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Keratin subsets in papillary and follicular thyroid lesions

A paraffin section analysis with diagnostic implications

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Abstract Previous studies indicate that keratins 7, 8 and 18 are present in all thyroid papillary and follicular lesions, but the distribution of other keratins has been incompletely characterized. The profile of individual keratin (K) polypeptides was evaluated immunohistochemically in over 200 non-neoplastic and neoplastic thyroid papillary and follicular lesions. Monoclonal antibodies to K19, K17, K16, K5/6 and K10 were applied in paraffin sections of formaldehyde-fixed tissue. K19 was present variably, often only focally in goitres, and was present only sporadically in papillary hyperplasia. However, K19 was strongly and uniformly expressed in virtually all papillary carcinomas, indicating differential diagnostic usefulness in differentiating papillary hyperplasia and papillary carcinoma. About half of the follicular carcinomas (defined as tumours strictly excluding the follicular variant of papillary carcinoma) were also strongly K19-positive, suggesting that K19 patterns are not reliable in differentiating papillary and follicular carcinoma. K17 and K5/6 were present in cysts and squamous metaplasia of goitres, and focally in papillary but only exceptionally in follicular carcinoma in areas of squamous differentiation and tumour cells in desmoplastic stroma. K16 in turn was present only focally in well-developed squamous metaplasia in goitres but was not found in differentiated thyroid carcinomas. K10, a high-molecular-weight keratin typical of epidermal differentiation, was identified neither in non-neoplastic nor in neoplastic differentiated thyroid lesions, including squamous metaplasia. These results indicate that papillary carcinomas differ from other differentiated thyroid tumours in their varying, usually focal, expression of stratified epithelial keratins that are partly but not exclusively related to squamous differentiation in such lesions. However, papillary carcinomas do not express truly epidermally restricted keratins; their previously described reactivity with polyclonal "epidermal keratin" antibodies most probably results from the reactivity of such antibodies with K19.

Key words Keratins · Thyroid · Immunohistochemistry

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Introduction

Analysis of keratin subsets in tumours has become simpler with the availability of antibodies specific to individual keratin polypeptides. Most of the early, widely used monoclonal keratin antibodies reacted with simple epithelial keratins (K) of low molecular weight K8/18 and K19. More recently, individual stratified epithelial keratins of higher molecular weight, initially only identifiable electrophoretically or in frozen section material by the classification of Moll et al. [13] and Sun et al. [23], have become identifiable with specific antibodies in formaldehyde-fixed and paraffin-embedded tissue [8, 12, 25].

Differentiated thyroid tumours include a histological spectrum of lesions that are not easy to classify morphologically, as illustrated by the problems of reproducibility of diagnosis [6, 17, 18]. It has been suggested that the differences in keratin polypeptide patterns might be useful in the classification of thyroid lesions, but most previous studies have analysed small series of thyroid tumours on frozen sections [2, 4, 7, 11, 16, 19, 20] or have been based on antibodies reacting with a range of different keratins. Both the earlier studies [4, 5] and our experience have demonstrated the presence of K7, K8/18 in all types of differentiated thyroid lesions and normal thyroid tissue. However, K19 expression appears to be more

limited, and it has been suggested by a study based on a small series of frozen tumours [19] that it might distinguish papillary thyroid carcinoma from follicular carcinoma and follicular thyroid adenoma. We also discuss the findings of a very recent paraffin-section based study that employed both simple and stratified epithelial keratin antibodies [5]. The previously observed reactivity of papillary thyroid carcinoma with keratin antisera raised to plantar callus keratins has not been fully explained in terms of keratin subtypes [10, 15].

Materials and methods

Formaldehyde-fixed tissue from over 200 selected representative and neoplastic thyroid papillary and follicular lesions were obtained from surgical pathology files available to the authors. Sections (4–5 μm) were cut onto neoprene-coated slides.

Immunohistochemical detection was performed by using the ABC technique (Vector Elite, Vector Laboratories, Burlingame, Calif.) and automatic immunostainers (Techmate 1000, Ventana Medical Systems, Tucson, Ariz.; Cadenza, Shandon, Pittsburgh, Pa.). All the procedures included overnight incubation of the primary antibody following the appropriate pretreatment. Incubations with the secondary antibody, ABC complex and colour development were completed the next day. Diaminobenzidine supplemented with hydrogen peroxide was used as the chromogen. The primary antibodies, their sources and dilutions and the pretreatments used prior to the immunostainings have been listed in Table 1. Enzymatic predigestion with pepsin (0.05% crude pepsin, Merck, Darmstadt, Germany) in HCl, pH 2.0, was applied for 20–30 min at 37°C prior to the immunostaining with CAM5.2 and 34ßE12 antibodies. The microwave-based antigen recovery step (“Heat-induced epitope retrieval, HIER”) was carried out in a Panasonic mi-

Table 1 Monoclonal antibodies specific to individual keratin polypeptides used in this study (*NT* no pretreatment. *MW* microwave, *Pepsin* pepsin digestion, as specified in the text)

Polypeptide	Clone	Isotype	Pretreatment Antibody dilution	Source
Keratin 8	CAM 5.2	IgG2a	Pepsin, 1:40	Beckton-Dickinson, Mt View, Calif.
Keratin 19	RCK 108	IgG1	MW, 1:50	Dakopatts, Carpinteria, Calif.
Keratin 5*	34ßE12	IgG1	Pepsin, 1:80	Dakopatts
Keratins 5/6	D5/16 B4	IgG1	MW, 1:20	Boehringer-Mannheim, Indianapolis, Ind.
Keratin 16	LL025	IgGM	MW, 1:80	Novocastra, Newcastle, UK
Keratin 17	E3	IgG2b	MW, 1:80	Novocastra
Keratin 10	DEK10	IgG1	NT, 1:40	Biogenex, San Ramon, Calif.

* Probably includes reactivity with other high molecular weight keratins

Table 2 Distribution of keratins 19, 5 and 17 in nonneoplastic thyroid and thyroid tumours. The number of positive cells is quantified as follows: *0* no positive cells present, + scattered positive cells present amounting to less than 1%; *1* 1–10% of lesional, cells positive, *2* 10–50% of lesional cells positive *3* more than 50% of lesional cells positive)

	Positive cells found of total of cases		Quantification of positive cells				
			0	+	1	2	3
Keratin 19							
Nodular goiter	89	89	0	35	28	22	4
Papillary hyperplasia	15	16	1	15	1	0	0
Chronic lymphocytic thyroiditis	38	38	0	0	14	21	3
Follicular adenoma, non Hürthle	49	54	5	17	19	5	8
Follicular adenoma, Hürthle cell	6	7	1	4	2	0	0
Papillary carcinoma	137	137	0	0	4	3	130
Follicular carcinoma, non Hürthle	19	22	3	3	3	3	10
Follicular carcinoma, Hürthle cell	6	6	0	2	3	1	0
Keratin 5/6							
Nodular goiter	29	86	0	29	0	0	0
Papillary hyperplasia	0	16	0	0	0	0	0
Chronic lymphocytic thyroiditis	17	32	15	14	3	0	0
Follicular adenoma, non Hürthle	4	45	41	4	0	0	0
Follicular adenoma, Hürthle cell	0	8	8	0	0	0	0
Papillary carcinoma	45	57	12	34	10	1	0
Follicular carcinoma, non Hürthle	2	23	21	2	0	0	0
Follicular carcinoma, Hürthle cell	0	10	10	0	0	0	0
Keratin 17							
Nodular goiter	9	28	19	9	0	0	0
Papillary hyperplasia	0	16	16	0	0	0	0
Chronic lymphocytic thyroiditis	9	18	9	8	1	0	0
Follicular adenoma, non Hürthle	4	45	41	4	0	0	0
Follicular adenoma, Hürthle cell	0	10	10	0	0	0	0
Papillary carcinoma	29	63	34	24	4	1	0
Follicular carcinoma, non Hürthle	1	23	22	1	0	0	0
Follicular carcinoma, Hürthle cell	0	5	5	0	0	0	0

crowave oven Model no. NN-5602 (800 W, Franklin Park, Ill.). The slides were submersed in 200 ml of acidic buffer (Chem Mate HIER buffer, pH 5.5–5.7, Ventana Medical Systems). The slide holder with slides was placed in the microwave oven for 5 min on the high-energy setting. Immediately afterwards 50 ml of distilled water was added to the vessel to replenish the evaporative loss and an additional 5 min heating on the high setting was applied. The holder and slides were then removed from the oven and cooled for 20 min before the immunostaining procedure was continued.

Because Hürthle cells often gave variable background, especially following microwave-based epitope retrieval, all such cases underwent avidin–biotin block [27] (kit from Vector Laboratories) according to the manufacturer's instructions. This included consecutive incubations with avidin and biotin following the normal serum block with horse antimouse antiserum. The block eliminated the background resulting from the endogenous biotin content (avidin binding) in the Hürthle cells.

Results

The distribution of keratins K19, K5/6 and K17 in thyroid papillary and follicular lesions is discussed below and summarized in Table 2. Because the antibodies 34βE12 and D5/16B4 for keratin 5/6 showed identical patterns, the results on these antibodies are shown together in Table 2. None of the tumours studied for K10 or K16 was positive. However, all the thyroid lesions studied showed practically uniform K8 reactivity.

The goitres usually showed focal K19 reactivity. The positive areas were typically seen in follicles lined by flattened epithelia (Fig. 1) or showing squamous metaplasia. About 30% of the goitres showed more extensive K19 reactivity, which was often concentrated to areas of small or apparently atrophic follicles with attenuated epithelium.

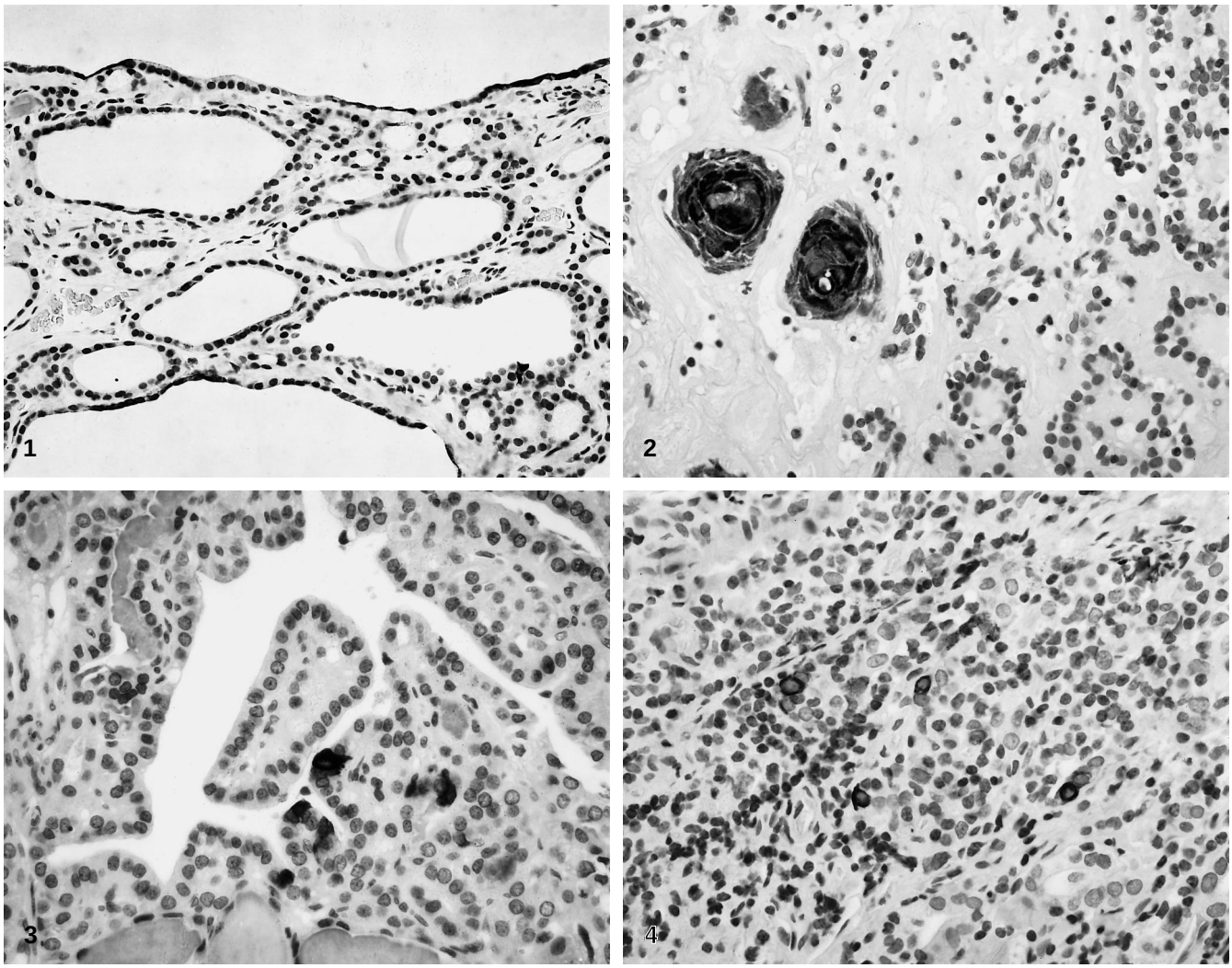
K5/6 had a markedly narrower distribution. Approximately a third of cases showed focal immunoreactivity, mostly limited to scattered cells in the flattened epithelium lining the cysts, or in small foci of well-developed

Fig. 1 Nodular goitre shows focal keratin 19 reactivity in the flattened epithelia of dilated follicles

Fig. 2 A focus of squamous metaplastic epithelia in goitre shows strong keratin 17 reactivity

Fig. 3 Papillary hyperplasia of thyroid shows sporadic keratin 19 immunoreactivity

Fig. 4 Chronic lymphocytic thyroiditis shows scattered keratin 17-positive cells



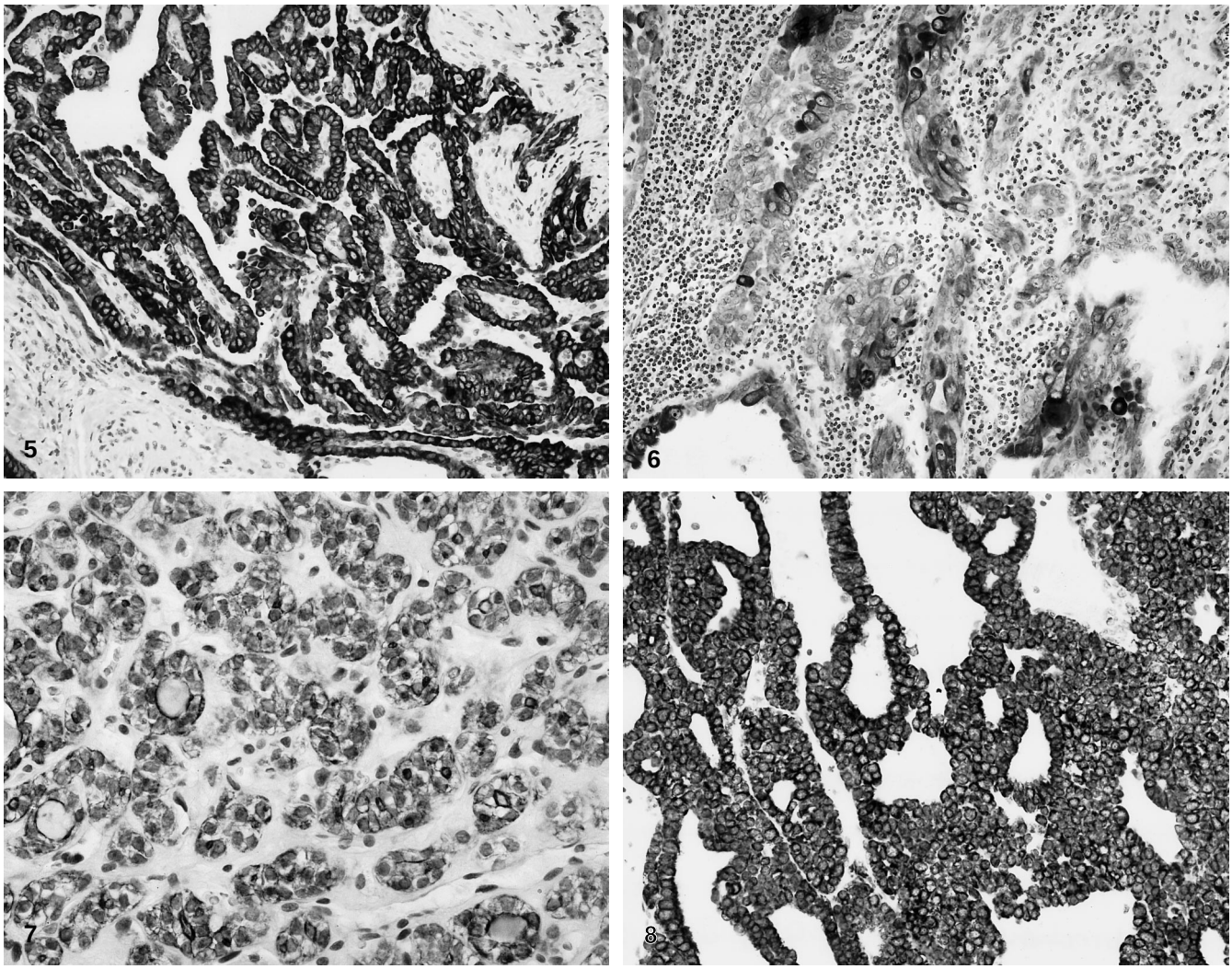


Fig. 5 Papillary thyroid carcinoma shows strong and uniform keratin 19 immunoreactivity

Fig. 6 Papillary carcinoma shows foci of keratin 5/6-positive tumour cells that have a squamoid appearance

Fig. 7 Follicular adenoma cells are keratin 19 positive, but show a delicate staining pattern

Fig. 8 All follicular carcinoma cells are strongly positive for keratin 19

squamous metaplasia. K17 showed a similar distribution, and was seen in well-developed squamous metaplasia and in some lining epithelia of cysts (Fig. 2). K16 was observed very focally in well-developed nests of mature squamous metaplastic epithelium in two cases (2/20). K10 was not identified in goitres. Cases that showed squamous metaplasia that were tested, (0/7) were all K10 negative.

The papillary hyperplasias, about half of which occurred in connection with Graves' disease, typically showed K19 reactivity limited in scattered epithelial cells (Fig. 3). Stratified epithelial keratins K5/6, K10, K16 and K17 were not identified.

Chronic thyroiditis typically showed more extensive K19 reactivity than the goitres. Strong K19 reactivity was seen in flattened and apparently atrophic epithelium, which was abundant in most such lesions. Small foci of spherical squamous-like cells often seen in the middle of lymphoid infiltrates were strongly positive for K19 and K5/6, and occasionally for K17. In addition, scattered K5/6- and K17-positive cells were present in half the cases (Fig. 4). Hürthle cell metaplasia was negative for K19, K5/6, K17, and K16. K10-positive cells were not present in thyroiditis.

Papillary carcinomas were nearly always strongly and uniformly positive for K19, irrespective of the histological appearance (Fig. 5). Papillary carcinomas of follicular type were also strongly positive. K5/6 was present focally in the areas of squamous metaplasia or in areas showing a stratification-like pattern, often with larger, squamoid-like tumour cells (Fig. 6). Infiltrative streaks of carcinoma cells in desmoplastic stroma were often K5/6 positive. These cases corresponded with diffuse sclerosing type of papillary carcinoma, or represented similar foci present in ordinary papillary carcinoma. However, cases showing exclusively papillary structures

were usually K5/6 negative. K17 was present in similar areas as K5/6, but was typically observed in a smaller number of cells. K16 and K10 were not seen in the papillary carcinomas tested (0/25).

Follicular adenomas were heterogeneous in their K19 reactivity, but positive cells were seen in most cases. Most adenomas showed either sporadic positive cells or reactivity limited to less than 10% of tumour cells. Extensive reactivity (more than 50% tumour cells positive) was seen in 15% of the cases. However, the staining showed a delicate pattern, and was always less prominent (less dense) than that seen in papillary carcinoma (Fig. 7). About 10% of adenomas showed sporadic K5/6- and K17-positive cells that were limited to degenerative areas showing evidence of squamous cell metaplasia.

All follicular carcinomas were either of a widely invasive type with conclusive evidence of vascular invasion or represented distant metastasis. Papillary carcinomas of follicular type were strictly excluded by cytohistological features that included the lack of overlapping nuclei, and lack of open chromatin pattern and lack of nuclear grooves. The follicular carcinomas were heterogeneous in their K19 expression. About 50% of the cases showed K19 reactivity in all or more than half of all of the tumour cells (Fig. 8); the reactivity was often as strong as seen in papillary carcinoma, and typically stronger than seen in K19-positive follicular adenomas. Only 3/22 (15%) of the cases were entirely negative for K19. Only rare cases showed occasional K5/6- and K17-positive cells, which were restricted to areas of squamous differentiation.

Benign Hürthle cell tumours and those malignant examples that were classified earlier as follicular carcinomas on the basis of vascular invasion or metastasis, had near-identical keratin profiles. These tumours typically showed scattered keratin 19-positive cells that were slightly more prevalent in carcinomas. Keratins 5, 17, 16 and 10 were not seen in Hürthle cell tumours. However, if avidin–biotin block was not performed, Hürthle cell tumours showed light to bright brown staining with all antibodies attributable to endogenous avidin binding in such cells, especially following microwave-based epitope retrieval.

Discussion

We have analysed the keratin subsets of thyroid papillary and follicular tumours, focusing specifically on the presence of stratified epithelial keratins in the tumours. We also studied a large number of papillary and follicular carcinomas to investigate whether the expression of K19 reliably separates these tumour types, as suggested previously [17].

While all differentiated thyroid tumours contain simple epithelial keratins K8 and 18 and K7 according to our experience and to previous studies [4], the presence of other keratins, K19 and keratins typical of stratified epithelia (K5/6, K17), appears to vary in different types of lesions. K19, the lowest molecular weight keratin (40 kDa) is widely present in simple epithelial cells, typically excluding only hepatocytes and renal tubular cells and corresponding carcinomas, while its expression is focal or restricted to basal-cells in complex and stratified epithelia [1, 9, 21]. The distribution of K19 shows significant differences in various thyroid lesions. While it is typically present only focally in goitres, often in areas of epithelial alteration such as cysts and squamous metaplasia, its expression is strong and uniform in papillary carcinoma. However, altered epithelia, including atrophic areas in thyroiditis, are also strongly positive, indicating that increased K19 expression is not specific for malignancy. Similar neo-expression of K19 in normally K19-negative simple epithelia has been described in atrophic renal tubular cells in tubulointerstitial nephritis [14] and in some pathologically altered hepatocytes in alcoholic liver cell injury [26].

With regard to the differential diagnosis between papillary hyperplasia and papillary carcinoma, our observations showing only focal K19 reactivity, if any, in the former and strong reactivity in the latter confirm the previous impressions based on frozen section material: K19 is a helpful marker in separating papillary hyperplasia from papillary carcinoma [17]. In such cases K19 may be used together with monoclonal antibody HBME-1, which typically shows no or sporadic staining in papillary hyperplasia but exhibits strong reactivity in papillary carcinoma [10]. Histochemical differential diagnosis may also be possible, as Damiani et al. [3] noted that papillary thyroid carcinomas show an apical cytoplasmic rim of alcian-blue positive acid mucopolysaccharide generally not present in papillary hyperplasia.

The finding that half of all follicular carcinomas are uniformly and strongly K19 positive indicate that K19 positivity cannot reliably be used to separate papillary and follicular carcinoma, as previously suggested [19]. We emphasize that the follicular carcinomas included in this study strictly excluded the follicular type of papillary carcinoma that reacted like other papillary carcinomas, being uniformly K19 positive. Interestingly, follicular carcinomas often show much stronger K19 reactivity than follicular adenomas, suggesting that malignant transformation increases keratin expression; a similar situation applies in papillary hyperplasia vs papillary carcinoma.

K5, together with K14 and K17, can be considered markers for stratified epithelia. They are present in basal cells of complex (stratified) glandular epithelia [12, 21, 24, 25). In normal squamous epithelia, K5 and K14 (but not K17), are present in basal cells, but they are all more widespread in squamous cell carcinomas [12, 23]. The distribution of K5/6 and K17 in non-neoplastic thyroid is limited to foci of squamous metaplasia in accordance with this concept.

The presence of stratified epithelial keratins in papillary and follicular carcinomas is markedly different. Papillary carcinomas, especially those with squamous differentiation show K5/6 and K17, but follicular carcinomas are almost uniformly negative.

Table 3 Summary of the typical main patterns of keratinpolypeptides K19,K5/6 and K17 in thyroid papillary and follicular tumours (– negative, ((+)) very rarely and focally, if ever, positive (+) rarely positive, and only focally, + focally positive, ++ widely positive)

	K19	K5/6	K17
Nodular goitre	+	(+)	(+)
Papillary hyperplasia	+	–	–
Papillary carcinoma	++	+	+
Follicular adenoma	+	(+)	(+)
Follicular carcinoma	+/++	((+))	((+))

Interestingly, infiltrating streaks of tumour cells are also often K5/6 and K17 positive, suggesting that the stromo–epithelial interaction may induce complex epithelial differentiation in these tumours. Alternatively, K5/6- and K17-positive tumour cells in papillary carcinoma may be better adapted in the microenvironment of a desmoplastic stroma.

In contrast to papillary carcinomas, follicular carcinomas (and also follicular adenomas) show a narrower spectrum of keratins and typically lack the focal K5/6 and K17 expression variably seen in papillary carcinomas. However, exceptional cases that showed focal K5/6 and K17 reactivity in squamous-like areas highlight that fact that the expression of K5/6 and K17 is related to squamous differentiation and not to the principal type of carcinoma. The typical patterns of expression of the keratins showing variable expression in thyroid tumours are summarized in Table 3.

A probable explanation for the previously observed strong reactivity of papillary but not follicular thyroid carcinoma to polyclonal antibodies to human plantar callus keratins [11, 15] can be proposed on the basis of the present results. Polyclonal keratin antibodies raised to epidermal callus keratins were typically poorly characterized in terms of their exact reactivity for individual keratins, as they antedated sophisticated biochemical analysis systems and were soon replaced by better defined monoclonal antibodies. The fact that many such antibodies, including the ones used by us, typically reacted widely with different epithelia and only excluded hepatocytes and renal tubular cells, as described by Sun et al. with similar antibodies [22], strongly suggests that such antibodies included reactivity to keratin 19 but excluded reactivity to keratins 8 and 18. It becomes obvious that these antibodies are not specific for epidermal keratins of high molecular weight and that reactivity to them does not indicate the presence of epidermal keratins in the positive tumours. Although we initially believed that the observed strong and global epidermal keratin reactivity indicated the presence of epidermal keratins in thyroid papillary carcinoma, the global reactivity of polyclonal epidermal keratin antibodies most probably results from the cross-reactivity of these antibodies with keratin 19. The variable, usually focal presence of stratified epithelial keratins in papillary carcinoma can be a contributing factor, but would not explain the strong epidermal keratin reactivity observed in all papillary carcinomas [11, 15].

Keratin 10, a high-molecular-weight keratin typically restricted to keratinizing squamous epithelia and variably present in squamous cell carcinomas [12, 18, 23], was not identified in any of the thyroid lesions we studied, including the squamous metaplasia, indicating the rarity of true epidermal differentiation in thyroid lesions. However, it has been found in frozen section material in rare papillary carcinomas [7] by some workers, although not by others [4]. Conceivably, small undetectable amounts of K10 may be present in papillary carcinomas; this may be undetectable in formaldehyde-fixed and paraffin-embedded tissue.

Hürthle cell tumours are subject to a notable immunohistochemical pitfall, namely endogenous avidin binding probably resulting from their biotin content. The endogenous biotin is particulary notable in cells such as hepatocytes and renal tubular cells, especially in frozen section immunohistochemistry. It can interfere with the interpretation of immunoreactivity unless blocked by incubation with avidin and biotin [27]. Hürthle cell tumours may appear to be immunoreactive for a wide variety of antigens, including the different keratins. Typically, pale brown staining of Hürthle cell epithelia occurs, and it is intensified by epitope retrieval, pointing out that such retrieval techniques can also enhance background by retrieving the reactivity of endogenous biotin. The elimination of this staining by avidin–biotin block confirms that such apparent immunoreactivity results from endogenous avidin binding and indicates that avidin–biotin block is necessary fur Hürthle cell tumours, especially if microwave-based epitope retrieval techniques are used.

In summary, our series shows differences in the keratin subsets in various thyroid tumours and indicates that K19 is useful in separating papillary carcinomas from papillary hyperplasia and in evaluating the complex epithelial differentiation typically restricted to papillary carcinoma among differentiated thyroid tumours. The practically useful patterns of keratins K19, K5/6 and K17 in differentiated thyroid tumours are summarized in Table 3.

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