Cribriform-Morular Variant of Papillary Thyroid Carcinoma

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28.1 Introduction

Cribriform-morular variant of papillary thyroid carcinoma (CMV-PTC) is rare and constitutes less than 0.5% of all PTC [1]. CMV-PTC typically affects young adults with a female predominance, showing a female-to-male ratio of 17:1 [1]. It is commonly associated with familial adenomatous polyposis (FAP) and has a germline mutation in the adenomatous polyposis coli (*APC*) gene [2, 3]. However, sporadic form without FAP has been also reported.

Preoperative diagnosis of CMV-PTC is important. As CMV-PTC with FAP usually displays multifocal nodules, total thyroidectomy is required. On the other hand, lobectomy is sufficient for sporadic cases because of solitary nodule and excellent prognosis. In addition, the fact that colonic polyposis may be detected after the diagnosis of CMV-PTC indicates the necessity of preoperative colonoscopy and/or *APC* gene analysis [1]. Therefore, aspiration cytology bears an important responsibility in the management of this variant. Herein, we described the diagnostic clue of CMV-PTC.

28.2 Case

The case was a 21-year-old woman. She was pointed out to have nodules in the anterior neck by a medical checkup. As aspiration cytology was suspicious for malignancy, she was referred to our hospital for surgical therapy. Ultrasonographic examination revealed two nodules in the thyroid. The nodule

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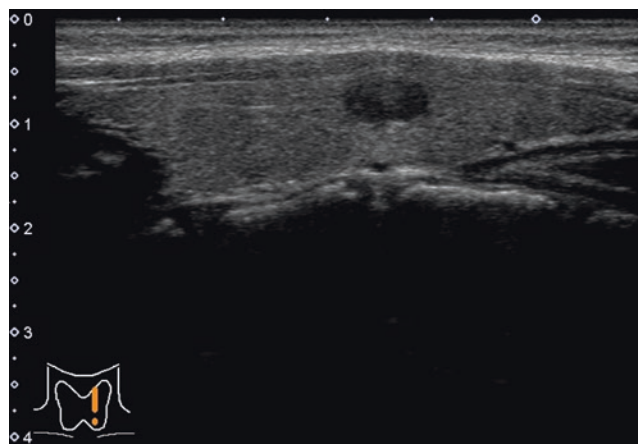University, Yufu, Oita, Japan

Fig. 28.1 A hypoechoic mass with well-defined border is seen. (Ultrasound B-mode image)

located in the left lobe measured 8 mm × 5 mm × 7 mm. It was hypoechoic, homogeneous, and not associated with fine strong echoes. The border of the mass was well-defined (Fig. 28.1). Color Doppler ultrasound showed that it was hypovascular. Ultrasonographic interpretation was a malignancy, and CMV-PTC was suspected by aspiration cytology. Another nodule located in the right lobe, measuring 11 mm × 3 mm × 6 mm, was interpreted as a benign nodule by ultrasonographic and cytological examinations. She underwent a left thyroid lobectomy including isthmus with central neck dissection. Colonic examination performed after the microscopic diagnosis of CMV-PTC did not detect any abnormalities. A test for *APC* gene mutation was not permitted. Her parents had no history of polyposis coli and thyroid tumors.

28.3 Cytological Findings

Aspirated material was cellular. There were a small number of foamy histiocytes in the background. Colloid materials were not seen. Carcinoma cells appeared as papillary or cribriform clusters. The cribriform clusters exhibited slit-like

empty spaces and anastomosing bars (Fig. 28.2). Papillary clusters partially showed nuclear palisading (Fig. 28.3). Some clusters contained small hyaline materials. Carcinoma cell nests with eddy formation were scattered (Fig. 28.4). Most of the carcinoma cells were tall columnar and their N/C ratios were low. Isolated carcinoma cells looked like spindle or elongated cells. The cytoplasm was weakly stained with light green, even in the carcinoma cells forming morules. A few carcinoma cells showed vacuolated cytoplasm (cytoplasmic lipid accumulation, CLIA) (Fig. 28.5). Metaplastic cytoplasm showing dense cytoplasm was not observed. Tail-like cytoplasmic elongation was observed at the periphery of the cell clusters (Fig. 28.6). The nuclei were round, oval, or short spindle and exhibited nuclear grooves and intranuclear cytoplasmic inclusions. The nuclear chromatin was not ground glass-like, but granular (Fig. 28.7). Some morular cells showed peculiar nuclear clearing that occupied most of the nuclei and directly surrounded by a nucleoplasm (Fig. 28.8).
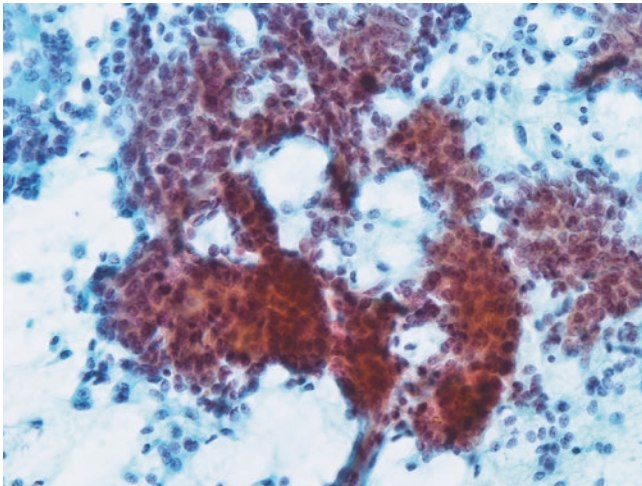
28.4 Pathological Findings

The tumor was located in the left lobe of the thyroid and measured 7 mm × 5 mm. On cut surface, it was solid and lobulated (Fig. 28.9). It was well-encapsulated and did not invade the surrounding thyroid tissue. Microscopically, the carcinoma cells showed cribriform (Fig. 28.10), papillary, solid, and follicular pattern. The cribriform pattern was formed by anastomosing bars and arches of carcinoma cells without intervening stroma. There was no colloid in the lumen. The morules were scattered in the solid area. Papillary area was composed of tall columnar carcinoma cells. The cytoplasm was slightly eosinophilic. The nuclei were round to spindle and represented cytoplasmic inclusions (Fig. 28.11). Peculiar nuclear clearing was observed in some of the morular cells (Fig. 28.12). The chromatin pattern was granular. Ground glass pattern consistent with classic papillary carcinoma was not observed. There were no psammoma bodies. Lymph node

Fig. 28.2 The cribriform clusters showing slit-like empty spaces and anastomosing bars are seen. There are no colloid materials in the lumen and background. (Papanicolaou, 100×)
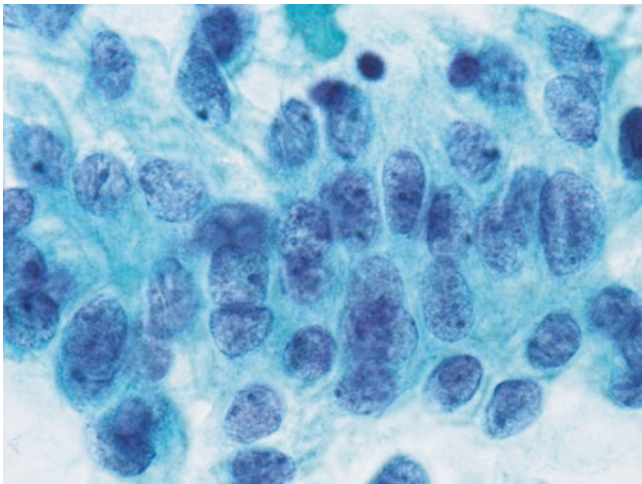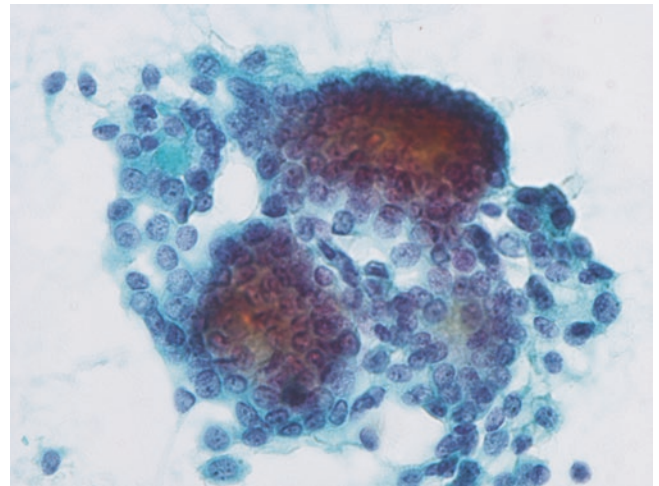

Fig. 28.4 Two eddies, called "morules," composed of carcinoma cells are seen. (Papanicolaou, 400×)

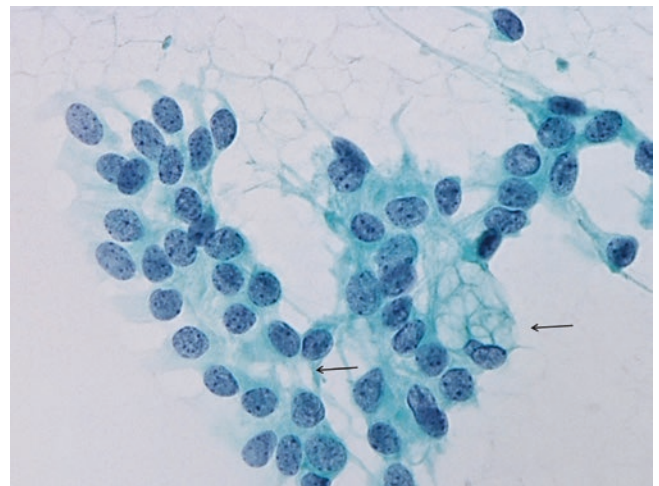**Fig. 28.3** Some nuclei show palisading. (Papanicolaou, 1000×)

Fig. 28.5 A few carcinoma cells show cytoplasmic vacuolation due to lipid accumulation (arrow). (Papanicolaou, 400×)
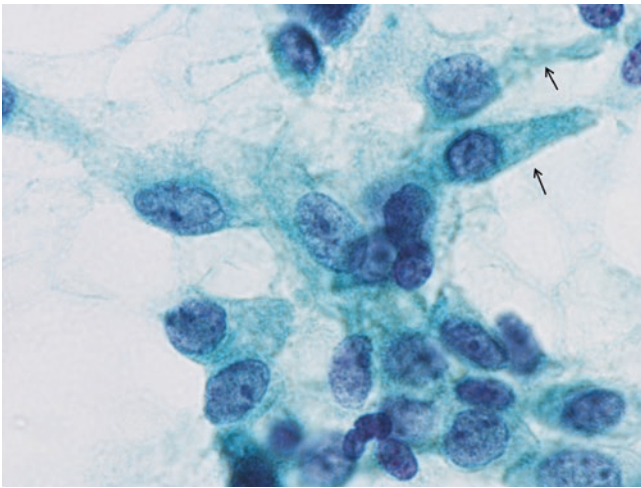
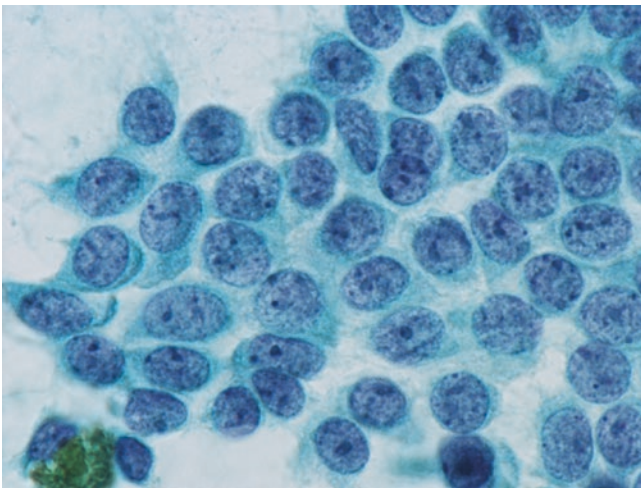**Fig. 28.6** The carcinoma cells exhibit tail-like cytoplasmic elongation (arrow). (Papanicolaou, 1000×)

Fig. 28.7 The nuclear chromatin is not ground glass pattern. (Papanicolaou, 1000×)
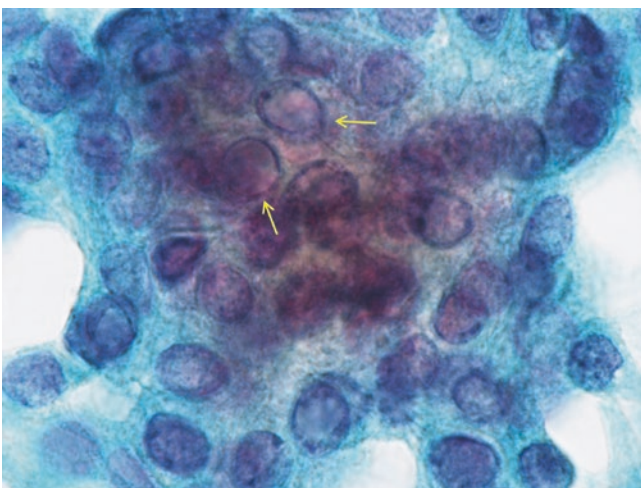

Fig. 28.8 Some nuclei show peculiar nuclear clearing that occupies most of the nuclei and is directly surrounded by a nucleoplasm (arrow). (Papanicolaou, 1000×)

was not identified. Immunohistochemically, the carcinoma cells showed nuclear and cytoplasmic positivity for beta-catenin (Fig. 28.13). Thyroglobulin was almost negative (Fig. 28.14). Estrogen receptor was positive except for morular cells (Fig. 28.15).

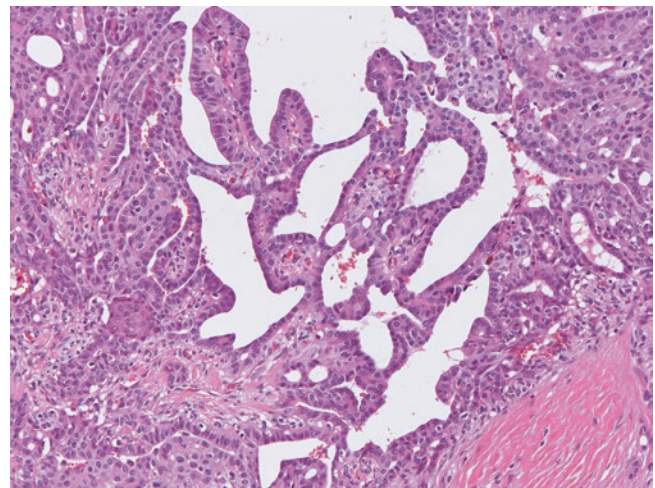**Fig. 28.9** An encapsulated and lobulated tumor is present in the thyroid

Fig. 28.10 Cribriform structure composed of anastomosing bars and arches of carcinoma cells is seen. There are no colloid materials in the lumen. (HE, 200×)
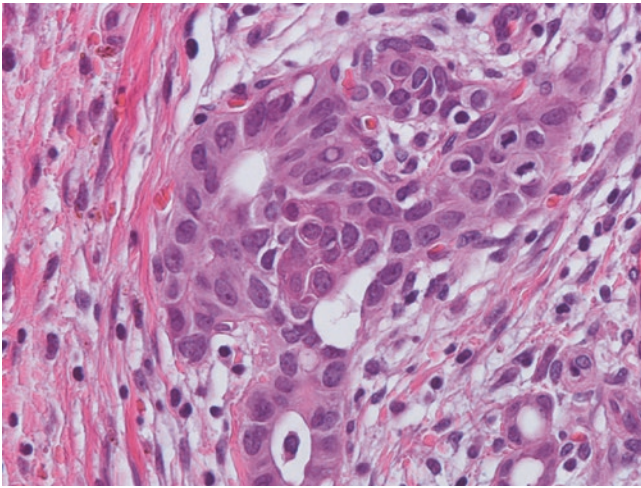
Fig. 28.11 The nuclei are dark, and intranuclear cytoplasmic inclusion is noticed. (HE, 400×)
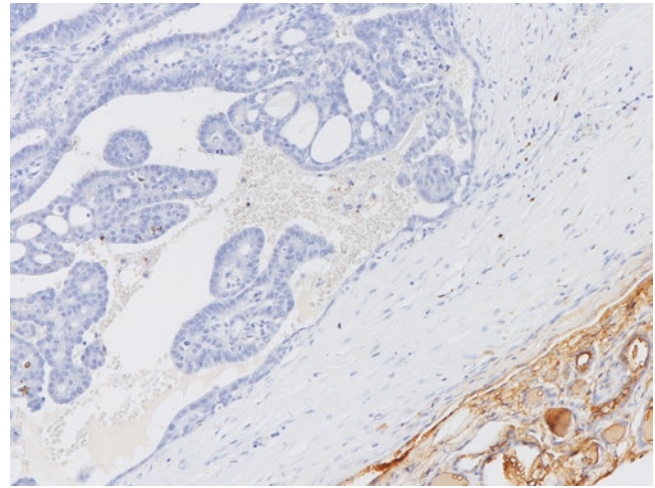

Fig. 28.14 The carcinoma cells do not express thyroglobulin. The normal follicular cells are positive for it (right lower). (Thyroglobulin immunostaining, 200×)
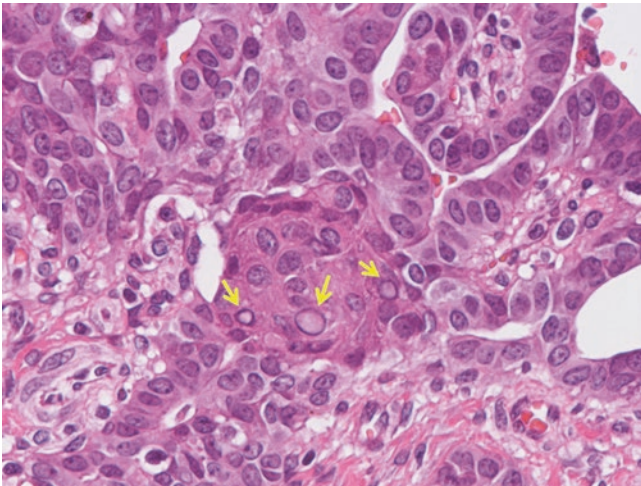

Fig. 28.12 Three carcinoma cells show peculiar nuclear clearing (arrows). (HE, 400×)
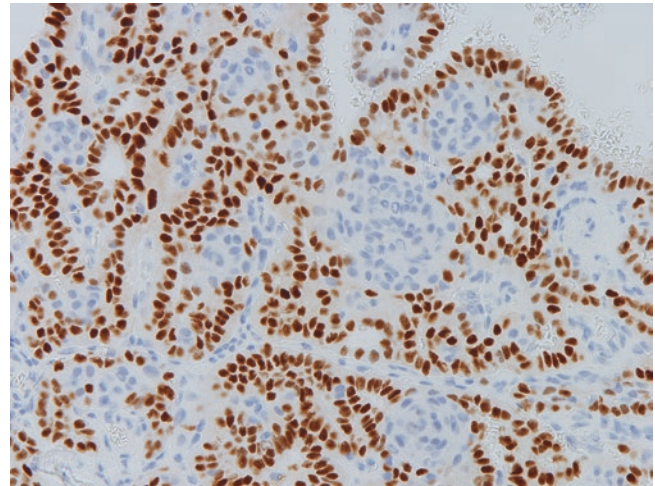

Fig. 28.15 The carcinoma cells are positive for estrogen receptor, except for morular cells. (Estrogen receptor immunostaining, 400×)

28.5 Discussion

CMV-PTC is considered by some to constitute a distinct category of thyroid carcinoma. It can occur in a sporadic form or as a manifestation of FAP. It occurs almost exclusively in young adult females. A sporadic form occurs in patients who do not carry a germline mutation of *APC* gene. Sporadic cases are usually solitary, whereas cases associated with FAP are often multifocal [4]. The prognosis is excellent, and nodal metastasis is relatively rare (Table 28.1) [5].

This variant is histologically characterized by an intricate blending of cribriform, follicular, papillary, trabecular, and solid patterns with the morules (Table 28.2). The cribriform pattern is formed by anastomosing bars and arches of carcinoma cells without intervening stroma and resembles ductal carcinoma of the breast. The lumen of the cribriform pattern
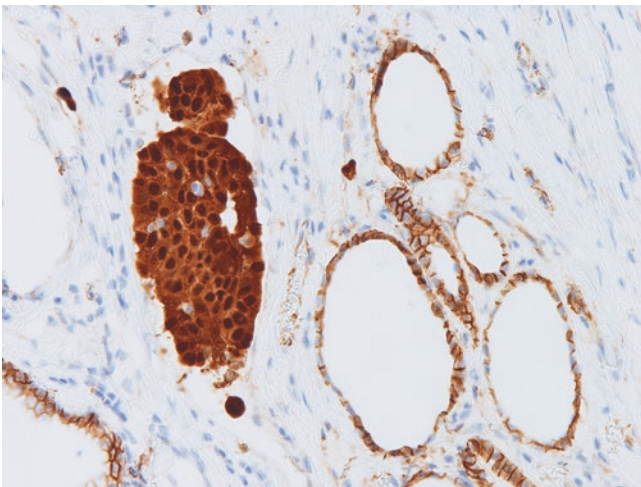

Fig. 28.13 Normal follicular cells show membranous positivity for beta-catenin (right). The carcinoma cells show nuclear and cytoplasmic positivity for it (left). (Beta-catenin immunostaining, 400×)

Table 28.1 Clinical features of cribriform-morular variant of papillary thyroid carcinoma

Age	Young adults
Gender	Female predominance (F/M ratio, 17:1)
Genetic background	*APC* gene abnormality (not all)
Focus	Multifocal in FAP-associated cases
	Solitary in non-FAP-associated cases
Prognosis	Excellent
Nodal metastasis	10–20%

Table 28.2 Pathological features of cribriform-morular variant of papillary thyroid carcinoma

Gross	Well-demarcated or encapsulated
	Solid, may be focally cystic
Microscopy	
Growth pattern	Cribriform, trabecular, solid, papillary, follicular morules (characteristic)
Cell shape	Tall columnar, cuboidal, round, spindle
Cytoplasm	Moderately abundant, eosinophilic
Nuclei	Peculiar nuclear clearing (characteristic)
	Fine granular chromatin, Obscure ground glass appearance
Colloid	Absent
Psammoma bodies	Very rare
Immunohistochemistry	
Thyroglobulin	Almost negative
Beta-catenin	Nuclear and cytoplasmic positivity
Estrogen receptor	Positive except for morules
Progesterone receptor	Positive except for morules

Fig. 28.16 The carcinoma cells are positive for adipophilin, especially in the subnuclear portion. (Adipophilin immunostaining, 400×)

is usually devoid of colloid. The carcinoma cells showing papillary growth are tall columnar, and the nuclei frequently display pseudostratification. Trabecular arrangement may be reminiscent of hyalinizing trabecular tumor (see Chap. 34). Among thyroid carcinomas, the morules appear limited to this variant. Nuclear chromatin is fine granular and ground glass appearance is obscure. Peculiar nuclear clearing characteristic of this variant tends to be observed in the morules [6]. According to the report by Hirokawa et al., the cytology of CMV-PTC is characterized by (1) hypercellularity, (2) papillary arrangement composed of tall columnar cells, (3) cribriform pattern, (4) morules, (5) spindle cells, (6) obscure ground glass nuclei, (7) pale-staining nuclei with thickened nuclear membranes (peculiar nuclear clearing), (8) foamy or hemosiderin-laden histiocytes, (9) hyaline materials, and (10) no colloid in the background [7].

Papillary arrangement is frequently seen in CMV-PTC. However, the finding is not important to diagnose CMV-PTC, because it is common to conventional PTC. Cribriform structure is characterized by slit-like empty spaces and anastomosing bars within cell clusters [8]. Insular carcinoma and follicular neoplasm may also present cribriform pattern. In such tumors, the spaces are small in size and round and may contain colloid. In contrast, the spaces seen in CMV-PTC are larger in size and not round and do not contain any colloid. Tall columnar cells are easily identified in CMV-PTC as carcinoma cells showing nuclear palisading and low N/C ratio. Tail-like cytoplasmic elongation is also consistent with tall columnar cells [9]. Tall columnar cells are also seen in tall cell variant and columnar cell variant of PTC (see Chaps. 27 and 29). Pseudostratified nuclei, hyperchromasia, and nuclear atypia are helpful in distinguishing columnar cell variant from CMV-PTC. The distinction of columnar cells between CMV-PTC and tall cell variant is difficult. The age of the patient may be useful. The latter occurs in elder persons. Morules are cell clusters with eddy formations [8, 9]. They may mimic squamous metaplasia. Compared with squamous metaplasia, the cytoplasm of carcinoma cells forming the morules is not densely stained. The spindle cells singly appear in the background [10]. Recently, Takada et al. reported that CLIA is a characteristic feature of CMV-PTC [11]. The vacuoles tended to distribute in the subnuclear portion of carcinoma cells showing papillary growth and were positive for oil red O staining and adipophilin (Fig. 28.16).
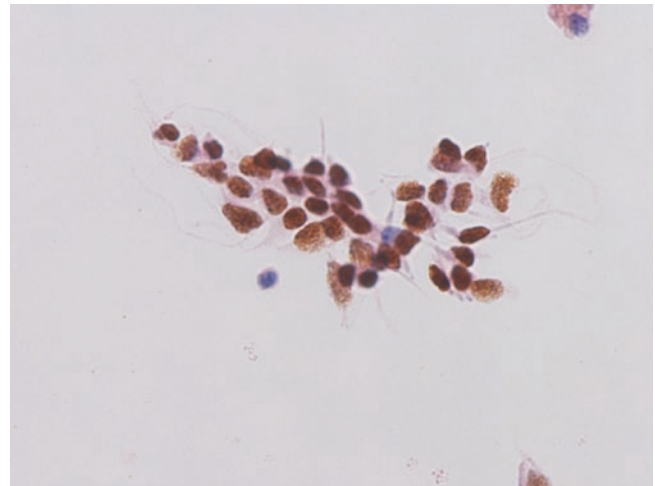
Similar to conventional PTC, CMV-PTC presents intranuclear cytoplasmic inclusions and nuclear grooves. However, ground glass appearance is obscure (Table 28.3). The chromatin seen in CMV-PTC is granular, and it mimics that of follicular neoplasm or medullary carcinoma. Intranuclear cytoplasmic inclusions are less common than in the conventional PTC (58% of cases) [12]. The presence of peculiar nuclear clearing is very useful for the diagnosis of CMV-PTC [9]. It is identified which as pale staining which is occupying most of the nuclei and usually accompanied by condensed chromatin at the periphery of the nuclei. It is distinguished from cytoplasmic inclusions by cytoplasmic staining and sharp circumscription with the nuclear membrane.

Table 28.3 Cytological differential diagnoses of cribriform-morular variant and conventional papillary thyroid carcinoma

	Cribriform-morular variant	Conventional
Arrangement	Papillary, cribriform	Papillary, follicular
	Nuclear palisading	
Morules	Occasionally present	Absent
Cell shape	Tall columnar, cuboidal, spindle	Round, cuboidal, columnar
Cytoplasm	Moderately abundant	Variable
	Tail-like elongation	
	Cytoplasmic lipid accumulation	Septated intracytoplasmic vacuole
Nuclei		
Peculiar nuclear clearing	Present	Absent
Ground glass appearance	Obscure	Present
Cytoplasmic inclusion	Present	Present
Background		
Colloid	Absent	Ropy strands
Lymphocytes	Absent	Occasionally present
Foam cells	Present	Occasionally present
Hyaline materials	Present	Absent
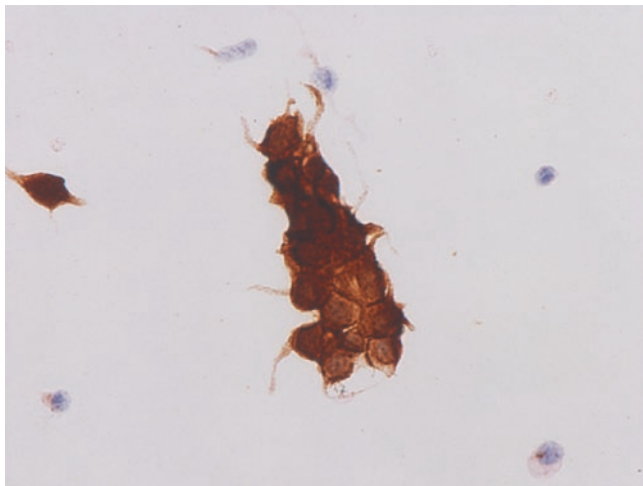
Fig. 28.17 The carcinoma cells show nuclear and cytoplasmic positivity for beta-catenin. (Beta-catenin immunostaining, LBC, 400×)

Fig. 28.18 The carcinoma cells are positive for estrogen receptor. (Estrogen receptor immunostaining, LBC, 400×)

Immunocytochemical staining is very useful in diagnosing CMV-PTC. When this variant is suspected, we routinely stain beta-catenin (Fig. 28.17), estrogen receptor (Fig. 28.18), and progesterone receptor. Beta-catenin reveals nuclear and cytoplasmic immunoreactivity [13, 14]. In contrast, conventional PTC reacts with the cell membrane against the antibody. CMV-PTC shows strong nuclear positivity for estrogen receptor and progesterone receptor, except for morular cells [15]. Conventional PTC is negative for them.

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