer, no family history of RP or other retinal degeneration, and a recent development of nystagmus and blurry vision. AF shows a
ring of hyper-AF around the central region of normal FAF (figure 4 between the solid and the dotted lines). Peripheral to the ring of hyper-AF, a ring of mottled hypo-AF extends into the arcades. By SD-OCT, the inner boundary of the hyper-AF rings begins at the peripheral border of the IS/OS junction. Across the area of hyper-AF, the ELM disappears and the ONL becomes progressively thinner. At the junction between the hyper-AF and hypo-AF, the ONL layer ends (dotted line). Normal retinal architecture, including the IS/OS junction, is limited to the fovea.

Patient 6 is a 68-year-old man with CAR and a diagnosis of bronchogenic lung cancer. Diagnosis of his malignancy was

### Table 1  Seven patients with AIR were identified

<table>
<thead>
<tr>
<th>Pt. #</th>
<th>Age</th>
<th>Gender</th>
<th>Cancer history</th>
<th>BCVA</th>
<th>Fundus exam findings</th>
<th>Goldman visual field</th>
<th>ERG</th>
<th>Antibodies (kDa)</th>
<th>IHC</th>
<th>FAF</th>
<th>OCT</th>
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<tr>
<td>1</td>
<td>54</td>
<td>M</td>
<td>Small cell lung</td>
<td>20/20</td>
<td>Attenuated vessels</td>
<td>Generalised constriction</td>
<td>Non-detectable rod response, significantly reduced cone responses</td>
<td>23, 42, 46, 50, 67</td>
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<tr>
<td>2</td>
<td>73</td>
<td>F</td>
<td>Breast</td>
<td>20/80 20/52</td>
<td>Attenuated vessels ERM and MH (OD)</td>
<td>Generalised constriction with decreased central sensitivity</td>
<td>Significantly diminished rod and cone response</td>
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<td>Y</td>
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<tr>
<td>3</td>
<td>24</td>
<td>F</td>
<td>AML</td>
<td>20/40</td>
<td>Attenuated vessels General RPE Atrophy</td>
<td>Generalised constriction with central island ~5° around fixation</td>
<td>Significantly diminished rod and cone response</td>
<td>40</td>
<td>NP</td>
<td>Y</td>
<td>Y</td>
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<td>31</td>
<td>F</td>
<td>Small cell cervical neuroendocrine</td>
<td>20/250 CF</td>
<td>Attenuated vessels Vitreous opacity ERM</td>
<td>NP due to poor vision</td>
<td>Non-detectable rod and cone response</td>
<td>40, 46, 72</td>
<td>NP</td>
<td>U</td>
<td>Y</td>
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<tr>
<td>5</td>
<td>63</td>
<td>F</td>
<td>None</td>
<td>20/32 20/40</td>
<td>Attenuated vessels Bull’s eye maculopathy</td>
<td>Generalised constriction, enlarged blind spot</td>
<td>Significantly diminished rod function, moderate cone dysfunction</td>
<td>30, 46, 60, 70</td>
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<tr>
<td>6</td>
<td>68</td>
<td>M</td>
<td>Bronchogenic Lung</td>
<td>20/20 20/32</td>
<td>Attenuated vessels Photo-receptor</td>
<td>Generalised constriction</td>
<td>Non-detectable rod response, delayed cone response</td>
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<td>7</td>
<td>57</td>
<td>M</td>
<td>Met. Melanoma</td>
<td>20/25 20/25</td>
<td>Normal exam</td>
<td>Generalised constriction</td>
<td>Non-detectable rod response, delayed cone response</td>
<td>33, 62, 72</td>
<td>OPL, bipolar</td>
<td>N</td>
<td>N</td>
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</tbody>
</table>

Six patients had abnormal FAF or SD-OCT findings (Y). One patient did not have abnormalities on FAF or SD-OCT (N). AIR, autoimmune retinopathy; AML, acute myelogenous leukaemia; BCVA, best corrected visual acuity; ERG, electroretinograms; ERM, epiretinal membrane; FAF, fundus autofluorescence; MH, macular hole; NP, not performed; OPL, outer plexiform; RPE, retinal pigment epithelial; SD-OCT, spectral domain optical coherence tomograms; U, uninterpretable.

**Figure 1**  Colour fundus, autofluorescence and spectral domain optical coherence tomography (SD-OCT) imaging of the right and left eyes of a patient with cancer associated retinopathy (patient 1). Hyper-AF (white double arrows) surrounds a central area of oblong and variegated normal fundus AF. The horizontal SD-OCT image shows a loss of outer retinal layers including the IS/OS junction, the ELM and ONL in the area of hyper-AF (white double arrows). Normal retinal architecture is maintained centrally (IS/OS+).
made during the systemic evaluation initiated as part of an AIR/CAR workup. AF shows a multilobed area of normal AF with interspersed and surrounding hyper-AF. Perivascular mottled hypo-AF is also present around the nerve and in the arcades. By SD-OCT the areas of hyper-AF correspond to loss of the outer retinal layers including the IS/OS and ELM in the smaller hyper-AF regions temporal to the fovea, and the complete outer retinal complex nasal to the fovea. Interspersed areas of normal AF correspond to areas of retained retinal architecture including the IS/OS junction, ELM and ONL.

Patient 7 is a 57-year-old man with a history of metastatic melanoma. This patient demonstrated concentric visual field loss by GVF testing and had ERG abnormalities consistent with severe rod or inner retinal dysfunction. Antiretinal antibodies were detected by western blot and by IHC to human retinal sections, staining of the OPL layer and bipolar cells was reported. This is the only patient with remarkably normal imaging. No outer retinal abnormalities were seen on SD-OCT, and FAF was unremarkable.

DISCUSSION

The diagnosis of an AIR remains a challenge, and there is significant controversy regarding how to weigh the pertinent findings in the history, physical exam and studies. For the seven patients presented here, the diagnosis was suggested by visual field loss out of proportion to exam, and was confirmed by a combination of ERG testing and the presence of circulating antiretinal autoantibodies. Heckenlively et al has proposed a system of diagnostic criteria that segregates evidence into ‘strong’, ‘supportive’ or ‘helpful’.19 However, in the absence of a specific test, clinicians will continue to use their own judgement to weigh the evidence for each patient.

Imaging technologies such as AF and SD-OCT are becoming more commonly available, and have the ability to suggest retinal pathology that is not readily apparent by fundus examination. In this series of patients, we show that for a majority of patients with an AIR, AF and SD-OCT imaging abnormalities can be identified that may suggest this rare diagnosis before ERG and laboratory results are available.18 20 The patients described here have hyper-AF surrounding a parfoveal region of normal AF. Furthermore, by SD-OCT, loss of outer retinal complex components was noted in the area of hyper-AF. In areas of normal FAF retinal architecture was relatively preserved.

A previous study described a ring of hyper-AF in four patients with AIR, and identified an association between the loss of IS/OS junction and the inner border of the hyper-AF ring.18 We found a similar association in some of our patients (patients 2, 5 and 6). In addition, the initial image for patient 1 shows the AF border occurring in the location of loss of all outer retinal complex structures. However, in the 8-month follow-up image, the borders of the inner and outer hyper-AF rings were associated with the loss of the ELM or ONL, respectively. Regardless of the exact structure lost, both studies identified progressive loss of outer retinal structure within the area of hyper-AF.

We found more variety in the appearance of the AF then previously reported.18 The highly variable appearance of the two acute cases shown here (patients 1 and 6), and the evolution of patient 1 over 8 months to the ring of hyper-AF as described in Lima et al suggests that acute cases of CAR may present with a wider spectrum of AF appearances, and that the hyper-AF ring may be a more common finding in subacute or chronic cases of AIR. In contrast to these acute patients, patient 3 was seen 2 years after her vision loss. It is possible that at this late stage, the disease has stabilised, and in the absence of progression the hyper-AF ring is replaced by hypo-AF. It may be the case that as more patients with AIR are identified and imaged, the more common patterns and their association with disease stage and risk of progression will emerge.
Interestingly patient 7, despite severe vision loss did not have posterior imaging changes suggestive of RPE or retinal cell loss; we propose several explanations. First, it is possible that this patient was identified very early in the disease process whereby outer retinal and RPE loss has not yet occurred. Second, in some patients the autoantibodies could alter normal retinal function but not cause cell loss. This mechanism could explain the loss of vision in the absence of posterior imaging abnormalities. However, for this patient we favour a third possibility; that the loss of the B-wave by ERG in conjunction with IHC specific for the OPL and bipolar cells represents vision loss is due to inner retinal dysfunction than photoreceptor disruption or loss. There are likely multiple mechanisms to explain the vision loss in patients with AIRs and additional studies will be required.

This study is limited by the small number of patients, variable lengths of follow-up, potential lead-time bias in the initial presentation of our patients and detection of imaging changes, and the heterogeneous disease population encompassed in the diagnosis of AIR. Currently, there are no definitive diagnostic criteria for AIRs, and alternative retinal degenerative diagnoses such as acute zonal occult outer retinopathy, RP, cone dystrophy and toxic retinopathy (chloroquine, hydroxychloroquine) must be considered in the differential diagnosis. Prospective analysis will be helpful to determine if FAF and SD-OCT imaging will be robust methods to identify patients with AIR, monitor response to therapy and follow disease progression.

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Competing interests None.

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REFERENCES


