Spectral-domain optical coherence tomography of retinal vessels in Waldenström’s macroglobulinemia

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ABSTRACT.

Purpose: To image retinal blood vessels in patients with Waldenström’s macroglobulinemia using optical coherence tomography (OCT).

Methods: Retrospective case series examining fundus photographs and OCT scans of 16 eyes in eight patients with Waldenström’s macroglobulinemia. Analyses included intravascular OCT reflectivity profiles and vessel diameters, and their relation to total immunoglobulin M (IgM) levels.

Results: In six out of eight patients, cross-sectional OCT scans of larger retinal vessels (diameter > 100 μm) showed normal intravascular reflectivity and retrovascular shadowing. In two patients with the highest total IgM > 60 g/l, altered intravascular reflectivity, distinct anterior and posterior vessel wall reflexes, and retrovascular hyposhadowing were seen. Normalization of the OCT reflectivity in these patients occurred after reduction of total IgM to < 17 g/l and was accompanied by decreasing venous tortuosity and disappearance of retinal haemorrhages and cotton wool spots.

Conclusion: This study found that Waldenström’s macroglobulinemia and total IgM > 60 g/l were associated with abnormal intravascular reflectivity and retrovascular shadowing on OCT. Awareness of these signs of hyperviscosity could potentially enable earlier detection of critical conditions in patients with Waldenström’s macroglobulinemia and improve the assessment of severity and treatment effect.

Key words: optical coherence tomography – retinal blood flow – retinal vessel diameters – retinal vessels – spectral-domain optical coherence tomography – Waldenström’s macroglobulinemia

Introduction

Waldenström’s macroglobulinemia is a malignant lymphoproliferative B-cell disorder characterized by overproduction of immunoglobulin M (IgM) (Gertz 2019). Immunoglobulin M (IgM) binds water through its carbohydrate component and can induce aggregate formation. Additionally, IgM coats red blood cells and thus promotes rouleau formation as can be seen on peripheral blood smears (Menke et al. 2006). Increasing IgM levels lead to increased intravascular viscosity and platelet dysfunction (Menke et al. 2006; Gustine et al. 2017) which may cause perfusion problems in vital organs (Dobberstein et al. 1999).

Ophthalmoscopically visible abnormalities in patients with Waldenström’s macroglobulinemia include dilated and tortuous retinal veins, retinal haemorrhages, microaneurysms, vein occlusions, optic disc swelling, serous retinal detachment and intraretinal ischaemia/cotton wool spots (Dobberstein et al. 1999; Menke et al. 2006, 2008; Roy et al. 2015).

Modern imaging methods may have an underexplored potential for assisting the diagnosis and monitoring of blood hyperviscosity. Of relevance, optical coherence tomography (OCT) has enabled imaging of flow patterns in the streaming blood in the retinal vessels. Under normal conditions, there is ordered laminar flow in retinal trunk vessels, which is seen as a characteristic intravascular figure-of-8 on cross-sectional OCT scans, with retinal and choroidal structures posterior to the vessel being masked by a shadow effect (Muraoka et al. 2013; Willerslev et al. 2014). The intravascular reflectivity pattern fades or disappears when blood
flow is slow or turbulent and in vessels from patients with some types of severe blood dyscrasia. In the absence of the normal structured intraluminal signal, the retrovascular shadow cast by the vessels is also weaker (Willerslev et al. 2017, 2019).

The present study examined patients with Waldenström’s macroglobulinemia to elucidate the consequences of hyperviscosity on the vascular and intravascular OCT reactivity of the vessels.

Methods

Observational, retrospective case series of eight patients with Waldenström’s macroglobulinemia. Patients had been referred from the Department of Hematology, Zealand University Hospital, Roskilde, between February 2012 and August 2016 for clinical eye examination and as part of a larger study of retinal changes in haematological diseases (Willerslev et al. 2017). The larger haematological study followed the tenets of the Declaration of Helsinki and was approved by the local medical ethics committee (H-1-2013-081). Inclusion in the current retrospective substudy required a diagnosis of Waldenström’s macroglobulinemia, image records in the form of fundus photographs (Topcon TRC50 DX, Topcon Corporation, Tokyo, Japan) and OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) and measurements of serum total IgM concentrations not more than 14 days prior to retinal imaging. Retinal vessel diameters were measured in digital greyscale (red-free) fundus photographs in all patients using a custom-developed semiautomatic computer algorithm. The six largest arteries and the six largest veins in the right eye were identified, and the central retinal artery equivalent diameter (CRAE), the central retinal vein equivalent diameter (CRVE) and the artery-to-vein diameter ratio (AVR) calculated according to formulae described by Knudtson et al. (2003). The AVR was defined as CRAE/CRVE.

Results

This retrospective case series reviewed data from 16 eyes in eight patients (three women, five men), median age 69 years (range: 48–76 years) and a median duration of Waldenström’s macroglobulinemia 2.6 months (range: four days to eight years). Total IgM concentration ranged from 37 to >60 g/l with a median level of 47 g/l (Table 1).

The time interval between the blood samples and the first retinal imaging was between 0 and 14 days with a median interval of 11 days.

In two patients, total IgM was >60 g/l and follow-up imaging after initialization of medical treatment was arranged. There was no structured follow-up imaging of the other six patients.

Fundus photographs showed manifestations of hyperviscosity in the form of dilated retinal veins, retinal haemorrhages, cotton wool spot and optic disc swelling in three patients. Median CRAVE diameter was 137 mm (range 114–158 mm), and median CRVE diameter was 235 mm (range 188–316 mm).

In six out of eight patients, cross-sectional OCT scans of larger retinal vessels (diameter > 100 mm) showed normal intravascular reactivity and retrovascular shadowing. In two patients with IgM >60 g/l, cross-sectional OCT scans of the retinal vessels showed abnormal intravascular reactivity, retrovascular hyposhadowing and very distinct vessel wall reflexes (Figs 1 and 2).

Follow-up OCT from these two patients at 3 and 4 months after initiating medical treatment showed normalization of the intravascular reactivity pattern and retrovascular shadowing. At the time of the second OCT scan, total IgM had been reduced from > 60 g/l to 12 g/l and to 16 g/l, respectively. Densitometric analysis of the anteroposterior OCT reflectivity pattern inside a large retinal vein before (Fig. 3, top panel) and after total IgM reduction (Fig. 3, bottom panel) in one of these patients showed a post-treatment decrease in venous diameter, a rise in the anteriormost intravascular reactivity peak and a largely unchanged density in the posterior half of the vessel. Follow-up fundus photography in the two patients showed that the haemorrhages and cotton wool spots had disappeared, venous tortuosity had decreased, and the AVR had changed from 0.53 to 0.76 and from 0.61 to 0.73, respectively, in tune with the reduction in venous congestion (Figs 1 and 2).

Large, non-cystoid cracks in the retina at or near arterial and venous vessel loops were seen in the two patients with the highest CRVE diameters (316 and 279 mm, Fig. 4). Neither patient had intraretinal haemorrhages or other funduscopy manifestations of hyperviscosity. Follow-up data were unavailable.

Discussion

This study of intravascular OCT in patients with Waldenström’s macroglobulinemia found that total
IgM > 60 g/l was associated with optically detectable structural abnormalities in the retina and in the blood flowing in its vessels. At total IgM concentrations > 60 g/l, cross-sectional OCT scans of retinal vessels showed subnormal luminal reflectivity, which made the anterior and posterior vessel wall reflexes exceptionally well defined. Likewise, the shadows cast by the retinal vessels on the retinal structures behind the vessels were markedly weaker than after treatment, demonstrating that subnormal intravascular reflectivity was associated with subnormal optical density of the blood. The reflectivity profiles returned to normal after treatment, presumably because of the reduction of IgM and thereby normalization of blood viscosity.

Optical coherence tomography findings agree with previous studies of blood dyscrasia (Willerslev et al. 2017) and could indicate blunting of the normal parabolic blood flow rate at the highest IgM (Menke et al. 2008). The upper measurable concentration in most laboratories is 60 g/l, and the odds of developing symptomatic hyperviscosity are 370-fold higher with serum IgM levels > 60 g/l (Gustine et al. 2017). Because blood is a shear-thinning fluid, the flowing blood becomes more viscous as flow slows down, resulting in jamming of blood cells and vascular occlusion (Stefansson et al. 2018).

Previous studies of healthy retinal trunk vessels have shown that the intravascular OCT reflectivity patterns are governed by the ordered laminar arrangement of erythrocytes in flowing blood which has a characteristic figure-of-eight pattern on cross-sectional scans (Muraoka et al. 2013; Willerslev et al. 2017). The ordered signal is reduced or disappears when flow is turbulent, too high or too slow to induce order in the blood column or in cases of severe blood dyscrasia (Willerslev et al. 2014, 2017). It cannot be ruled out, however, that the change in blood composition per se may change the optical reflectivity of the intravascular blood column, and new OCT methods that apply Doppler technology (Tayyari et al. 2014) have the added potential of providing quantitative estimates of retinal blood flow that can be cross-validated with the methods used in the present study.

Previous retinal flow studies of patients with Waldenström’s macroglobulinemia and hyperviscosity syndrome found significant reductions in venous diameter accompanied by significant increase in venous blood speed after patients had undergone plasmapheresis (Menke et al. 2006).
Retinal blood flow levels, however, remained at normal levels before and after treatment (Menke et al. 2008). Video fluorescein angiography studies found abnormally long arteriovenous passing times in patients with Waldenström’s macroglobulinemia (Dobbberstein et al. 1999). These findings suggest that not only the optical reflectivity of the flowing blood, but also its rheological properties undergo measurable changes in Waldenström’s macroglobulinemia.

The observation in this study of non-cystoid cracks near distended retinal vessels should be seen in the context of such structural discontinuity having been described in up to 40% of healthy eyes (Osaka et al. 2017). The presence of internal cracks in the retina in patients with Waldenström’s macroglobulinemia gives rise to suspicion that the openings may expand in relation to the distension that follows from vascular congestion and contract...
in relation to the abatement of hyperglobulinemia. This hypothesis awaits testing in future studies.

Major limitations of this case series include the small number of patients and that only ad hoc OCT follow-up scans were available for comparative image analysis. Other limitations include the lack of fluorescein angiography. Even though Waldenström’s macroglobulinemia is known to be ‘angiographically silent’ (Ho et al. 2000), an angiographic examination would have been necessary to completely rule out fluid leakage from the retinal vessels.

In summary, we imaged retinal blood vessels in patients with Waldenström’s macroglobulinemia using OCT and found that hyperviscosity in patients with total IgM > 60 g/l can be associated with subtle vascular changes on OCT. The skilled user of OCT should be aware of these signs because they can promote early diagnosis of hyperviscous blood dyscrasia and assessment of severity and effect of treatment.

References


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