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Alteration of the basement membrane in human thyroid diseases: an immunohistochemical study of type IV collagen, laminin and heparan sulphate proteoglycan

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Abstract. Basement membrane (BM) alteration in thyroid diseases was examined by immunohistochemistry using antibodies for the three major BM proteins: type IV collagen, laminin and heparan sulphate proteoglycan. Linear epithelial BMs surrounding follicles accompanied by vascular BMs forming loops, similar to those seen in the normal thyroid, were observed in Graves' disease and adenomatous goitre. Hashimoto's thyroiditis showed scant epithelial BMs as a result of follicle destruction. In follicular adenomas, development of epithelial BMs seemed to be related to follicle formation; well-developed epithelial BMs were frequently seen in normo- or large-follicular type, whereas trabecular or solid types revealed scant or poorly developed epithelial BMs. Lumpy accumulation of BM proteins was detected in hyalinizing trabecular adenomas. Papillary carcinomas revealed two different types of papillae; one type contained both epithelial and vascular BMs, and the other had only vascular BMs. Epithelial BMs in invasive areas of papillary carcinoma were distributed in an irregular, interrupted manner, and were completely absent in many foci. Anaplastic carcinomas showed scant or a total loss of epithelial BMs. These results suggest that alterations of BM in thyroid diseases clearly reflect their architectural variations, presumably in connection with their function and/or biological behaviour.

Key words: Basement Membrane – Thyroid disease – Type IV collagen – Laminin – Heparan sulphate proteoglycan

Introduction

The basement membrane (BM) separates the epithelium from the subjacent connective tissue. BMs are composed by collagenous (type IV) and non-collagenous (laminin, fibronectin) glycoproteins and proteoglycans (Kefalides et al. 1979). Of the various BM components, type IV collagen is the most abundant molecule and serves as the major structural framework (Martinez-Hernandez and Amenta 1983). Laminin is a smaller cross-shaped molecule that binds to collagen IV molecules through its globular domains (Engel et al. 1981). Heparan sulphate proteoglycan (HSPG) consists of a core protein, to which side chains of glycosaminoglycans are bound, and it probably plays a role in the attachment of cells to BMs (Hassel et al. 1980). Therefore, immunohistochemistry for these BM major proteins can be a method suitable for the observation of the BM structure in various pathological states.

Although considerable progress has been made during the past several years in understanding the composition and structure of BM, little is known about how BMs are structurally altered in disease, and how these structural abnormalities influence their functions. In addition, little attention has been focused on the distribution of BM proteins in thyroid diseases. Laminin has been detected in human thyroid tumours (Miettinen and Virtanen 1984; Charpin et al. 1985). Kendall et al. (1985) examined the distribution of type IV collagen and laminin immunohistochemically in follicular thyroid tumours, and found that the BM was lost in the widely invasive ones, while it was presented in most encapsulated ones.

In the present study, to evaluate the variation of BM distribution in human thyroid disorders, we examined thyroid specimens from 113 patients with various thyroid disorders immunohistochemically using antibodies to the three major BM components: type IV collagen, laminin, and HSPG. In addition, we sought to determine whether the alternation of BM has any value in differential diagnosis of thyroid diseases, especially between benign and malignant tumours.

Materials and methods

We reviewed the surgically resected specimens of various thyroid diseases from the files of the Department of Pathology at Yama-

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nashi Medical University, Kofu City Hospital and Iwate Medical University, and selected 113 cases for immunohistochemical studies of BM proteins. The materials consisted of tissues from 10 cases of Graves' disease, 5 of Hashimoto's thyroiditis, 10 of adenomatous goitre, 30 of follicular adenoma, 5 of follicular carcinoma, 41 of papillary carcinoma, 5 of anaplastic carcinoma, and 3 of medullary carcinoma. In addition, there were 4 cases of hyalinizing trabecular adenoma: 3 were surgical specimens from the Kuma hospital, and one was obtained from the consultation file of one of the authors (R.K.). The criteria for selection included representative morphological characteristics and adequate tumour mass. In tumour cases, the lesions were classified according to the diagnostic criteria of the WHO classification proposed in 1988. All specimens were processed routinely, and paraffin blocks were available in all cases. For light microscopy, stain was performed with haematoxylin and eosin, van Gieson and periodic acid Shiff methods.

For immunohistochemical analysis, the following antibodies were used: goat polyclonal antiserum to type IV collagen (dilution 1:400; Southern Biotechnology Associates, USA), mouse monoclonal antiserum to human type IV collagen (dilution 1:100; Dako, Denmark), rabbit polyclonal antiserum to laminin (dilution 1:100; Chemicon International, USA) and mouse monoclonal antiserum to HSPG (1:25; Chemicon).

Deparaffinized sections were first treated with 0.1% pronase for 60 to 90 min at room temperature and then were exposed to a 0.1% solution of hydrogen peroxide in absolute methanol to inactivate endogenous peroxidases. An indirect immunoperoxidase staining was used for the immunohistochemical study. The sections were treated overnight at 4° C successively with the antibodies for BM proteins. Anti-goat IgG or anti-mouse IgG conjugates were applied to the sections for 60 min at room temperature, and the peroxidase reaction was performed using diaminobenzidine tetrahydrochloride. The immunohistochemical preparations were counterstained with haematoxylin or methyl green. For controls, normal rabbit serum or phosphate-buffered saline were used instead of the primary antibody.

For the purpose of comparing BM patterns in neoplastic tissues, distributions of the epithelial and of the vascular BMs in a predominently histological pattern were divided into the following three grades: E1 when epithelial BMs were scanty or completely absent, E2 when epithelial BMs were discontinuous or focal, and E3 when epithelial BMs were well-developed; V1 when vascular BMs were scanty, V2 when vascular BM were moderately developed, and V3 when vascular BMs were well-developed.

Results

Pretreatment with 0.1% protease yielded constant immunoreactivity for type IV collagen, laminin and HSPG, while immunostaining without the pretreatment showed only focal or completely negative immunoreactivity. In thyroid tissue, the follicular BMs were divided into two components: epithelial BMs and vascular BMs. No immunohistochemical differences between type IV collagen and laminin were observed in vascular and epithelial BMs. Immunoreactivity for HSPG, however, was weaker and more focal than those for type IV collagen and laminin. Therefore, alteration of epithelial and vascular BM in various thyroid disease was mainly evaluated by type IV collagen or laminin staining.

In normal tissues thin continuous epithelial BMs and several vascular BMs forming loops were detected around the follicles in thyroid tissues (Fig. 1A). Distinct immunoreactivities for BM proteins were also observed in associated structures inside or outside the thyroid, such as vessels, adipocytes, perineurinum and endoneurinum of the peripheral nerve fibres, as well as the perimysium and endomysium of the striated muscles. In general, BMs of these associated structures were more readily stained than were follicular BMs, particularly after enzymatic pretreatment. No intracytoplasmic immunoreactivity for any of the three antibodies was observed throughout the tissues.

In Graves' disease immunostaining for BM proteins in epithelial BMs surrounding hyperplastic follicles was similar to that in normal thyroid tissues. However, in the areas showing marked proliferation of follicular epithelium, epithelial BMs were irregular in shape and thickness, and loops of vascular BMs were characteristically prominent (Fig. 1B). All cases of Hashimoto's thyroiditis showed remarkable destruction and degeneration of thyroid follicles accompanied by fibrosis and diffuse infiltration of lymphocytes and plasma cells. The degenerated follicles, composed of oxyphilic cells, exhibited scant or discontinuous immunoreactivities for the epithelial BMs (Fig. 1C). The patterns of BM staining in the hyperplastic follicles of adenomatous goitres were similar to those of normal thyroid follicles (Fig. 1D). In some parts, epithelial BMs were thickened and loops of vascular BMs surrounding the follicles were prominent.

The immunohistochemical results of BM proteins in neoplasms (type IV collagen and laminin) are summarized in Tables 1 and 2. The staining patterns obtained with the antibodies to the BM proteins varied with the histological architecture of the tumour. A grading system was used to compare BM patterns in neoplastic tissues, where normal thyroid tissue was regarded as having well-developed epithelial BMs (E3) and scanty vascular BMs (V1).

Well-developed epithelial BMs (E3) around the follicles were most frequently seen in normo- or large follicular types of follicular adenoma (Table 1, Fig. 2A). The tubular type mainly showed moderately developed epithelial BMs (E2). In one case of the tubular type of adenoma, continuous, thick epithelial BMs (E3) were dispersed in small follicles composed only of a few cells (Fig. 2B). All trabecular and/or solid types of adenoma revealed scanty or poorly developed epithelial BMs (E1) (Fig. 2C). The oxyphilic cell type showed scanty epithelial BMs even if tumour cells had formed follicular structures (Fig. 2D). On the other hand, loops of vascular BMs were prominent (V3) in the tubular, oxyphilic and solid-trabecular types of adenoma, and in contrast, poorly or moderately developed (V1 or V2) in the normoor large follicular types (Table 2). Small focal thickening or accumulation of epithelial BMs was observed in 3 cases of normo- or large follicular types of adenoma (Fig. 2E). Clumping or arborizing depositions of BM proteins were characteristically detected in all 4 cases of the hyalinizing trabecular type (Fig. 2F).

In papillary carcinomas, the tumour tissues had abundant BMs (Fig. 3A); 34 of 41 cases (82.9%) showed moderately or well-developed epithelial BMs (E2 or E3) and 39 of 41 cases (92.7%) had moderately or well-developed vascular BMs (V2 or V3) (Table 1). Immunostaining for BM proteins revealed two types of papillae in papillary carcinoma. In the first type, the papillae

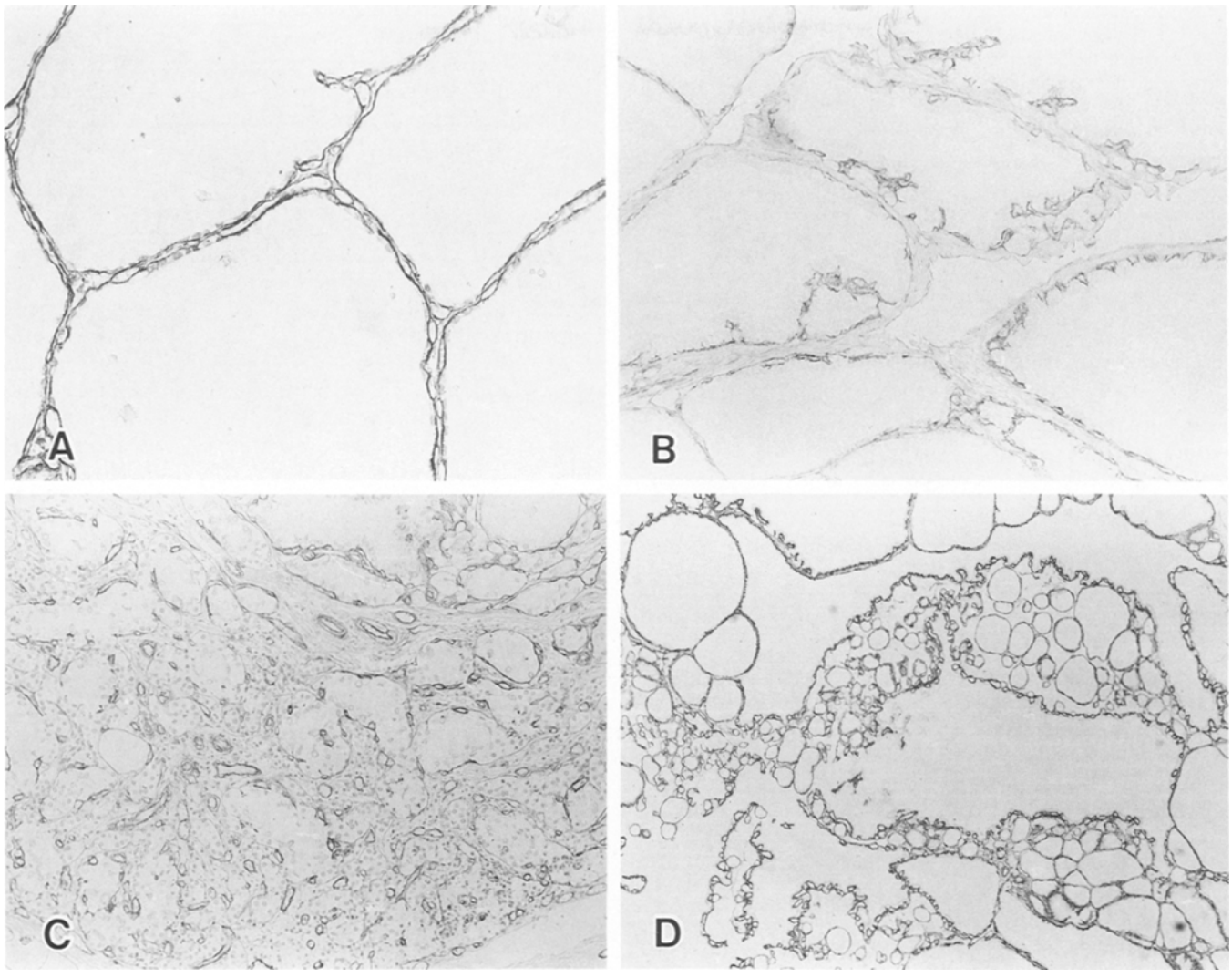

Fig. 1. A Normal thyroid gland. Staining for type IV collagen shows linear basement membranes (BMs) around the follicles. ×200. **B** Graves' disease. Staining for heparan sulphate-proteoglycan reveals a similar BM distribution as that of normal thyroid. Note prominent vascular BMs forming loops. ×100. **C** Hashimoto's thyroiditis. Staining for laminin shows scant or discontinuous distribution of epithelial BMs. ×200. **D** Adenomatous goitre. Staining for type IV collagen shows linear epithelial BMs around hyperplastic follicles. ×40

Table 1. Staining results of epithelial basement membrane (BM) in thyroid tumours

Histological types	No. of cases	Staining patterns of epithelial BM		
		E1	E2	E3
Follicular adenoma	34	12	16	6
Normo- or large-follicular type	10	1	4	5
Tubular type	10	2	7	1
Trabecular and/or solid type	5	5	0	0
Oxyphilic cell type	5	4	1	0
Hyalinizing trabecular type	4	0	4	0
Follicular carcinoma	5	3	2	0
Papillary carcinoma	41	7	20	14
Anaplastic carcinoma	5	5	0	0
Medullary carcinoma	3	0	0	3

E1, Negative or scanty epithelial BM; E2, focal epithelial BM; E3, well-developed epithelial BM

Table 2. Staining results of vascular basement membrane (BM) in thyroid tumour

Histological types	No. of cases	Staining patterns of vascular BM		
		V1	V2	V3
Follicular adenoma	34	7	22	5
Normo- or large-follicular type	10	4	6	0
Tubular type	10	3	5	2
Trabecular and/or solid type	5	0	3	2
Oxyphilic cell type	5	0	4	1
Hyalinizing trabecular type	4	0	4	0
Follicular carcinoma	5	0	4	1
Papillary carcinoma	41	2	27	12
Anaplastic carcinoma	5	1	3	1
Medullary carcinoma	3	0	3	0

V1, Scanty vascular BM; V2, moderately developed vascular BM; V3, well-developed vascular BM

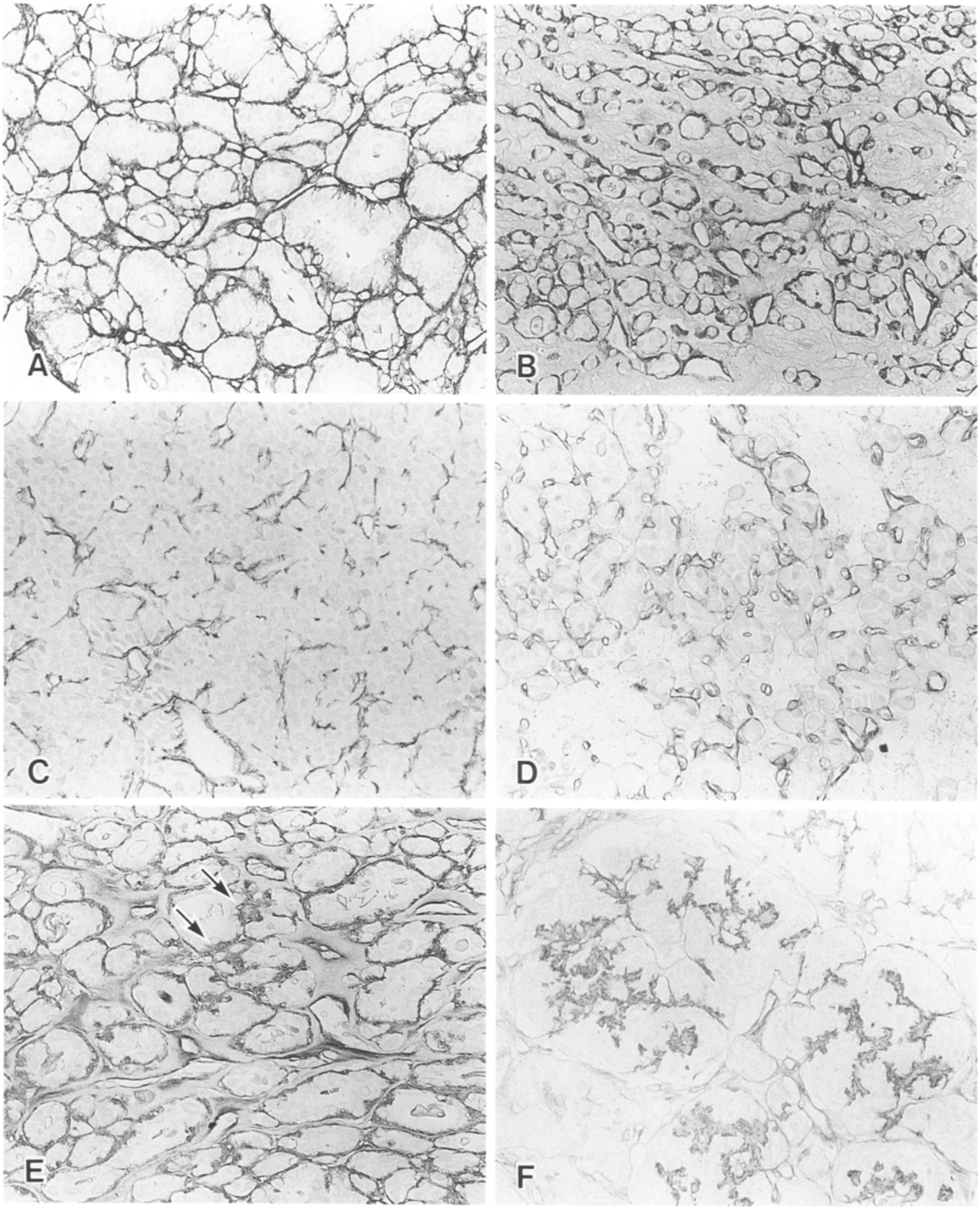

Fig. 2A–F. Follicular adenoma. Staining for type IV collagen shows linear epithelial BMs in the normo-follicular type (**A**, ×100) and tubular type (**B**, ×200), and scant epithelial BMs in the solid-trabecular type (**C**, ×100) and oxyphilic cell adenoma (**D**, ×200). Staining for laminin reveals focal thickenings *(arrows)* of epithelial BMs in the normo-follicular type (**E**, ×100) and lumpy depositions of BM materials in a hyalinizing trabecular adenoma (**F**, ×100)

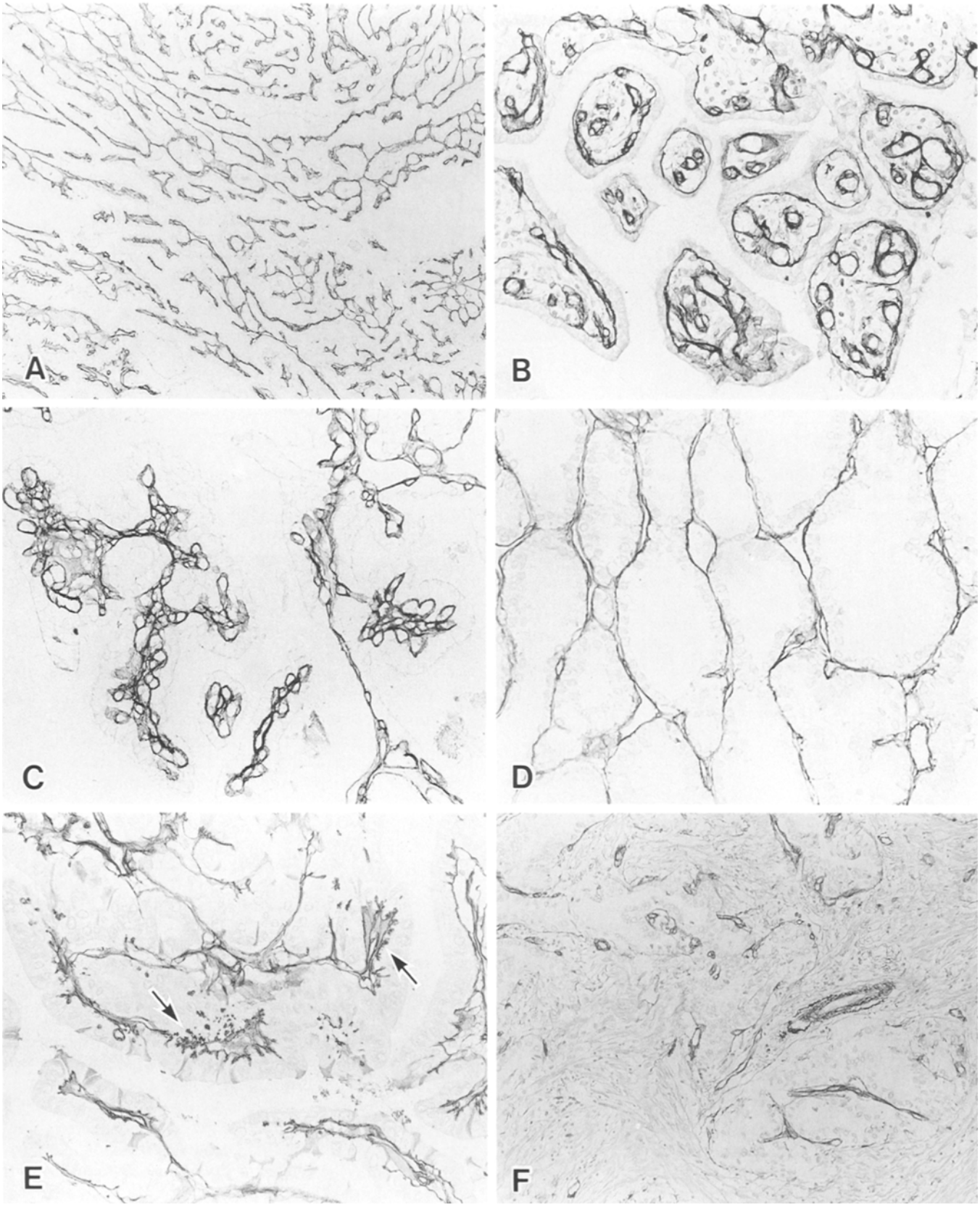

Fig. 3A–F. Papillary carcinoma. Staining for type IV collagen shows well-developed BM distribution (**A**, ×40). Some papillae have both epithelial and vascular BMs (**B**, ×100), but some have only vascular BMs (**C**, ×200). Follicular areas show linear BMs (**D**, ×200). Note focal thickenings *(arrows)* of epithelial BMs in the papillae (**E**, ×200). Loss of epithelial BMs were noted in invasive areas (**F**, ×100)

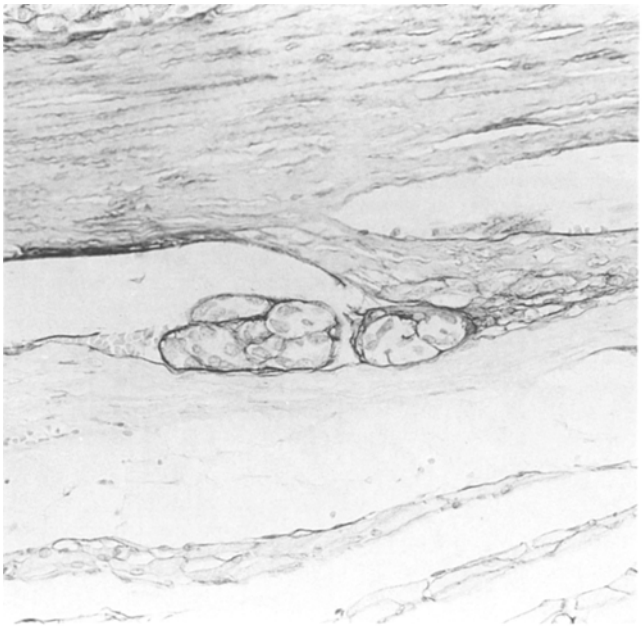

Fig. 4. Follicular carcinoma stained for laminin. Immunostaining defined vascular BMs within tumour capsule. Note that tumour plugs had linear BMs. × 200

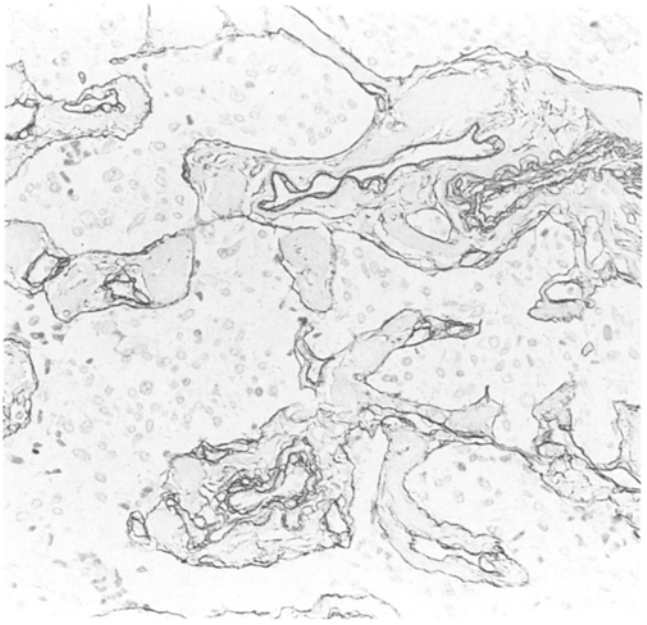

Fig. 6. Medullary carcinoma stained for type IV collagen. Immunostaining showed well-developed epithelial BM around tumour cell nests and amyloid masses. × 100

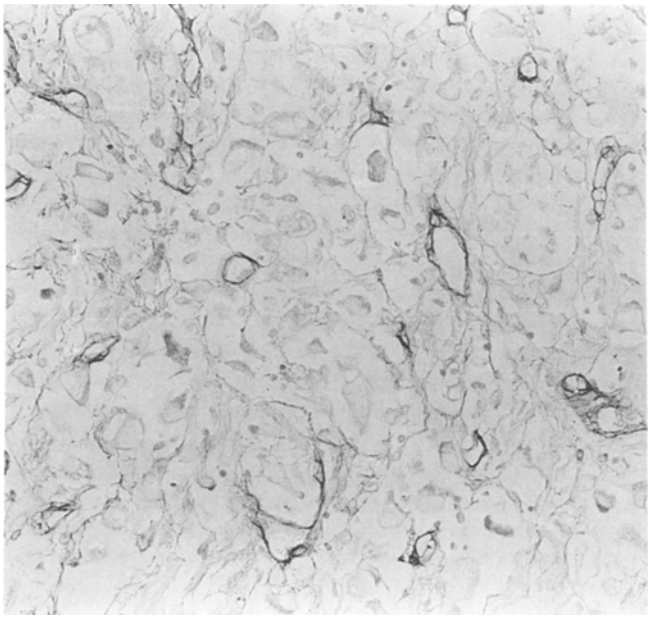

Fig. 5. Undifferentiated carcinoma stained for laminin. Immunostaining revealed scanty epithelial basement membranes. × 200

contained well-developed, linear epithelial BMs along the fibrovascular core beneath the lining of tumour cells (Fig. 3B). The other type of papillae had only vascular BMs forming loops and did not contain any epithelial BMs (Fig. 3C). The former was more common and usually larger in size. The follicular structures in the papillary carcinomas showed similar staining patterns to those of normal thyroid follicles (Fig. 3D). Focal accumulations of BM materials were seen in 4 cases of papillary carcinomas (Fig. 3E). In the invasive areas of papillary carcinoma, epithelial BMs were consistently scanty, focal and sometimes completely absent (Fig. 3F).

The distribution patterns of BM components in the follicular carcinomas was similar to those found in follicular adenoma. However, scanty or poor epithelial BMs (E1) were more frequent in the former than in the latter. By contrast, vascular BMs were more prominent in follicular carcinomas. Immunostaining for BM proteins also defined vascular walls within the capsule, and revealed that the tumour plugs had distinct continuous epithelial BMs (Fig. 4).

In all three medullary carcinomas, continuous staining of the epithelial BMs surrounded both the tumour cells nests and the amyloid masses (Fig. 5). Vascular BMs were prominent in the interstitium. Anaplastic carcinomas showed negative or scant immunoreactivity for BM proteins (Fig. 6).

Discussion

In this study, the presence of BMs around the thyroid follicles was demonstrated immunohistochemically only after pronase pretreatment. The selective immunoenhancing effect of pronase treatment on BM antigens has been described, but its exact mechanism remains unclear (Barsky et al. 1984) although it seems likely that the effect may be related to its ability to solubilize portions of the molecule masking immunoreactive BM epitopes (Leu et al. 1986). Immunoreactivity of type IV collagen and laminin is specific and reliable. No distinct differences in immunoreactivities between type IV collagen and laminin were seen in the tissue examined. The immunoreactivity of HSPG was, however, weak and

focal. The discrepancy of immunoreactivity between HSPG and other BM components (type IV collagen and laminin) has also been reported (Bonkhoff et al. 1991). Although there is a possibility that the weak HSPG immunoreactivity reflects a low content of HSPG in thyroid materials, a more exact interpretation appears to require further investigations. Intracellular localization of laminin or type IV collagen was reported in hyperplastic or neoplastic prostate epithelium (Sinha et al. 1989) and in salivary gland tumours (Skalova and Leivo 1992). However, we observed no intracytoplasmic type IV collagen or laminin in either normal, hyperplastic or neoplastic thyroid epithelium.

In adenomatous goitre and Graves' disease, some irregularities of epithelial BMs in their distribution pattern were seen in the hyperplastic follicles with marked epithelial proliferation. However, the epithelial BMs in Hashimoto's thyroiditis were revealed to be discontinuous or sometimes completely absent around the follicles. These alteration of epithelial BMs may reflect a functional abnormality or proliferative activity of the follicles, and the findings in Hashimoto's thyroiditis may be related to degeneration of follicular cells (oxyphilic change) and/or destruction of thyroid follicles.

The BM distributions in neoplastic tissues varied. However, there was a tendency for epithelial BMs to be more limited in their formation, and vascular BMs were more prominent in neoplastic tissues compared with normal thyroids. In follicular adenomas, the epithelial BMs were relatively well-preserved in the tubular and normo- or large follicular types. In contrast, trabecular and/or solid types of follicular adenoma exhibited scanty epithelial BMs. These findings suggest that formation of epithelial BMs is related to the follicular structure. However, oxyphilic cell adenomas showed scanty or complete loss of epithelial BM formation even if the tumour cells were present in the follicular structure. With regard to this finding, it is possible that oxyphilic cells may have impaired epithelial BM formation.

Hyalinizing trabecular adenoma (HTA) shows some of the features associated with medullary carcinoma, papillary carcinoma and paraganglioma on haematoxylin and eosin study which may pose considerable difficulties in histological diagnosis (Carney et al. 1987). One of US (Katoh et al. 1989) previously reported that one of the main histological features of HTA, the hyalin extracellular material, is due to over-production of a BM-like material by the neoplastic follicular cells. In this study, we also confirmed the existence of lumpy depositions of BM materials in all 4 cases of HTA. Therefore, the immunohistochemistry for BM components could be a useful diagnostic tool in distiguishing HTA from other tumours with similar histological findings, such as papillary carcinoma, medullary carcinoma and paraganglioma. Interestingly, focal depositions of epithelial BMs, but much smaller in size than those in HTA, were also observed in some cases of follicular adenomas and papillary carcinomas. Overproduction of BM proteins has also been reported in some malignant neoplasms such as adenoid cystic carcinoma and yolk sac tumour (Barsky et al. 1988).

The localization patterns of the BM components in follicular carcinomas did not differ essentially from those found in follicular adenoma. However, scanty epithelial BMs were more frequent in follicular carcinomas. In general, detection of vascular invasion within the capsule is considered to be of particular diagnostic importance in follicular thyroid tumours. In the present study, immunostaining for BM proteins defined the vascular walls within the capsule and revealed that the tumour plugs had distinct continuous epithelial BMs. Thus, immunohistochemistry for these BM proteins could be helpful for diagnosis of follicular carcinoma by their enhancing the detection of vascular invasion, (Kendall et al. 1985). The value of immunostaining of BM components for detecting vascular invasion has also been shown in breast cancer (Bettelheim et al. 1984).

Papillary carcinomas are characterized by papillary structures having fibrovascular cores. The present study revealed that these papillae can be divided into two types: one contained both epithelial and vascular BMs and the other had only vascular BMs forming loops. The latter papillae were usually small in size and did not contain prominent collagen. Therefore, the former could be regarded as being mature papillae and the latter as being immature.

Epithelial BM formation was rather poor or absent in undifferentiated carcinomas. This finding suggests the idea that BM deposition and the degree of differentiation of carcinoma may be correlated (Hay 1978; Bosman et al. 1985). However, in the present study, some follicular adenomas or well-differentiated carcinomas (follicular carcinoma and papillary carcinoma) also displayed scanty or total loss of epithelial BM. Therefore, such a correlation was less apparent in thyroid tumours, and it is too early to draw any conclusions. Nevertheless, the available information warrants further studies on the significance of basement membrane deposition as a differentiation marker in neoplasia (Bosman et al. 1985).

Our study showed that the epithelial BMs in invasive areas were distributed in an irregular, interrupted manner, and were completely absent in many foci. Previous studies have shown that the invasive properties of malignant cells are related to the interactions between the tumour cells and the extracellular matrix (Martinez-Hernandez and Amenta 1983). The invasive and metastatic potential of malignant cells have been shown to correlate with the expression of high levels of an extracellular matrix degrading the enzymes, particularly against the BM (Liotta et al. 1980; Monteagudo et al. 1990). Studies in breast, colon and hepatocellular carcinomas have shown that type IV collagenase immunoreactivity is increased in aggressive, invasive tumour cells (Barsky et al. 1983; Grigioni et al. 1991; Levy et al. 1991). Malignant cells have been shown to increase their expression ot cell surface receptors for laminin during the metastatic cascade, and this results in the loss of the usual polarized distribution of receptors at the basal portions of the cells (Wewer et al. 1987).

In the present study, most thyroid tumours showed more prominent vascular BMs compared with those of normal thyroid tissues. Staining patterns of vascular

BMs in tumour tissues varied, and were fairly well-related to histological types. In particular, papillary carcinomas usually had prominent vasculature in papillary areas, but this was, not so marked in follicular areas. This finding supports the hypothesis that tumours can induce angiogenesis and modulation of the microvasculature. In addition, it may be conceivable that the histological type of tumours can determine the vascular pattern, suggesting the heterogeneity of angiogenic stimuli among different histological types.

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References

Barsky SH, Togo S, Garbisa S, Liotta LA (1983) Type IV collagenase immunoreactivity in invasive breast carcinoma. Lancet 1:296–297

Barsky SH, Rao NC, Restrepo C, Liotta LA (1984) Immunocytochemical enhancement of basement membrane antigens by pepsin: applications and diagnostic pathology. Am J Clin Pathol 82:191–194

Barsky SH, Layfield L, Varki N, Bhuta S (1988) Two human tumors with high basement membrane-producing potential. Cancer 61:1798–1806

Bettelheim R, Mitchell D, Gusterson BA (1984) Immunocytochemistry in the identification of vascular invasion in breast cancer. J Clin Pathol 37:364–366

Bonkhoff H, Wernert N, Dhom G, Remberger K (1991) Basement membranes in fetal, adult normal, hyperplastic and neoplastic human prostate. Virchows Arch [A] 418:375–381

Bosman FT, Havenith M, Cleutjens JPM (1985) Basement membranes in cancer. Ultrastruct Pathol 8:291–304

Carney JA, Ryan J, Goellner JR (1987) Hyalinizing trabecular adenoma of the thyroid. Am J Surg Pathol 11:589–591

Charpin C, Kopp F, Pourreau-Schneider N, Lissitzky JC, Lavaut MN, Martin PM, Toga M (1985) Laminin immunodetection in tumours and nontumours disorders of human thyroid. Bull Cancer (Paris) 72:6–15

Engel J, Odermatt E, Engel A, Madri JA, Furthmayer H, Rohde H, Timpl R (1981) Shapes, domain organization and flexibility of laminin, and fibronectin, two multifunctional proteins of the extracellular matrix. J Mol Biol 150:97–120

Grigioni WF, Garbisa S, D'Errico A, Baccarini P, Stetler-Stevenson, Liotta LA, Mancini AM (1991) Evaluation of hepatocellular carcinoma aggressiveness by a panel of extracellular matrix antigens. Am J Pathol 138:647–654

Hassel JR, Robey PG, Baranch HJ, Wilczek J, Rennard SI, Martin GR (1980) Isolation of heparan sulphate proteoglycan from basement membrane. Proc Natl Acad Sci USA 77:4494–4498

Hay ED (1978) Role of basment membranes in development and differentiation. In: Biology and chemistry of basement membranes. Kefalides N, (ed) Academic Press, New York, pp. 119–136

Katoh R, Jasani B, Williams ED (1989) Hyalinizing trabecular adenoma of the thyroid. A report of three cases with immunohistochemical and ultrastructural studies. Histopathology 15:211–224

Kefalides NA, Alper R, Clark CC (1979) Biochemistry and metabolism of basement mambranes. Int Rev Cytol 61:167–228

Kendall CH, Sanderson PR, Cope J, Talbot IC (1985) Follicular thyroid tumours: a study of laminin and type IV collagen in basement membrane and endothelium. J Clin Pathol 38:1100–1105

Leu FJ, Engvall E, Damajanov I (1986) Heterogeneity of basement membranes of the human genitourinary tract revealed by sequential immunofluorescence staining with monoclonal antibodies. J Histochem Cytochem 34:483–489

Levy AT, Cioce V, Sobel ME, Garbisa S, Grigioni WF, Liotta LA, Stetler-Stevenson WG (1991) Increased expression of the Mr 72,000 type IV collagenase in human colonic adenocarcinoma. Cancer Res 51:439–444

Liotta LA, Tryggvason K, Garbisa S, Garbisa S, Hart I, Foltz CM, Shafie S (1980) Metastatic potential correlates with enzymatic degradation of basement membrane collagen. Nature 284:67–68

Martinez-Hernandez A, Amenta PS (1983) The basement membrane in pathology. Lab Invest 48:656–677

Miettinen M, Virtanen I (1984) Expression of laminin in thyroid gland and thyroid tumors: an immunohistologic study. Int J Cancer 34:27–30

Monteagudo C, Merino MJ, San-Juan J, Liotta LA, Stetler-Stevenson WG (1990) Immunohistochemical distribution of type IV collagenase in normal, benign, and malignant breast tissue. Am J Pathol 136:585–592

Sinha AA, Gleason DF, Wilson MJ, Staley NA, Furcht LT, Palm SL, Reddy PK, Sibley RK, Martinez-Hernandez A (1989) Immunohistochemical localization of laminin in the basement membranes of normal, heperplastic, and neoplastic human prostate. Prostate 15:299–313

Skalova A, Leivo I (1992) Basement membrane proteins in salivary gland tumours. Distribution of type IV collagen and laminin. Virchows Arch [A] 420:425–431

Wewer UM, Taraboletti G, Sobel ME, Albrechtsen R, Liotta LA (1987) Role of laminin receptor in tumor cell migration. Cancer Res 47:5691–5698