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Immunohistochemical study of granular cell tumours

Demonstration of neurone specific enolase, S 100 protein, laminin and alpha-1-antichymotrypsin*

Walter B.J. Nathrath and Klaus Remberger

Pathologisches Institut der Universität München, Thalkirchner Straße 36, D-8000 München 2, Federal Republic of Germany

Summary. Nine granular cell tumours were investigated with poly- or monoclonal antisera to neurone specific enolase (NSE), glial enolase (GE), S 100 protein, alpha-1-antichymotrypsin, lysozyme, laminin, neurofilament (NF), glial fibrillary acidic protein (GFAP), brain creatine kinase (CK), different cytokeratins (Keratin Dako, PKK1), tissue polypeptide antigen (TPA), carcinoembryonic antigen (CEA), desmin, myoglobin and leukocyte common antigen (LCA), using immunoperoxidase-methods on formalin fixed paraffin embedded sections.

While five tumours from adults show specific cytoplasmic staining for NSE and S 100, three congential tumours, two from the gingiva and one from palatine, show only a weak reaction for NSE, reflecting a possible origin from mature and immature Schwann cells, respectively. However, one subcutaneous tumour from near the clavicule of a ten year old girl differs from the other eight tumours by its specific cytoplasmic staining for alpha-1-antichymotrypsin only, supporting the view that there are granular cell tumours of histiocytic origin. In addition, the five adult NSE-S100 tumours show strong laminin-immunostaining around the single small or syncytial granular cells, whereas pericellular laminin is not detectable in the histiocytic nor in the three congenital tumours.

None of the tumours shows any staining for lysozyme, epithelial, muscular, leukocyte, neurofilament or glial antigens.

Key words: Granular cell tumours – Epulis congenita – NSE – S 100 – Alpha-1-antichymotrypsin – Laminin – Immunohistochemistry

Introduction

Granular cell tumours are composed of large, round or elongated cells with abundant granular eosinophilic cytoplasm (Enzinger 1969). This char-

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Offprint requests to: W. Nathrath at the above address

acteristic appearance led to their separation as a histological entity originally referred to as granular cell myoblastoma because of possible derivation from striated muscle cells (Abrikossoff 1926; Klinge 1928; Abrikossoff 1931). Subsequent investigators favoured a neural origin, in particular from Schwann cells (Feyrter 1935; Fust and Custer 1949; Bangle 1953; McCormack et al. 1954; Fisher and Wechsler 1962; Garancis et al. 1970; Weiser 1978) or from mesenchymal cells, including perineural histiocytes and fibroblasts (Fischer 1928; Leroux and Delarue 1939; Pearse 1950; Azzopardi 1956; Sobel and Marquet 1974). Comparable histological appearances suggest that congenital epulis (Neumann 1871) was related to granular cell tumours (Lauche 1928; Sternberg 1928; Wegelin 1947; Sobel and Marquet 1974; Dixter et al. 1975; Skoglund and Holst 1983), a view not accepted by some authors (Fuhr and Krogh 1972; Slootweg et al. 1983).

The recent immunohistochemical demonstratioin of S 100 protein (Nakazato et al. 1982; Stefansson and Wollmann 1982; Armin et al. 1983; Dhillon and Rode 1983; Weiss et al. 1983; Vanstapel et al. 1985), neurone specific enolase, the neural differentiation antigen PGP 9.5 and the myelin associated glycoprotein Leu 7 (Rode et al. 1982; Rode et al. 1985; Smolle et al. 1985) in adult granular cell tumours supports their neural, possibly Schwann cell derivation. Here we report on the immunohistological findings in nine granular cell tumours of different localisation in patients of different ages, using a wide range of cell and tissue marker antisera.

Material and methods

Tumours, normal tissues. Nine granular cell tumours were selected from the files of the Munich University Pathology Institute.

Details of localisation, patient's age and sex are given in Table 1. For comparison, normal gingiva, tongue, palatine, skin and spinal root ganglion tissues were taken from adult and

Table 1. Granular cell tumours

Case No.	Patient		Tumour localisation	Size
	Age[a]	Sex		(cm)
1	1 month	f	maxillary gingiva, "epulis congenita"	0.5
2	2 days	f	maxillary gingiva	1.0
3	2 days	f	palatine	2.0
4	17 years	f	left vocal cord	0.5
5	45 years	m	tongue	1.0
6	31 years	m	3rd finger, volar side, middle phalanx	1.5
7	27 years	m	5th finger, right hand, distal joint	0.5
8	77 years	f	skin of breast	1.0
9	10 years	f	right clavicular skin	1.0

Abbreviations: d = day, m = month, y = year, f = female, m = male

[a] at time of operation

newborn autopsy cases within 24 h post mortem. The tumours and normal tissues had been routinely fixed in 10% formalin and embedded in paraffin (Nathrath et al. 1985).

Serial 5 μ sections were cut from each tissue block and were mounted on glass slides, using egg albumin. After overnight incubation at +37° C the slides were deparaffinised and brought to water for the routine HE, EVG, Ag, PAS-Alcianblue, Diastase-PAS and for the immunohistochemistry staining.

Antisera. The antisera specific for a wide range of antigens were obtained from different sources (see Table 2).

Immunohistochemistry. An indirect immunoperoxidase method was used as described previously (Nathrath et al. 1985) for the antisera to tissue polypeptide antigen (TPA), human epidermal keratin (Kera D) (Dakopatts, Denmark; MW 64 and 56 KD), myoglobin, alpha-1-antichymotrypsin, lysozyme, laminin, carcinoembryonic antigen (CEA) (Dakopatts), creatine kinase BB and glial enolase (GE, alpha-alpha) (Gerbitz et al. 1983; Gerbitz et al. 1984).

To demonstrate keratin PKK1 (Labsystems; MW 56, 48, 45, 41 KD; Holthöfer et al. 1983), desmin, S 100 protein, neurone specific enolase (NSE, gamma-gamma), neurofilament (NF), glial fibrillary acidic protein (GFAP), CEA (Euro-Diagnostics) and leukocyte common antigen (LCA), the Avidin-Biotin-Complex-method (Vector) for the respective rabbit or mouse IgG was employed; for monoclonal antibodies, sections were incubated for 30′ at 37° C and then overnight at +4° C.

For both methods, amino-ethyl-carbazole (AEC) was employed as the visualising peroxidase substrate. Pretreatment with protease (Sigma VII, St. Louis, MO, USA) was necessary to demonstrate TPA, PKK1, Kera D (Dakopatts), alpha-1-antichymotrypsin and S 100, as described previously (Nathrath and Meister 1982; Nathrath et al. 1985).

For visualisation of laminin, previously described methods were followed (Burns et al. 1980; Ekblom et al. 1982; Reibel et al. 1985).

Table 2. Antisera employed

Antigen designation	Animal	Source
Tissue polypeptide antigen (TPA)	rabbit	Dr. Björklund
Keratin PKK1 (simple epithelia, MW 56, 48, 45, 41 KD)	mouse monoclonal	Labsystems
Keratin (Kera D) (epidermis, MW 56 and 64 KD)	rabbit	Dakopatts
Carcinoembryonic antigen (CEA)	rabbit[a]	Dakopatts
Carcinoembryonic antigen (CEA)	mouse monoclonal	Euro-Diagnostics
Desmin	rabbit	Dakopatts
Myoglobin	rabbit	Dakopatts
Lysozyme	rabbit	Dakopatts
Alpha-1-antichymotrypsin	rabbit	Dakopatts
Laminin	rabbit	Bethesda Research Corporation
S 100 protein	rabbit	Dakopatts
Neurone specific enolase (NSE)	rabbit	Dakopatts
Glial enolase (GE)	rabbit	Dr. Gerbitz
Neurofilament (NF)	mouse monoclonal	Labsystems
Glial fibrillary acidic protein (GFAP)	mouse monoclonal	Labsystems
Brain creatin-kinase (CK)	rabbit	Dr. Gerbitz
Leukocyte common antigen (LCA)	mouse monoclonal	Dakopatts

[a] Antiserum absorbed with normal human lung and spleen and diluted 1:200 (Nathrath et al. 1984)

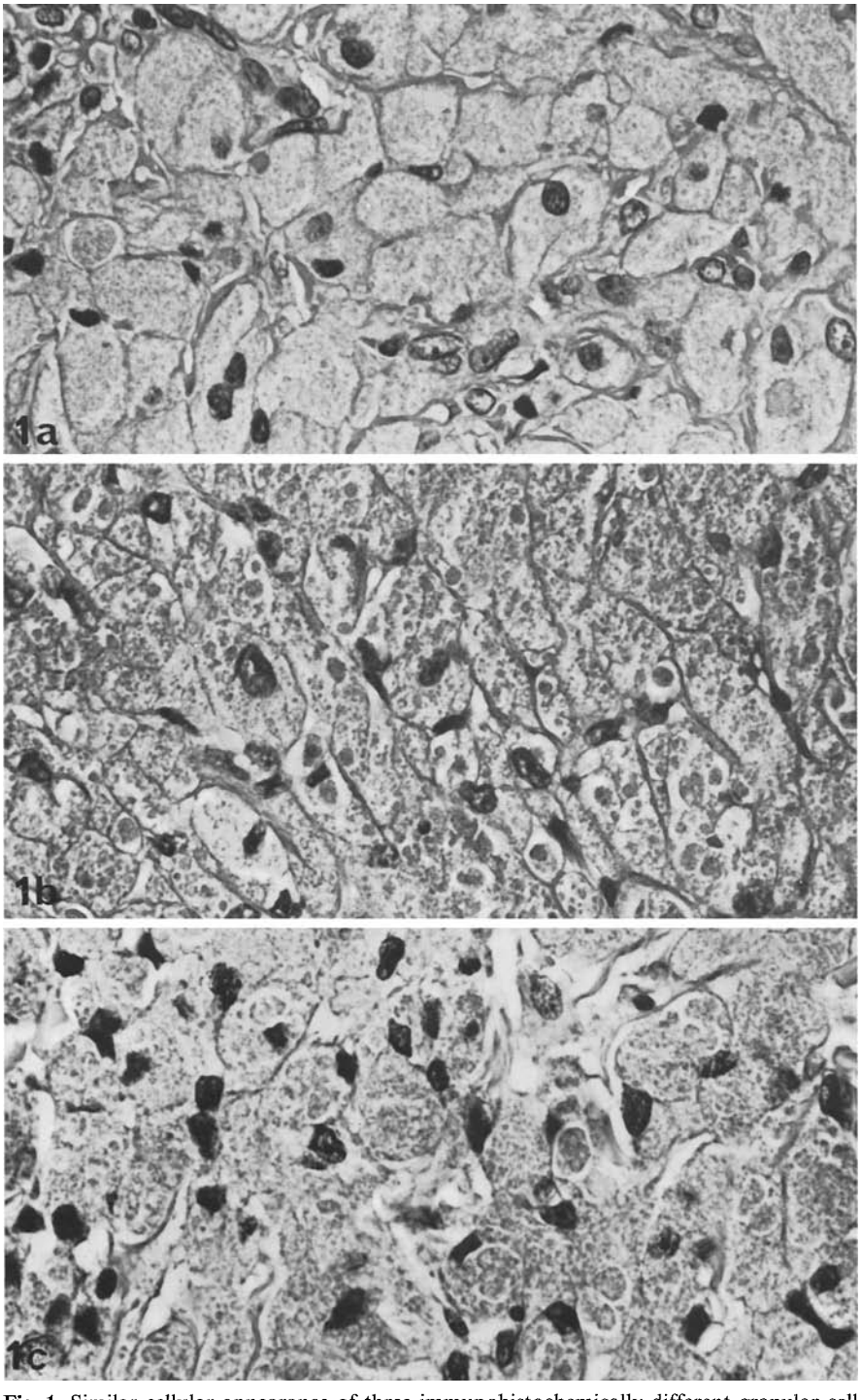
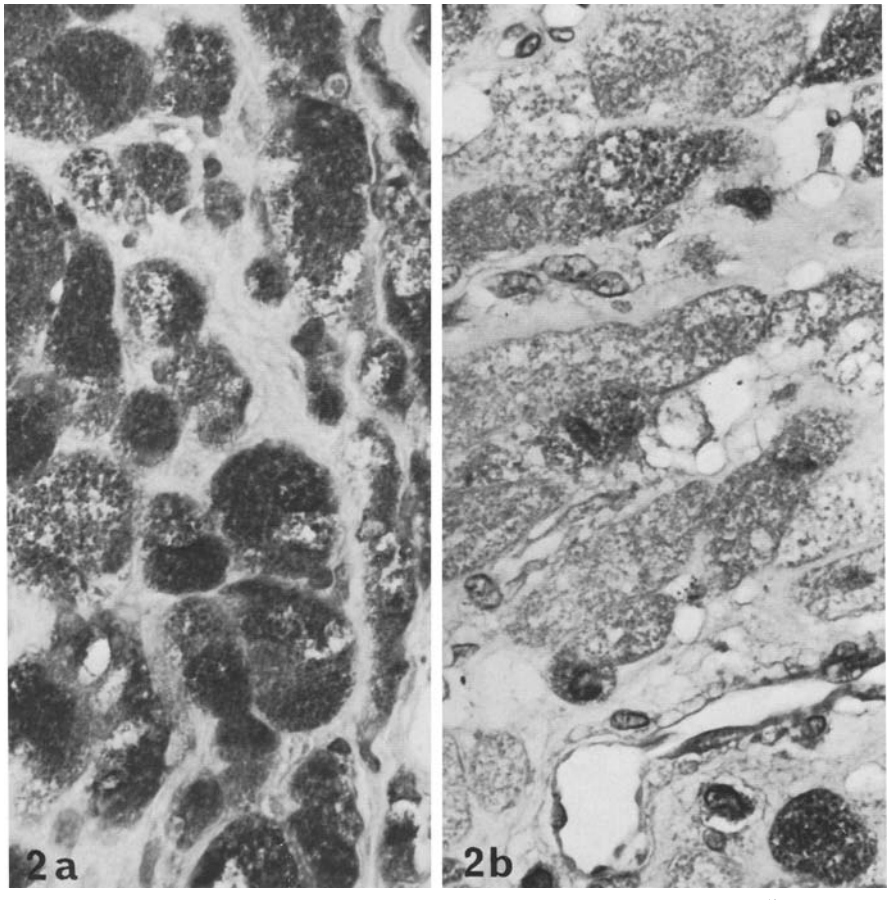


Fig. 1. Similar cellular appearance of three immunohistochemically different granular cell tumours, HE. × 560. **a** Epulis congenita (case 1 in Table 1 and 3), **b** adult from tongue (case 5), **c** adult from clavicule (case 9)



Figs. 2–5. Immunoperoxidase staining of granular cell tumours, haematoxylin counterstain. × 560

Fig. 2. Variable staining for NSE: **a** strongly positive reaction in adult 3rd finger tumour (case 6), **b** irregular and partly weak staining in congenital palatine tumour (case 3)

Rabbit anti-CEA serum (Dakopatts) had been absorbed with normal human lung and spleen, in particular to remove antibodies to the "non specific cross-reacting antigen" and was then used in a dilution of 1:200, at which normal colon epithelium showed a weak luminal membrane reaction, but normal human lung, liver and spleen did not react (Nathrath et al. 1984). The monoclonal anti-CEA serum (Euro-Diagnostics) showed the same specificity, at a 1:100 dilution.

Results

The nine granular cell tumours presented here form a non-homogenous group in localisation, age and sex distribution (for details see Table 1). They were nodular in appearance, not larger than 2 cm, with well defined but not sharply demarcated boundaries. Histologically, they have in com-

Table 3. Specific immunostaining in granular cell tumours[a]

Case no. tumour-localisation	Specific antisera to[b]				
	TPA, PKK1, Kera D, CEA, GFAP, GE, CK, NF, Desmin, Myoglobin, LCA, Lysozyme	Alpha-1-antichymotrypsin	Laminin[c]	S 100	NSE
1 Maxillary gingiva	−	−	−	−	+/−
2 Maxillary gingiva	−	−	−	−	+/−
3 Palatine	−	−	−	−	+/−
4 Vocal cord	−	−	+	+	+
5 Tongue	−	−	+	+	+
6 3rd finger volar	−	−	+	+	+
7 5th finger distal joint	−	−	+	+	+
8 Breast skin	−	−	+	+	+
9 Clavicule	−	+	−	−	−

[a] Symbols represent: − = no staining, +/− = irregular or weak staining,
[b] + = any staining of granular tumour cells (for details see results section). For abbreviations of antigens see Table 2
[c] Pericellular staining

mon their composition of compactly arranged plump cells with abundant cytoplasm, containing many acidophilic granules of varying size (Fig. 1) and of diastase resistant PAS-stainability. Pericellular reticular fibres are weakly developed in most of the nine tumours and are particularly scarce between the syncytial cells of the vocal cord tumour; however, the tumours from the clavicule and from the 3rd finger (case 6) contain well developed collagen bundles.

A survey of the specific staining patterns with the different antisera is given in Table 3. All tumours except the one localised near the clavicule, show a cytoplasmic immunostaining for NSE (Fig. 2a), which is strong to moderate in the five adult cases, but irregular and partly weak in the three congenital tumours (2b). In the palatine tumour, occasional intranuclear NSE-staining is observed.

S 100 protein is not found in the clavicular or the three congenital tumours. However, the five adult tumours show specific S 100 staining of generally moderate strength in the cytoplasm (Fig. 3a), at places in a segmental distribution, and occasionally in the nuclei.

Only the clavicular tumour shows a reaction for alpha-1-antichymotrypsin, which is moderately strong, often distributed segmentally within individual tumour cells (Fig. 3b), leaving part of the granular material unstained.

Nerve fibres are found in and around two of the NSE-S 100 adult tumours, i.e. from the 5th finger (case 7) and from the tongue, and in the two congenital gingival tumours. In and around the latter, small poorly myelinated fibres are seen in close contact with small vessels, and the 5th finger adult tumour is closely attached to a tactile body. The axons of

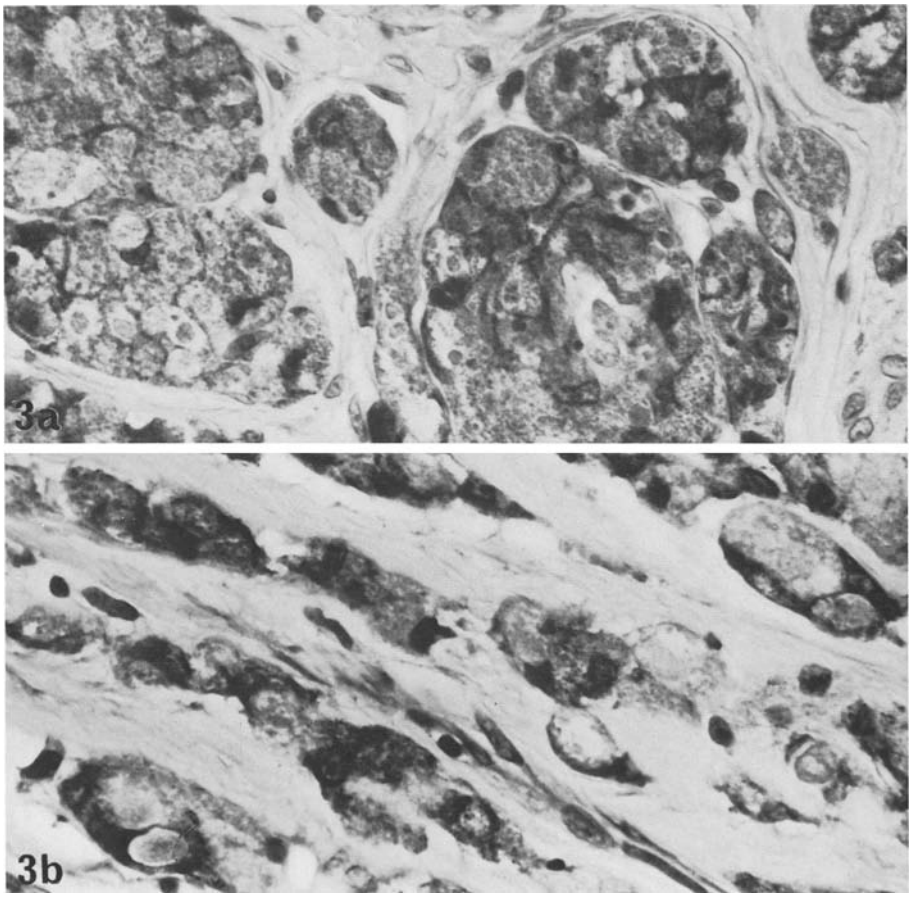


Fig. 3. **a** Staining for S 100 protein in adult tongue tumour (case 5). **b** Staining for alpha-1-antichymotrypsin in adult tumour from clavicular skin, in a segmental distribution in some cells

the intratumour nerve fibres in these four cases react strongly for NSE (Fig. 4a) and NF (Fig. 4c) but not for S 100 (Fig. 4b). However, the surrounding tumour cells react for both NSE and S 100 only in the two adult cases, while in the two congenital cases the tumour cells react weakly for NSE only. The tumour cells in all cases are negative for NF.

By comparison, normal peripheral nerves in adults show specific immunostaining for NF in nerve fibre axons only, for S 100 in Schwann cell cytoplasm only, and for NSE in axons and – differing from previous findings (Schmechel et al. 1978) – also occasionally in Schwann cell cytoplasm. S 100 and NSE are also seen at the periphery of the myelin sheaths and occasionally in Schwann cell nuclei. However, the reaction in newborn nerves, when compared with adult tissues appears stronger and involves the whole nerve diameter for NSE, appears weaker for S 100 and the same for NF. Except Schwann cells, no other endoneural cells are seen to react for S 100 or

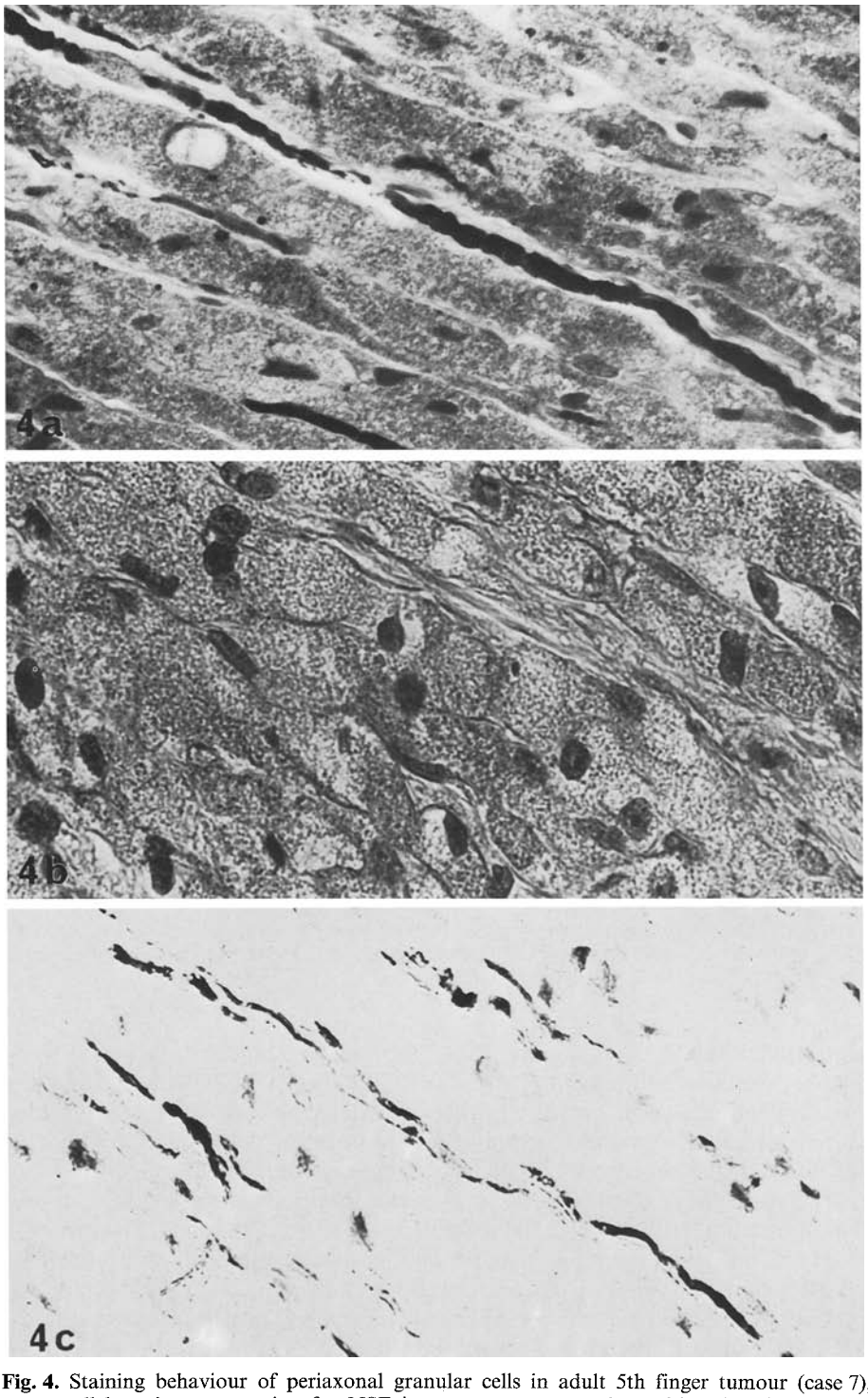


Fig. 4. Staining behaviour of periaxonal granular cells in adult 5th finger tumour (case 7), **a–c** parallel sections: **a** reaction for NSE in axons more strongly positive than in granular cells, **b** staining for S 100 protein in granular cells only, **c** staining for neurofilament in axons only

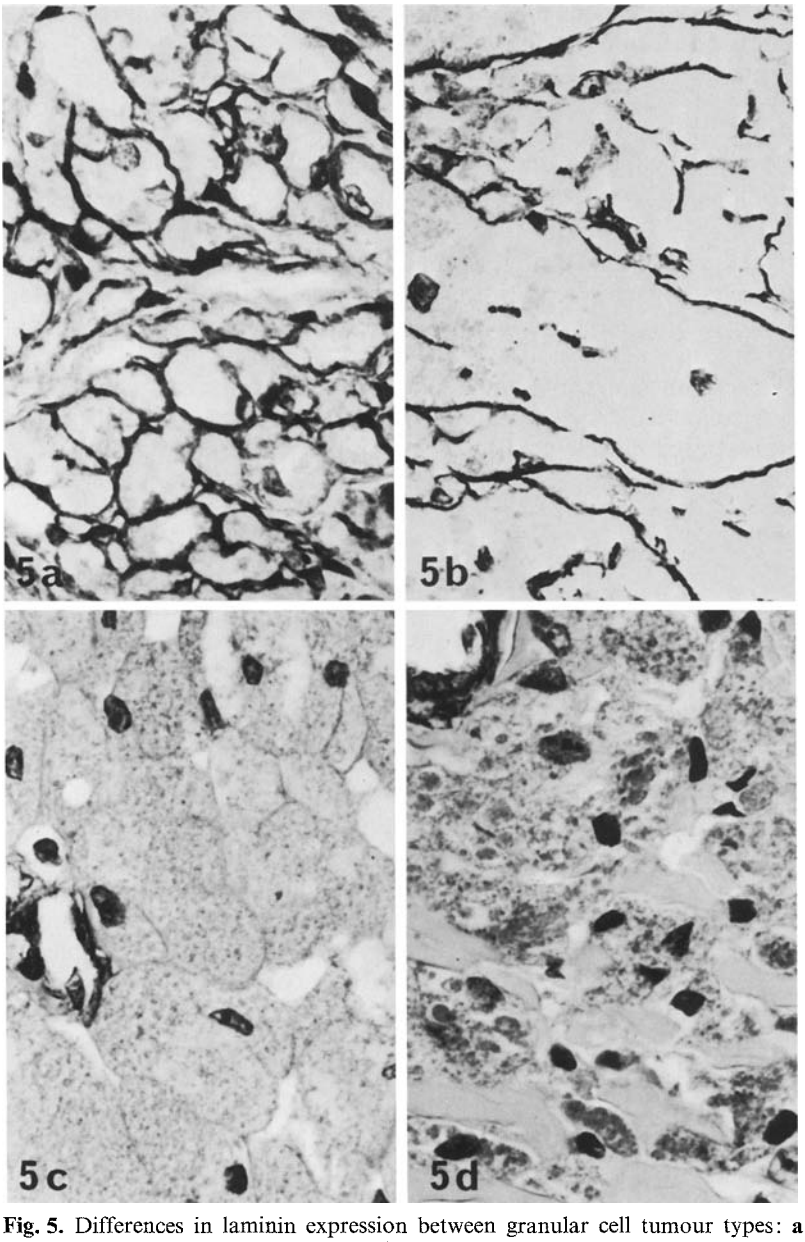


Fig. 5. Differences in laminin expression between granular cell tumour types: **a** staining for laminin around single cells in adult 5th finger tumour (case 7) **b** staining for laminin around single cells and around and also within syncytial cells in adult vocal cord tumour (case 4); **c** and **d**) lack of pericellular staining in congenital palatine and adult clavicule tumour, respectively

NSE. Normal perineural cells do not stain for NSE or S 100; alpha-1-antichymotrypsin is not found at all in nerves.

In the five adult NSE-S 100 positive tumours, laminin is seen in a basal membrane like distribution around the individual small and syncytial granular cells (Fig. 5a, b), in the latter giving the wrong impression of a group phenomenon (Miettinen et al. 1984; Reibel et al. 1985): remnants of former bounderies of smaller granular cells can be recognised in the syncytial cells and are particularly obvious in the vocal cord tumour (Fig. 5b). Laminin is not expressed pericellularly in the three congenital tumours nor in the clavicule tumour (Fig. 5c, d), despite broad collagen fibres in the latter. However, these tumours appear to give weak intracytoplasmic staining for laminin (Fig. 5c, d).

None of the tumours shows any reaction with the sera to lysozyme, epithelial, muscular, leukocyte and glial antigens. Normal epithelia, histiocytic cells and striated muscle next to or within the tumours are well stained with the respective antisera.

Discussion

Although non-homogenous in localisation, age and sex distribution and fibre content, all nine tumours are distinctly characterized as granular cell tumours by their identical cellular appearance and small nodular size. Immunohistochemically, none of these tumours expresses lysozyme or epithelial, muscular, leukocyte, neuro- or glia-filament qualities, in agreement with other investigations (Matthews and Mason 1982; Slootweg et al. 1983; Miettinen et al. 1984; Schwechheimer et al. 1983) The failure of all nine tumours to react with the monoclonal and absorbed antisera to CEA (Shousha and Lyssiotis 1979) is explained by the lack of non-specific cross reactive antibodies in the antisera used (Primus et al. 1978; Matthews and Mason 1982).

However, three patterns can be distinguished by the specific immunostaining for NSE, S 100 protein and alpha-1-antichymotrypsin: An alpha-1-antichymotrypsin-reaction is only found in the clavicular tumour, which does not express NSE or S 100. The five remaining adult tumours show reaction for NSE and S 100, whereas the three congenital tumours show a weak or irregular reaction for NSE only. The distinction between these three groups is further supported by the pericellular laminin staining in the NSE-S 100 tumours (Miettinen et al. 1984; Reibel et al. 1985) and its is lacking in the clavicular and the congenital tumours.

The demonstration of NSE in eight of the nine tumours, the additional demonstration of S 100 in five of these tumours and the presence of nerve fibres not only in the adult tumours but, in contrast to previous findings (Fuhr and Krogh 1972; Matthews and Mason 1982) also in the congenital tumours, relates both these groups to nervous system cells. The lack of NF-staining in the tumour cells (Dhillon and Rode 1983; Slootweg et al. 1983; Trojanowski and Lee 1983; Miettinen et al. 1984) would exclude an origin from neurons, the only normal structure reactive for NF (Trojanowski and Lee 1983).

The expression of both NSE and S 100 (Nakazato et al. 1982; Rode

et al. 1982; Stefansson and Wollmann 1982; Dhillon and Rode 1983) in the five adult tumours and the clearly periaxonal tumour cell localisation in two of these tumours strongly support the view, that they correspond to Schwann cells (Feyrter 1935; Fisher and Wechsler 1962; Garancis et al. 1970; Weiser 1978). S 100 and – from our observations – NSE are also found in normal Schwann cells and in Schwannomas (Stefansson et al. 1982a, b; Weiss et al. 1983; Vinores et al. 1984; Rode et al. 1985; Vanstapel et al. 1985). Dhillon and Rode (1983) have already drawn attention to a similar joint expression of both antigens in melanomas and a specific subclass of neural crest cells has been considered to be the origin of melanocytes and Schwann cells (Stefansson et al. 1982a).

The association of nerve fibres with two of the congenital tumours may indicate that this group is also related to Schwann cells. The lack of S 100 in these tumours is in agreement with the finding of Weiss et al. (1983) who found this protein also lacking in malignant granular cell tumours and thus considered it to be an expression of considerable Schwann cell differentiation (Cicero et al. 1972; Stefansson and Wollmann 1982). This would also agree with our impression that in normal newborn in contrast to normal adult tissues the neural reaction for S 100 is weaker than that for NSE, as the neural sheaths may still be in a developmental stage. Thus, the varying staining behaviour of S 100 and NSE in our eight "neurogenic" tumours seems to be related to different maturity of the precursor Schwann cell. In addition, Vimentin has been found to a lesser degree in adult than in congenital granular cell tumours (Slootweg et al. 1983), probably also as in index of nerve system maturation (Tapscott et al. 1981). We thus agree with the assumption, that both the NSE-S 100 adult and the congenital tumour types are basically identical (Wegelin 1947; Skoglund and Holst 1983) and of Schwann cell origin, but differently mature. The relation of some of these tumours to the peripheral ends of sensory nerve fibres near tactile bodies (Bangle 1953; Rode et al. 1982) or small vessels (regulation of blood flow?) may invite speculation that this localisation plays a role for the development of granular cell tumours.

In contrast to the eight NSE positive tumours, there is no indication of neurogenesis in the clavicular tumour. However, although also negative for lysozyme (Schwechheimer et al. 1983; Miettinen et al. 1984) it shows, by virtue of its reaction for alpha-1-antichymotrypsin, some histiocytic quality (Travis et al. 1978; Meister and Nathrath 1981; Nathrath and Meister 1982; Permanetter and Meister 1984). This would be in line with the assumption that there are granular cell tumours of mesenchymal-fibrocytic origin (Pearse 1950; Haisken and Langer 1962; Sobel and Marquet 1974). The intracytoplasmic segmental distribution of the alpha-1-antichymotrypsin immunostaining in the clavicular tumour may indicate a distinction between a functioning cell compartment and the more granular stored material (Lauche 1944). Whether this is of endogenous (Pearse 1950) or of exogenous (Wegelin 1947) origin, cannot be decided from this study; however there is no indication that the clavicular tumour is a traumatic "reactive granular lesion" (Sobel and Marquet 1974).

In context with the other results, the different staining patterns of laminin

in these cases may also represent differences in tumour cell-maturity and a basic difference in granular cell type, respectively.

The characterisation of one of these tumours as histiocytic, and the previously published descriptions of granular cell lesions of epithelial (Gilliet et al. 1973), myogenic (Christ and Ozello 1971) and astrocytic (Burston et al. 1962; Schwechheimer et al. 1983) origin lent some support to the assumption that in a minority of cases the granular cell phaenotype may be acquired by tumours of different cytogenic origin (Leroux and Delarue 1939; Moscovic and Azar 1967; Slootweg et al. 1983), whereas one can expect the majority to be of neural crest, most likely of Schwann cell origin. In all cases a similar metabolic defect may produce identical tumour appearances (Leroux and Delarue 1939; Azzopardi 1956; Haisken and Langer 1962; Moscovic and Azar 1967; Garancis et al. 1970; Christ and Ozello 1971).

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