BMJ Case Reports

TITLE OF CASE

Bilateral macular drusen in acquired partial lipodystrophy with type 2 membranoproliferative glomerulonephritis

SUMMARY

A 35 year old female with acquired partial lipodystrophy (PLD) and features of type 2 membranoproliferative glomerulonephritis (MPGN-II), presented with difficulty in her fine detailed vision over the past year. She had a right amblyopia from a hypermetropic anisometropia with astigmatism, displaying a best corrected visual acuity of 0.50 and 0.00 LogMAR, in the right and left eye, respectively. Fundoscopy showed bilateral symmetrical drusenoid deposits most prominent in the temporal macula with clusters in the superior and inferior retina, outside the temporal vascular arcades. Multimodal retinal imaging was performed which confirmed hyperautofluorescent drusen located between the retinal pigment epithelium and Bruch's membrane. Electroretinography showed bilateral mild peripheral macular dysfunction but normal central macular function on the pattern electroretinogram. Both PLD and macular drusen, are rare as distinct disease entities, but an association does exist and may be linked to type 2 membranoproliferative glomerulonephritis. This must be considered to assemble the correct multidisciplinary team, and to also distinguish it from a potential hereditary macular dystrophy in younger patients.

BACKGROUND

Lipodystrophy is an ultra rare condition characterised by generalised or partial loss of adipose tissue (lipoatrophy), often with corresponding pathological accumulation of adipose tissue (lipohypertrophy) elsewhere in the body. The global prevalence of lipodystrophy is approximately 1.3-4.7 per 1,000,000.[1] The condition can be acquired or inherited, with the ratio of affected males to females varying significantly depending on subtype; congenital generalised and familial partial lipodystrophy 1:1-2, acquired generalised lipodystrophy 1:3 and acquired partial lipodystrophy 1:4.[2] Changes in the *AGPAT2*, *LMNA* and *PPARγ* genes give rise to familial forms of the condition.[3] There are no known monogenic causes for acquired partial lipodystrophy, but risk alleles in *LMBN2* have been associated with an increased likelihood of developing the condition.[4] The acquired form is most commonly seen in HIV patients receiving highly active anti-retroviral therapy.[5]

Lipodystrophy is commonly associated with metabolic dysfunction such as insulin resistance, altered lipid metabolism and renal disease.[6] This is unsurprising as the adipose tissue is metabolically dynamic and integral to the endocrine system in regulating metabolic homeostasis. Due to its rarity and heterogeneity, patients with lipodystrophy syndrome may frequently be missed or misdiagnosed. This is of concern as the condition is progressive with significant metabolic consequences which may potentially be life-threatening.

Very little is known about the ocular manifestations of lipodystrophy syndrome. Previously, retinal drusen, retinal pigment epithelium (RPE) atrophy,[7] choroidal neovascularisation (CNV),[8] vitreous haemorrhage and enophthalmos secondary to lipid atrophy have been reported.[9] Here we provide detailed structural and functional correlation for macular drusen associated with acquired partial lipodystrophy syndrome, a rare and important differential for inherited macular dystrophies.

CASE PRESENTATION

A 35-year-old female had noticed over the past year she was straining to see fine detail and suffering from evening tension headaches. She visited an optician who noted bilateral retinal drusen and referred her to Moorfields Eye Hospital NHS Foundation Trust. She reported photosensitivity but no issues with dark adaptation, photopsia, colour vision, distortion, nyctalopia or visual field loss. Her previous ocular history included right amblyopia from childhood. The patient had a past medical history of acquired partial lipodystrophy, in a cephalothoracic distribution, which was diagnosed at age 7. Her condition was managed by the National Severe Insulin Resistance Service at the Addenbrooke's Hospital, Cambridge. She had previous cosmetic treatment involving adipose tissue transposition from the thighs to the face. She suffered from renal dysfunction with one affected kidney, and was found to be C3 nephritic factor positive with a low serum C3 suggestive of type 2 membranoproliferative glomerulonephritis (MPGN-II). She had no drug history or known allergies. She was a non-smoker with no alcohol intake, and worked as a graphic designer. She was born full-term and the pregnancy had been uncomplicated. Her mother is of Scottish descent, and her father is Syrian, no consanguinity. She had a family history of diabetes on her paternal side. Otherwise, there was no relevant family history other than her older sister had a squint and amblyopia.

INVESTIGATIONS *If relevant*

Best corrected visual acuity was 0.50 and 0.00 LogMAR in the right and left eye, respectively. Refraction was +4.50/-1.00x115 in the right eye and +2.50/-1.00x85 in the left eye, indicating a hypermetropic anisometropia with astigmatism. General inspection of the face revealed bilateral deep sulci. Examination of the eyelids revealed bilateral anterior and posterior margin blepharitis. Anterior segment examination was remarkable for punctate epithelial erosions and an abnormal tear film, breakup time of <10 seconds consistent with evaporative dry eyes. Fundoscopy showed bilateral drusen, most dense in the temporal macula with clusters superior and inferior to the temporal vascular arcades (Figure 1), there was no evidence of RPE atrophy, macular haemorrhage, exudation or CNV. Multimodal retinal imaging was performed including ultra-widefield colour fundus and autofluorescence, which revealed hyperautofluorescent macular drusen (Figure 1). Spectral domain optical coherence tomography (SD-OCT) confirmed the location of the drusen between the RPE and Bruch's membrane and the absence of intra- and subretinal fluid (Figure 2). Humphrey visual field was normal in both eyes. Full-field and pattern electroretinogram (ERG) was performed; the full-field ERG was normal suggesting normal generalised retinal function. The pattern ERG was within normal limits to a standard field stimulus, however, to a large field stimulus it did not demonstrate the expected increase in amplitude in either eye, suggesting mild peripheral macular dysfunction with intact central macular function (Figure 2). Multifocal ERG was also performed and confirmed no central macular dysfunction, but far eccentric areas were subnormal. Given the higher density of drusen in the peripheral macula, we postulated that this accounted for the mild peripheral macular dysfunction.[10] The patient underwent genetic testing with a retinal and macular dystrophy targeted gene panel consisting of 236 causal genes, but no pathogenic variants of significance were detected.[10]

DIFFERENTIAL DIAGNOSIS *If relevant*

Sorsby fundus dystrophy is a progressive autosomal dominant macular dystrophy. This condition is caused by mutations involving the *TIMP3* gene. It is known to present between the third and sixth decade of life with characteristic thickening of the basement membrane and drusenoid deposits that later develop into areas of atrophy. Typically, patients demonstrate disrupted dark adaptation and nyctalopia, progressing to a loss of central vision.[11]

Doyne honeycomb retinal dystrophy, also known as dominant drusen or Malattia Leventinese, is caused by one specific variant in *EFEMP1* (p.Arg345Trp). Characteristically, small radial and large round drusen are visible in the posterior pole and juxta papillary area.[11,12] Patients are generally asymptomatic. If visual symptoms are apparent, these may include reduced central vision, metamorphopsia and photopsia.

Familial benign fleck retinopathy is an autosomal recessive condition that belongs to the group of flecked retina syndromes. It is caused by biallelic variants in the *PLA2G5* gene.[11] Affected individuals do not suffer from visual dysfunction, nor do they demonstrate electrophysiological deficits. They present from an early age with non-progressive subretinal drusenoid deposits that extend far into the peripheral retina; however, unlike our patient, these deposits are foveal sparing.[12]

Pattern dystrophy is an autosomal dominant condition, comprising a heterogenous group of macular disorders with various patterns of macular pigmentary alterations. The most common mutation is in the *PRPH2* gene although variants in other genes such as *CTNNA1* have been reported.[13] It is often an incidental finding on routine examination as affected individuals are often asymptomatic although mild reduction in vision and metamorphopsia may occur.

Certain systemic disorders such as MPGN-II and lipodystrophy can manifest as early-onset retinal drusen or drusen-like deposits. MPGN-II can present with basal laminar (also known as cuticular) drusen, in the second decade of life. These small yellow-white clustering drusen are found in the macula and peripheral retina. They are easily visualised by fluorescein angiography (FA) and were first described as having a ‘starry sky’ appearance. Over time reduced central vision secondary to choroidal neovascularisation, serous macular detachment and macular atrophy may ensue.[11]

TREATMENT *If relevant*

Despite the extensive macular drusen, the patient retained normal vision in her left eye, hence no intervention was required. An Amsler grid was provided so the patient could monitor for any changes such as distortion or scotomas associated with a possible CNV. The patient was advised to maintain a healthy balanced diet rich in antioxidants and avoid cigarette smoke. Lid hygiene advice and ocular lubricants were prescribed for her blepharitis and dry eyes.

The mainstay metabolic management of lipodystrophy includes dietary macronutrient restriction and regular exercise, as well as the use of hypoglycaemic and hypolipidemic medications where indicated. Currently, the only drug approved for metabolic control in lipodystrophy is metreleptin, which can be used as an adjunct to diet, and has been found to be more effective in those with general, rather than partial lipodystrophy.[6] Additional first line treatments include metformin for treatment of diabetes and insulin resistance, statins for hyperlipidaemia, angiotensin converting enzyme inhibitors or angiotensin receptor blockers for hypertension. Consideration should be given regarding the psychological impact of the condition and referrals should be made accordingly for psychological therapy and cosmetic surgery.[6]

OUTCOME AND FOLLOW-UP

Annual follow-up was arranged to monitor the retinal findings. The patient remained stable without any deterioration in vision or associated symptoms over a one-year period. There was no evidence of CNV or RPE atrophy. The blepharitis was well controlled with conservative management.

DISCUSSION *Include a very brief review of similar published cases*

Generalised and acquired lipodystrophy have a prevalence of 0.23 and 2.84 cases per 1,000,000, respectively.[1] The percentage association with retinal drusen is unknown but it is ultra rare with few reported cases.[14-23] This case highlights the importance of knowing the associated ocular and systemic features of lipodystrophy, including the following: diabetes, dyslipidaemia, non-alcoholic fatty liver disease, cardiovascular disease, renal disease and reproductive dysfunction.[12] This ensures input from the correct multidisciplinary teams. It also helps to forewarn patients that macular drusen may develop, allowing for annual retinal screening to be pre-emptively organised with a local optometrist.

The association between lipodystrophy syndrome and MPGN-II is described in the literature,[24] with 22% of lipodystrophy patients developing this condition.[25] MPGN-II, also known as dense deposit disease, is a rare renal disorder with 2-3 cases per 1,000,000, arising from nephritic factor induced dysregulation of the alternate complement pathway and consequent low levels of serum C3. This condition presents with proteinuria and haematuria in childhood, often progressing to renal failure. It is characterised by electron-dense deposits in the glomerular basement membrane of the kidney and, owing to the systemic nature of the disease, can also be found within the spleen, and between the choriocapillaris and Bruch's membrane of the retina.[26] MPGN-II and age-related macular degeneration (ARMD) are known to share a common pathophysiological process through dysregulation of the alternate complement cascade. Patients with MPGN-II can present with early onset macular drusen from their second decade, which advances peripherally and is associated with thickening of the Bruch's membrane.[24] Interestingly, there is no correlation between the degree of retinal disease and severity of the renal disease. However, a correlation between the duration of renal disease and the likelihood of retinal disease developing has been described; all patients with MPGN-II in one study (n=23) demonstrated drusen after ≥16 months.[19]

In a long-term follow-up study by D'Souza et al in 2008 nearly 80% of their patients with MPGN-II (n=20) exhibited cuticular drusen.[27] As such, it is recommended that patients presenting with this feature undergo screening for nephropathy.[24] Previous attempts at systemic treatment of MPGN with IV immunoglobulins, plasmapheresis and B-cell suppression have all been relatively unsuccessful. Nevertheless, recent studies on Eculizumab, a monoclonal antibody that prevents formation of the membrane attack complex by binding C5, and compstatin, a C3-targeted complement inhibitor have demonstrated promising results.

Ophthalmic management involves monitoring of drusen and associated complications such as CNV. Treatment of CNV involves the use of vascular endothelial growth factor (VEGF) antagonists to control the underlying neovascular process and prevent central vision loss. Signs of dry eyes such as disruption of the tear film, keratitis and blepharitis are common amongst lipodystrophy patients, with up to 87%, of patients suffering from them.[28] Treatment of lipodystrophy associated keratitis varies depending on severity. Mild symptoms may be managed with the use of lubricating eye drops and/or ointments to maintain tear film stability and reduce ocular irritation.

In summary, due to the extremely low prevalence of lipodystrophy syndrome, accurate diagnosis remains a challenge to clinicians. Patients who are diagnosed with this condition must be warned of the associated features that may manifest later in life, so they can have appropriate follow-up and investigations can be performed by the correct multidisciplinary team. If patients present to ophthalmology with early onset macular drusen, they should be aware of this association but may have to exclude an underlying macular dystrophy. More detailed ophthalmological assessment including electrophysiology with pattern electroretinograms can detect early macular changes, advice and monitoring for possible CNV can be offered.

LEARNING POINTS/TAKE HOME MESSAGES *3-5 bullet points*

1) Lipodystrophy is an ultrarare, progressive disease with severe metabolic sequelae that may be life-threatening if not appropriately diagnosed and managed.
2) Management of patients with acquired partial lipodystrophy may require regular screening for metabolic and renal complications such as type 2 membranoproliferative glomerulonephritis (MPGN-II).
3) Ocular manifestations of acquired partial lipodystrophy, especially in those with renal involvement (MPGN-II), include dry eyes and retinal drusen. Long term follow-up to monitor for complications such as choroidal neovascularisation, which can lead to severe visual impairment, should be considered.

REFERENCES

1) Chiquette E, Oral EA, Garg A, *et al*. Estimating the prevalence of generalized and partial lipodystrophy: Findings and challenges. Diabetes, Metab Syndr Obes Targets Ther. 2017 Sep 13;10:375–83.
2) Handelsman Y, Oral EA, Bloomgarden ZT, *et al*. The clinical approach to the detection of lipodystrophy - An AACE consensus statement. Endocr Pract. 2013;19(1):107-116.
3) Garg A. Acquired and Inherited Lipodystrophies. Obe Metab. 2004;1(2):42-44.
4) Hegele RA, Cao H, Liu DM, *et al*. Sequencing of the reannotated LMNB2 gene reveals novel mutations in patients with acquired partial lipodystrophy. Am J Hum Genet. 2006;79(2):383-389.
5) Mallon PWG, Cooper DA, Carr A. HIV-associated lipodystrophy. HIV Med. 2001;2(3):166-173.
6) Brown RJ, Araujo-Vilar D, Cheung PT, *et al*. The diagnosis and management of lipodystrophy syndromes: A multi-society practice guideline. J Clin Endocrinol Metab. 2016;101(12):4500-4511.
7) Patel D, Page B. Images in medicine ocular complications in acquired partial lipodystrophy. Postgrad Med J. 2006;82(973):774.
8) Broadhead GK, Chang A. Choroidal Neovascularization in acquired partial Lipodystrophy. Eur J Ophthalmol. 2013;23(3):439-441.
9) Nasr AM, Ayyash I, Karcioglu ZA. Unilateral enophthalmos secondary to acquired hemilipodystrophy. Am J Ophthalmol. 1997;124(4):572-575.
10) Patel A, Hayward JD, Tailor V, *et al*. The Oculome Panel Test: Next-Generation Sequencing to Diagnose a Diverse Range of Genetic Developmental Eye Disorders. Ophthalmology. 2019;126(6):888-907.
11) Khan KN, Mahroo OA, Khan RS, *et al*. Differentiating drusen: Drusen and drusen-like appearances associated with ageing, age-related macular degeneration, inherited eye disease and other pathological processes. Progress in Retinal and Eye Research. 2016;53:70-106.
12) Guigui B, Leveziel N, Martinet V, et al. Angiography features of early onset drusen. Br J Ophthalmol. 2010;95(2):238-244.
13) Tanner, A., Chan, H. W., Pulido, J. S., *et al*. (2020). Clinical and Genetic Findings in CTNNA1-Associated Macular Pattern Dystrophy. Ophthalmology, S0161-6420(20)31034-4. Advance online publication. https://doi.org/10.1016/j.ophtha.2020.10.032.
14) Gaboriau T, Rigalleau V, Rougier M-B, *et al*. LIFELONG PROGRESSIVE RETINAL ATROPHIC LESIONS IN A PATIENT WITH PARTIAL ACQUIRED LIPODYSTROPHY (BARRAQUER–SIMONS SYNDROME). Retin Cases Brief Rep. 2019;:1
15) Pratyusha G, Votruba M. Retinal changes in a patient with acquired partial lipodystrophy (Laignel-Lavastine and Viard Syndrome). Acta Ophthalmol. 2015;93(7):e598–9.
16) Jansen J, Delaere L, Spielberg L, *et al*. Long-term fundus changes in acquired partial lipodystrophy. BMJ Case Rep. 2013;2013(nov18 1):bcr2013201218-bcr2013201218.

17) Askar A, Mushtaq F, Al Shuaibi F, *et al*. Rare case of spot diagnosis of nephrotic syndrome in a Saudi male. Saudi J Kidney Dis Transpl. 2011;22(5):1003–7.
18) D'souza YB, Jones CJP, Short CD, *et al*. Oligosaccharide composition is similar in drusen and dense deposits in membranoproliferative glomerulonephritis type II. Kidney Int. 2009;75(8):824-827.
19) D'souza Y, Short CD, McLeod D, *et al*. Long-term follow-up of drusen-like lesions in patients with type II mesangiocapillary glomerulonephritis. Br J Ophthalmol. 2008;92(7):950-953.
20) Trabucchi G, Sannace C, Introini U, *et al*. Partial lipodystrophy with associated fundus abnormalities: An optical coherence tomography study [1]. British Journal of Ophthalmology. 1998;82(3):326-326.
21) O'Brien C, Duvall-Young J, Brown M, *et al*. Electrophysiology of type II mesangiocapillary glomerulonephritis with associated fundus abnormalities. Br J Ophthalmol. 1993;77(12):778-780.
22) Raines MF, Duvall-Young J, Short CD. Fundus changes in mesangiocapillary glomerulonephritis type II: Vitreous fluorophotometry. Br J Ophthalmol. 1989;73(11):907-910.
23) Davis TME, Holdright DR, Schulenberg WE, *et al*. Retinal pigment epithelial change and partial lipodystrophy. Postgrad Med J. 1988;64(757):871-874.
24) Mansour A, Lima L, Arevalo J, *et al*. Retinal findings in membranoproliferative glomerulonephritis. American Journal of Ophthalmology Case Reports. 2017;7:83-90.
25) Misra A, Peethambaram A, Garg A. Clinical Features and Metabolic and Autoimmune Derangements in Acquired Partial Lipodystrophy: Report of 35 Cases and Review of the Literature. Medicine. 2004;83(1):18-34.
26) Appel GB, Cook HT, Hageman G, *et al*. Membranoproliferative glomerulonephritis type II (dense deposit disease): An update. J Am Soc Nephrol. 2005;16(5):1392-1403.
27) McAvoy CE, Silvestri G. Retinal changes associated with type 2 glomerulonephritis. Eye. 2004;19(9):985-989.
28) FERNANDES VO, GOMES LMA, MONTENEGRO APDR, *et al*. Ophthalmologic Findings in Congenital Generalized Lipodystrophy—A Possible Marker of Metabolic Disorders. Diabetes. 2018;67(Supplement 1):628-P.

FIGURE/VIDEO CAPTIONS

Figure 1: Multimodal imaging of patient with acquired lipodystrophy and macula drusen. (A,B) Ultra-widefield colour images demonstrating bilateral drusen, contained mainly within the arcades, and involving the macula (C,D) Short wavelength autofluorescence also demonstrating bilateral macula drusen.

Figure 2: (A) Infrared reflectance (IR) demonstrating macula drusen in right eye. (B) Optical Coherence Tomography (OCT) demonstrating macula drusen in right eye. (C) IR demonstrating macula drusen in left eye. (D) OCT demonstrating macula drusen in left eye. (E) Pattern electroretinogram (ERG) to a standard stimulus field are normal and relatively symmetrical. To a large stimulus field response shows some increase in amplitude bilaterally, but not quite as much as would be expected suggesting the possibility of mild peripheral macular dysfunction with no evidence of central macular dysfunction. The right eye has existing amblyopia.

PATIENT'S PERSPECTIVE

Unavailable

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