

# Medullary carcinoma of the thyroid with carcinoid-like features

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## Abstract

**Aims:** To show that medullary carcinomas of the thyroid are morphologically indistinguishable from gut carcinoids: the value of histochemistry in their identification and differential diagnosis from metastatic carcinoid tumours to the thyroid and some follicular cell neoplasms.

**Methods:** 15 thyroid medullary carcinomas with features of gut carcinoids were histochemically studied for the presence of argyrophil and argentaffin granules, and calcitonin, thyroglobulin, and serotonin immunoreaction.

**Results:** Histological features of midgut (classic) carcinoids were observed in two tumours, foregut carcinoids in 12, and hindgut carcinoids in one. All tumours showed, to a greater or lesser extent, a calcitonin immunoreaction and argyrophilia. These markers were present only in a small area showing a classic pattern of thyroid medullary carcinoma in the hindgut carcinoid-like neoplasm. Argentaffin granules and serotonin immunostaining occurred in occasional cells from four foregut carcinoid-like tumours. Thyroglobulin was not expressed in all cases and amyloid stroma was expressed in three.

**Conclusions:** In some cases a diagnosis of metastatic carcinoid tumour to the thyroid can be considered only after ruling out clinically and histochemically medullary carcinoma of the thyroid. Immunolocalisation techniques are also essential for the differentiation between medullary carcinoma and thyroid follicular cell neoplasms that resemble carcinoid tumours. It is proposed that this tumour variant to be incorporated into current classifications as another histological subtype of C cell carcinoma.

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Medullary carcinoma of the thyroid (MCT) was recognised as a true clinicopathological entity in 1959 by Hazard, Hawk, and Crile,<sup>1</sup> and its importance as a separate type of thyroid tumour originating from the parafollicular cells was suggested by Williams in 1966.<sup>2</sup> Solid nests of polygonal, round, or spindle-shaped cells surrounded by fibrous tissue and amyloid deposition were originally considered to be important histological features of MCT.<sup>1,3,4</sup> Lately, C cell tumours resembling papillary,<sup>5</sup> follicular,<sup>6,7</sup> and undifferentiated carcinomas of the thyroid<sup>8,9</sup> have been recognised.

Early studies implied that MCT might resemble gut carcinoids on cytochemical, ultrastructural, and clinical grounds.<sup>4,10,11</sup>

Morphologically, trabecular, ribbon, palisading, insular, or carcinoid patterns have been described in MCT,<sup>1,3,4,12,13</sup> and a differential diagnosis from rare carcinoid tumours metastatic to the thyroid was considered.<sup>12,14,15</sup>

We studied MCTs showing histological features indistinguishable from gut carcinoids to find out the value of immunohistochemistry in their identification and in their differential diagnosis from metastatic carcinoid tumours to the thyroid and some follicular cell neoplasms.

## Methods

Fourteen of the 15 MCTs studied were found in a review of 122 thyroid C cell carcinomas available from the National Board of Health and Welfare in Sweden. Clinical data of the patients are summarised in table 1. One of the cases was found in a review of 179 non-MCTs from the Swedish Cancer Registry. No clinical details were available in this 68 year old woman (case 15).

Representative, formalin fixed, and paraffin wax embedded tissue from each case was selected for histological and histochemical evaluation. In 13 cases the primary tumour was analysed, while in the other two cases (cases 7 and 13) only metastatic tumour in lymph nodes of the neck was available. The cases were stained with haematoxylin and eosin, Alcian blue (pH 2.5)-PAS diastase method (14 cases), slightly modified Grimelius argyrophil,<sup>16</sup> and Masson argentaffin silver techniques,<sup>17</sup> and Congo red for amyloid. Further sections were immunostained for the demonstration of thyroglobulin, calcitonin, and serotonin (13 cases) using the biotin-avidin complex method (Vectastain, Vector Labs, Inc., USA) with diaminobenzidine as chromogen. Polyclonal antisera to thyroglobulin (Dakopatts, Copenhagen, Denmark, code A251) and calcitonin (Immuno Nuclear Corporation, Stillwater, Minnesota, USA, code 207), and monoclonal antibody to serotonin (Sera-Lab, Ltd, Crawley Down, Sussex, England, code MAS 055), were used at dilutions of 1 in 15 000, 1 in 600, and 1 in 800, respectively. The sections were incubated overnight at room temperature. Follicles and C cells from tumour free background thyroid and normal human gastric antrum were used as positive controls. In control tests where the primary antiserum was substituted by neutral serum, immunostaining was absent. Negative immunostaining also occurred when the relevant antigen was added to the diluted antiserum for 24 hours at 4°C prior to incubation with the sections.

The tumours were histologically diagnosed as MCT based on the WHO system<sup>18</sup> and then grouped histologically according to current

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Table 1 Clinical data of 14 patients with MCT

Case No	Sex/Age	Initial complaint	Clinical type	Follow up
1	F 67	Mass in neck	Sporadic	13 y: hypercalcaemia
2	M 52	Mass in neck	Sporadic	7 y: death not related to tumour
3	F 54	Mass in neck	Sporadic	1 y: death with disseminated tumour
4*	M 34	Mass in neck	MEN 2b	7 y: death with disseminated tumour
5	M 37	Mass in neck	Sporadic	26 y: alive and free of disease
6	F 63	Mass in neck	Sporadic	3 y: death with disseminated tumour
7	F 78	Mass in neck	Sporadic	2 y: alive with metastatic disease
8	F 57	Mass in neck	Sporadic	8 y: death with disseminated tumour
9	F 30	Mass in neck	Sporadic	16 y: alive and freed of disease
10	F 73	Mass in neck	Sporadic	2 y: death with disseminated tumour
11	F 69	Mass in neck	Sporadic	5 y: alive and free of disease
12	F 51	0.5 cm tumour found on screening	Sporadic	16 y: hypercalcaemia
13	M 75	Mass in neck	Sporadic	12 y: alive with metastatic disease
14	F 68	Mass in neck	Sporadic	3 y: alive with metastatic disease

\* Mucosal neurinomas and bilateral pheochromocytoma present.

classifications of gut carcinoids,<sup>19 20</sup> namely, anastomosing solid islands and nests surrounded by fibrohyaline stroma as for classic midgut carcinoids; a tendency to a trabecular pattern as for hindgut carcinoids; and a wide architectural variety such as trabecular, palisading, lobular, ribbonny and glandular (tubular and rosette-like) patterns as for foregut carcinoids. The latter group also included the pattern seen in the so-called atypical carcinoid (central necrosis, cell atypia, and high mitotic rate).

## Results

### HISTOLOGICAL FINDINGS

MCT from cases 1 and 2 showed histological features of midgut (classic) carcinoids (table 1). The tumours were composed of round to polygonal cells showing clear or slightly eosinophilic cytoplasm with uniform nuclei, and arranged in solid islands, and anastomosing nests surrounded by fibrohyalinising septa (fig 1). Sometimes a palisading pattern occurred as well as occasional glandular lumens within solid islands (insular pattern) (fig 1).

In case 3 the tumour resembled a hindgut carcinoid both histologically and histochemically because it was largely composed of cells with abundant cytoplasm and regular nuclei forming trabeculae, as well as some tubular structures lined by tall cells and nests surrounded by delicate fibrous stroma (fig 2). The cells did not stain for calcitonin and argyrophil granules and no amyloid stroma was present. Only about 10% of the tumour showed typical histological and histochemical features of MCT, including amyloid and calcitonin immunostaining (fig 8).

The other 12 tumours showed a variety of patterns as seen in foregut carcinoids. They were often composed of round to oval and polygonal cells with regular nuclei arranged mainly in lobular, nesting, and trabecular structures usually surrounded by delicate fibrous stroma (fig 3–5). Ribbonny and cribriform patterns predominated in two cases (fig 4), a palisading arrangement of tumour cells occurred in another two cases (figs 3 and 6) and glandular structures in four (fig 3). Some giant cells with pleomorphic nuclei were observed in one tumour. Oxyphilic cells pre-

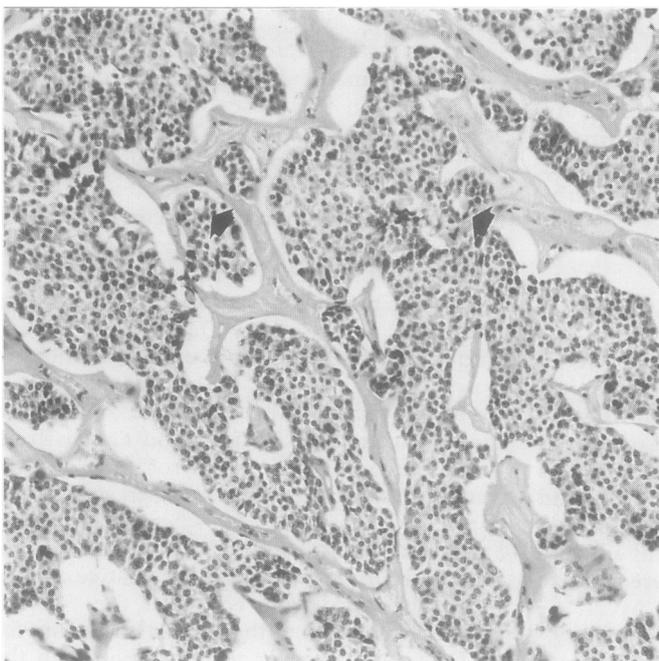


Figure 1 Case 1: solid anastomosing nests composed of round regular cells and surrounded by delicate amyloid-free hyaline stroma with thin-walled vessels. Glandular structures within solid islands are arrowed (haematoxylin and eosin).

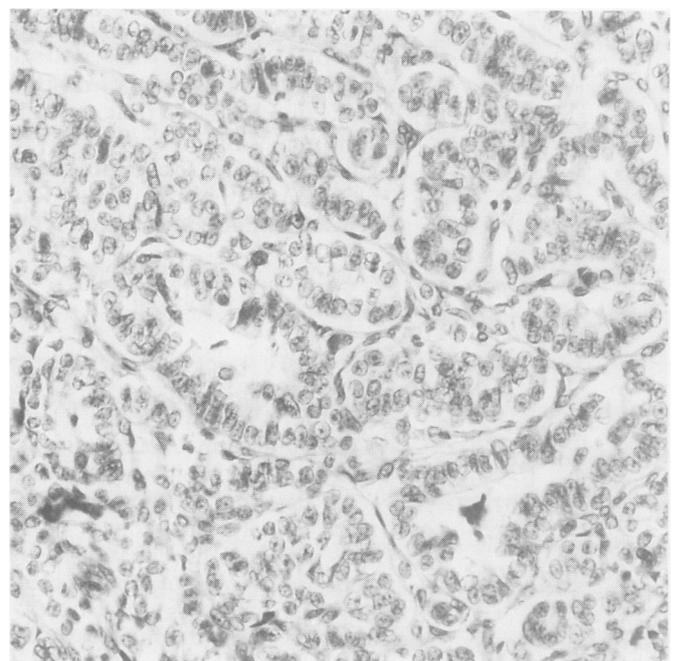


Figure 2 Case 3: trabecular and tubular structures lined by tall clear cells and surrounded by delicate fibrous stroma (haematoxylin and eosin).

Table 2 Semiquantitative analysis of the degree of cellular staining and extent of amyloid deposits in 15 cases of MCT

Case No	Amyloid	Argyrophil granules	Calcitonin	Argentaffin granules	Serotonin
1	**	++	++	-	-
2	*	+++	+++	-	-
3	*	+	+	-	-
4	**	++++	+	+	+
5	***	++++	++	+	-
6	*	++++	+++	-	-
7	-	+	+++	-	-
8	**	++++	+++	-	-
9	**	+++	+++	+	+
10	-	++++	++++	-	-
11	**	++++	++++	+	-
12	*	++	++++	-	+
13	**	++++	++	-	+
14	-	++++	++++	-	-
15	*	++++	+++	-	-

- = negative staining; + = 1-5% cells; ++ = 5-25%; +++ = 25-50%; ++++ = > 50%.  
 - = absent; \* = isolated focus; \*\* = few foci or small areas; \*\*\* = large areas.

dominated in three cases; in one of them (case 10) they were arranged in solid islands with central necrosis and showed a high mitotic rate, resembling an atypical bronchial carcinoid (fig 5). Case 15 showed large pseudoglandular structures with papillary infoldings lined by multiple layers of neoplastic cells resembling pancreatic islet cell tumours (fig 7). Cases 4, 6, and 11 showed typical features of MCT in about 60%, 15%, and 20% of the tumour area, respectively.

#### HISTOCHEMICAL AND IMMUNOHISTOCHEMICAL FINDINGS

Congo red positive amyloid stroma showing green birefringence after polarisation was usually present in small amounts in 12 tumours. It was restricted to areas showing typical features of MCT in cases 3, 4, 6 and 11 from this series (table 2). Foci of calcium deposition occurred in seven tumours, in four of them it was partially related to amyloid deposits. All cases showed variable argyrophilia. Argentaffin granules and acid mucin were detected in isolated cells from four and five MCTs with features of foregut carcinoids, respectively (table 2).

All tumours showed a variable grade of cellular calcitonin reaction (table 2). The staining intensity was usually stronger in areas showing the typical pattern of medullary carcinoma (figs 6 and 8). A positive reaction was also observed in amyloid deposits. In case 3 calcitonin immunoreactivity and argyrophilia were negative in the areas showing a hindgut carcinoid pattern and strongly positive in the areas with typical features of MCT (fig 8). Serotonin immunoreaction was present in occasional cells from four tumours with features of foregut carcinoids, two of them showed occasional argentaffin cells as well (table 2). Thyroglobulin immunoreactivity was not observed in neoplastic cells but it was identified in normal trapped thyroid follicles at the periphery and in fibrous strands of eight tumours. In five cases the tumour cells near to normal thyroid follicles stained weakly positive for this glycoprotein.

#### Discussion

The differential diagnosis of MCT has been complicated in the past few years by the wide spectrum of morphological variants described

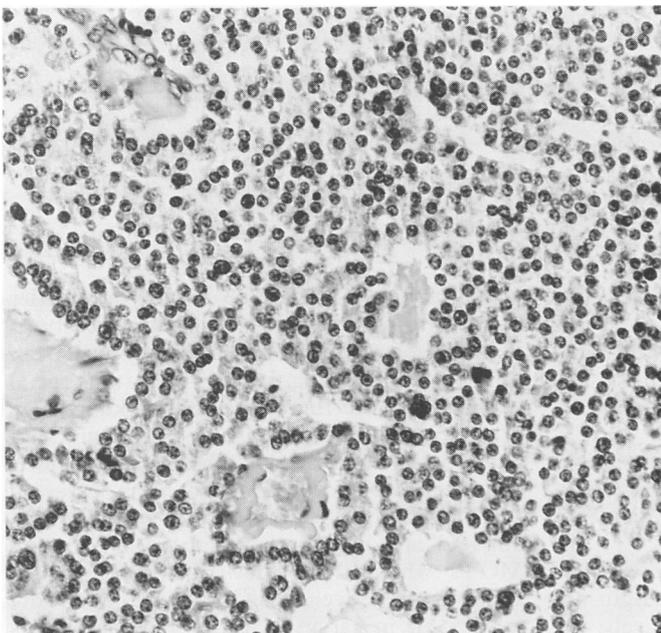


Figure 3 Case 5: neoplastic round cells with regular nuclei arranged in a solid pattern and forming few glandular structures. Note palisading of some peripheral neoplastic cells (haematoxylin and eosin).

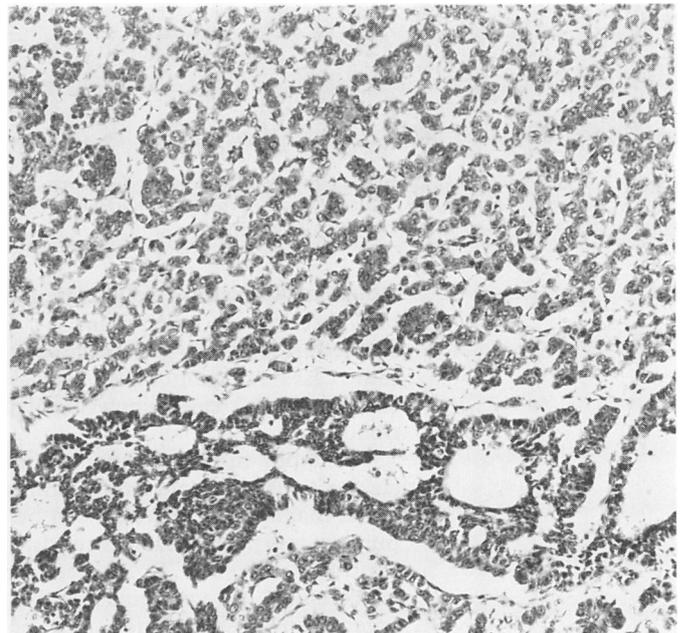


Figure 4 Case 7: cribriform and ribbon patterns (haematoxylin and eosin).

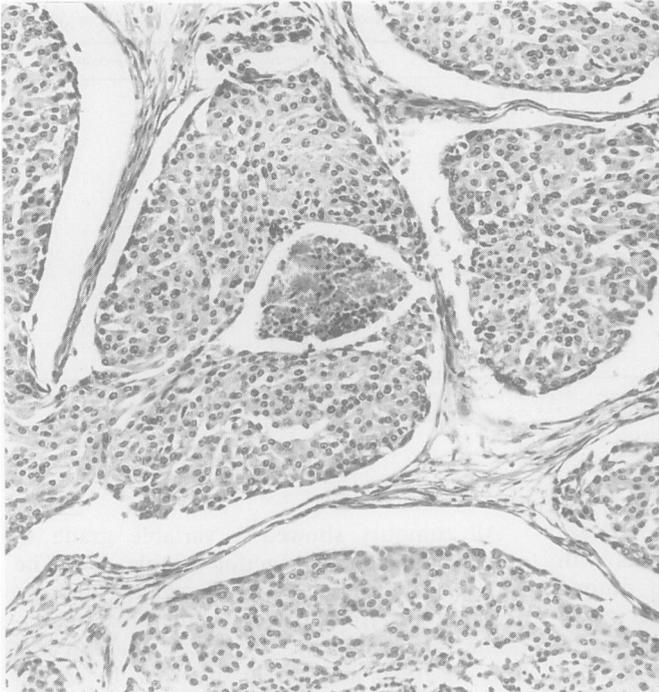


Figure 5 Case 10: solid anastomosing tumour areas of oxyphilic cells with central necrosis and surrounded by delicate fibrous stroma with thin-walled vessels (haematoxylin and eosin).

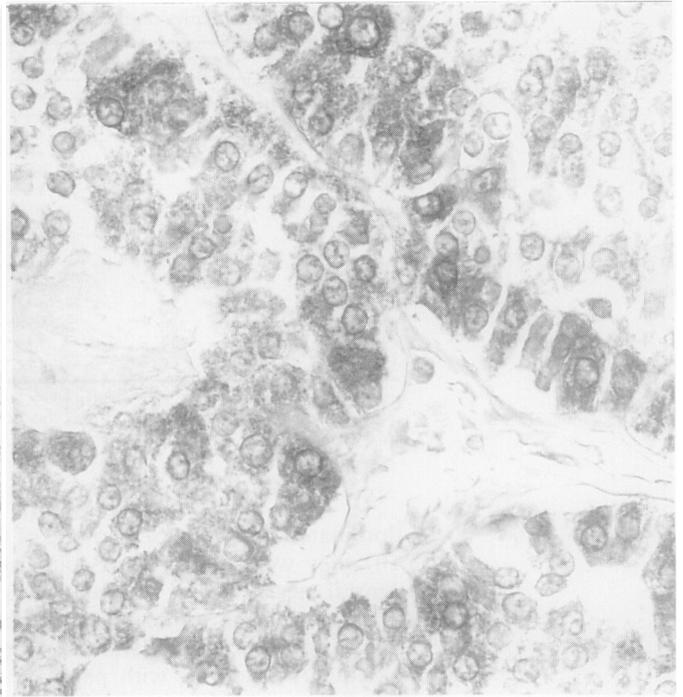


Figure 6 Case 5: tumour cells stained for calcitonin and showing palisading arrangement.

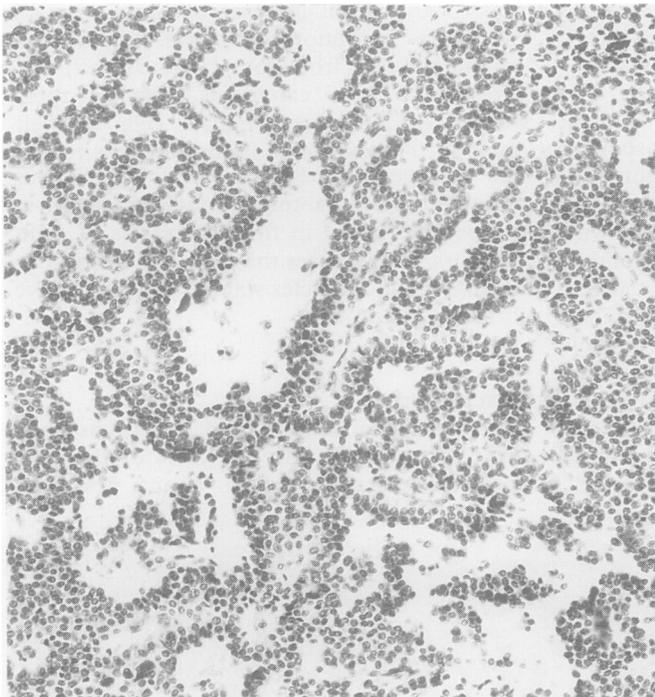


Figure 7 Case 15: pseudoglandular structures with papillary infoldings lined by multiple layers of round neoplastic cells with regular nuclei and lying in delicate stroma tissue (haematoxylin and eosin).

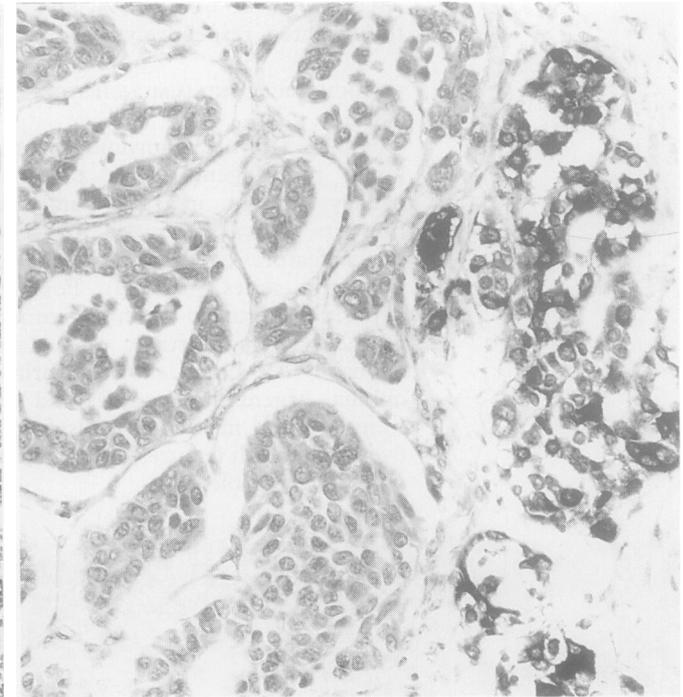


Figure 8 Case 3: strong calcitonin reaction in neoplastic cells from an area of typical medullary carcinoma (right) contrasting with adjacent negatively stained tissue with features of carcinoid tumour.

which may resemble follicular, papillary, and undifferentiated carcinomas.<sup>5-9</sup> The MCTs studied resembled gut carcinoids with only four cases showing areas typical of C cell carcinoma. All cases showed calcitonin reaction.<sup>18 21</sup>

Carcinoid tumours can occasionally metastasise to the thyroid and histological differential diagnosis with MCT can be difficult on purely morphological grounds.<sup>12 14 15 22</sup> In contrast to the MCTs studied, classic enterochromaffin cell carcinoids of the midgut are argentaffin positive and stain positively for serotonin; hindgut carcinoids may not show argyrophilia and, together with foregut carcinoids, generally do not show calcitonin immu-

nostaining.<sup>19 23 24</sup> Case 3 from our series showed histological and histochemical features of hindgut carcinoids. This case may have been difficult to differentiate from a metastatic rectal carcinoid to the thyroid<sup>15</sup> without knowledge of clinical data if the small area of typical MCT had not been present. Differential diagnosis may be even more complicated in cases of MCT that are not argyrophilic and show no amyloid and calcitonin reaction, and in rare MCTs where there may be large areas of serotonin reactive cells.<sup>25 26</sup> Amyloid stroma may occur in carcinoid tumours,<sup>27</sup> as well as calcitonin reactive cells, but usually to a much lesser extent than in MCT.<sup>23 24 28</sup> Additional analysis of clinical data, investigation of further

sections of the tumours, and the more sophisticated in situ hybridisation techniques may help to elucidate the diagnosis in such difficult cases.

The tumours studied here displayed a variety of additional morphological features, such as glandular and papillary structures, large cells and oxyphilic cells. These can be expected to occur even as a dominant pattern in medullary carcinomas.<sup>5-8</sup> Three cases were amyloid free.<sup>18-21</sup> Differential diagnosis should be considered with follicular adenomas, especially the hyalinising trabecular variant, moderately and poorly differentiated follicular carcinomas, papillary carcinoma, and the mixed medullary-follicular carcinoma of the thyroid. All these neoplasms show, among other features, thyroglobulin reaction in neoplastic cells unlike MCT.<sup>29-33</sup> Neoplastic cells with acid mucin were also present in five cases. Mucin production has been documented in MCT<sup>3,7,21</sup> and their histogenesis has been linked to thyroid mucinous C cells.<sup>34</sup>

Eight cases showed thyroglobulin reactive normal thyroid follicles at the periphery and in fibrous stands of the tumours. In five this glycoprotein also gave a weakly positive reaction in some neoplastic cells adjacent to normal thyroid follicles. These findings should be carefully interpreted to avoid a misdiagnosis of mixed medullary-follicular tumours of the thyroid.<sup>30,31</sup> Several mixed carcinomas have been reported in some series, mainly based on the identification of thyroglobulin reactivity in neoplastic cells from the central part of the tumours,<sup>25</sup> as well as in metastases.<sup>30</sup> The alternative explanation for thyroglobulin reaction in neoplastic cells is phagocytosis by neoplastic cells near to disrupted normal intratumoural follicles.<sup>7,21</sup> The latter contention is, in our opinion, relevant to the tumours studied here.

In MCTs with carcinoid features the diagnosis can be suspected on routine microscopy, especially when there are areas with typical histological and histochemical patterns of C cell neoplasia. However, it might not always be an easy diagnosis, particularly when carcinoid tumours metastatic to the thyroid may occur as well as primary thyroid follicular and mixed medullary-follicular neoplasia showing similar morphological features.

These 15 cases of MCT are reported because we believe that this pattern may be mistakenly considered to be of follicular cell origin or metastatic, leading to inappropriate treatment and failure to obtain a careful family history. These cases also illustrate the great value of histochemical methods in establishing what might otherwise be a difficult diagnosis. We propose that this tumour variant should be incorporated into accepted histological subtypes of MCT.<sup>18,21</sup>

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