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ORGANSCHAFTEN: Vereinigung für ästhetische Dermatologie und Lasermedizin e.V.
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FALLSTUDIE ZUM SCHLEIMHAUT-NEUROM-SYNDROM

ERATUM

Issue 6 – 2010: pages 298-305

Mucosal Neuroma Syndrome without mutations of the RET-protooncogene: A clinical and histologic study on a case, supported by molecular genetic analysis

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SCHLEIMHAUT-NEUROM-SYNDROM OHNE MUTATIONEN DES RET-PROTOONKOGENES:
KLINISCHE UND HISTOLOGISCHE FALLSTUDIE SOWIE MOLEKULARGENETISCHE ANALYSE

Mucosal Neuroma Syndrome without mutations of the RET-protooncogene: A clinical and histologic study on a case, supported by molecular genetic analysis

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KEY WORDS

mucosal neuroma, histopathology, DNA sequencing, MEN2b syndrome

SUMMARY

Mucosal neuromas are nerve hamartomas of the digestive tract and larynx, usually observed in the setting of Multiple Endocrine Neoplasia type 2b (MEN2b), i.e. in the presence of typical mutations and in association with medullary thyroid carcinoma, pheochromocytoma and marfanoid habitus. Exceptionally, they arise without the accompanying mutations and endocrine tumors, and in this paper we are reporting on a case of mucosal neuromas lacking the specific mutations. The patient was an adolescent girl with marfanoid habitus, with a left-sided epidermal nevus of the neck, and a bulging left upper lip and cheek. The left side of her tongue was considerably enlarged and studded with multiple protrusions. The histologic examination of the tongue showed a proliferation of tortuous gigantic nerve trunks, composed of multiple small bundles of argyrophilic and fully myelinated axons, invested by extremely hyperplastic perineurium and epineurium. These architectural distortions and disproportions, in the absence of disorders of polarity, imparted to the picture a dysmorphic, rather than neoplastic imprint. Although the required follow-up procedures were hindered by the patient's unavailability, DNA sequencing, performed on the paraffin specimen, demonstrated that none of the RET mutations reported to date in MEN 2b were present in our case. Therefore, this syndrome could be reasonably excluded and a final diagnosis of Multiple Neuroma Syndrome was assessed. Awareness of mucosal neuroma can be critical for the patient's survival, since this rare and often underrated neoplasm is likely to be an early marker of MEN2b, a life-threatening syndrome which requires early prophylactic surgery.

INTRODUCTION

Mucosal neuromas are multiple hamartomatous growths of nerve bundles which involve the mucosae of the oral cavity, larynx, and gastrointestinal tract, usually in patients with multiple endocrine neoplasia type 2b (MEN2b) [1]. This is an autosomal dominant cancer syndrome characterized by the association of the mentioned mucosal neuromas with medullary thyroid carcinoma and pheochromocytoma, in patients with

SCHLÜSSELWÖRTER

Schleimhautneurom, Histopathologie, DNA-Sequenzierung, MEN2b-Syndrom

ZUSAMMENFASSUNG

Schleimhaut-Neurome sind nervale Hamartome des Verdauungstraktes und Larynx, die für gewöhnlich im Rahmen der multiplen endokrinen Neoplasie Typ 2b (MEN2b) vorkommen. Somit lassen sich die typischen Mutationen und Assoziationen zum medullären Schilddrüsenkarzinom, zum Phäochromozytom und zum marfanoiden Habitus nachweisen. Selten treten sie ohne entsprechende Mutationen und endokrine Neoplasien auf. Über einen solchen Fall berichten wir in dieser Arbeit. Es handelte sich um eine Jugendliche mit marfanoiden Habitus und einem linksseitigen epidermalen Nävus von Hals, Wange und vorgewölbter Oberlippe und Wange. Die Zunge war ipsilateral vergrößert und wies multiple Protrusionen auf. Bei histologischer Untersuchung zeigte sich eine Proliferation geschlängelter, erheblich vergrößerter Nervenstränge, die aus argyrophilen und komplett myelinisierten Axonen aufgebaut sind. Perineurium und Epineurium sind extrem hyperplastisch. Diese architektonischen Störungen und Abnormalitäten und das Fehlen von Polaritätsstörungen impliziert eher dysmorphe als neoplastische Prozesse. Leider waren Nachfolgeuntersuchungen durch Nichterreichbarkeit der Patientin vereitelt worden. Eine DNA-Sequenzierung am Paraffinmaterial zeigte, dass keine der RET-Mutationen des MEN2b nachweisbar waren. Die Kenntnis der Schleimhautneuroms kann für den Patienten kritisch sein, da dieser seltene Tumor ein früher Marker des MEN2b sein kann, welches frühzeitige prophylaktische chirurgische Resektion erfordert.

marfanoid habitus and facial deformities [2–14]. It is caused by germline activating mutations in the RET-protooncogene, a gene which affects neural crest derived tissues and cells, such as the thyroid C cells, the adrenal medulla, and the enteric nervous system [15–20].

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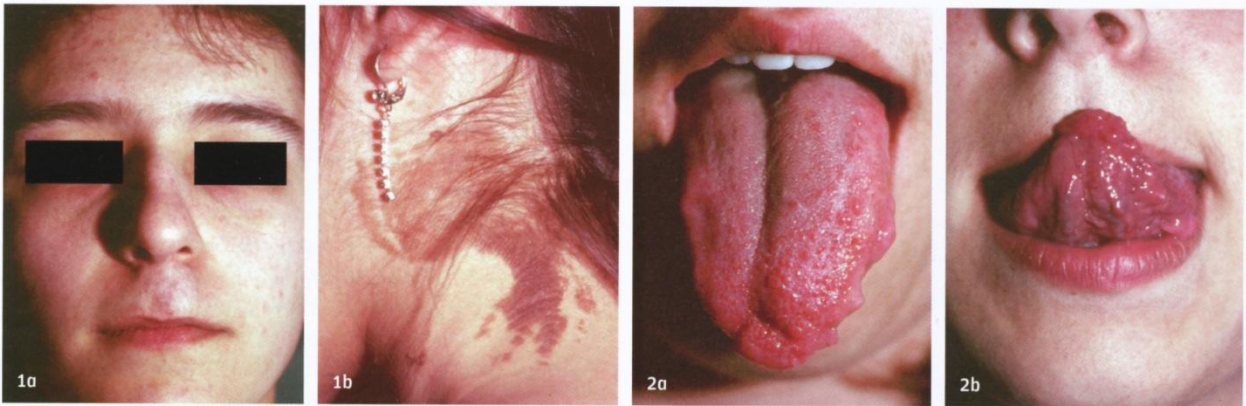


Fig. 1a, b: a) Asymmetric face and bulging left upper lip. b) Bulging left cheek and epidermal nevus on the neck, on the same side as the neuromas. **Fig. 2a, b:** Left sided tumefaction of the tongue with tooth imprints a) dorsal aspect showing the numerous papules and papulo-nodular lesions scattered over its surface. b) ventral aspect with irregular protrusions.

However, exceptional cases of either multiple or isolated neuromas of the mucosae have been described, in which, neither associated thyroid and adrenal neoplasm, nor mutations of the RET gene had been detected [21–23]. We report herein a clinical and histological study on a case of mucosal neuroma of the tongue associated to linear epidermal nevus, in an adolescent girl, in which none of the known mutations of MEN2b syndrome was revealed by molecular genetic analysis.

CASE REPORT

A 16-year-old adolescent girl was referred to our department for the evaluation of a remarkable left sided enlargement of her tongue, which had been present since early childhood. The patient had a slightly marfanoid habitus, being over height with long limbs and fingers, and an asymmetric face. Her upper left lip and cheek were hypertrophic and bulging (Fig. 1a and b). The left half of her tongue was noticeably enlarged with tooth imprints on its edge. Its dorsal surface was studded with numerous, unevenly distributed, dome-shaped nodules and papules, which merged together on the tip giving shape to a cobblestone pattern (Fig. 2a). Its inferior surface presented several irregularly sized and shaped protrusions (Fig. 2b).

The posterior-lateral left side of the patient's neck showed a brown, verrucous linear plaque, which was clinically identified as epidermal nevus (Fig. 1b). The patient did not complain of any systemic symptoms and was ostensibly in good health except for a slight nuisance in articulating and swallowing due to the conspicuous size of her tongue. Her parents were both alive and healthy.

HISTOLOGY AND IMMUNOHISTOCHEMISTRY

Methods: A 10 X 8 mm biopsy, including a large papule, was taken from the dorsal aspect of the left side of the tongue, and the specimen was fixed in buffered formalin and processed for histology. The sections were stained with hematoxylin – eosin

and treated with Bodian's silver impregnation for nerve fibers. Moreover, immunohistochemistry was performed employing a two-step polymeric detection/amplification system with a monoclonal Anti-Epithelial Membrane Antigen (anti-EMA) antibody for the detection of perineurial epithelial cells, and a polyclonal anti-S100 antibody for the detection of Schwann cells, myelin sheaths and nerve fibers. The reaction product was visualized with diamino-benzidine.

Histologic features: The lesion was characterized by a large number of tortuous hyperplastic nerve trunks, which lay from the covering mucous membrane throughout the lamina propria, up to the dense collagen bundles between the tongue muscles (Fig. 3). They were haphazardly distributed and randomly oriented in all directions and were loosely invested by a few circular layers of collagen bundles (Fig. 4). These formations comprised all the micro-anatomical constituents of normal nerves, i.e. epineurium, perineurium and endoneurium, the

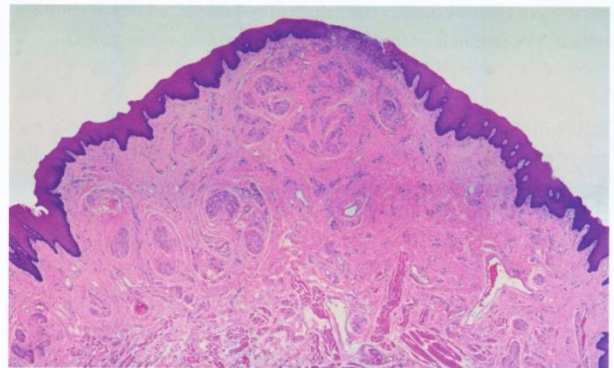


Fig. 3: Dome-shaped protrusion of the mucosa, lined by stratified, non keratinizing epithelium and edged by a collarette, reminiscent of a distorted fungiform papilla. The formation contains an ill-delimited proliferation of hyperplastic nerve trunks, haphazardly distributed and oriented in all directions. (Hematoxylin-Eosin, 10X).

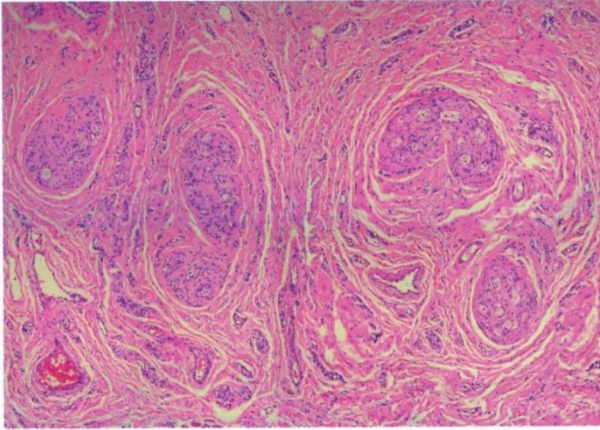


Fig. 4: Large and tortuous nerve trunks in the background of the normal lamina propria of the tongue. They are loosely invested by a few circular layers of collagen bundles (Hematoxilin-Eosin, 40X).

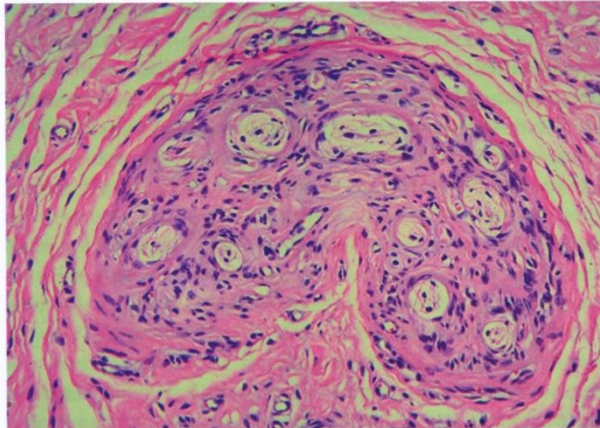


Fig. 5: One of the dysmorphic nerve trunks of Fig.4, shown in detail. The endoneural/axonal component is fragmented in several, tiny fascicles, each invested by hyperplastic perineurium and bound together by thickened epineurium. The endoneurium is recognizable by its delicate connective network and by the Schwann cell nuclei, while neurites are not easily detectable with this stain. (Hematoxilin-eosin, 100X).

latter including true myelinated nerve fibers, and all the structures were properly organized into a typical architecture, without disorders of polarization (Fig. 4–5).

However, unlike normal terminal nerves, which are usually composed of a single fascicle, these malformed nerves included several tiny fascicles of one or two axons, ensheathed by hugely hyperplastic perineurium (Fig. 5–6). The neurites were typically argyrophilic (Fig. 7), and were invested by well formed, S100 positive myelin sheaths (Fig. 8), and enveloped in a delicate endoneurial connective tissue, with a regular number of Schwann cells and fibroblasts.

The perineurium represented the largely preponderant component, of which both the inner, cellular stratum and the outer, collagenous stratum exhibited remarkable concentric hyper-

plasia (Fig. 9). This resulted in an onion bulb pattern, which was further enhanced by the prominent plumping of the EMA positive perineurial epithelial cells of the inner stratum (Fig. 10–11). Similarly to major nerves, the perineurium merged externally with a thick layer of epineurium, which bound the nerve fascicles together and was peripherally condensed to form a strong, intensely eosinophilic, cylindrical sheath around the whole structure.

In the central portion of the lesion, the mucosa protruded giving shape to a dome-like formation, reminiscent of a distorted fungiform papilla, which was lined by stratified, non keratinizing epithelium, and edged by a collarette of elongated rete ridge (Fig. 1). The hamartomatous tissue did not have a well-defined outline, and the malformed nerves decreased progressively in size, becoming more and more similar to normal ones, toward the periphery of the specimen. Thus the neuroma as a whole seemed to result from multiple neural growths merging together.

A histologic diagnosis of mucosal neuroma was rendered and, accordingly, the hypothesis of multiple endocrine neoplasia type IIb (MEN2b) was formulated. However, the instrumental investigations and laboratory tests planned by us to detect the other expected neoplasms could not be carried out, because the patient, although we repeatedly tried to contact her, was no longer reachable. In order to establish whether or not the mucosal neuroma was in the setting of MEN2b syndrome, molecular genetic analysis was performed on the histologic paraffin specimen.

MOLECULAR GENETICS

Methods: Six 10 µm sections, cut from the histologic specimen with the standard procedure required to prevent DNA contamination, were sent to the BMR-Genomics laboratory for the detection of the following possible mutations in the RET gene (gene ID5979, position; 43572517 to 43625799, according to the GRCh37¹⁾ assemblage, on chromosome 10):

- ATG to ACG on codon 918, exon 16, replacing Methionine with Threonine (M918T), codon position: 43617415- 43617417 (GRCh37 assemblage);
- GCT to TTT on codon 883, exon 15, replacing Alanine with Phenylalanine (A883F), codon position: 43615568-43615570 (GRCh37 assemblage);
- GTG to ATG on codon 804, exon 14, replacing Valine with Methionine (V804M), codon position: 43614996-43614998 (GRCh37 assemblage);
- GAG to AAG on codon 805, exon 14, replacing Glutamate with Lysine (E805K), codon position: 43614999-43615001 (GRCh37 assemblage);
- TAC to TGC on codon 806, exon 14: replacing Tyrosine with Cysteine (Y806C), codon Position: 43615002-43615004 (RCh37 assemblage);
- TCC To TGC on codon 904,exon 15: replacing Serine with Cysteine (S904C), codon position: 43615631-43615633 (GRCh37 assemblage).

1) Genome Reference Consortium human 37/hg Feb. 19, 2009

DNA was extracted from the paraffin sample and the regions of interest were identified and amplified through polymerase chain reaction. Finally DNA was sequenced in single-strand with the Sanger dideoxy chain-termination method, using forward primers. Three sequences were achieved, comprising: codon 918, codons 804/805/806, and the codons 883 and 904, and spanning 150 bases, 148 bases and 188 bases, respectively. All the reactions were first performed on a normal (non pathologic) control, while a blank paraffin-extraction sample and a negative control, without template, accompanied each of our specimens along the amplification phase.

Results: The resulting chromatograms showed that none of the substitutions searched for by us were present, nor were there other mutations in the probed sequences (Fig. 12). The chromatograms, instead, closely overlapped the normal controls, while the blank and the negative controls did not give rise to any amplicons.

DISCUSSION

Multiple mucosal neuromas are neural hamartomas characterized by nerve proliferation affecting the mucosal aspect of the mouth, eyelids, larynx and, in the form of ganglioneuromas, the gastrointestinal tract [1]. In most cases, they are observed in the setting of multiple endocrine neoplasia type 2b (MEN2b), in association with medullary thyroid carcinoma (MTC), thyroid C-cell hyperplasia, bilateral pheochromocytoma and adrenal medullary hyperplasia [2–14]. MEN2b is an autosomal dominant inherited tumor syndrome, caused by germline activating mutations of the RET gene (locus 10q11.2), which normally codifies for the RET transmembrane protein [15–20]. This is a receptor tyrosine kinase that is involved in the development of neural crest derived tissues and cells, such as the thyroid C cells, the adrenal medulla, and the enteric nervous system [15].

The first mutation to be described in MEN2b, and by far the most frequent, is a single base ATG to ACG transition on codon 918, which causes the substitution of a threonine for methionine (M918T) [15, 16]. Alternatively, the other, much rarer, possible mutations, comprise: the two base substitution A883F [17], or one of the following combined single-base substitutions: V804M/E805K [18], V804M/Y806C [19], and V804M/S904C²⁾ [20]. All the mentioned alterations lie in the tyrosine kinase domain of the RET protein and are able to enhance its catalytic activity, either freeing it from its ligand-dependence or decreasing its selectivity in regards to substrates³⁾ [15–20].

In rare instances, isolated or multiple mucosal neuromas (Multiple Neuroma Syndrome), without associated thyroid or adrenal neoplasms, or detected mutations of the RET gene, have been reported [22, 23], and our case can currently be ascribed to this group, since it has not shown any of the mutations discovered in MEN2b until the present day.

The hamartomatous – rather than neoplastic – imprint of mucosal neuroma is evident in its histology, whose singular features have been illustrated in our study. In fact, the configuration of this growth is produced by a multitude of authentic,

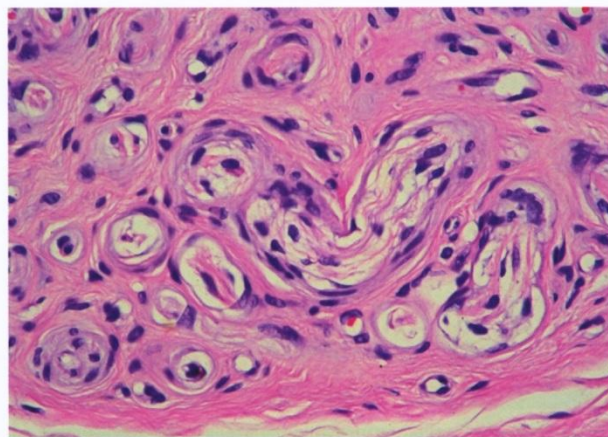


Fig. 6: Detail of a nerve trunk showing a few small nerve fascicles with noticeable hyperplasia of the perineurium. In the center of the field, a few axons of a fascicle are discernible in the endoneurium, together with several Schwann cells (Hematoxylin-Eosin, 250X).

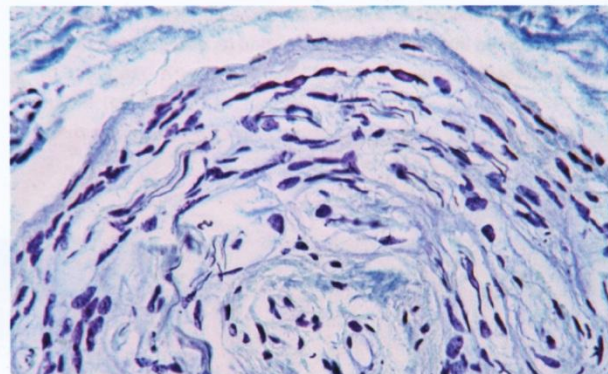
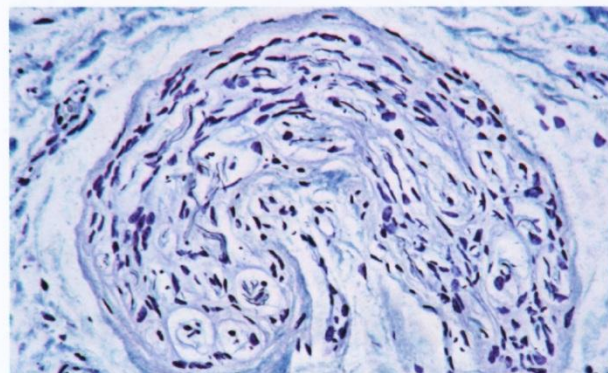


Fig. 7a, b: a) Argyrophilic neurites in the endoneurium of a hamartomatous nerve trunk. b) detail of a (Bodian's silver impregnation for nerve fibers; a) 250X, b) 400X.

2) V804M = substitution of Valine (V) with Methionine (M) on codon 804 (GTG → ATG)
E805K = substitution of Glutamate (E) with Lysine (K) on codon 805 (GAG → AAG)
Y806C = substitution of Tyrosine (Y) with Cysteine (C) on codon 806 (TAC → TGC)
A883F = substitution of Alanine (A) with Phenylalanine (F) on codon 883 (GCT → TTT)
S904C = substitution of Serine (S) with Cysteine (C) on codon 904 (TCC → TGC)

3) Interestingly, an increase in the RET protein expression due to M918T and A883F mutations has been locally revealed in Sporadic Medullary Thyroid Carcinoma through immunohistochemical methods (21).

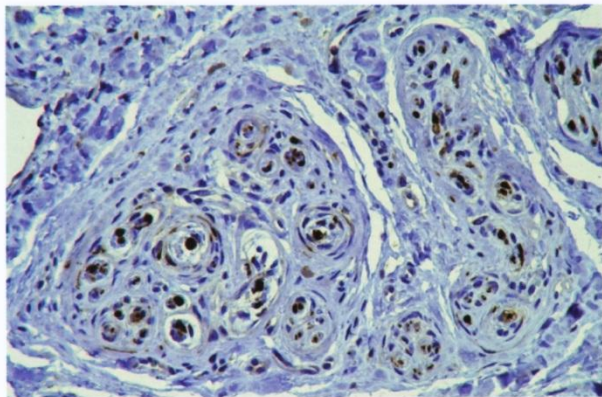


Fig. 8: Thick myelin sheaths investing the axons in two hamartomatous nerve trunks, which are seen cut in a transversal- and in a longitudinal plane of section, respectively (S100 immunostain; X100).

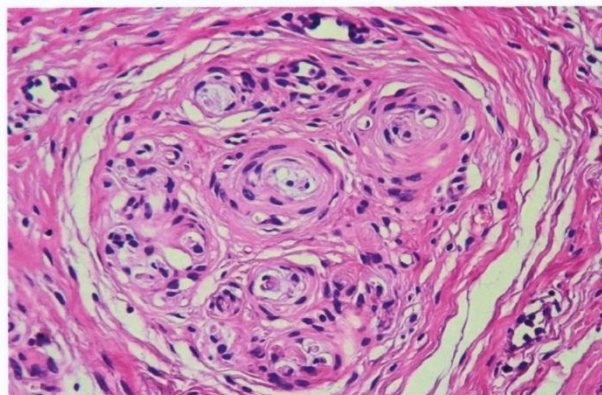


Fig. 9: Transversal section of another hamartomatous nerve, showing the onion-like, concentric hyperplasia of the perineurium, which involves both its inner, cellular stratum, and its outer, connective stratum (Hematoxylin-Eosin, 100X).

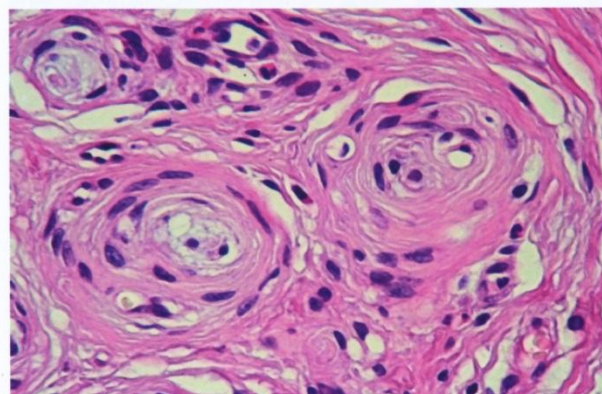


Fig. 10: Detail of the onion-like hyperplasia of the perineurium shown in Fig. 8. The concentric multiplication of its layers and the plumping of the perineurial cells is evident. In the center of the "onion bulbs" the faint connective network marking the endoneurium is visible (Hematoxylin-Eosin, 250X).

although deformed, gigantic nerve trunks, which result from the proper arrangement of all the cells and tissues normally composing peripheral nerves, and reside in the background of unchanged connective tissue. True argyrophilic nerve fibers, regularly embedded in their endoneurium, constitute integral part of the hamartoma and participate in the proliferation, accompanied by their S100 positive myelin sheaths. Similar changes have been observed in the intestinal ganglioneuroma, with the addition of a conspicuous proportion of mature ganglion cells [1, 3, 13].

The cell bundles, the whorls and the storiform pattern to which the inversion of polarity gives shape in neural tumors are missing in mucosal neuroma. Instead, the difference between its dysmorphic nerves and their normal counterpart resides in their number and size, in their tortuous course, as well as in the modified architecture and remarkable disproportion between their constitutive elements. Specifically, the huge hyperplasia and the overwhelming preponderance of perineurium and epineurium over the endoneurial/axonal component are noteworthy, as well as the onion bulb pattern resulting from the extraordinary concentric multiplication of the perineurial layers and from the prominence of the perineurial cells. Another striking feature is the fragmentation of the endoneurium in several, exceedingly minute fascicles, each including one or two argyrophilic fibers and individually encased in its perineurial sheath. The whole results in a unique picture, clearly distinguishable from that of any other growth or from normal terminal nerve trunks.

Finally, the number of myelinated axons and the thickness of the myelin sheaths in mucosal neuroma are increased in comparison to small peripheral nerves. Similar alterations, although without tumor formation, have been demonstrated, histologically and in electron microscopy, in the clinically normal skin of patients affected by MEN2b syndrome, thus suggesting that the disturbance of nerve development which the mutation gives rise to involves all of the skin and mucosae [24].

On account of its distinguishing histologic picture, the diagnosis of mucosal neuroma is obvious, as long as its existence is considered. Although clinically similar to it, terminal neurofibroma consists histologically of loose bundles of wavy Schwann cells and endoneurial connective tissue oriented in various directions. It does contain argyrophilic fibers, but these are paltry pre-existing neurites, belonging to the affected nerve and entrapped in the tumor [1]. In the presence of a syndrome, a histologic differential diagnosis between the two neoplasms allows the clinician to readily differentiate MEN2b from neurofibromatosis, with crucial implications in the management of the disease [25, 26].

Schwannoma is mainly composed of Schwann cells arranged with a typical biphasic pattern: compact Antoni A areas, characterized by interlacing fascicles of spindle cells with twisted nuclei, sometimes with a storiform, whorled or palisading configuration, and hypocellular, Antoni B areas, with cells haphazardly punctuating the loosely textured matrix. In this tumor, residual argyrophilic nerve fibers are found only underneath

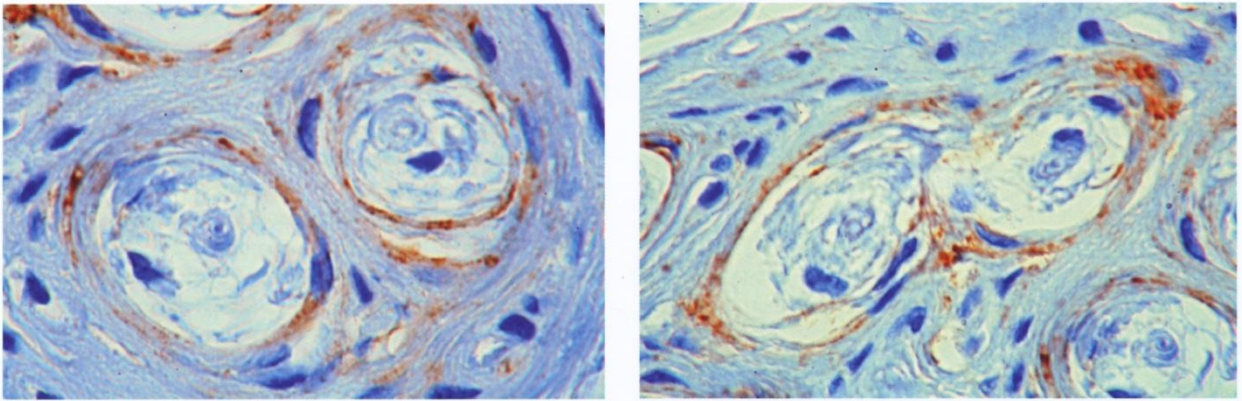


Fig. 11a, b: Details of a hamartomatous nerve trunk. EMA positivity marks the multiple layers of the ensheathing perineurial epithelial cells: a reverse staining pattern in comparison to that of silver impregnation and S100 immunostain, which highlight the axons and their myelin sheaths in the center of the "onion bulbs" (EMA immunostain, 400X).

the capsule of the tumor, being dislodged at the periphery by the newly-formed tissue [1].

Similarly to mucosal neuroma, intraneural perineuroma forms onion bulbs composed of concentric layers of EMA-positive perineurial cells, each bulb ensheathing a single central axon and Schwann cell. This tumor, however, results from clonal proliferation of the only perineurial cell component and involves major nerves of the upper extremities, which it expands, usually remaining confined inside the epineurium [1].

Among true neuromas, i.e. benign nerve tissue growths characterized by concurrent proliferation of neuritis and endoneurial connective tissue, palisaded encapsulated neuroma, must be considered. This is usually found on the face of middle-aged individuals and consists of a solid proliferation of Schwann cells and argyrophilic axons, forming well developed, interweaving nerve-trunk-like fascicles, clustered together in a single nodule [1, 27]. Thus, the fascicles are not scattered in the dermis as in mucosal neuroma, nor are they individually invested by a perineurium, which, instead, forms a single thin sheath of EMA-positive cells and connective tissue around the tumor.

Traumatic neuroma is a reactive nerve growth, resulting from a proliferative response to injury or surgery, which can take place if apposition between the stumps of a severed nerve has been lost. It consists of an exuberant proliferation of variously oriented nerve bundles, complete with myelinated axons and individual perineurial sheaths [1]. The bundles are crammed together in a background of collagen and not dispersed, as observed in mucosal neuroma.

The diagnosis of mucosal neuroma does not represent mere academic exercise, since this tumor is a very likely herald of MEN2b, a life-threatening syndrome whose timely diagnosis is decisive for the patient's survival. In fact, the recognition of MEN2b implies the necessity of early prophylactic thyroidectomy, in order to prevent the onset of medullary thyroid carcinoma, which in this syndrome arises in early adolescence and is characterized by aggressive clinical behavior [2, 28, 29].

In our case, the diagnostic procedures which should have followed the histologic identification of the lesion⁴⁾ were hindered by the patient's unavailability, as was a slit lamp examination for the detection of medullated corneal nerve fibers, a

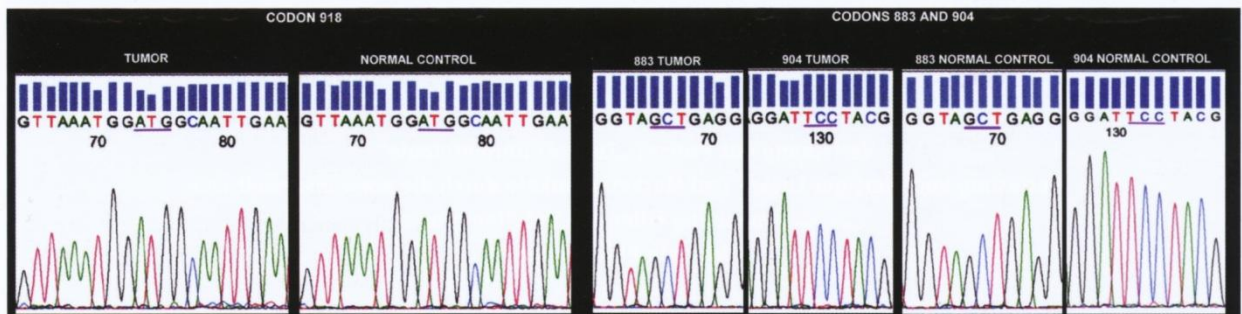


Fig. 12: Chromatograms of DNA sequencing from the paraffin specimen, showing the absence of MEN2b mutations. The codons of interest have been underlined. a) Mucosal neuroma: regular ATG sequence of codon 918; b) Normal control for a; c) Mucosal neuroma: regular GTG, GAG and TAC sequences of codons 804, 805 and 806; d) Normal control for c; e) Mucosal neuroma: regular GCT and TCC sequences of codons 883 and 904; f) Normal control for E.

4) Measurement of serum levels of calcitonin, carcinoembryonic antigen and catecholamines, search for urinary catecholamine metabolites, ultrasonography of the thyroid gland, and abdominal computed tomography scan or magnetic resonance for the detection of pheochromocytoma

frequent, but non-specific feature of MEN2b. However, since, to our knowledge, the typical thyroid and adrenal neoplasms have never been reported in association to mucosal neuromas, in the absence of the diagnostic RET mutations, MEN2b could be reasonably ruled out on the basis of DNA sequencing, along with its potentially associated malignancies. Therefore, the final diagnosis of Multiple Neuroma Syndrome, fully consistent with the bulging lip and cheek, as well as, with the marfanoid habitus [22], was issued. The association with an epidermal nevus on the same side of the neck, which – as far as we know – has never been reported before, can be more than coincidental, although only generic conjectures about a common neuroectodermic disorder for the two lesions can currently be offered in this regard.

Acknowledgements: The Authors thank Giorgio Malacrida, Doctor of Biology, Responsible for the Kinship Identification Service at the BMR-Genomics, for projecting and performing the DNA sequencing, and for his thorough consultation in this regard.

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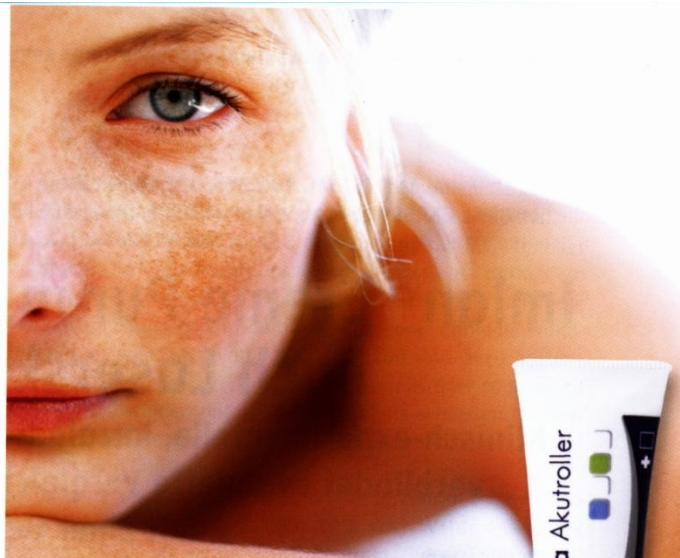
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