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SHORT COMMUNICATION

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Typical ocular findings in a patient with multiple endocrine neoplasia type 2b syndrome

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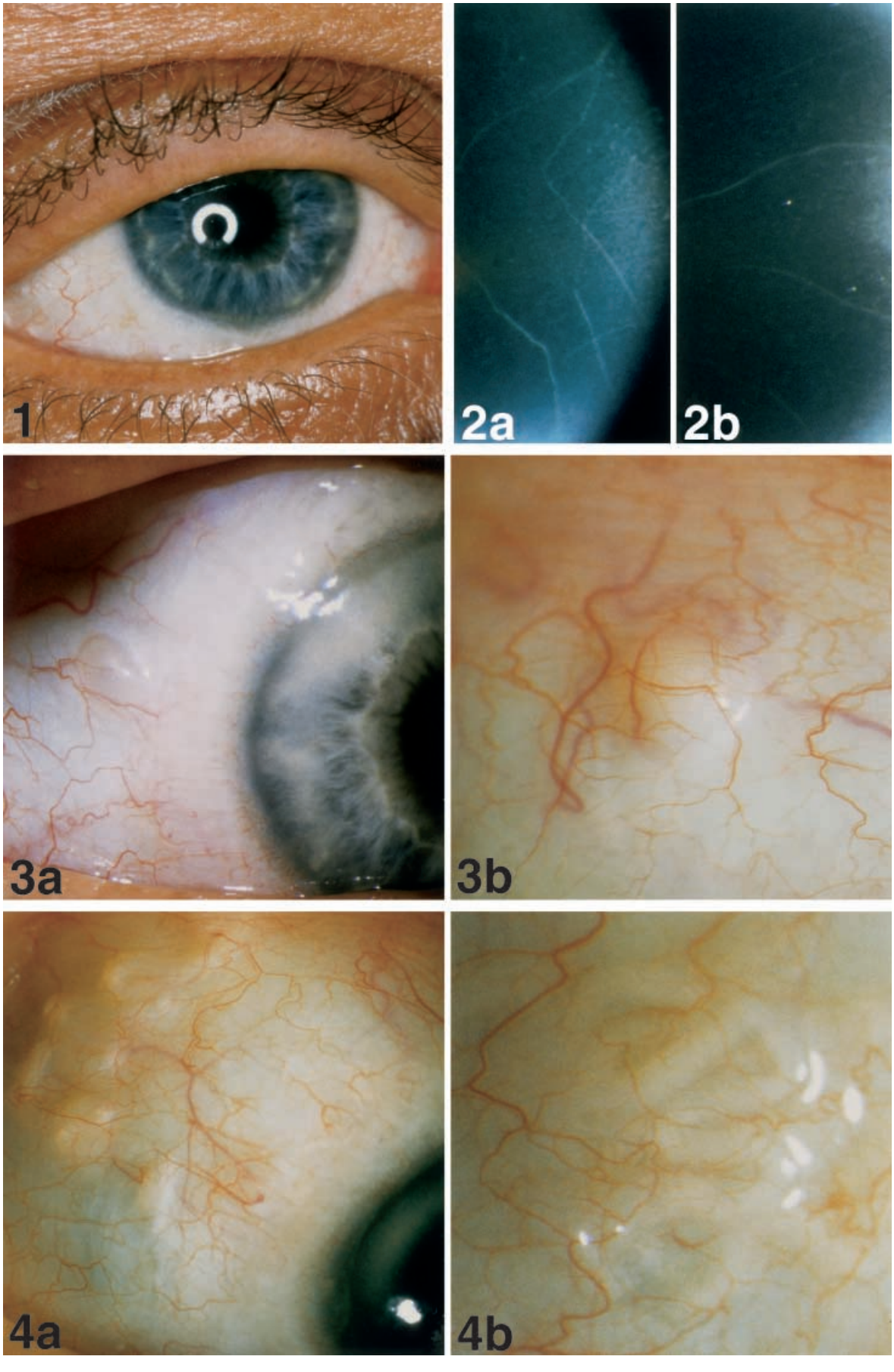
Abstract *Background:* Multiple endocrine neoplasia (MEN) type 2b syndrome is accompanied by typical ocular findings; however, the disease is often only diagnosed at an advanced stage by symptoms of C-cell carcinoma or pheochromocytoma and is then fatal in most cases. Therefore, the importance of ophthalmic assessment in making the diagnosis has to be stressed.
Methods: The history and ocular findings of a patient with MEN 2b syndrome are described, and a brief overview of the syndrome is given.
Results: Slit-lamp examination showed extremely thickened corneal nerves as well as multiple small plexiform and nodular subconjunctival tumors. Both eyes also displayed thickened upper and lower eyelids. A molecular genetic study of the RET proto-oncogene showed a heterozygous ATG to ACG mutation in codon 918 of exon 16.
Conclusion: Greatly thickened corneal nerves and subconjunctival tumors may be the first hint of MEN 2b. Whenever greatly thickened corneal nerves are detected, MEN 2b must be ruled out.

Introduction

Three different types of multiple endocrine neoplasia syndrome (MEN) exist. All of them are characterized by the occurrence of tumors in two or more endocrine glands. The combination of pheochromocytoma and carcinoma of the thyroid gland was first described by Sipple in 1961. Soon after that, the combination of pheochromocytoma, medullary thyroid carcinoma and parathyroid tumors or hyperplasia was referred to as "multiple endocrine neoplasia type 2" (MEN 2). Several years later MEN 2 was subdivided into two types, a and b. MEN type 2a patients display the common phenotype associated with medullary carcinoma, pheochromocytoma and parathyroid disease.

The MEN 2b syndrome is characterized by the association of medullary carcinoma of the thyroid gland, pheochromocytoma and multiple mucosal neuromas. The onset of the disease is significantly earlier than in MEN 2a; the age at diagnosis ranges from 2 days to 52 years (mean 18.9 years) [2]. Other typical findings of this disease include a marfanoid habitus, a long history of diarrhea and/or constipation, thickened lips with nodules, nodules on the anterior aspect of the tongue and nodules on the cheek mucosa. The ophthalmic findings include conjunctival and lid neuromas, thickened upper eyelids, keratoconjunctivitis sicca and thickened corneal nerves. MEN 2b is inherited in an autosomal dominant pattern. However, up to 60% of the cases are due to de novo mutations. The gene for MEN type 2b is located on chromo-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some 10 [5]. It encodes the Ret receptor tyrosine kinase, a transmembrane protein expressed in neuroendocrine cells that transduces signals for growth and differentiation. Recently, maxillofacial and orthopedic changes have also been found to be typical for MEN type 2b, such as a broadened nasal bridge, a markedly enlarged and bifurcated inferior alveolar channel and shortened roots of the lower incisor teeth, slipped captor femoral epiphysis, pes cavus, talipes equinovarus, kyphosis, scoliosis, lordosis, increased joint laxity and weakness of the proximal muscles of the extremities [3, 12]. If the disease is discovered late, patients usually die of metastatic thyroid carcinoma.

Case report

A 34-year-old white male was referred to the Department of Ophthalmology for ophthalmologic examination by the Department of Clinical Biochemistry. He complained of strong bilateral conjunctival hyperemia in the morning, which had first appeared in childhood and had increased ever since. He was seeing an ophthalmologist occasionally and was prescribed vasoconstrictant eye drops, which decreased the redness immediately. His ophthalmologic history was otherwise unremarkable.

At the age of 22 years, a medullary thyroid carcinoma was diagnosed, and thyroidectomy ensued. Further investigation disclosed a pheochromocytoma of the left adrenal, which was removed surgically. Five years later a pheochromocytoma of the other adrenal was diagnosed and removed surgically. Since then he had been receiving hydrocortisone 30 mg, fludrocortisone 0.1 mg and levothyroxine 150 µg per day. Two years ago, he was referred to the Department of Clinical Biochemistry for further follow-up. Calcitonin levels were found to be 123 pg/ml (normal: <100 pg/ml); serum tests concerning catecholamines were negative.

The patient's father had died at the age of 31 from myocardial infarction. No links with endocrine neoplasias were found. The mother and sister of the patient had been examined elsewhere. The mother had been diagnosed as having a goiter, but no thyroid malignancy had been found. All other findings, including a pentagastrin-stimulated calcitonin test, were reported to have been unremarkable. Neither the mother nor sister was available for ophthalmologic examination.

The patient had no further close relatives.

On examination, uncorrected visual acuity was 20/20 in both eyes, intraocular pressure was normal and ophthalmoscopic findings were unremarkable. Slit-lamp examination showed thickened upper and lower eyelids (Fig. 1). Extremely thickened corneal nerves in the superficial and midcorneal stroma could be recognized (Fig. 2). Both eyes displayed multiple small plexiform and nodular subconjunctival tumors (Fig. 3a,b). The conjunctiva at the corneoscleral limbus was irregularly thickened and appeared almost chemotic (Fig. 3a). Only the left cornea showed an arcus lipoides.

◀ **Fig. 1** The patient's right eye, showing a thickened upper and lower eyelid

Fig. 2a, b Thickened corneal nerves of both eyes

Fig. 3a, b Both eyes of the patient, showing subconjunctival nodular tumors

Fig. 4a, b Both eyes of the patient, showing plexiform subconjunctival tumors

Break-up time was 15 s OD and 5 s OS; basal tear secretion was 1 mm OD and 4 mm OS. Orthoptic findings were unremarkable. The patient was diagnosed as having MEN type 2b. The diagnosis was confirmed by genetic analysis. A molecular genetic study of the RET proto-oncogene showed a heterozygous ATG to ACG mutation in codon 918 of exon 16, which is present in 95% of patients with MEN type 2b [4].

Discussion

MEN type 2b syndrome is characterized by medullary thyroid gland carcinoma and typical mucosal neuromas found in all patients described in the literature. Pheochromocytoma, marfanoid habitus and other features are variably expressed. In all cases described in the literature, thickened corneal nerves were found, no matter how old the patients were. Robertson et al. [11] described two families with MEN 2b. In one of the families thickened corneal nerves were found in two children aged 2 and 4 years, too young for marfanoid habitus to be determined. In the 4-year-old a medullary thyroid gland carcinoma could already be detected. The 2-year-old showed elevated calcitonin levels, and total thyroidectomy revealed C-cell hyperplasia.

Although our patient had been seen by ophthalmologists long before any other symptoms were apparent, the diagnosis of MEN 2b was first established when a medullary thyroid gland carcinoma and a pheochromocytoma occurred on one side.

Among the other signs, greatly thickened corneal nerves formed an irregular lace pattern across the entire cornea. The enlargement of corneal nerves may be caused by the increase in the number of axons found by Riley et al. [10] in histopathologic sections of the cornea. An increased number of Schwann cells may also contribute to the large size of the corneal nerves [10]. Myelination of corneal nerves as the cause for increased visibility has also been suggested [1, 7]. In histopathologic sections Riley et al. [10] found the myelination of the corneal nerves to terminate near the corneoscleral limbus. Thickened corneal nerves rarely occur in other diseases; however, they have been described to appear occasionally in patients with MEN 2a, MEN 3, neurofibromatosis, pheochromocytoma, congenital ichthyosis, leprosy and medullary C-cell carcinoma without known mutations for MEN 2a and 2b. Corneal nerves also appear more visible in some corneal diseases, such as herpes simplex, herpes zoster, posterior polymorphous dystrophy, Fuchs' bullous keratopathy and keratoconus [6, 8].

Enlarged, prominent nerves are also common in the subconjunctival region of patients suffering from MEN 2b, leading to a swelling of the overlying conjunctiva, as we found in the perilimbal conjunctiva. These nerves can also occur in bundles as relatively flat neuromas, appearing as nodules. Perilimbal neuromas are often associated with dilated perilimbal conjunctival blood vessels, lead-

ing to chronically red eyes. Although our patient complained of redness of the eye in the morning, no dilated perilimbal conjunctival vessels could be found during the examination. Dryness in the morning could be related to keratoconjunctivitis sicca, which is demonstrated by decreased tear production.

The patient had been referred to the Department of Clinical Biochemistry because of increasing levels of calcitonin. This indicates metastases from the former thyroid carcinoma, implying a poor prognosis. Because MEN 2b is often only diagnosed at an advanced stage on the basis of elevated serum levels such as calcitonin or catecholamines present in medullary C-cell carcinoma and pheochromocytoma, respectively, the disease is fatal in most cases. An ophthalmologic examination is therefore important in helping to detect the typical ophthalmic signs in MEN 2 patients. In particular, the thickened corneal nerves in an otherwise unremarkable corneal stroma rarely appear in any other disease and may be the first hint of MEN 2b (or perhaps MEN 2a [13] or MEN 3 [9]) syndrome. Thus, whenever greatly thickened corneal nerves are detected during an ophthalmologic examination, MEN 2b must be considered.

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