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Case Report

Desferrioxamine-Related Pseudo-Vitelliform Dystrophy and the Effect of Anti-Vascular Endothelial Growth Factor

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Keywords
Anti-VEGF · Desferrioxamine (desferal, deferoxamine) · Desferrioxamine-related maculopathy · Pseudo-vitelliform dystrophy

Abstract
We report a case of a 72-year-old female who developed bilateral pseudo-vitelliform dystrophy after taking desferrioxamine for the treatment of chronic iron overload. The patient then developed a right superior hemiretinal vein occlusion associated with intraretinal fluid in the right eye and was treated with monthly intravitreal aflibercept injections for 3 months followed by as required treatment. In addition to the intraretinal fluid responding to anti-VEGF treatment, there was a reduction in the size of the pseudo-vitelliform subfoveal deposit height, which was not seen in the untreated eye. Our case of an uncommon presentation of desferrioxamine-related maculopathy associated with a vein occlusion and the changes associated with intravitreal anti-VEGF treatment may help with the potential hypotheses of the pathophysiology of desferrioxamine-related pseudo-vitelliform retinal lesions and help with the potential future treatments of the condition.

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Introduction

Desferrioxamine is an iron chelating agent used in the treatment of chronic iron overload and iron poisoning. The medication is most commonly used in patients with thalassaemia and other haematological conditions which require regular blood transfusions. Desferrioxamine can cause a large array of adverse effects in most major organ systems including the eye. Ocular signs of desferrioxamine toxicity include cataract, optic neuropathy and retinopathy and it is advised that the medication is promptly discontinued in symptomatic patients without life-threatening iron overload [1].

We report a patient who presented with bilateral macular pseudo-vitelliform lesions as a result of long-term treatment with desferrioxamine. Due to a comorbid hemiretinal vein occlusion (HRVO) associated with macular oedema in the right eye, the patient was treated with intravitreal anti-vascular endothelial growth factor (VEGF). We report the effect of this treatment on the macular pseudo-vitelliform lesion.

Case Report

A 72-year-old Caucasian female was referred by her haematology team for desferrioxamine toxicity monitoring. The patient had myelodysplastic syndrome which was managed with monthly blood transfusions and had therefore been started on subcutaneous desferrioxamine 1,600 mg five times a week for the treatment of iron overload 16 months prior. She had no previous past ocular history. She had a past medical history of ischaemic heart disease and, in addition to desferrioxamine, took the following medications regularly: aspirin, felodipine, isosorbide mononitrate, lansoprazole and simvastatin. There was no family history of inherited retinal disease.

At the first Ophthalmology visit, the patient was asymptomatic. On examination, visual acuity was 75 ETDRS letters (6/9) in the right eye and 80 letters (6/7.5) in the left eye, colour vision measured with Ishihara chart was 17/17 in both eyes and slit lamp examination of the eyes was normal. Optical coherence tomography (OCT) of both eyes was normal (Fig. 1a). The patient was reviewed again 6 and 12 months later with no evidence of desferrioxamine toxicity. A Humphrey visual field carried out 12 months after presentation was normal.

26 months after the patient first presented to the Ophthalmology Department, she reported a “net curtain” effect in the right eye. At this point, the patient had been on desferrioxamine for 3.5 years but had stopped treatment 2 weeks prior to this Ophthalmology review because of concerns over her vision. On examination, visual acuity was 47 (6/36) letters (improved to 66 [6/15] with pinhole) in the right eye and 70 letters (6/12) in the left eye. Ishihara in the right eye was 14/17 and in the left eye 16/17. Examination showed bilateral macular pigmentary changes and blot haemorrhages in the superior fundus of the right eye indicating superior HRVO. OCT showed probable bilateral subretinal deposits. The patient was referred to a specialist medical retina clinic.

2 months later, the patient was seen in a subspecialist medical retina clinic and reported blurred vision in the right eye which was noted especially in changing light conditions. On

examination, visual acuity was 55 letters (6/24) in the right eye and 67 (6/15) in the left eye. The patient had bilateral subretinal vitelliform deposits and a right superior HRVO as previously described (Fig. 2a). Fundus autofluorescence showed minimal hyperautofluorescence in both eyes (Fig. 2b). OCT showed a combination of subfoveal hyperreflective material and hyporeflective space (subretinal fluid/space) on either side and also new IRF in the right eye (Fig. 1b). FFA showed bilateral late macular hyperfluorescence and evidence of a right HRVO. Electrophysiological investigations also carried out at this time showed normal multifocal, full-field electroretinography and electro-oculogram.

The patient was started on a course of monthly intravitreal injections of aflibercept to the right eye for 3 consecutive months in order to improve the macular oedema associated with the HRVO. She was reviewed after these 3 loading doses of aflibercept where OCT showed resolution of the IRF in the right eye but also some improvement of the subretinal fluid/space in the right eye (Fig. 1c).

The patient underwent further intravitreal aflibercept as required for recurrent intraretinal and subretinal fluid. 5 years after first presenting (approx. 2 years after first starting aflibercept injections), the patient had received 16 intravitreal aflibercept injections to the right eye and her vision was 45 letters (6/36) in the right and 71 letters (6/12) in the left. OCT of the right eye at this point was dry but with retinal thinning (Fig. 1e). Though both eyes show persistent subretinal deposits, the size and volume has significantly reduced on the right side with gradual reduction to the current state compared to the left.

Conclusions

The mechanisms of desferrioxamine toxicity has been extensively studied; however, the pathophysiology of its ocular side effects are still not well understood. Some have examined and shown the direct toxic effect that desferrioxamine has on RPE cells [2], whereas others believe that the retinopathy caused may be related to abnormal serum or intracellular metal levels due to the drug chelating properties [3]. Histological examination of eyes with desferrioxamine retinopathy showed abnormalities that resembled apoptotic changes of the RPE including swelling and calcification of mitochondria, enlarged RPE cells with melanin accumulation and thickening of Bruch's membrane [4].

Cataract, optic neuropathy and retinal pigment epithelial changes resembling pattern dystrophy have commonly been described as ocular side effects but less frequently the finding of pseudo-vitelliform lesions [1]. We believe our case is that of desferrioxamine-related pseudo-vitelliform dystrophy rather than adult vitelliform dystrophy as the macular changes appeared relatively quickly, there is no family history of inherited retinal disease, the patient had significant visual symptoms and the electrodiagnostic tests were normal. Figure 3 shows a comparison of OCTs between our case and a patient with adult vitelliform dystrophy. In addition to the differences described above, in a typical patient with adult vitelliform dystrophy the subretinal macular lesions are about one-third to one-half the disc diameter in size, are centred by a pigmented spot, are often associated with drusen and often have characteristic clinical and OCT changes with time [5], all of which are absent in our case.

Our patient's history, examination and multiple imaging modalities are also very similar to previously described cases of desferrioxamine-related pseudo-vitelliform maculopathy. In two cases described by Gonzales et al. [6] patients demonstrated vitelliform-like macular lesions after prolonged treatment with low-dose desferrioxamine. These cases showed granular changes, mottling of the RPE and FFA showed hyperfluorescence of the macula in the arterial phase of the FFA. Another case described by Genead et al. [7] in a patient with a 20-year history of desferrioxamine use showed accumulation of material in the sub-RPE space associated with intense autofluoresence. All available case reports studied have shown normal electrophysiology results other than Bui et al. [8] who described a case of reduced rod function seen on electroretinography and markedly abnormal electro-oculogram. Although there are a variety of findings in the cases of desferrioxamine-related pseudo-vitelliform lesions, our case of a patient with prolonged desferrioxamine use, subretinal deposits, increased autofluorescence and normal electrophysiological tests does correspond with previously published cases. Although there has been a case of bull's eye maculopathy likely caused by iron overload, to our knowledge vitelliform lesions have never been a described association [9]. We therefore believe that this case is a rare presentation of an uncommon disease, but the case also shows the effect of intravitreal anti-VEGF therapy on these lesions, which, to our knowledge, has not been described before.

Other than discontinuing desferrioxamine treatment in symptomatic patients without life-threatening iron overload, there is no proven treatment for desferrioxamine-related retinopathy [1]. In the UK, intravitreal anti-VEGF agents are licensed for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusions. This unique case of an uncommon presentation of desferrioxamine retinopathy combined with a vein occlusion gives the opportunity to see if there are any changes to desferrioxamine-related pseudo vitelliform lesions with intravitreal anti-VEGF treatment and also offers a comparison with the untreated other eye. Our case showed that there did seem to be some effect on the subretinal changes secondary to desferrioxamine. Both eyes at presentation showed evidence of subretinal deposits with underlying hypo-reflective area and with anti-VEGF treatment there was significant reduction in the size of the subfoveal deposit height, which was not seen in the untreated eye. With anti-VEGF treatment to the right eye, the subfoveal deposit height, central retinal thickness and macular volume all progressively reduced over the course of 2 years with no significant change in the same parameters in the left eye (Table 1).

The reduction in the subfoveal deposit height was not, however, associated with improvement in vision, with long-term follow-up and repeated aflibercept injections for recurrent IRF; there was evidence of inner retinal thinning in the treated eye. Although there is of course the confounding factor of the comorbid vein occlusion in the right eye, which can cause the sequalae of inner retinal thinning, we believe that the retinal changes are related to intravitreal aflibercept treatment. Our main reasoning for this is that the size of the whole macular lesion has reduced rather than just the superior half, which would be predicted if the change were related to the associated superior HRVO. Gradual reduction of the subretinal deposit in the right eye with continued anti VEGF therapy also points to the effect of treatment rather than the natural course of retinal vein occlusion.

Interestingly, it has previously been noted that subretinal fluid associated with subretinal vitelliform lesions seen in Best disease is often noted to fluctuate and wax and wane over time [10]. In patients with Best disease complicated by choroidal neovascular membranes, the presence of subretinal fluid alone was not a useful guide to treatment and SRF can be expected to both predate and postdate choroidal neovascular membrane discovery/activity [11]. The interplay between subretinal lesions and associated subretinal fluid as well as the response to anti-VEGF is therefore poorly understood, but this case provides evidence of some effect on the subretinal changes secondary to desferrioxamine. Even though we are unable to postulate a hypothesis to explain the resorption of the subretinal deposit on the right side with anti-VEGF therapy, there potentially is an element of the disease which might respond to anti-VEGF therapy in these patients with pseudo-vitelliform deposits resulting from desferrioxamine therapy. More research is needed to understand the pathogenesis of these pseudo-vitelliform lesions.

We hope that our case of an uncommon presentation of desferrioxamine maculopathy associated with a vein occlusion and the changes associated with intravitreal anti-VEGF treatment may help in understanding the pathophysiology of desferrioxamine-related pseudo-vitelliform retinal lesions and help with the potential future treatments of the condition.

Acknowledgements

None.

Statement of Ethics

All procedures followed were in accordance with the tenets of Declaration of Helsinki. Ethical approval was not necessary as this is an individual case report. Written informed consent was obtained from the patient to publish their case and images.

Conflict of Interest Statement

The authors have no conflict of interest and no proprietary interest to declare.

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Author Contributions

Michael Grinton, Yanmei Chen and Ajay Kotagiri: Acquisition, analysis and interpretation of the case, drafting and revising the work. All authors approve the final version of the manuscript for publication.

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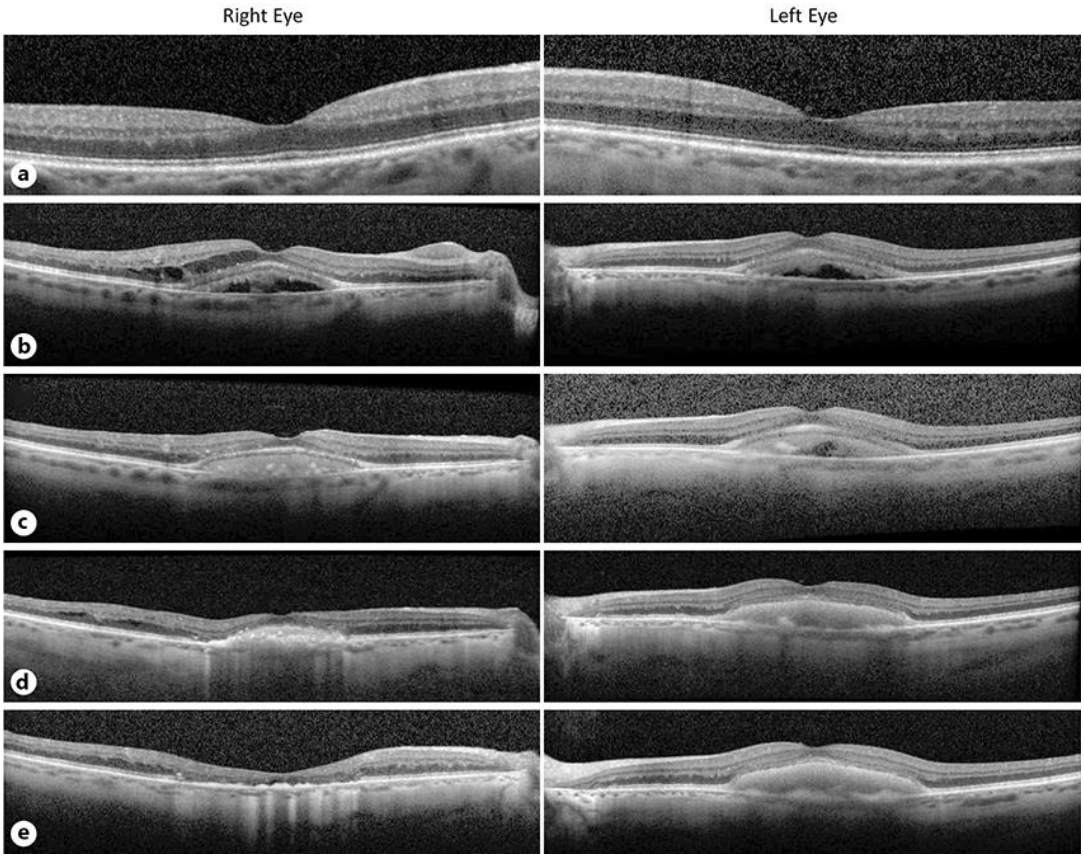

Fig. 1. Serial OCT scans of both eyes: 2 years prior to treatment with aflibercept (**a**), prior to treatment with aflibercept to the right eye (**b**), 4 months after commencing treatment (after 3× loading doses of aflibercept) (**c**), 16 months after commencing treatment (13× aflibercept injections to right eye) (**d**), and 24 months after commencing treatment (16× aflibercept injections to right eye) (**e**).

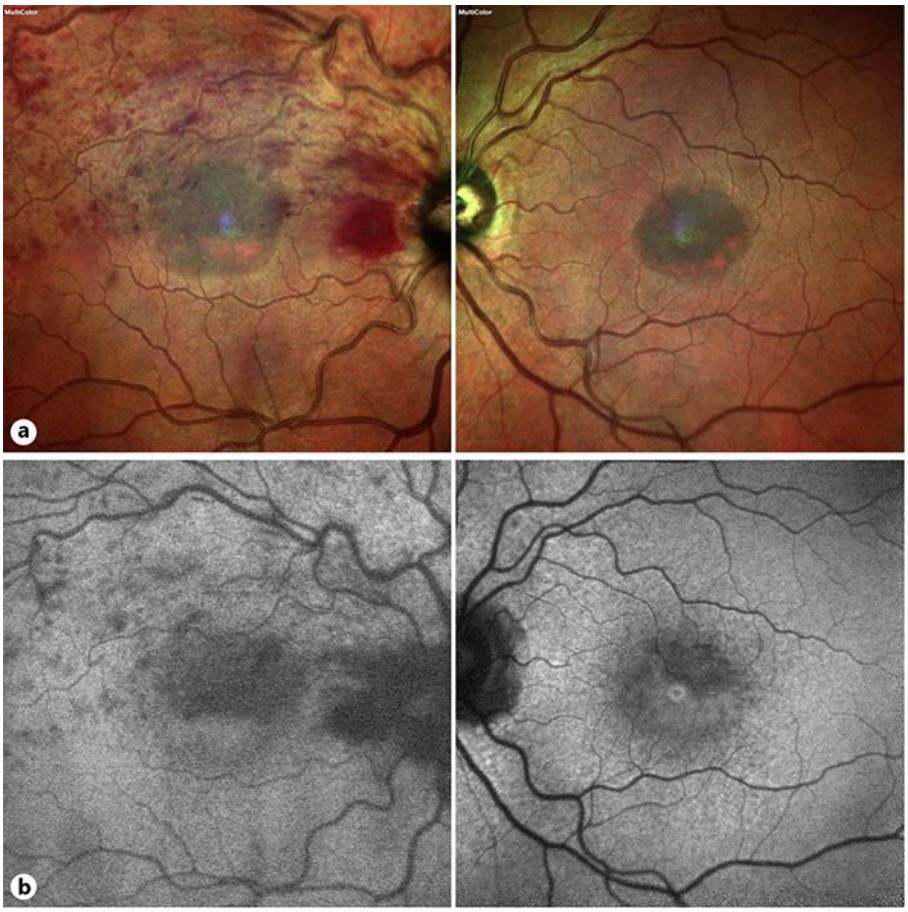

Fig. 2. Multicolour Heidelberg photos (**a**) and fundus autofluorescence (**b**) of both eyes prior to treatment with aflibercept to the right eye.

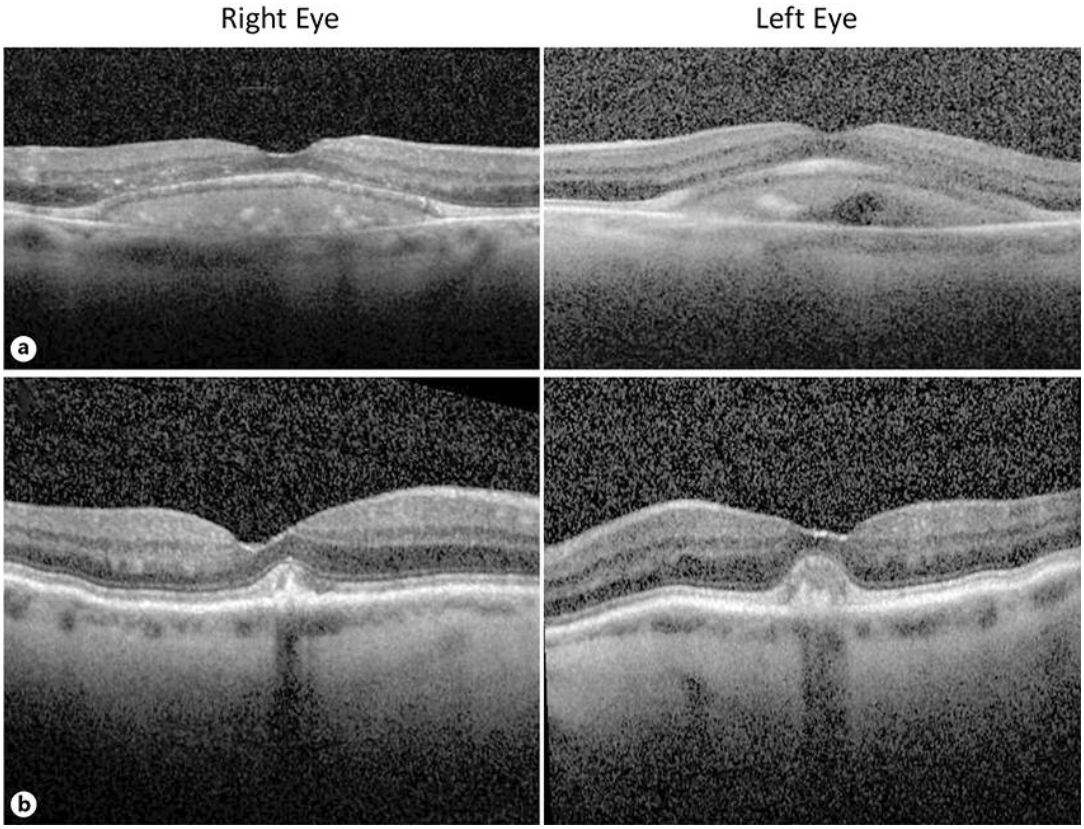

Fig. 3. OCT scans of both eyes in our case of desferrioxamine-related pseudo-vitelliform dystrophy (**a**) and a patient with adult vitelliform dystrophy (**b**).

Table 1. Serial subfoveal deposit heights, macular volumes and central retinal thicknesses in both eyes over 2 years of treatment with aflibercept to the right eye

	Right eye (treated eye)			Left eye		
	subfoveal deposit height, μ	macular volume, mm^3	central retinal thickness, μm	subfoveal deposit height, μm	macular volume, mm^3	central retinal thickness, μm
Pre-treatment	361	0.42	538	329	0.40	509
4 months after starting treatment (3× aflibercept)	296	0.34	429	326	0.42	530
16 months after starting treatment (13× aflibercept)	206	0.24	303	316	0.41	527
24 months after starting treatment (16× previous eylea)	64	0.15	192	381	0.42	533