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Coexpression of cytokeratin, neurofilament and vimentin in carcinoid tumors

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Summary. The immunohistochemical expression of intermediate filaments was investigated in 56 carcinoid tumors from 50 cases including 31 rectal and 25 non-rectal sites. Cytokeratin was the most frequently expressed in 55 of the tumours. Only one tumour of the stomach was negative for cytokeratin. Neurofilament (68 kd and 160 kd) was positive in 25 (44.6%) tumours with no preferential pattern of expression in particular tumours. Vimentin was positive in 18 out of the 31 rectal carcinoids (58%), and 3 of the 25 non-rectal carcinoids (12%). There was a significant difference in vimentin immunoreactivity between rectal and non-rectal carcinoids. The coexpression of cytokeratin and neurofilament was 44.6% and that of cytokeratin and vimentin was 37.5%. The coexpression of all three types of intermediate filament was 35.5% in rectal carcinoids, but 8% in non-rectal carcinoids. The present study revealed coexpression of cytokeratin, neurofilament and vimentin in carcinoids and an especially high incidence of vimentin expression in those of rectal origin.

Key words: Intermediate filament coexpression – Cytokeratin – Neurofilament – Vimentin – Carcinoid tumours

Introduction

Carcinoid tumours are a group of diffuse neuroendocrine tumours (Pearse 1977) which characteristically express a common neuroendocrine program, manifest by their ability to produce biologically active neuroamines, peptides, neuron-specific enolase, chromogranin (Kimura et al. 1988) and synaptophysin (Gould et al. 1987; Miettinen et al. 1987). Although it has not been emphasized it has been noticed that there are large numbers of filaments in the cytoplasm of these tumours, when examined by electron microscopy (Pearse 1969).

While earlier studies suggested that the intermediate filaments of carcinoid tumours belonged to only one biochemical class, either neurofilament (Lehto et al. 1984) or cytokeratin (Gown and Vogel 1985; Miettinen et al. 1985) recent evidence from several laboratories indicates that the tumours might be able to coexpress both types of filament within the same cell (Blobel et al. 1985; Moll et al. 1986).

The analysis of intermediate filaments should give a further insight into the neoplastic process, and also clarify the characteristics of carcinoid tumours. Rectal carcinoid occurs at a high frequency and has a unique marker in prostate specific acid phosphatase, which is rarely seen in carcinoids at other sites (Kimura and Sasano 1986; Sobin et al. 1986). This study was designed to see what kind of intermediate filament was expressed in carcinoid tumours and whether there was any difference between rectal and non-rectal carcinoids.

Materials and methods

The study group of 56 carcinoid tumours from 50 cases consisted of 31 rectal, 13 gastric and small intestinal, 5 bronchial, 2 ovarian and 2 testicular, and 1 each of appendicular, epipharyngeal and uterine origin. Most of the specimens were removed surgically, but 2 rectal, 1 gastric and 2 bronchial cases were obtained by autopsy. The size and depth of the invasion of examined tumours are summarized in Table 1. Four cases, including 2 rectal, 1 gastric & 1 of ileal origin were multiple.

Formalin-fixed, paraffin-embedded materials were cut serially at 2.5 μm and stained with haematoxylin-eosin, Grimelius's argyrophil and occasionally Masson-Fontana's argentaffin reactions.

Immunoperoxidase staining was performed using the biotin streptavidin technique and a commercial kit (BioGenex Lab,

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Table 1. Intermediate filaments in carcinoid tumours

Case	Size (cm)	Invasion	Cytokeratin	Neurofilament	Vimentin	Comments
Rectum						
1. [1]	0.8	sm	+	+++	−	multiple
[2]	0.8	sm	+	+	−	
[3]	0.5	sm	++	+	−	
[4]	0.3	sm	+	++	−	
2.	1.0	sm	+++	−	+++	
3.	1.0	sm	+++	+++	+++	
4.	1.0	sm	+++	++	+++	
5.	0.5	sm	+++	+	+++	
6.	0.3	sm	++	−	+++	
7.	1.1	sm	++	++	+++	
8.	2.0	sm	++	+	+++	
9.	0.5	sm	++	−	−	
10.	2.0		+++	+	−	autopsy
11.	0.1	sm	+	−	−	
12.	9.0	a	+	+++	+++	liver metastasis
13.	0.1	sm	+++	−	+++	
14.	1.0	sm	+	+++	+++	
15.	1.0	sm	+++	−	+++	
16.	1.5	sm	+	−	+++	
17. liver	10.0		++	+++	++	died of multiple metastases
kidney	2.0		++	+++	+++	
18.	1.3	sm	+	+++	−	
19.	1.0	sm	++	−	+	
20.	0.8	sm	+++	−	−	
21.	0.3	sm	+	−	−	
22.	0.4	sm	+++	−	−	
23.	0.2	sm	+	−	+++	
24.	0.5	sm	+++	+	+	
25.	0.5	sm	++	−	−	
26.	2.4	pm	+++	+++	+++	
27.	0.2	sm	+++	−	−	multiple
Stomach and Small Intestine						
1.	2.0		+++	++	+	died of multiple metastases
2.	2.0	sm	+	−	−	
3.	2.0	sm	+	−	−	
4. [1]	0.3	sm	+++	−	−	multiple
[2]	0.3	sm	+++	−	−	
[3]	0.2	sm	+++	−	−	
5.	1.0	sm	+++	+++	−	
6.	2.0	sm	−	−	−	
7.	1.0	sm	+++	+++	−	
8.	0.2	sm	+++	−	−	
9.	2.0	sm	+++	−	−	lymph node metastasis
10.	1.0	sm	+	−	−	multiple
Appendix						
1.	1.0	sm	+++	−	−	
Lung						
1.	2.0		+++	+++	++	ACTH producing with lymph node metastasis
2.	2.7		+++	+++	−	
3.	2.0		++	−	−	died of multiple metastases
4.	1.0		+++	+	−	died of multiple metastases
5.	2.0		++	−	−	
Epipharynx						
1.	1.0		+++	−	−	

Table 1 (continued)

Case	Size (cm)	Invasion	Cytokeratin	Neurofilament	Vimentin	Comments
Ovary						
1.	9.0		+ + +	−	−	
2.	2.0		+ + +	−	+ + +	strumal carcinoid
Uterus						
1.	3.0		+ + +	+ + +	−	combined with endocervical adenocarcinoma
Testis						
1.	2.5		+ + +	+ +	−	
2.	3.0		+ + +	−	−	

+ + +: over 50% are positive; + +: 10–50% are positive; +: under 10% are positive
sm: submucosal layer; pm: propria muscularis; a: adventitia

Dublin, CA). Mouse monoclonal antibodies for cytokeratin, which react to 40, 46, 50, 52, 56.6, 58, 65–67 kd cytokeratins (BioGenex Lab, Dublin, CA) and vimentin (Boehringer, Manheim, FRD) were obtained commerically. The preparation of neurofilament proteins of 68 kd and 160 kd and their antibodies is described elsewhere (Nakazato et al. 1984). In summary, neurofilament proteins were obtained from human spinal nerve roots. Each neurofilament protein was emulsified with Freund's complete adjuvant and injected into New Zealand white rabbits. The specificity of the antiserum was examined by Ouchterlony's double diffusion test. Each antiserum was absorbed with normal human serum by affinity chromatography for immunohistochemical staining. The working dilution of both neurofilaments was 1:3000.

Endogenous peroxidase was blocked with methyl alcohol and hydrogen peroxide. Normal rabbit serum for monoclonal antibodies and normal goat serum for polyclonal antibodies were used to decrease the background. Cytokeratin and vimentin antibodies required treatment for the tissue with 0.1% trypsin in phosphate buffered saline (pH 7.8) for 1 h at 37° C before incubating the antibodies. All primary antibodies were incubated for 18 h at 4° C. The colour reaction was developed with diaminobenzidine. Sections were counterstained with methyl green and mounted in permount. Each series of immunostaining included positive controls (for cytokeratin, sections from rectum, for vimentin, sections from connective tissue, for neurofilaments, sections from peripheral nerve). Negative controls included slides for which the primary antibody had been omitted.

Results

All tumours showed the typical features of carcinoids with trabecular, insular or glandular structures (Fig. 1). Grimelius's argyrophilic reaction was characteristically observed in all tumours. Some lesions of the rectum and epipharynx showed some mucin production.

Cytokeratin and vimentin were observed diffusely in the cytoplasm, however, staining of the 68 kd neurofilament was observed in dot-like or peri-nuclear clumps or tufts around the nucleus. The staining of 160 kd neurofilament was observed to be more intense and more widely evident around the nucleus than that of 68 kd.

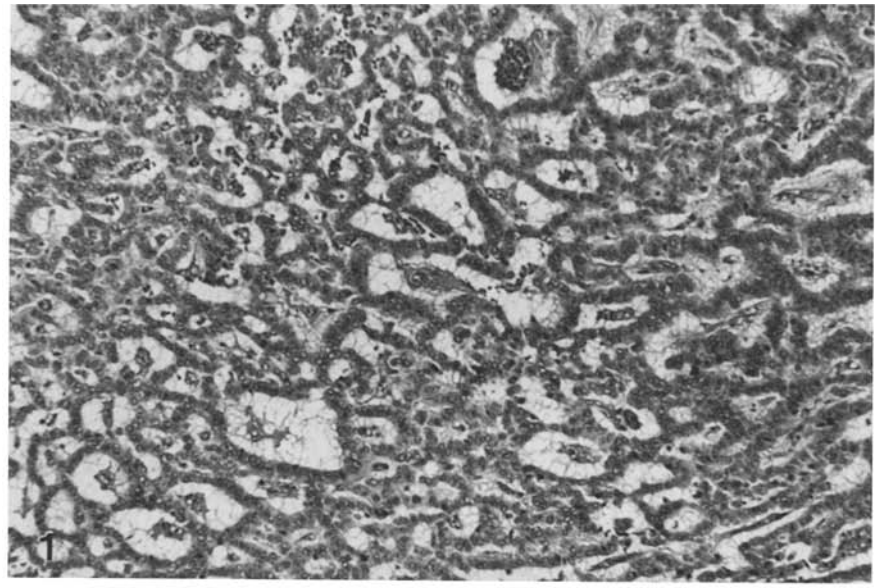
Table 2. Expression of intermediate filaments in carcinoid tumours

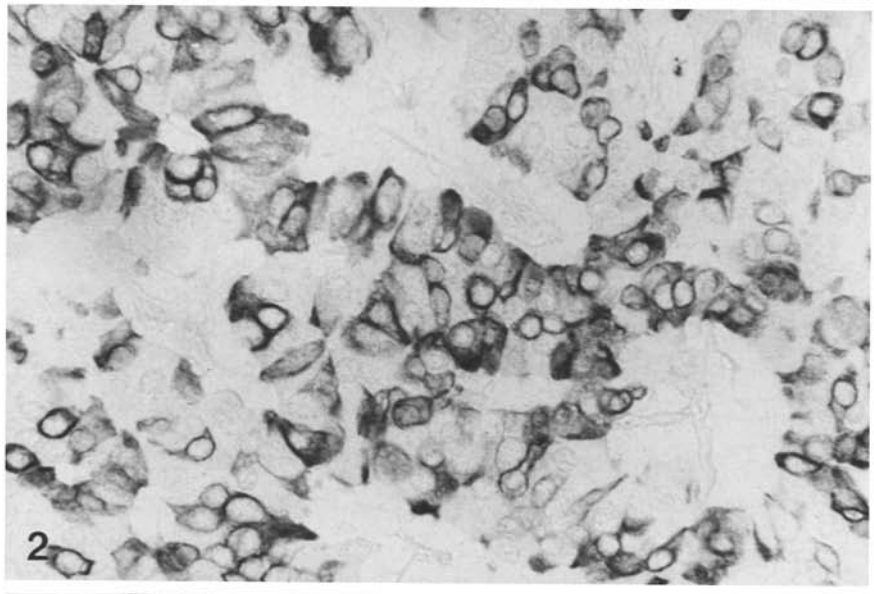
Location	Cytokeratin		Neurofilaments		Vimentin	
Rectum ($n=31$)	31	(100%)	17	(54.8%)	18	(58.1%)
Stomach and Small intestine ($n=13$)	12	(96%)	3	(32.0%)	1	(12.0%)
Appendix ($n=1$)	1		0		0	
Lung ($n=5$)	5		3		1	
Epipharynx ($n=1$)	1		0		0	
Ovary ($n=2$)	2		0		1	
Uterus ($n=1$)	1		1		0	
Testis ($n=2$)	2		1		0	
Total ($n=56$)	55	(98.2%)	25	(44.6%)	21	(27.5%)

The pattern of reactivity of different tumours with the individual members of the antibodies was defined as follows: + + +, positive cells were over 50%, + +, indicated a sub-population of the tumour cells ranging 10 to 50% and +, a minor fraction of the tumour cells (<10%) displayed immunoreactivity.

The results are summarized in Table 2, in which the tumours are grouped according to their patterns of reactivity with the panel of antibodies. Because 68 kd and 160 kd neurofilament proteins occurred in the same cell, the results are presented only with reference to the neurofilament.

For the rectal carcinoids 22 of 31 tumours (71%) were less than 1.0 cm in diameter and 26 tumours (84%) were localized in submucosal layer. Two cases died of multiple metastases. Two other cases had multiple tumours. Immunohistochemical





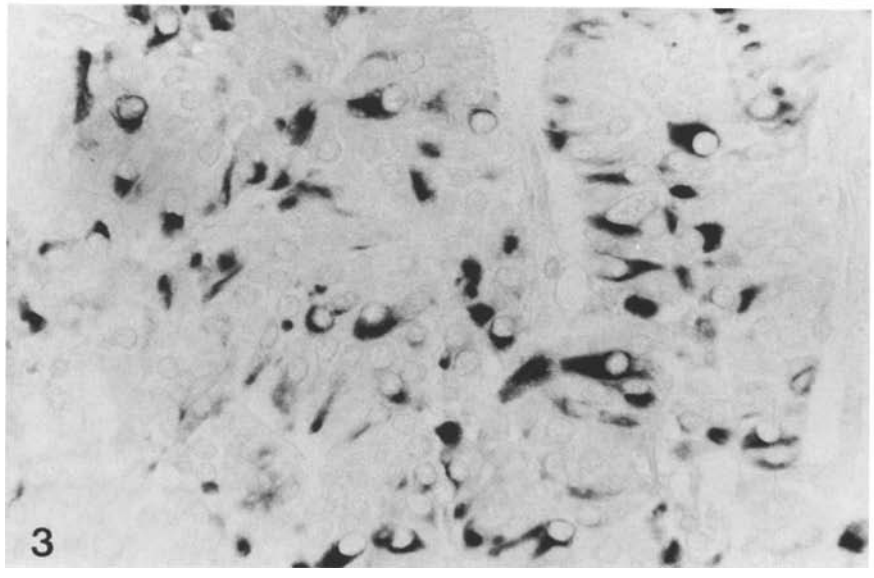


Fig. 1. Rectal carcinoid, case 26 showing a trabecular pattern (H & E, ×60)

Fig. 2. Same case as figure 1 showing cytokeratin immunoreactive cells. Cytokeratin is detected diffusely in cytoplasm (+++) (ABC, counterstained with methyl green, ×400)

Fig. 3. Same case as figure 1 showing immunoreactive cells for 160 kd neurofilament (+++) (ABC, counterstained with methyl green, ×400)

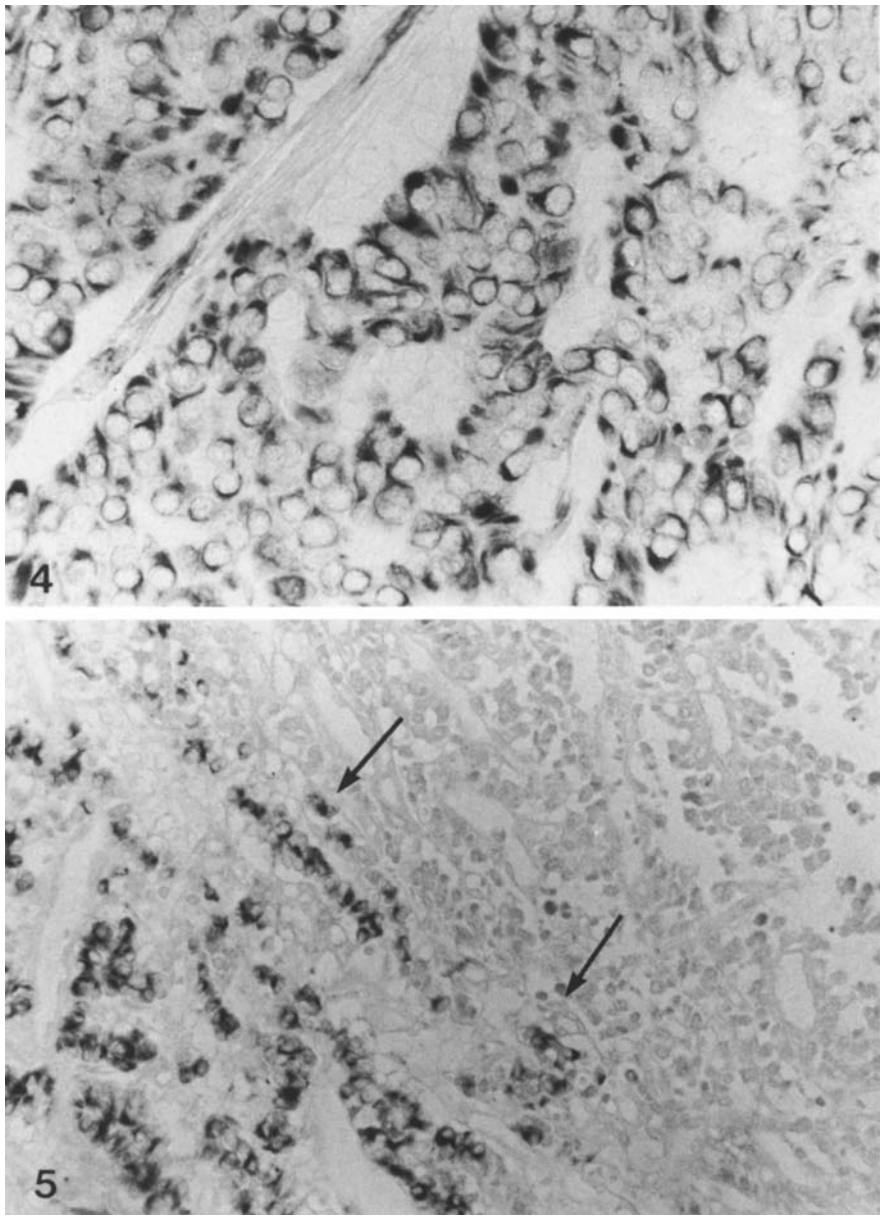


Fig. 4. Same case as Fig. 1 showing immunoreactive cells for vimentin (+ + +) (ABC, counterstained with methyl green, ×400)

Fig. 5. Bronchial carcinoid, case 2 showing 160 kd neurofilament protein immunoreactive cells. Outer area (arrow) of the tumour is strongly positive but the inner area is negative or sporadically positive to 160 NF. (ABC, ×60)

staining revealed that all of these tumours had cytokeratin positive cells, and, neurofilament and vimentin were also observed in 17 (55%) and 18 (58%) of the tumours, respectively. Eleven tumours (36%) showed immunoreactivity to all 3 types of antibodies; cytokeratin, neurofilament and vimentin. Five (16%) were immunoreactive to both cytokeratin and neurofilament but were negative to vimentin. Seven (23%) were positive to both cytokeratin and vimentin but negative to neurofilament. Seven (23%) reacted only to cytokeratin.

Although all three types of intermediate filament were observed simultaneously in some tumour cells, most showed a heterogeneous distribution of immunoreactivity; some areas were strongly reactive to neurofilament but were weak or negative to cytokeratin and vimentin. The reverse of this phenomenon was also true in some areas (Figs. 2, 3, 4). In general, the immunoreactive cells to the same antibody were grouped in part, but they were sometimes intermingled with other cells which reacted to the different antibodies. There was no relationship between the expression of the types of intermediate filament and size or depth of invasion of the tumours.

Normal mucosa of the rectum, small intestine

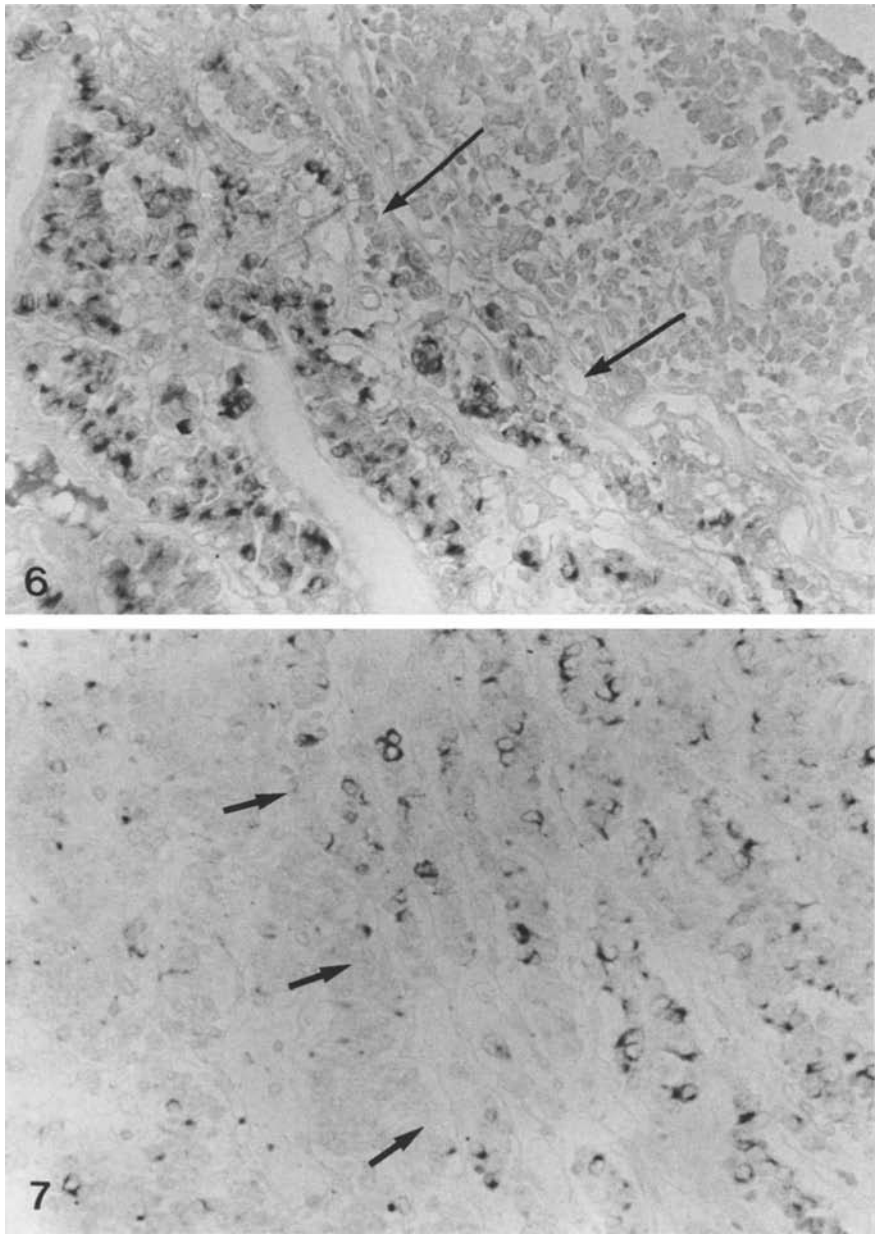


Fig. 6. Bronchial carcinoid, case 2. Neurofilament protein 68 kd is detectable in the same area (arrow) as shown in Fig. 5 (ABC, ×60)

Fig. 7. Bronchial carcinoid, case 2. Cytokeratin is strongly immunoreactive in the inner (arrow) area but negative in the outer area. Distribution of the immunoreactive cells shows heterogeneity. Figs. 5, 6, 7 were serially cut (ABC, ×60)

and stomach adjacent to the tumours was strongly stained by cytokeratin antibody. They reacted negatively to neurofilament and vimentin antibodies.

One patient with a stomach tumour died of multiple metastases. Two stomach tumours had lymph node metastases. Two of the stomach and two of the ileal tumours were multiple. The size ranged from 0.2 to 2.0 cm in diameter.

Only 1 of the stomach tumours was negative to cytokeratin, as were the normal pyloric glands adjacent to the tumours. The other 12 were positive to cytokeratin (92%), neurofilament was observed in 3 tumours (23%) but only 1 autopsy case with multiple metastases was positive for vimentin (8%).

In the lung cytokeratin was observed in all 5 tumours. Neurofilament was positive in 3 cases (60%). An heterogeneous distribution of immunoreactivity was remarkable; cytokeratin was strongly demonstrated in some areas but was weakly immunoreactive in others. Neurofilaments of both 68 kd and 160 kd were strongly positive in the area staining weakly for cytokeratin but negative in strongly positive areas (Figs. 5, 6, 7). Vi-

Table 3. Coexpression of intermediate filaments in carcinoid tumours

	CK+NF	CK+V	CK+NF +V
Rectum ($n=31$)	17 (54.8%)	18 (58.1%)	11 (35.5%)
Non-rectum ($n=25$)	8 (32%)	3 (12%)	2 (8%)
Total ($n=56$)	25 (44.6%)	21 (37.5%)	13 (23.2%)

Abbreviations: CK, cytokeratin; NF, neurofilament proteins; V, vimentin

mentin immunoreactivity was observed only in an atypical carcinoid which produced ACTH with Cushing's syndrome.

Cytokeratin was detectable in all tumours derived from epipharynx, ovary, uterus and testis. Neurofilament was detected in a uterine and a testicular carcinoid. (the uterine carcinoid was combined with endocervical adenocarcinoma). Although cytokeratin was observed in both the carcinoid tumour and uterine adenocarcinoma, neurofilament was detectable only in a part of the carcinoid tumour. Vimentin was detectable only in the strumal carcinoid of the ovary.

Cytokeratin reactivity occured at the highest frequency and neurofilament was sometimes coexpressed in carcinoid tumours. Although vimentin was found in rectal carcinoids, it was very rare at other sites. The coexpression of those filaments is summarized in Table 3.

Discussion

The immunological features of the intermediate filaments of tumour cells are those of their tissue of origin. It can be seen, therefore, that during neoplastic transformation, there are no major changes in the synthesis of intermediate filament proteins when compared with normal tissues (Gabbiani et al. 1981). A panel of monoclonal antibodies for human intermediate filament proteins can distinguish carcinomas unequivocally (Altmannsberger et al. 1984), melanomas (Leader et al. 1987) and lymphomas (Gown and Vogel 1985). Neural (Lehto et al. 1983a; Trojanowsky et al. 1984; Trojanowsky and Lee 1985) and neuroendocrine (Gown and Vogel 1985) tumours can be identified with the anti-neurofilament antibody. Recently published observations have indicated that cytokeratin-neurofilament coexpression is characteristically found in a number of neuroendocrine neoplasms including Merkel cell tumours (Mull et al. 1986), carcinoid tumours, small cell carcinomas, pancreatic islet cell tumours (Gown and Vogel 1985; Miettinen et al. 1985) and medullary thyroid carcinomas (Gould et al. 1987; Schroeder et al. 1986). However only one type of cytokeratin (Biobel et al. 1985; Miettinen et al. 1985; Van Muijen et al. 1984) or neurofilament (Lehto et al. 1983b; Lehto et al. 1984) has been detected in those groups of tumours. We have found that cytokeratin is universally present in all carcinoid tumours derived from various organs though intensity and distribution of immunoreactivity varies case by case. Only one tumour was negative for cytokeratin and this may have another subtype of cytokeratin not recognized by the antibody used in the present study. In normal human epithelia and carcinomas, 19 different cytokeratins have been identified and catalogued by their positions on two-dimensional gels (Moll et al. 1982).

Neurofilament expression was observed in 45% of carcinoid tumours in the present study. The antibodies used here were anti 68 kd and 160 kd. In neurons, the 68 kd protein forms the backbone of the filament, the 200 kd protein is periodically arranged in a more peripheral position. The 145 kd protein is revealed almost continuously along the filament (Sharp et al. 1982). In neoplasms of neurons, the largest number react with the antibody to 68 kd and the least with the antibody to 200 kd (Mukai et al. 1986). It is possible to detect tumour cells in which the 68 kd subcomponent exists by itself, but no tumour cells in which the 150 kd or 200 kd subcomponent exist alone have been detected (Mukai et al. 1986). In the present study, both 68 kd and 160 kd were observed in the same tumours, however, immunoreactive sensitivity was better with 160 kd than 68 kd, which may be dependant on the source of the antibodies. The occurrence of neurofilament proteins in many carcinoids is difficult to explain, since they were not detected in all of the corresponding normal tissues (the endocrine cells in the alimentary tract). It might be considered that in some tumours, the neurofilament can be formed *de novo* in the process of neoplastic transformation – as seen for chromogranin (Wiedenmann et al. 1986).

It is not easy to evaluate vimentin as a tumour marker. The earlier studies showed that vimentin was a sensitive and specific marker of mesenchymal derivation or differentiation (Leader et al. 1987). Although mature epithelial cells do not express vimentin in the cytoplasm, the coexpression of vimentin and cytokeratin has been observed in parietal endoderm cells of the early mouse embryo (Lane et al. 1983). It is also true that immature muscle cells (Bennett et al. 1979) and glial cells (Franke et al. 1981) express vimentin, which is later

replaced by the mature tissue specific intermediate filament type, desmin and glial fibrillary protein respectively. Vimentin is the first intermediate filament to appear in primitive cells and it may be a marker of immaturity as well as of mesenchymal origin.

The coexpression of cytokeratin and vimentin has been reported in the tumours of the kidney (Herman et al. 1983), salivary gland (Caselitz et al. 1981; Caselitz et al. 1984), thyroid gland (Buley et al. 1987) and in cells of epithelial origin present in effusions (Ramaekers et al. 1983). The coexpression of three types of intermediate filaments, cytokeratin, vimentin and neurofilament has been observed in the normal choroid plexus (Kasper et al. 1986) which is of neuroectodermal origin. In tumours, this phenomenon has been observed occasionally only in medullary thyroid carcinomas (Domagula et al. 1988; Schroeder et al. 1986).

The coexpression of three types of intermediate filaments in rectal carcinoids occurred in 11 of 31 tumours (36%) and vimentin positive cells were demonstrated in 18 tumours (58%). In nonrectal carcinoids, tumours immunoreactive for all three types and for vimentin were 2 of 25 (8%) and 3 of 25 (12%) respectively. Thus rectal carcinoids show some characteristic features for the expression of vimentin. It might be said that rectal carcinoids have a multi-directional ability or an undetermined directional program. This hypothesis is supported by other evidence that they produce multiple hormones (O'Brain et al. 1982) and have a high frequency of expression of prostate specific acid phosphatase (Kimura and Sasano 1986; Sobin et al. 1986) findings not common in carcinoids at other sites.

According to Godwin's analysis (Godwin 1975) of the incidence of carcinoid tumours, based on a large sample of the United States population, the most common sites were the appendix, 1,160 (65.7%), rectum, 400 (22.7%) and ileum 336 (11.8%) between 1950 and 1971. In a Japanese analysis (Sasano et al. 1984) however, of 270 carcinoid tumours from 1977 to 1981, 230 tumours (85.2%) were found in the rectum, and 12 were in the appendix (4.4%). This difference in the incidence of organs affected may be explained by the progress of endoscopic examination, in addition to differences between the races examined. However, rectal carcinoid still has a high incidence in both USA and Japan and further characterisation is of value to pathologists.

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