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# Retinal pigment epithelial detachments and tears, and progressive retinal degeneration in light chain deposition disease

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## ABSTRACT

**Background/purpose** Light-chain deposition disease (LCDD) is a rare condition characterised by deposition of monoclonal immunoglobulin light chains (LCs) in tissues, resulting in varying degrees of organ dysfunction. This study reports the characteristic clinical ocular findings seen in advanced LCDD upon development of ocular fundus changes. This is the first report to describe this entity in vivo in a series of patients.

**Methods** A case series of ocular fundus changes in three patients with kidney biopsy-proven LCDD. All patients underwent best corrected visual acuity (BCVA) exam, perimetry, colour fundus photography and fluorescein angiography; two patients underwent indocyanine green angiography, optical coherence tomography, ultrasound and electroretinography; and one patient underwent fundus autofluorescence.

**Results** Three patients, 53–60 years old at initial presentation, were studied. All three presented with night blindness, poor dark adaptation, metamorphopsia and visual loss. Examination revealed serous and serohaemorrhagic detachments, multiple retinal pigment epithelial (RPE) tears, diffuse RPE degeneration and progressive fibrotic changes. Neither choroidal neovascularisation nor other vascular abnormalities were present. Final best corrected visual acuity (BCVA) ranged from 20/40 to 20/300.

**Conclusions** Progressive LC deposition in the fundus seems to damage RPE pump function with flow disturbance between choroid and retina. This pathogenesis can explain the evolution to RPE detachments and subsequent rips and progressive retinal malfunction.

membrane, especially at the distal tubules and Henle's loops.

Although renal disease is most frequently the primary manifestation, LCs can also deposit in organs such as the heart, liver, lungs, bone marrow, spleen, pancreas, gastrointestinal tract, abdominal vessels, skin, endocrine glands and central nervous system.<sup>3–5</sup> Renal insufficiency manifests in the great majority of patients, rapidly progressing to uraemia despite early and aggressive treatment.<sup>6</sup> Rarely, LCDD occurs without renal involvement.<sup>7</sup> Survival from onset of symptoms varies from 1 month to 10 years.<sup>8</sup>

Ocular posterior segment involvement in LCDD has been reported in two single case reports,<sup>9 10</sup> and in a presentation of the current case series of three patients at Association for Research in Vision and Ophthalmology.<sup>11</sup> A single-patient, post-mortem histopathological study has also been reported.<sup>12</sup> In this paper we report extensively on the observed fundus changes and imaging of the lesions with long term follow-up of one case, and we discuss what we believe to be the LCDD-related fundus changes with associated poor visual outcome of the condition.

## CASE SERIES

The present study included three subjects with biopsy-confirmed LCDD and visual symptoms. The subjects were aged 60 (Cases 1 and 2) and 53 (Case 3) at the time of the first ophthalmic examination.

Case 1 concerns a 60-year-old woman who presented to the medical retina department in 1998 with a best corrected visual acuity (BCVA) of 20/20 OU despite metamorphopsia right eye (OD). Fundus examination showed a serous retinal pigment epithelial (RPE) detachment OD and mild RPE changes in the left eye (OS) (figure 1A,B). Medical history revealed the diagnosis of end-stage renal disease and biopsy-proven LCDD 9 years earlier, at the age of 51. In 1998, she underwent kidney transplantation, which suffered acute vascular rejection. Dialysis was immediately instituted and continued until 2004, when she underwent a second kidney transplantation. This transplant failed as well. Histology showed LC deposition in the transplanted kidney. Electron microscopy detected LCs in the basement membrane of the renal tubules. Dialysis was recommenced.

Significantly, neither corticosteroids nor other immunosuppressants were used for long periods of time. Further, blood pressure was always very

## INTRODUCTION

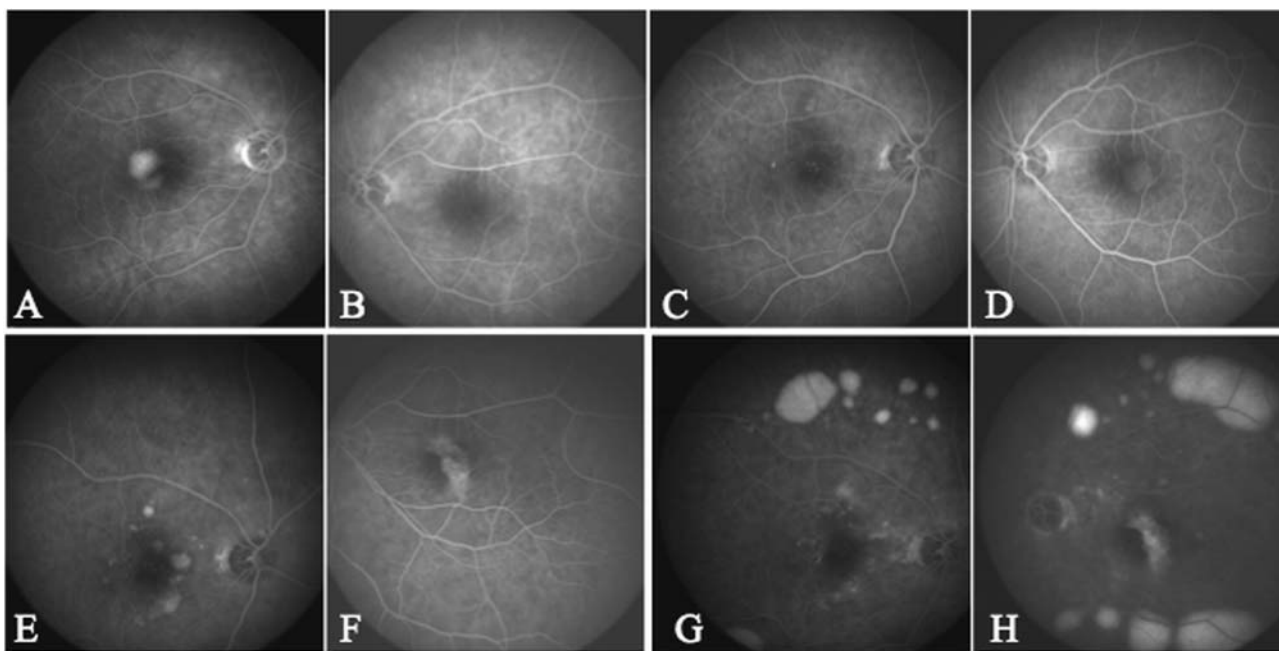
Light-chain deposition disease (LCDD) is a systemic disorder characterised by the deposition of monoclonal immunoglobulin light chains (LCs) in tissues. It is associated with B cell immunoproliferative disorders such as plasma cell dyscrasias and other lymphoproliferative disorders in which LCs are overproduced and deposit in the organs in a non-organised, granular form.<sup>1</sup>

The disease's clinical manifestations depend on the tissues involved, the LC load in the tissues and the resulting organ dysfunction. The kidney is a prominent location for LC deposition, and the clinical picture of LCDD is generally dominated by the kidney's involvement in the disease.<sup>2</sup> Accumulation of LCs in the kidney may involve glomeruli, tubules, interstitium and vessels, either independently or concurrently. The histopathological hallmark of LCDD is the evidence of monoclonal LC deposition along the renal tubular basement



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**Figure 1** Fluorescein angiography of case 1 (female patient; age 60 years at first ophthalmic examination). Serous retinal pigment epithelial (RPE) detachment in the right eye (A) and mild RPE changes in the left eye (B; 1998). One year after initial presentation, the macula was flat in the right eye (C), but the left eye had developed a serous RPE detachment (1999). Two years after initial presentation, the left eye had developed an unusual tear of the RPE, not at the border of the RPE detachment, but rather in the middle of the detachment (F). Several small serous RPE detachments were observed bilaterally (E and F; 2000). Four years after initial presentation, new serous RPE detachments had developed in the mid-periphery of both eyes (G and H). There were no signs of subretinal neovascularisation (2002).

tightly regulated. The patient had neither diabetes mellitus nor primary renal disease.

One year after initial presentation, the right macula was flat, but the left eye had developed a serous RPE detachment (figure 1C,D). Two years after initial presentation, the left eye also developed an unusual tear of the RPE, and several small serous RPE detachments were observed bilaterally (figure 1E, F). This tear was not located at the border of the RPE detachment, but rather in the middle. Four years after initial presentation, new serous RPE detachments had developed in the mid-periphery of both eyes (figure 1G,H). There were no signs of subretinal neovascularisation.

Five years after initial presentation, the patient began to complain of poor vision. BCVA was 20/25 and 20/30. Marked loss of visual field was recorded bilaterally. At that time, a large tear of the RPE and numerous serous RPE detachments were seen in the right eye (figure 2A). In the left eye, a very large serous detachment with recent tears of the RPE was present in the nasal retina of the right eye (figure 2B) and the other sectors also had RPE detachments and tears. On indocyanine green angiography, the deep fluorescence was totally blocked in the area of the large RPE detachment (figure 2C). The indocyanine green angiography showed no subretinal neovascularisation, and the perfusion was normal in retinal and choroidal vasculature. Lesions continued to develop 11 years after initial presentation (figure 2D,E), and the large serous detachment in the left eye eventually flattened out (figure 2E). Old and new tears of the RPE were visible. Optical coherence tomography (OCT) initially showed RPE detachments, RPE tears and progressive structural disorganisation of the overlying retina. Enhanced depth imaging OCT (EDI-OCT; figure 2F) was available starting in 2011. Besides a disorganised retina and multifocal atrophy of RPE, the EDI-OCT images show choroidal thinning and disappearance of

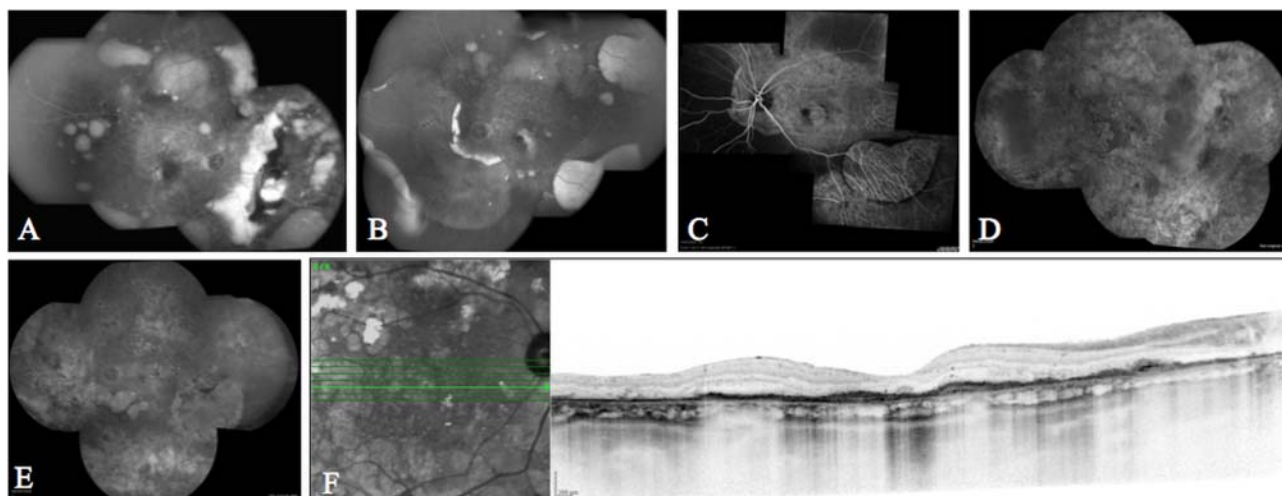
choriocapillaris. Perivascular hyperreflectivity is visible around choroidal vessels, particularly in areas where RPE is atrophic. The black and grey areas around choroidal vessels likely correspond with the LC dense deposits. In sum, widespread damage included RPE detachments, which induced RPE tears, leading to scarring and fibrosis.<sup>13</sup>

Autofluorescent images taken at 9 years, 12 years and 14 years from initial presentation, displayed a rapid increase of hypofluorescent regions, which is indicative of severely diseased RPE and retina (figure 3). These areas correspond to severe visual field narrowing and deterioration of the electroretinographic (ERG) response. Indeed, the ERG deteriorated to nearly flat.

In 2009, treatment with Revlimid (lenalidomide; Celgene; Summit, New Jersey, USA), a derivative of thalidomide, was initiated to lower the load of LCs. However, leucopenia led to the temporary cessation of treatment, which was later restarted. This second trial was again stopped due to side effects. The last recorded BCVA was 20/200 OD and 20/100 OS in August 2012. The patient was very unhappy, due to progressive loss of visual acuity and constriction of the visual field, with multiple large scotomata.

Case 2 concerns a 60-year-old man who presented in 2003 with a 2-year history of poor vision in the left eye and a 5-month history of visual loss in the right eye. He had a history of multiple myeloma diagnosed 16 years earlier, which was treated with chemotherapy. Six years before initial presentation to the medical retina department, the patient had developed end-stage renal disease. Kidney biopsy showed LC deposits. Renal failure was treated with haemodialysis. Arterial hypertension was medically controlled. The patient had neither diabetes mellitus nor primary renal disease.

A general ophthalmologist's report, dating from 2001, 2 years before presentation to our department, indicated a peripheral

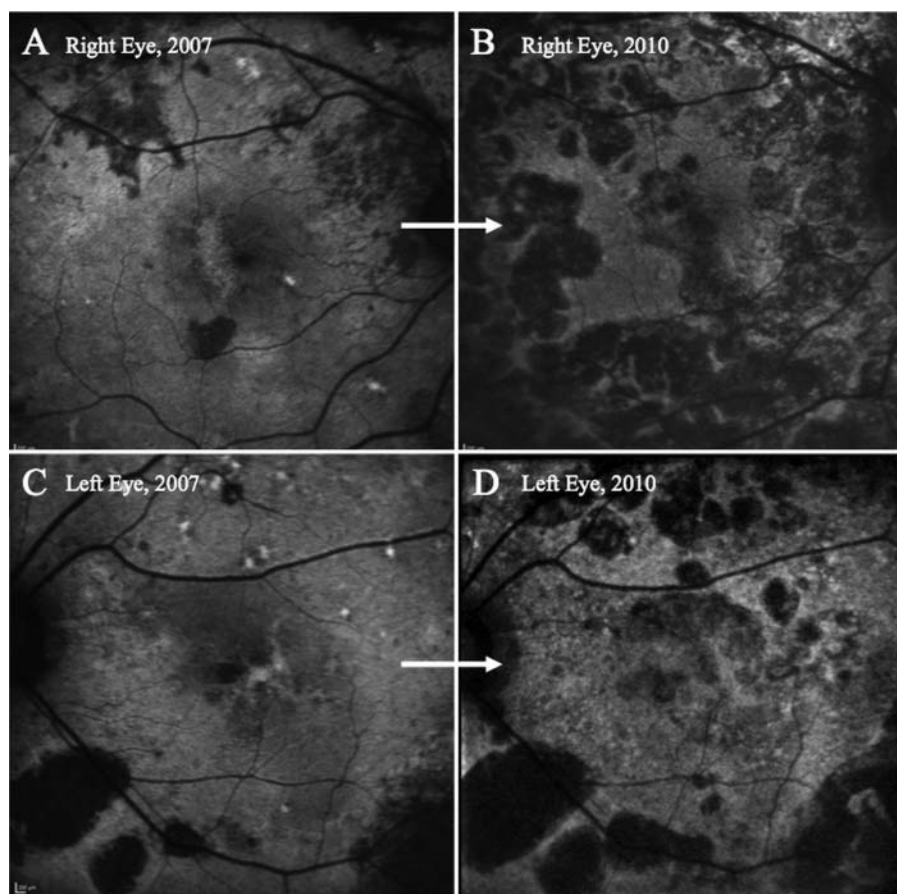


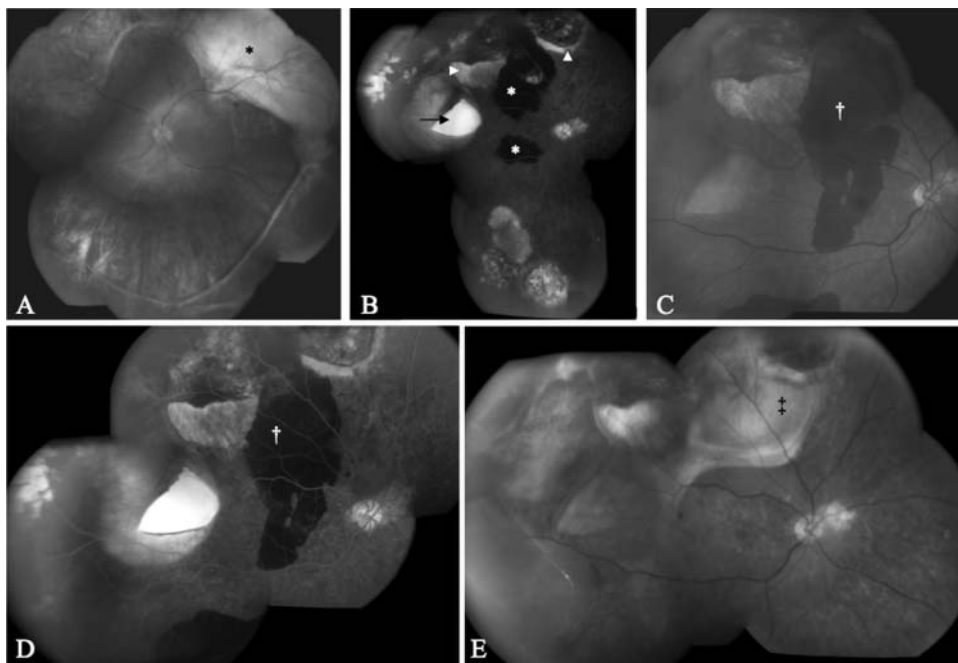
**Figure 2** Fluorescein angiography and indocyanine green angiography (ICGA) of case 1. Five years after initial presentation, the patient complained of poor vision. Visual acuity was 20/25 and 20/30. Marked loss of visual field was recorded bilaterally. At that time, a large tear of the retinal pigment epithelium (RPE) was seen in the right eye and there were numerous serous RPE detachments. Identical changes are noted in the left eye, with several RPE tears and serous detachments. A very large serous detachment with recent tears of the RPE is visible in the nasal area left eye (2003). Composite ICGA image (C) of the left eye, taken 5 years after initial presentation. A serous RPE detachment is visible superiorly. An old RPE tear, with sharp borders and enhanced visibility of choroidal vessels, is visible inferiorly. A prominent serous RPE detachment is visible nasally. Here, the deep fluorescence is completely blocked. Note that there are no retinal vascular lesions, no choroidal neovascularisation and no choroidal vascular abnormalities (2003). Composite fluorescein angiogram images of the right (D) and left (E) eyes, taken 11 years after initial presentation. These images show widespread damage to the RPE, including scars due to RPE tears and detachments (2009). Enhanced depth imaging OCT (EDI-OCT) of the right eye (F), showing a very thin choroid and perivascular hyperreflectivity round choroidal vessels (2011). This hyperreflectivity is especially well demonstrated in areas of RPE pigment atrophy. Subfoveal choroidal thickness is 191 microns (mean: 251 microns).<sup>13</sup>

RPE detachment and retinal detachment in the left eye and no obvious changes in the right eye. At initial presentation in our department, BCVA was 20/200 and 20/60 with bilateral

metamorphopsia. The left eye had annular fibrosis in the mid-periphery (figure 4A). Fluorescein angiography of the right eye (figure 4B) showed a macular neurosensory detachment and a

**Figure 3** Autofluorescence images of the posterior pole of Case 1, taken in 2007 (A and C) and 2010 (B and D), respectively 9 years and 12 years after initial presentation. Note the rapid increase of hypofluorescent regions, indicative of severely diseased retinal pigment epithelium and retina. These areas correspond to a severe visual field loss and electroretinographic deterioration.





**Figure 4** Case 2 was a 60-year-old man who presented with a 2-year history of poor vision in the left eye and recent loss of vision in the right eye. Fibrosis (\*) was present in the left eye at initial presentation (A). Fluorescein angiography (FA) of the right eye (B) showed a recent retinal pigment epithelial (RPE) tear (arrow) and two older RPE tears (arrowheads), as well as extensive haemorrhages (\*). At 1 month after initial presentation, red-free photography (C) and FA (D) showed confluence of the haemorrhages (†) in the right eye. Nine months after initial presentation, fibrotic changes (‡) were evident in the right eye (E), similar to those which were present in the left eye at presentation. Progressive devastation of the posterior pole continued until 13 months after initial presentation.

recent and two older tears of the RPE, as well as extensive supramacular and inframacular haemorrhages in the right eye. There was no evidence of choroidal neovascularisation (CNV).

One month later, there was a confluence of haemorrhages in the right eye (figure 4C,D). Nine months after baseline, fibrotic changes were also evident in the right eye (figure 4E). Progressive devastation of the posterior pole was seen at 13 months after baseline. BCVA was 20/300 OD and 20/70 OS. The patient succumbed to systemic complications related to renal failure shortly thereafter. No ocular pathological study could be performed.

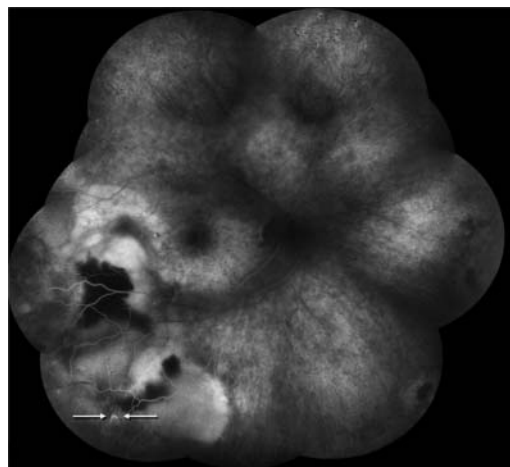
Case 3 concerns a 53-year-old man with end-stage renal disease and biopsy-proven LCDD. The patient had neither diabetes mellitus nor primary renal disease. He presented to the department of ophthalmology with complaints of night blindness and dark adaptation difficulty. The ERG was highly abnormal bilaterally. BCVA was 20/30 and 20/25. The visual fields were mildly constricted bilaterally, with a large deficit in the superonasal sector of the right eye. Colour fundus photography and red-free photography of the posterior pole of the right eye showed lipid exudates and a serohaemorrhagic RPE detachment temporal to the macula. Fluorescein angiography showed pooling of fluorescein in the region of the RPE detachment. A small RPE tear was also noted in the right eye (figure 5). Fibrosis and deep, subretinal bleeding were present in the peripheral retina of the right eye. Despite the abnormal retinal function tests, the fundus of the left eye was normal upon examination.

## DISCUSSION

LCDD is the result of the deposition of amorphous, non-fibrillar deposits of immunological origin in plasma cell dyscrasias or other lymphoproliferative disorders. This is the first report that

describes the clinical, in vivo ocular fundus changes that occur in three patients with LCDD. Although no ocular histopathological study was performed for this report, all three patients had renal biopsy-proven LCDD. None of the most common ocular signs of plasmacytomas, such as corneal crystals,<sup>14 15</sup> and ciliary epithelial cysts<sup>16 17</sup> were present in these three cases. Our three patients had similar ocular signs and symptoms, which together represent what we believe to be the typical clinical ocular fundus features for advanced LCDD.

The involvement of the posterior segment of the eye in LCDD has been reported in several case studies<sup>9 10</sup> and a single-patient, postmortem histopathological study is available.<sup>12</sup> In



**Figure 5** Composite fluorescein angiography of the right eye of case 3. A small, peripheral tear in a serohaemorrhagic retinal pigment epithelial detachment is visible (arrows).

1987, Khan *et al*<sup>10</sup> described ischaemic retinopathy in a patient with hyperviscosity syndrome and LCDD. Severe retinal vasculopathy associated with LC deposition and damage to the retinal vasculature was described in 1990.<sup>9</sup> The authors suggested that LC deposition in the retinal vessels had led to focal thrombosis. However, ocular histology was not available in these cases.

In 1995, Daicker *et al*<sup>12</sup> reported a postmortem histopathological analysis of both globes of a 32-year-old woman who succumbed to LCDD soon after biopsy-confirmed diagnosis. No in vivo ocular fundus examination was reported. Of note, the fundus changes observed in the patients in the present case series correspond to the histopathology described by Daicker *et al*. Neither ischaemic nor thrombotic retinopathy was present. Macroscopically, a single black and yellow subretinal patch was visible in the left peripheral fundus. Histological examination of the lesion revealed a haemorrhagic RPE detachment and a subretinal haemorrhage with signs of organisation.

Light microscopy, immunofluorescence and electron microscopy identified extensive deposition of  $\kappa$  LCs, which were primarily present in the uvea, including the ciliary body, pars plana and choroid. No deposits were found in the iris. LCs were present beneath the basement membrane of the ciliary pigment epithelium, on vessels of the ciliary body, within the collagenous zones of Bruch's membrane and in the innermost part of the choroid. In the ciliary body, the deposits closely resembled those of Kimmelstiel-Wilson's disease in the kidney, forming a similar periodic acid-Schiff-positive layer beneath the pigment epithelium.

In the choroid, the deposited layer was more pronounced in the central fundus, with its dense capillary network, than in the periphery, suggesting local circulatory origin. The dense deposits in the posterior pole were associated with partial choriocapillary occlusion. Overlying this obstructed area was a recent exudative retinal detachment. The retinal vessels remained unaffected. The authors hypothesised that the RPE acted as a barrier against internal deposition, and there was no obvious RPE damage visible under light microscopy.

We hypothesise that the choroidal LC deposition is responsible for significant impairment of RPE function, a finding that was reported at the Association for Research in Vision and Ophthalmology in 2010.<sup>11</sup> The RPE plays an important role as a fluid pump for the reabsorption of subretinal fluid. Defects in this pump function, as well as in the RPE's outer blood-retinal barrier, can lead to fluid retention and RPE detachment and tears. Although steroids have been shown to induce central serous chorioidopathy (CSC), whose manifestations include RPE and neurosensory detachments, corticosteroid-associated RPE tears are quite rare, as are RPE tears in the context of CSC. The classic variant of CSC consists of a shallow neuroretinal detachment located at the posterior pole of the ocular fundus. Bilateral and multifocal serous RPE detachments represent an atypical form. Further, although these patients were prescribed corticosteroids, this was low-dose and for short duration, and was thus unlikely to be responsible for the RPE changes observed.

No obvious inflammatory reaction of the LC-laden connective tissue was present in either the present series or in the case described by Daicker *et al*. Further, fresh haemorrhages were only observed in association with new RPE tears. None of the patients had associated CNV.

In sum, we have reported a series of three cases of biopsy-proven LCDD who displayed similar signs and symptoms over

the course of their follow-up. All cases presented with night blindness, poor dark adaptation, metamorphopsia and visual loss. Serous and serohaemorrhagic RPE detachments, multiple RPE tears and diffuse degeneration of the retinal pigment epithelium as well as progressive fibrotic changes were noted. Neither CNV nor other vascular abnormalities were observed. We believe this to be the classic presentation of fundus changes due to long-term progression of LCDD.

**Contributors** All three authors (LHS, JRH, AML) made substantial and approximately equal contributions to the conception and design of the study, the acquisition of data, and the analysis and interpretation of the data. The drafting of the manuscript, as well as its critical revision for important intellectual content was conducted by all three authors. Final approval of the final manuscript was granted by all authors.

**Competing interests** None.

**Patient consent** Obtained.

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## REFERENCES

- Ronco PM, Alyanakian MA, Mougnot B, *et al*. Light chain deposition disease: a model of glomerulosclerosis defined at the molecular level. *J Am Soc Nephrol* 2001;12:1558–65.
- Pozzi C, D'Amico M, Fogazzi GB, *et al*. Light chain deposition disease with renal involvement: clinical characteristics and prognostic factors. *Am J Kidney Dis* 2003;42:1154–63.
- Buxbaum JN, Chuba JV, Hellman GC, *et al*. Monoclonal immunoglobulin deposition disease: light chain and light and heavy chain deposition diseases and their relation to light chain amyloidosis. Clinical features, immunopathology, and molecular analysis. *Ann Intern Med* 1990;112:455–64.
- Rho L, Qiu L, Strauchen JA, *et al*. Pulmonary manifestations of light chain deposition disease. *Respirology* 2009;14:767–70.
- Popović M, Tavčar R, Glavac D, *et al*. Light chain deposition disease restricted to the brain: the first case report. *Hum Pathol* 2007;38:179–84.
- Heilman RL, Velosa JA, Holley KE, *et al*. Long-term follow-up and response to chemotherapy in patients with light-chain deposition disease. *Am J Kidney Dis* 1992;20:34–41.
- Casiraghi MA, De Paoli A, Assi A, *et al*. Hepatic amyloidosis with light chain deposition disease. A rare association. *Dig Liver Dis* 2000;32:795–8.
- Kyle RA. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N Engl J Med* 1997;336:1202–7.
- Enzenauer RJ, Stock JG, Enzenauer RW, *et al*. Retinal vasculopathy associated with systemic light chain deposition disease. *Retina* 1990;10:115–18.
- Khan P, Roth MS, Keren DF, *et al*. Light chain disease associated with the hyperviscosity syndrome. *Cancer* 1987;60:2267–8.
- Lays A, Spielberg L, Heckenlively JR. Retinal pigment epithelial detachments and tears in light chain deposition disease. Association for Research in Vision and Ophthalmology (ARVO) E-Abstract 2010.
- Daicker BC, Mihatsch MJ, Strøm EH, *et al*. Ocular pathology in light chain deposition disease. *Eur J Ophthalmol* 1995;5:75–81.
- Margolis R, Spaide RF. A pilot study of enhanced depth imaging optical coherence tomography of the choroid in normal eyes. *Am J Ophthalmol* 2009;147:811–15.
- Auran JD, Donn A, Hyman GA. Multiple myeloma presenting as vortex crystalline keratopathy and complicated by endocapsular hematoma. *Cornea* 1992;11:584–5.
- de Alba Campomanes A, Rutar TM, Crawford JB, *et al*. Crystal-storing histiocytosis and crystalline keratopathy caused by monoclonal gammopathy of undetermined significance. *Cornea* 2009;28:1081–4.
- Bowman Z, Peiffer RL Jr, Bouldin TW. Pathogenesis of ciliary-body cysts associated with multiple myeloma. *Ann Ophthalmol* 1988;20:292–5.
- Omoti AE, Omoti CE. Ophthalmic manifestations of multiple myeloma. *West Afr J Med* 2007;26:265–8.