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Solitary mastocytoma of the eyelid

A case report with special reference to the immunocytology of human tissue mast cells, and a review of the literature

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Summary. Solitary mastocytoma (mast cell naevus) of the skin represents a relatively rare dermal tumour. Its occurrence on the lower eyelid is exceptional. We report the case of a 4 month old male infant who exhibited a firm, yellowish nodule (1 cm in maximum diameter) on the lower lid of the right eye from birth. Histologically, the tumour consisted of strongly metachromatic tissue mast cells (TMC) infiltrating the whole dermis, the adjacent subcutaneous tissue and the lid muscle. Since comparable skin lesions in other sites were not observed, a diagnosis of solitary mastocytoma was made. Immunocytological investigations revealed strong reactivity of the TMC to antisera against vimentin, common leucocyte antigen (CLA), α1-antitrypsin (α1-AT) and α1-antichymotrypsin (α1-ACT). A minor proportion of the TMC reacted to antisera against lysozyme and KiB3. Surprisingly, the TMC also reacted to antisera against certain regulatory peptides (RP), namely adrenocorticotropic hormone (ACTH), peptide histidine isoleucine (PHI), leu-enkephalin and met-enkephalin. However, absorption controls revealed that the immunostaining for ACTH and the two enkephalins was non-specific. The immunocytological phenotype of TMC suggests a close relationship to the myeloid-monocytic lineage, but a possible relationship between TMC and the diffuse neuroendocrine system needs further investigation.

Key words: Eyelid tumour – Immunocytology – Mastocytoma – Tissue mast cell

Introduction

Tumourous accumulations of tissue mast cells (TMC) in the dermis often present clinically as disseminated, maculopapular or (rarely) bullous or telangiectatic rashes. These common forms of cutaneous mastocytosis are designated urticaria pigmentosa. Solitary mastocytomas (mast cell naevi) of the skin, however, occur infrequently and arise most commonly in infants. Mastocytomas are mainly seen on the limbs and the trunk (Holmberg 1970; Burkhardt 1982). The occurrence of a mastocytoma on the face seems to be extremely rare and, to the best of our knowledge, a mastocytoma of the eyelid has not been described before. This case also offered the opportunity to evaluate the immunoreactivity of human TMC with a broad spectrum of monoclonal and polyclonal antisera against various haematopoietic and non-haematopoietic cell markers.

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Case report

A 4 month old male infant was seen in the Department of Faciomaxillary Surgery (University of Tübingen, FRG) in November 1986 because of a slowly-growing, non-tender eyelid tumour which had been present since birth. On clinical examination, a firm, yellowish nodule with a maximum diameter of 1 cm was noted laterally on the lower lid of the right eye. No other skin lesions were detected. A diagnosis of lymphangioma was suspected clinically. At operation, it became evident that the tumour was infiltrating the subcutaneous tissue and the lid muscle and reached down to the infraorbital periosteum. Nevertheless complete surgical resection of the tumour was possible. A definitive diagnosis was not possible on frozen section examination, although the histological picture resembled a naevus in some respects. Further histological investigations using paraffin-embedded tissue and special stains revealed the tumour to be a mastocytoma (mast cell naevus). The patient's postoperative course was without complication and neither local recurrence nor dissemination of the tumour has occurred after a period of 8 months.

Material and methods

The surgical specimen of the eyelid tumour was fixed in 10% buffered formalin and embedded in paraplast. 6 μm thick sec-

Table 1. List of primary antibodies

Antibody, species	Titre	Source	Method
Common leucocyte antigen, m	1: 20	DAKO	ABC
KiB3, m	1:8000	*	ABC
Lysozyme, r	1: 500	DAKO	PAP
α1-antitrypsin, r	1: 250	DAKO	PAP
α1-antichymotrypsin, r	1: 250	DAKO	PAP
Cytokeratin, r	1: 100	DAKO	PAP
Carcinoembryonic antigen, r	1: 100	DAKO	PAP
α-fetoprotein, r	1: 50	DAKO	PAP
Factor VIII-related antigen, r	1: 50	DAKO	PAP
Vimentin, r	1: 50	Laboserv	PAP
Desmin, r	1: 50	Laboserv	PAP
Neuron-specific enolase, r	undiluted	Camon	PAP
S-100 protein, r	1: 100	DAKO	PAP
Serotonin, r	1:1000	INC	PAP
Adrenocorticotropic hormone, r	1: 400	INC	PAP
β-endorphin, r	1: 400	INC	PAP
Leu-enkephalin, r	1: 400	INC	PAP
Met-enkephalin, r	1: 400	INC	PAP
Substance P, r	1: 400	INC	PAP
Human peptide histidine isoleucine, r	1: 500	Medac	PAP
Vasoactive intestinal peptide, r	1: 500	Medac	PAP
Chromogranin A, m	1: 200	Ortho	ABC

Abbreviations: m: mouse, monoclonal antibody; r: rabbit, polyclonal antiserum; ABC: avidin-biotin complex method; PAP: peroxidase-antiperoxidase method

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tions were subjected to the following dyes and enzyme reactions: haematoxylin and eosin (HE), periodic acid-Schiff (PAS), Giemsa (Merck, Darmstadt, FRG), toluidine blue at different pH's ("toluidine blue pH-series", Lennert and Schubert 1959), Gomori's silver impregnation, naphthol AS-D chloroacetate esterase (Leder 1964) and the argyrophil reaction of Grimelius (1968). Immunocytochemical reactions were performed either with the peroxidase-antiperoxidase (PAP) method of Sternberger (1979) or with the avidin-biotin complex (ABC) method of Hsu et al. (1981). The primary antibodies are summarized in Table 1. The reagents for both the PAP method and the ABC method i.e. swine anti-rabbit IgG, PAP complex, biotinylated rabbit anti-mouse IgG and AB complex were purchased from Dako (Denmark). The individual steps of the methods were performed either according to Polak and Van Noorden (1986) (PAP-method) or according to the instructions given by Dako (ABC method). All sections were pretreated for 20 min with a solution of 0.3% hydrogen peroxide in methanol to inhibit endogenous peroxidase activity. In cases of polyclonal antisera the sections were incubated for 30 min with 10% normal swine serum (Dako, Denmark) prior to the application of the primary antiserum to decrease nonspecific background staining. The immunoreactive sites were visualized by incubation with diaminobenzidine tetrahydrochloride (DAB, Sigma, FRG). Controls included non-immune sera in the first layer, secondary antisera not specific to the primary antisera, omission of essential steps in both methods and the demonstration of positive immunoreactivity in appropriate human control tissue (Table 2). In addition, absorptions controls were carried

Table 2. Main specificity of primary antibodies and reactivity of tissue mast cells (TMC)

Antibody	Main specificity/ Control tissue	Reactivity of TMC
Common leucocyte antigen	All leucocytes	++
KiB3	B-lymphocytes	+
Lysozyme	Macrophages, histiocytes	+
α1-antitrypsin	Macrophages, histiocytes	++
α1-antichymotrypsin	Macrophages, histiocytes	++
Cytokeratin	Epithelial cells	−
Carcinoembryonic antigen	Fetal and neoplastic epithelium	−
α-fetoprotein	Fetal and neoplastic epithelium	−
Factor VIII-related antigen	Endothelial cells	−
Vimentin	Mesenchymal cells	++
Desmin	Muscle cells	−
Neuron-specific enolase	Neural and neuroendocrine cells	−
S-100 protein	Glial cells, immune accessory cells	−
Serotonin	Endocrine cells (gut)	−
Adrenocorticotropic hormone	Cells of pineal gland	++[1]
β-endorphin	Brain, nerve fibres	−
Leu-enkephalin	Brain, nerve fibres	++[1]
Met-enkephalin	Brain, nerve fibres	++[1]
Substance P	Nerve fibres, endocrine cells (gut)	−
Peptide histidine isoleucine	Autonomic nerves	++[2]
Vasoactive intestinal peptide	Autonomic nerves	−
Chromogranin A	Endocrine cells	−

[1] immunostaining for regulatory peptide not quenched in absorption controls
[2] for evaluation of immunoreactivity see discussion
− no reactivity of TMC; + few TMCs positive; ++ nearly all TMCs positive

out with the following peptides obtained from SIGMA: ACTH (1–39) human, synthetic; leu-enkephalin, synthetic; met-enkephalin, synthetic. Prior to use, antibodies were incubated with the appropriate antigen at 4° C for 24 hrs at the following maximum antigen-concentrations: ACTH, 140 µg/ml; leu-enkephalin, 500 µg/ml; met-enkephalin, 500 µg/ml. Absorption controls with PHI were not carried out.

Results

The skin biopsy specimen consisted of a firm nodule (maximum diameter 1 cm) elevating the overlying epidermis which showed no erosive or ulcerative defects on pathological examination. The cut surface of the tumour was yellowish.

Routine staining with HE revealed a dense, non-encapsulated infiltrate consisting of large, slightly pleomorphic cells with round or reniform, sometimes indentated nuclei and abundant eosino-

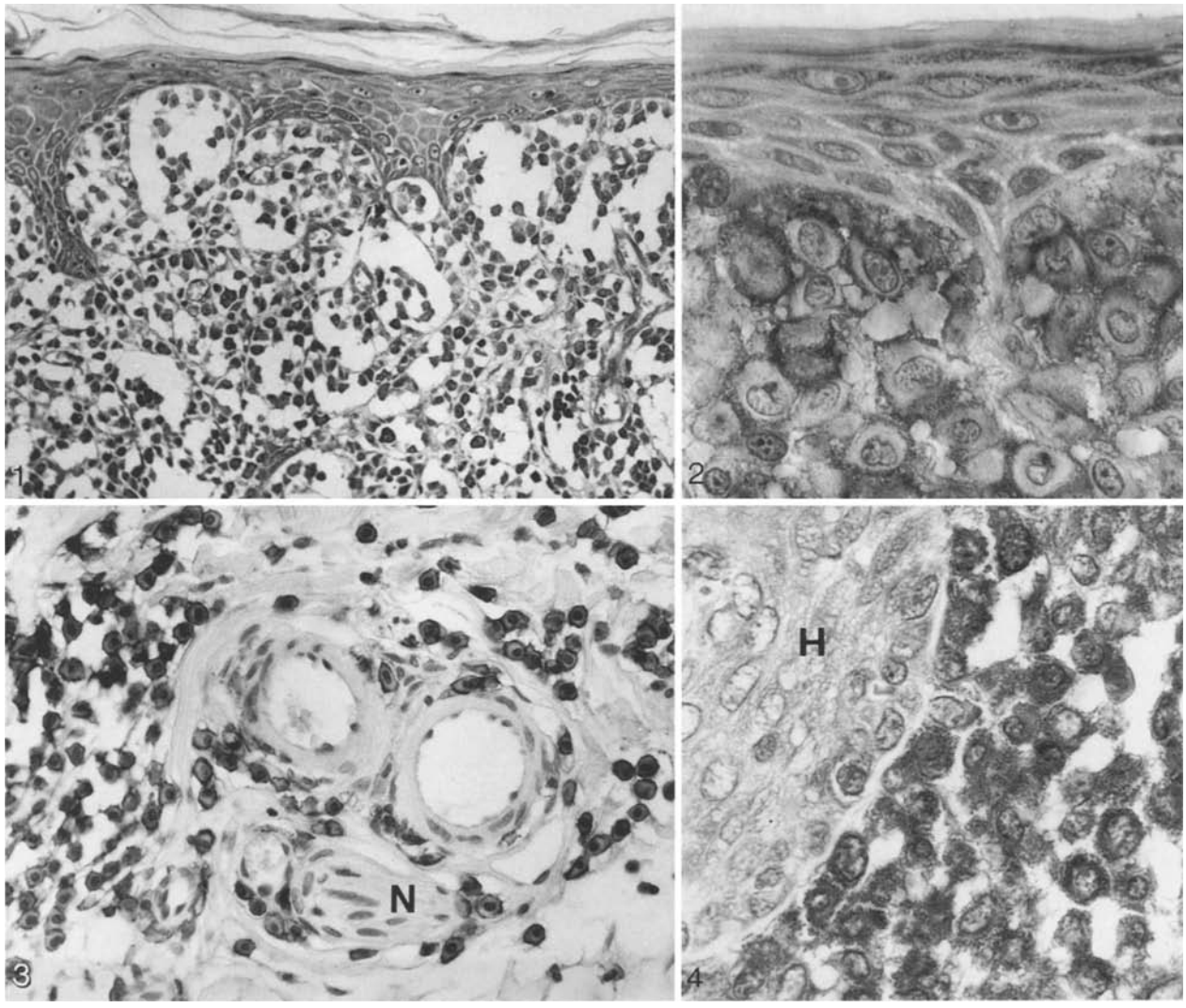

Fig. 1. Solitary mastocytoma of the lower eyelid. The stratum papillare of the corium is diffusely infiltrated by roundish, large tissue mast cells (for cytological details compare Fig. 2). Note the prominent intercellular oedema. The epidermis is intact. Toluidine blue, 272 ×

Fig. 2. Solitary mastocytoma of the lower eyelid. The ring-shaped, membrane-bound staining of tissue mast cells by the common leucocyte antigen (*CLA*) is clearly visible. The TMC nuclei are slightly pleomorphic and often contain one or two prominent nucleoli. Some nuclei exhibit an indentated ("monocytoid") shape. Anti-CLA, ABC-method, 448 ×

Fig. 3. Solitary mastocytoma of the lower eyelid. The deeper edge of the tumour reveals infiltration of the perivascular and perineural (*N* = nerve) spaces by small clusters of TMC. Anti-CLA, ABC-method, 280 ×

Fig. 4. Solitary mastocytoma of the lower eyelid. Dense infiltration of tissue mast cells around a hair follicle (*H*). Staining with anti-α1-antichymotrypsin reveals strong, granular, intracytoplasmic reaction of the tumour cells. Anti-α1-ACT, PAP-method, 448 ×

philic cytoplasm. The tumour occupied the whole corium. Strands and columns of tumour cells infiltrated the adjacent subcutaneous tissue layer and parts of the lid muscle. Prominent intercellular oedema was observed in the stratum papillare of the corium (Fig. 1). The epidermis was atrophic but erosion was not seen. There were many eosinophilic granulocytes loosely intermingled among the tumour cells. In PAS staining, the tumour cells exhibited a prominent purple colour of the cytoplasm. The argyrophil reaction was completely negative. Gomori's silver impregnation showed an increase in reticulin fibres which were forming a loose alveolar network. In the tumour cells Giemsa stain revealed densely-packed, monomorphic, intracytoplasmic granules which partially overlapped the periphery of the karyoplasm and which were strongly metachromatic. Metachromasia of the tu-

mour cells was also observed in toluidine blue stains of different pH's with a peak between pH 4.5 and 5.5. Most of the TMC were also positive for naphthol AS-D chloroacetate esterase, displaying a distinct red staining in the cytoplasm.

The majority of the TMC reacted strongly to antisera against vimentin, CLA, α1-AT, α1-ACT, ACTH, PHI, leu-enkephalin and met-enkephalin, whereas only a minority were positive for lysozyme and Ki B3 (Table 2). Two different patterns of immunoreactivity were observed: 1) the application of anti-CLA produced ring-shaped, brownish staining of the cell membrane (Figs. 2 and 3); 2) the reactions with antisera against vimentin, the anti-proteases and regulatory peptides (RP) yielded a prominent, granular staining of the cytoplasm (Fig. 4). No immunoreactivity could be detected after the replacement of primary antibodies by non-immune sera or after the omission of essential steps in the staining procedure. However, the positive immunostaining of mastocytoma cells for ACTH, leu-enkephalin and met-enkephalin was not quenched after preabsorption of the antibody with the appropriate antigen, whereas staining in positive control tissues was completely abolished. All other antisera tested, including antisera against cytokeratin and other epithelial markers, desmin, F VIII-related antigen, as well as various neural and neuroendocrine cell markers, were consistently negative.

Discussion

A review of the literature revealed 18 cases of solitary mastocytoma reported since 1969. The most important clinical data are summarized in Table 3. Multiple nodular mastocytic infiltrates (Burkhardt 1982) and urticaria pigmentosa evolving from a solitary mastocytoma (Lantis and Koblenzer 1969) were excluded from this review. The age of onset ranged between birth and 16 years with a median of 1 week. The limbs (15/18 cases) were the most common sites of occurrence reported, whereas only 3 tumours occurred on the trunk. A mastocytoma arising in the head and neck region has been reported only once; this occurred in the previously mentioned case with multiple mastocytomas (Burkhardt 1982). The size of the mastocytomas reported generally varied between 1.0 cm and 1.5 cm (range: 0.5 cm to 3.5 cm).

The solitary (often congenital) mastocytoma of the human skin was first described by Gross in 1934. About 75 cases had been reported in the literature up to the late sixties (Holmberg 1970); we thus add a further 18 cases which have been described since 1969. Since mastocytoma can only be identified by the demonstration of metachromasia of the tumour cells (especially in toluidine blue or Giemsa staining), its true incidence is presumably higher than might be inferred.

Our case of solitary mastocytoma conforms well to the data reported in the literature with re-

Table 3. Solitary mastocytoma. List of cases reported since 1969

Case No.	Age/sex (onset)	Site/ size (cm)[a]	Remarks	Reference
1.	18 yr/m (16 yr)	l. thigh 0.5	–	Baraf and Shapiro 1970
2.	5 mo/f (birth)	l. thigh 2.2	flush, D+ blister	Holmberg 1970
3.	nr/nr (2 wk)	trunk nr	flush, D+	Holmberg 1970
4.	nr/nr (1 wk)	l. forearm nr	obstr. bronchitis, D+	Holmberg 1970
5.	nr/nr (9 mo)	l. forearm nr	blister, D+	Holmberg 1970
6.	10 mo/m (birth)	l. forearm 2.0	[b]	Holmberg 1970
7.	nr/nr (8 mo)	r. forearm nr	hypoglycaemia, D+	Holmberg 1970
8.	nr/nr (2 mo)	l. forearm nr	D+	Holmberg 1970
9.	nr/nr (birth)	sole of r. foot, nr	blister	Holmberg 1970
10.	birth/f (birth)	l. thigh nr	blister, flush, D+	Kilburn 1974
11.	5 mo/m (nr)	suprascap. arca, 2.0	[c]	Kilburn 1974
12.	4 yr/m (3 wk)	trunk 1.5	blister blister	Kilburn 1974
13.	15 yr/m (infancy)	l. shoulder nr	–	
14.	10 mo/f (1 wk)	hand 1.5	–	Andrade 1975
15.	8 mo/m (birth)	l. thigh 1.5	bullous lesion	Barth and Haustein 1978
16.	4 mo/m (birth)	l. leg 3.5	–	Magana Lozano 1978
18.	8 mo/m nr	l. forearm 1.5	[d]	Wesley et al. 1982

D+: Darier's sign positive; nr: not reported; l: left; r: right

[a] maximum diameter
[b] flush, irritability, loose stools, blister, D+
[c] obstructive bronchitis, respiratory wheezing, D+
[d] significant elevation of vasoactive intestinal peptide level in serum, normalization after tumour resection

gard to the age and sex of the patient and size of the tumour. However, the site of this lesion was exceptional, since a mastocytoma occurring on the eyelid has not been reported before. Cutaneous mastocytosis (either solitary mastocytoma or the disseminated maculopapular lesions of urticaria pigmentosa) may be suspected when Darier's sign (urticaria produced by rubbing) is positive. However, the lesion in the case described did not urticate, and the clinical diagnosis was that of a vascular tumour (lymphangioma). Only the application of toluidine blue and Giemsa stains finally enabled the diagnosis of mastocytoma to be established by the histological demonstration of metachromatic intracytoplasmic granules. Similar metachromatic granules can be observed only in the blood basophil, which represents the rarest subtype of granulocyte. However, the granules of the blood basophil are water-soluble and would have been destroyed by routine fixation in (aqueous) formol (Parwaresch 1976), whereas mast cells granules, by contrast, are well preserved in common fixatives like formalin (Lennert and Schubert 1959).

Although on histological examination widespread infiltration of the subcutis and lid muscle was observed, a diagnosis of mast cell sarcoma would not have been consistent with other cytological findings. Mast cell sarcoma, which is exceedingly rare and has been described in man only once (Horny et al. 1986), characteristically displays neoplastic TMC with clear cytological atypia; metachromatic granules, in particular, are extremely scarce. Nevertheless, from a histological point of view, a more aggressive variant of mastocytoma cannot be excluded with certainty in this special case, in as much as typical mastocytoma is usually confined to the upper (subepidermal) layers of the corium.

The origin of human TMC, which must be distinguished from the so-called mucosal mast cells, still remains a topic of discussion (Kitamura et al. 1987; Parwaresch et al. 1985). Kitamura et al. (1981) have demonstrated that rodent mast cell precursors originate in the bone marrow. Results of investigations in man favour a close relationship of TMC to the myeloid-monocytic lineage, thus suggesting a bone marrow origin of these enigmatic cells too (Lennert and Parwaresch 1979; Zucker-Franklin 1980; Horny et al. 1985; Dalton et al. 1986). This hypothesis is further supported by immunocytochemical findings described in this report, namely the strong membrane-bound reaction to the antiserum against the CLA and the marked, granular, intracytoplasmic reaction to antisera against the antiproteases α1-AT and α1-ACT.

The positive reaction of a minority of the TMC to KiB3, which is regarded as a B-lymphocyte marker (Dr. Wacker, Kiel, FRG, personal communication), is difficult to explain. Cross-reactivity seems to be more likely than a cytogenetic relationship between TMC and the lymphoid system, although the T-cell lineage and TMC have formerly been thought to be interrelated (Ginsburg 1963; Burnet 1977). Non-specific staining of the TMC by avidin-biotinylated peroxidase complexes (ABC) as reported by Bussolati and Gugliotta (1983) was not observed in our case. We found, however, three different staining patterns when the ABC method was applied. First, the TMC were completely negative for chromogranin A. Second, a minority of the TMC reacted with KiB3 and, third, all the TMC showed a typical membrane-bound immunoreaction to anti-CLA.

It is well known that mast cell granules in man contain various mediators including preformed substances which are rapidly eluted under physiological conditions (e.g. histamine, eosinophil chemotactic factors of anaphylaxis, neutrophil chemotactic factors, exoglycosidases and kininogenase), newly generated substances (e.g. slow-reacting substances like leukotrienes, prostaglandins, monohydroxyeicosatetraenoic acids, thromboxanes and platelet activating factor) and preformed, granule-associated mediators (e.g. heparin, chymotrypsin/trypsin, arylsulfatase B and inflammatory factors of anaphylaxis, for review see Marom and Casale 1983; König et al. 1986). In this connection, it seems of particular interest that the TMC in this case of mastocytoma were found not only to share cytological and immunocytochemical properties with leucocytes, but also to show strong immunostaining for certain RP, namely ACTH, enkephalins and PHI. However, the ACTH-, leu-enkephalin- and met-enkephalin-like immunoreactivity of the TMC studied here could not be confirmed by absorption controls. Under these circumstances the demonstration of PHI-like immunoreactivity in this tumour must be viewed with great scepticism, as an absorption control was not carried out and this peptide has never been found in TMC before.

Vasoactive intestinal peptide (VIP) could not be demonstrated immunohistochemically in our case, while Wesley et al. (1982) have reported the finding of an elevated serum VIP level in an 8 month old infant with a solitary mastocytoma on the left forearm (compare Table 3), and Giachetti et al. (1978) have detected VIP in rat mast cells by radioimmunoassay. In previous studies concerning the immunoreactivity of human TMC Mo-

toi et al. (1980) found lysozyme, α1-antitrypsin and α1-antichymotrypsin, and Forni et al. (1983) found serotonin, prostaglandin, a heparin-like compound and fibronectin in mast cell granules, but absorption controls were not carried out in Forni's study. In contrast to the latter authors, we were unable to demonstrate serotonin in the TMC in the case we studied.

It should be mentioned that non-specific immunostaining for certain RP has also been observed in "normal" TMC in lymph nodes with chronic non-specific lymphadenitis, in neoplastic TMC of a patient with malignant mastocytosis (Horny et al. 1988) and in TMC of the human appendix (own unpublished observations). Thus when evaluating immunohistochemical staining one should bear in mind the fact that human TMC react non-specifically with certain antisera. We are at present carrying out a more detailed investigation into the problem of non-specific immunostaining of TMC. Altogether, the data presented do not allow definite conclusions to be drawn regarding a possible relationship between TMC and the diffuse neuroendocrine system. Further studies, preferably combining immunohistochemical and biochemical methods, should therefore be performed.

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