Utility of in Vivo Corneal Confocal Microscopy in Atypical MEN2B Findings. A Case Report

Štorm Josef[1], Hrdličková Enkela[2], Mahelková Gabriela[1,3]

[1]Department of Ophthalmology, 2nd Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic
[2] Department of Ophthalmology 3rd Faculty of Medicine, Charles University and University Hospital Kralovske Vinohrady, Prague, Czech Republic
[3]Department of Physiology, 2nd Faculty of Medicine, Charles University, Prague, Czech Republic

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MUDr. Josef Štorm

Correspondence address
Oční klinika dětí a dospělých 2. lékařské fakulty Univerzity Karlovy a Fakultní nemocnice v Motole
V Úvalu 84
150 00 Praha 5
Czech Republic
E-mail: storm.vyzkum@gmail.com

SUMMARY

Purpose: To describe atypical biomicroscopical and histological changes in corneal and conjunctival structures in multiple endocrine neoplasia type 2 (MEN2b) and bring attention to common characteristics and atypical features.
Methods: Retrospective case series.
Results: Two patients, female, and male, with previously confirmed MEN2B diagnosis were examined at our clinic to evaluate corneal and conjunctival pathologies using in vivo corneal confocal microscopy (IVCM). The female patient showed all hallmark signs of MEN2b features despite a recent unilateral herpetic infection. The male was examined at a very late stage of the disorder and showed only partial features of typical ocular MEN2b manifestations. Two notable deviations were observed: an opaque corneal mass of the right eye and absence of prominent corneal nerves in both eyes IVCM conjunctival neuroma scans correlated with scans of the corneal mass, ascertaining its histological nature.
Conclusions: This case series is, to our knowledge, the first to describe the absence of prominent corneal nerves in MEN2b. It also highlights the utility of IVCM in superficial lesion analysis. Its non-invasive nature is of great benefit to the patient.
Key words: MEN2B, corneal nerve fibers, neuroma, corneal confocal microscopy, ocular surface

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INTRODUCTION

Multiple endocrine neoplasia type 2b (MEN2b) belongs to a group of rare hereditary disorders, characterized by endocrine gland enlargement or even benign or malignant tumor growth. MEN2b is notable for mucosal neuromas alongside Marfanoid habitus and the greater risk of rapid thyroid carcinoma development and spread. Current literature also presents ocular involvement e.g., dry eye, conjunctival neuromas, eyelid thickening, and pronounced thickening of corneal nerve fibers [1–4]. We present a case series of two MEN2b confirmed patients, examined using in vivo corneal microscopy (IVCM, Heidelberg Retinal Tomograph III – Rostock Cornea Module) at our clinic, with varying symptoms and ocular findings, both macro- and microscopic.

MATERIALS AND METHODS

This case series involves two patients with previously confirmed MEN2b diagnoses made through genetic testing, referred for IVCM examination at the Department of Ophthalmology, 2nd Faculty of Medicine, Charles University and Motol University Hospital. Each patient was questioned for relevant history, underwent a thorough ocular examination including VA, biomicroscopic examination, anterior segment imaging and IVCM. Informed Consent forms for image acquisition and anonymized publishing were signed by all participants. The study was conducted following the World Medical Association Declaration of Helsinki.

CASE REPORT H

A 35-year-old female patient was referred to our

clinic for in vivo corneal confocal microscopy (IVCM) evaluation of prominent corneal nerve fibers and perilimbal conjunctival masses in both eyes, with a recent recurrence of herpetic keratitis in the left eye (OS). She had been previously treated for herpetic keratitis in OS as early as 2012 at our clinic. At the age of 16 years, a thyroidal carcinoma was diagnosed and removed. Subsequent genetic analysis established the MEN2b diagnosis. Her history revealed long-term contact lens wear as well.

Clinical evaluation showed conjunctival hyperemia with white semi-transparent perilimbal subconjunctival thickening, as well as notable circular vasculature following the perilimbal cornea in both eyes. Another bilateral biomicroscopic finding was the significant thickening of stromal nerve fibers. The right eye (OD) showed no corneal epitheliopathy, while OS had minimal superficial epitheliopathy. Sensitivity was decreased in both eyes, significantly more in OS.

IVCM verified thick hyperreflective nerve fiber bundles of varying widths in both eyes. There was a notable decrease in corneal subbasal nerve fiber length (9.3044 mm/mm^2) as well as density (7.4995 fibers/mm^2) in OS. These parameters were within normal ranges in OD. In addition, OS scans of the subbasal plexus showed a marked increase in activated dendritic cells. Focusing on the conjunctival masses, stromal images reveal tangled, disorganized fibrous-like structures with scattered hyperreflective strands. Figure 1.

CASE REPORT Z

A 54-year-old male patient, who is being followed closely at our clinic due to a suspected metastatic choroidal nodule in OD, had been diagnosed with MEN2B at the age of 23 years, following surgical intervention and radiation treatment for medullary thyroid carcinoma. In the subsequent years, several more interventions were necessary due to recurring neoplasms. 2016 was the year of our first contact with the patient for a suspected metastatic choroidal nodule in OD and secondary glaucoma. He has been in our care since then. In 2019, OD was treated with a gamma knife, but the nodule responded poorly. IVCM examination was requested, following a conjunctival biopsy of OD.

OD examination revealed conjunctival hyperemia, discrete nasal and lateral conjunctival thickening, perilimbal neovascularization, and an opaque white superficial protruding mass on the inferior cornea. OS findings were similar, with significantly more pronounced conjunctival thickening, but with no corneal growths present. Sensitivity was similarly decreased in OU. There were no further atypical or pathological findings in the anterior segment. No biomicroscopically prominent corneal nerve fibers were described in the available history.

IVCM examination results were similar in OU. The superficial epithelium was intact, but the subbasal nerve plexus was significantly diminished and we were unable to perform a standard subbasal plexus analysis. There was mild stromal edema and only marginal thickening of stromal nerve fibers. Endothelial images showed no pathology. Scanning the perilimbal conjunctival masses as well as the superficial corneal nodule in OD showed structures like those seen in Patient H.

Bioptic samples from the OS superior nasal conjunctival mass were predominantly populated by elongated spindle cells, with sporadic cytoplasmic melanin deposits. Of note were nerve fascicle-like structures with myelinated axons scattered throughout the sample. Figure 2.

DISCUSSION

MEN 2b ocular features have been extensively described in the past, considering stromal corneal nerve fiber thickening as one of its hallmarks alongside conjunctival neuromas [1–6]. In one of our presented cases, thickened corneal nerve fibers were not observed, despite a definite MEN2b diagnosis confirmed by genetics. To our knowledge, this is the first published case where this feature of MEN2b was not apparent.

Patient H demonstrated all the notable characteri-

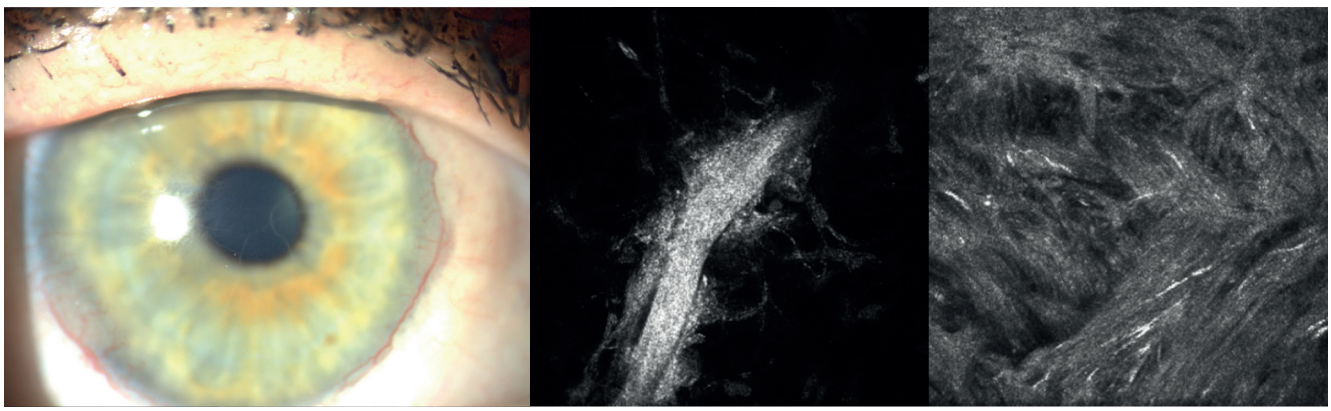

Figure 1. Prominent corneal nerve fibers and perilimbal subconjunctival thickening with their respective ultrastructure as seen with IVCM
IVCM – in vivo confocal microscopy

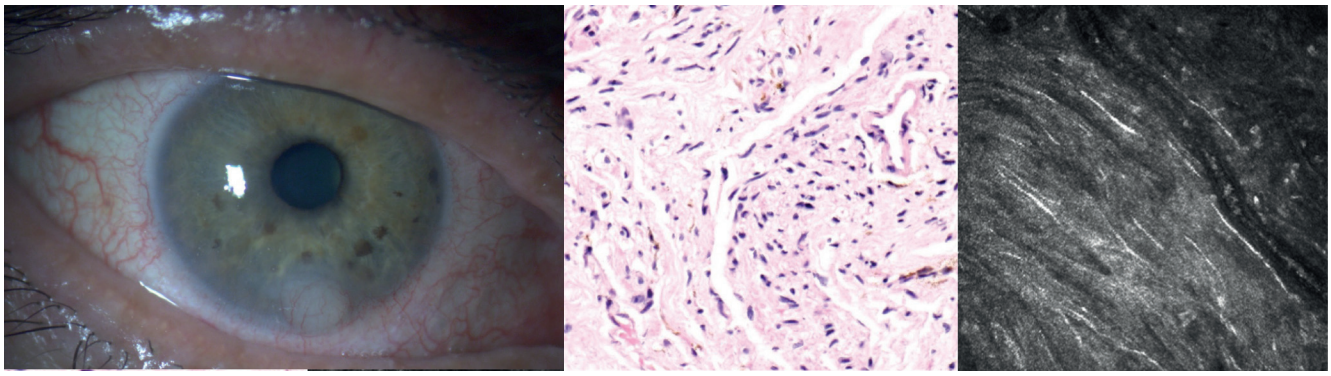

Figure 2. No thickening of corneal nerve fibers, corneal mass and notable perilimbal subconjunctival thickening. Histological section sample from the thickened perilimbal conjunctiva. IVCM ultrastructure of the corneal mass
IVCM – in vivo confocal microscopy

stic findings. Perilimbal conjunctival masses as well as notably thickened corneal nerves were observed. Our findings were possibly altered by a recent corneal herpetic infection in OS, which led to a decrease in sensitivity and the extensive presence of dendritic cells in the Bowman's layer. In this case, the subbasal plexus was significantly reduced in OU. However, this may have been the result of chronic contact lens wear or previous herpetic infections. Nevertheless, this did not change the constitution of stromal corneal fibers as confirmed by IVCM.

The findings were much more subtle in patient Z. Subconjunctival thickening was present, but discreet in both eyes, whereas biomicroscopy did not reveal any significant corneal nerve fiber thickening. Of note was the opaque corneal mass in OD of uncertain origin, which we were able to examine using IVCM.

Focusing on the subconjunctival masses in both patients, IVCM showed comparable ultrastructure. We were able to obtain a biopsy sample from patient Z and to verify them as conjunctival neuromas. The characteristic IVCM findings of these benign growths were also observed in the corneal mass of patient Z.

CONCLUSION

This case series also demonstrates the ease of use and availability of IVCM in the clinical setting, especially its role in diagnosing superficial lesions of the eye. The characteristic structure of neuromas, particularly the hyperreflective strands, is easily recognizable [1,2,7], so an early examination could spare the patient from invasive biopsies.

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