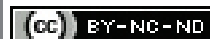


Cribriform Morular Thyroid Carcinoma, Elusive Malignancy with Difficult Diagnosis: A Case Series of Five Cases

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ABSTRACT

Cribriform-Morular Thyroid Carcinoma (CMTC) are very rare thyroid carcinoma and has been recently renamed in the 2022 WHO classification as a thyroid tumour of uncertain histogenesis. Preoperative diagnosis of CMTC is challenging due to overlapping cytomorphological features, between Papillary Thyroid Carcinoma (PTC) and cribriform thyroid carcinoma. Authors analysed clinicopathological and Immunohistochemical (IHC) features of five cases of CMTC diagnosed at our centre. Clinical characteristics, treatment received, and follow-up data were obtained from electronic medical records. Haematoxylin and Eosin (H&E) stained slides and Immunohistochemistry (IHC) slides were reviewed, histomorphological and IHC profile of all the cases were analysed. The salient histomorphological features noted were cribriform pattern, tall cell areas, solid growth with squamoid morules, absent/scant colloid and rare psammoma bodies. All the five cases consistently expressed beta-catenin. TTF1 was positive in all cases, with negative staining in squamoid areas. Diagnosis of CMTC warrants initiation of genetic screening for APC mutation.

Keywords: Cytomorphology, Familial adenomatous polyposis, Genetic testing, Thyroid cancer, WNT/Beta catenin pathway

INTRODUCTION

The CMTC is rare and now considered as distinct clinical entity according to the 2022 World Health Organisation classification representing 0.16% to 0.30% of all thyroid carcinomas [1]. The CMTC occurs almost exclusively in women, with an average age of presentation of 25 years and is more common in the Asian population with lower rate of lymph node as well as distant metastasis, recurrence, and mortality as compared to classic PTC [2,3]. It was considered as a distinctive follicular cell neoplasm sharing some features of PTC and Follicular Thyroid Carcinoma (FTC), as well as having a tendency to multicentricity [1,4]. The CMTC was included as a subtype of PTC in the 2017 WHO classification of thyroid tumours [5]. Subsequently, this tumour is considered as distinctive thyroid carcinoma with a peculiar endodermal (intestinal-like) phenotype associated with the activation of the WNT/ β -catenin signalling pathway [6]. CMTCs lack the definitive biomarkers of thyroid follicular cell differentiation and the presence of morulae with co-expression of CK5 and CD5 along with the positivity for Caudal - type homeobox transcription factor 2 (CDX2) could represent thymic/ultimobranchial pouch-related differentiation [7]. Currently, in the new fifth edition of the WHO classification of endocrine and neuroendocrine tumours, the CMTC is considered an independent thyroid neoplasm of uncertain histogenesis [8]. These carcinomas uniformly express Thyroid Transcription Factor 1 (TTF1), lack thyroglobulin reactivity, and are known for their distinct cytomorphological features. The features include cribriform architecture, morules without keratinisation, papillary architecture, spindle cells, and scant/absent colloid and psammoma bodies [9].

A unique feature of CMTC is its strong association with Familial Adenomatous Polyposis (FAP), which is caused by germline mutations in the APC gene [6]. Germline and somatic disease are associated with alterations in the Wnt/beta-catenin pathway. Around 53% to 60% of CMTC cases are associated with FAP, and in approximately 40% to 48% of cases, thyroid carcinoma diagnosis precedes the discovery of FAP [3,6]. Literature shows sporadic CMTC with unifocal disease have larger tumour size, and FAP associated tumours were multifocal and shows an earlier disease onset [7].

Despite being a well differentiated tumour with low risk of recurrence and metastasis, its association with FAP begets the need for prompt genetic testing and expeditious colonoscopy since individuals with FAP have nearly complete penetrance of colorectal carcinoma [10].

For sporadic cases, total thyroidectomy or lobectomy is an appropriate surgical treatment whereas total thyroidectomy is recommended for FAP-associated CMTC, but modified neck lymph node dissection is not necessary [11].

The aim of this case series is to retrospectively review the cases of this rare diagnosis and assess the clinico-pathological features that help to reach the diagnosis. We present a series of CMTC of five cases, evaluating the clinical and pathological parameters reported at our institution.

MATERIALS AND METHODS

This was a retrospective case series of one year and eight-month duration from January 2024 to August 2025. Following approval by the Institutional Review Board at our centre, case records and all the available haematoxylin and eosin-stained slides and IHC slides of all the five cases of CMTC during the study period were retrieved from the archives. Clinical characteristics, treatment received, and follow-up data were obtained from the medical records. Histomorphological features assessed were growth pattern, cell morphology, nuclear features, psammoma bodies, mitosis, presence or absence of necrosis and colloid, mitotic count, lymphovascular and capsular invasion, presence or absence of lymph node metastases and extra thyroidal extension. Out of the five cases, two cases were recurrence presenting as lymph node metastases of thyroid carcinoma which were diagnosed initially as columnar cell and tall cell subtype of PTC four and 12 years back respectively. Panel of IHCs done includes: TTF1, Beta catenin, Oestrogen Receptor (ER), CD10, CDX2 and pattern of IHC staining were assessed.

RESULTS

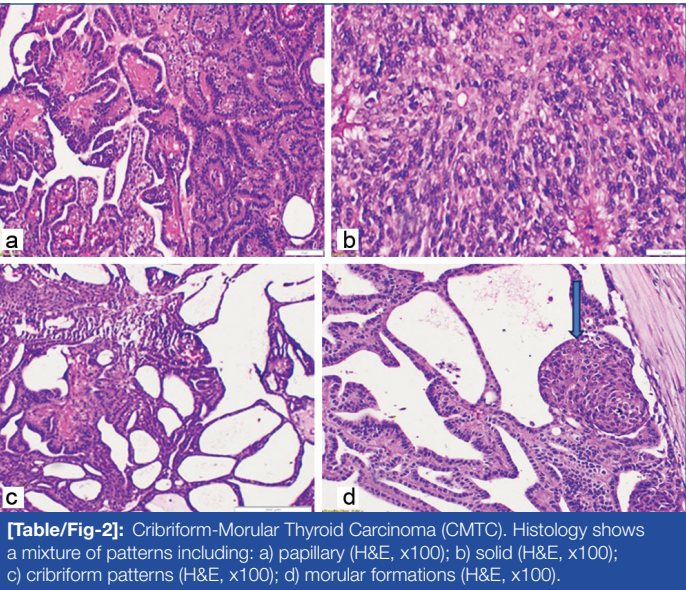
A total of five cases of CMTC were identified in the study period, all (100%) were females. The mean age at diagnosis was 28.2 years (range, 19-47). History of colonoscopically diagnosed FAP

syndrome was present in single case (20%) with family history of FAP and PTC. [Table/Fig-1] shows the clinicopathological details of all the five cases.

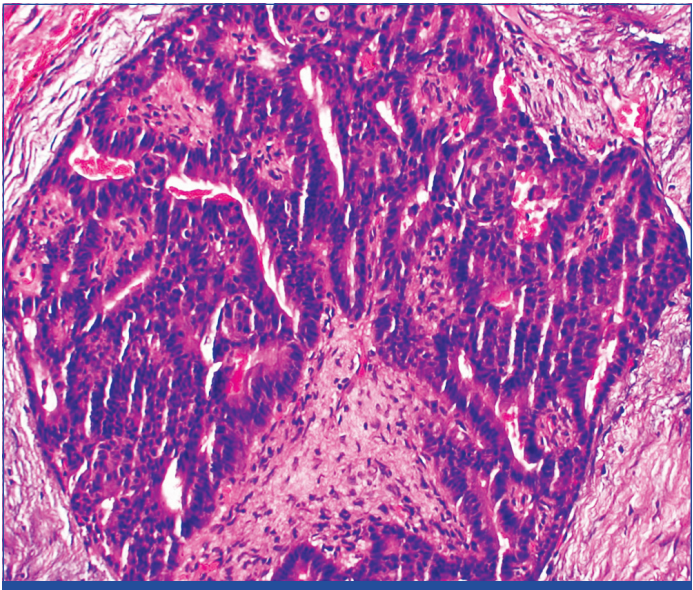
architecture Whorls and squamoid nests (morules) [Table/Fig-5a] were conspicuous in some and focal in others. Individual cells were tall, columnar, vesicular nuclei, with nuclear clearing (not suffice to

Clinical parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Age at presentation (in years)/sex	21/F	19/F	47/F	35/F	19/F
Clinical presentation/Duration	Incidental detection	Anterior neck swelling×6 months	Left-side neck swelling×4 months	Anterior neck swelling×6 months	Left-side neck swelling×1 year
Focality	Multifocal	Multifocal	Multifocal	Unifocal	Multifocal
Growth pattern [Table/Fig-2]	Cribriform, solid, branching papillae, nests and whorls	Branching papillae, [Table/Fig-2a] cribriform, nest, whorls	Arborising papillae, follicular, solid, [Table/Fig-2b] rosettoïd, cribriform, [Table/Fig-2c] squamoid cells nest [Table/Fig-2d]	Papillary architecture with columnar cells	Branching papillae, irregular follicle, cribriform, nests, whorls
Psammoma bodies	Absent	Absent	Absent	Absent	Absent
Nuclear features	Oval vesicular nuclei, inconspicuous nucleoli, few with nuclear grooves	Oval vesicular nuclei	Oval vesicular nuclei	Hyperchromatic nuclei	Ovoid irregular nuclei with vesicular chromatin, tiny inconspicuous nucleoli and occasional grooving
Colloid	Scant colloid	Absent	Absent	Absent	Scant colloid
Mitosis	Not evident	Not evident	Not evident	Not evident	Not evident
Necrosis	Absent	Absent	Absent	Absent	Absent
Lymphovascular invasion	Present	Present	Present	Absent	Present
Extrathyroidal extension	Absent	Present	Absent	Absent	Absent
Lymph node metastases	Absent	Present	Present	Absent	Absent
TTF1	Diffuse moderate positivity	Positive	Diffuse positive	Positive	Positive in cribriform component
CK7	IHC not performed	IHC not performed	Diffuse positive	IHC not performed	IHC not performed
Beta catenin	Diffuse strong positive	Diffuse strong positive	Diffuse positive	Positive	Positive
ER	IHC not performed	IHC not performed	Diffuse positive	IHC not performed	Negative
Thyroglobulin	Focal areas of cytoplasmic positivity	Negative	Negative	Negative	Patchy weak staining
PAX8	Negative	Negative	Negative	Negative	Occasional scattered cells show positivity
Synaptophysin	IHC not performed	IHC not performed	Negative	IHC not performed	IHC not performed
Chromogranin	IHC not performed	IHC not performed	Negative	IHC not performed	IHC not performed
CD10	IHC not performed	IHC not performed	Positive in squamoid morules	IHC not performed	Positive in morular component
CDX2	IHC not performed	IHC not performed	Negative	Negative	A few cells in morules show positivity
Initial diagnosis	CMTC	Columnar cell subtype of PTC [Table/Fig-3]	Tall cell subtype of PTC [Table/Fig-4]	CMTC	CMTC

[Table/Fig-1]: Clinicopathological details.



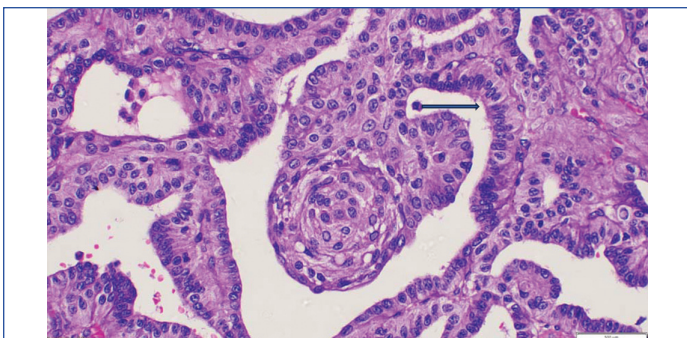
[Table/Fig-2]: Cribriform-Morular Thyroid Carcinoma (CMTC). Histology shows a mixture of patterns including: a) papillary (H&E, ×100); b) solid (H&E, ×100); c) cribriform patterns (H&E, ×100); d) morular formations (H&E, ×100).



[Table/Fig-3]: Cribriform Morular Thyroid Carcinoma (CMTC) mimicking columnar cell subtype of PTC. Thin papillae or glandular spaces lined by pseudostratified epithelium (H&E, ×400).

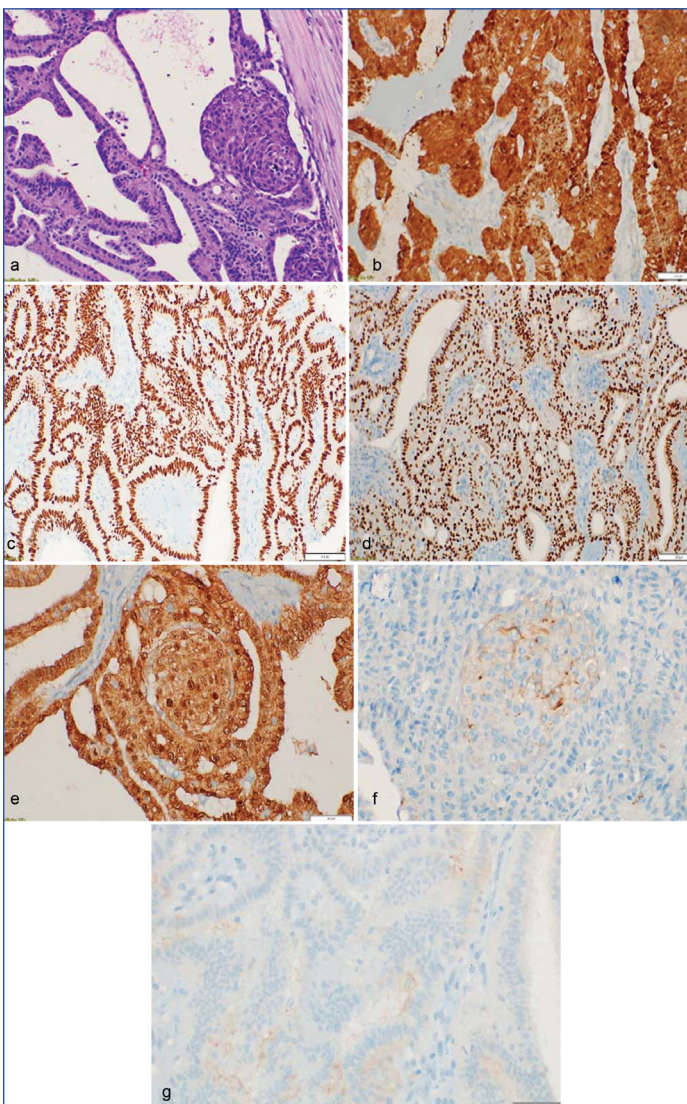
All the five cases were reviewed. Grossly, lesion is fairly circumscribed grey white granular. On microscopy lesions showed arborising papillary pattern, solid and follicular pattern, rosettoïd areas and cystic spaces formed by arches and bars forming a cribriform

diagnose classical PTC) inconspicuous nucleoli and few showing nuclear grooves. One case showed elongated hyperchromatic nuclei.



[Table/Fig-4]: Cribriform Morular Thyroid Carcinoma (CMTC) mimicking tall cell subtype of PTC. Papilliferous tumour composed of tall cells (H&E, x400).

Classical nuclear features of PTC (nuclear enlargement, elongation, overlapping, grooves, membrane irregularity, pseudo inclusions, clearing, chromatin marginalisation) are often rare or absent. IHC; tumour cells in all cases (5/5) showed diffuse positivity for beta-catenin [Table/Fig-5b] and TTF1 (100%) [Table/Fig-5c]. ER showed nuclear positivity in single case, 1/5(20%) [Table/Fig-5d]. Morules showed positive staining for beta catenin and CDX2 [Table/Fig-5e,f]. Thyroglobulin was focally positive in two case, 2/5 (40%) [Table/Fig-5g].



[Table/Fig-5]: Cribriform-Morular Thyroid Carcinoma (CMTC): a) Morules lack keratinisation and the cells show nuclear clearing (H&E, x400); b) Strong nuclear and cytoplasmic immunoreactivity for β -catenin (IHC, x400); c) Tumour cells are consistently positive for TTF1 (IHC, x200); d) Tumour cells are also positive for oestrogen receptors (IHC, x200); e) Morules show positive staining for beta catenin (IHC, x400); and ; f) Morules show positive staining for CDX2 (IHC, x400); g) Tumour cells are negative for thyroglobulin (IHC, x200).

All the patients were surgically treated by total thyroidectomy followed by radioactive iodine therapy in view of metastatic disease,

multifocality and large primary tumour. One patient had nodal recurrence after four years of disease-free interval and required radical neck dissection. Another patient had multiple regional lymph node recurrences which required multiple local resections after disease-free interval.

DISCUSSION

The CMTC is a rare thyroid malignancy that can present as an extracolonic manifestation of FAP, but usually occurs as a sporadic neoplasm [5]. CMTC is known to occur almost exclusively in females and it is known for a very favourable outcome [12]. Mean age at diagnosis of 26 years (range 8-61 years), both for FAP associated and for sporadic CMTC [13]. CMTC can arise in patients who have had previous radiation to the head and neck [14].

Grossly, tumours are mostly well circumscribed and encapsulated, tan to white, solid and fleshy. Histologically, the tumour exhibits a complex merge of cribriform, follicular, papillary, trabecular and solid patterns of growth, with morular (squamous) areas [6]. The percentage of these growth patterns vary within and among these tumours. The cribriform pattern is composed of tumour cells without interposed stroma that merge with tubulo-glandular follicles without colloid, as well as with papillae. The papillae are lined by cuboidal or tall cells, often mimicking the tall-cell or columnar-cell subtypes of PTC [6,7]. Areas of trabecular pattern, solid areas with spindle-like cells can simulate hyalinising trabecular tumour [6,8]. Psammoma bodies are rare. Nuclei are round to oval, clear and can show irregular contours, grooves and pseudo inclusions. The defining feature of CMTC is the presence of morular structures, which are nests of nonkeratinised cells with characteristic chromatin clearance and with no keratinisation or intercellular bridges [6,8]. Morules are primarily seen in solid areas but also may occur in cribriform and trabecular areas. Rare cases with marked stromal hyalinisation and calcification, adamantinous-like pattern [15], adenoid cystic carcinoma-like areas [16] or focal squamous differentiation [12] have been reported in the literature. According to the criteria of the new edition of the WHO classification of thyroid tumours [8] rare cases of 'high-grade CMTC' with necrosis and/or high proliferative activity have also been reported [7,12,17].

The IHC profile shows strong diffuse nuclear and cytoplasmic immunostaining for β -catenin, and is the hallmark of CMTC [9]. Non morular tumour component show positive staining for CK7, CK19, 34betaE12, Phosphatase and TENsin homologue deleted on chromosome 10 (PTEN), B-cell lymphoma 2 (bcl2), vimentin, TTF1, p53, galectin -3, oestrogen and Progesterone Receptors (PR) [7,9]. Morular structures also show aberrant nuclear and cytoplasmic positivity for β -catenin and can be easily identified in the tumour by their characteristic cytoplasmic positivity for CD10, nuclear positivity for bcl2, and diffuse membranous positivity for CDX2, and E-cadherin [8,18]. However, morulae in CMTC do not represent metaplastic squamous epithelium since they lack p63, p40, TTF1, and Paired box gene 8 (PAX8) [8]. TTF1, ER and PR are negative [3]. Thyroglobulin show either focal or negative staining pattern [3,19]. Both non-morular and morular cells in CMV-PTC are positive for galectin 3 and p53 protein [9]. In addition, Lymphoid Binding Factor 1(LEF-1) is a sensitive and specific marker for CMTC [20].

The CMTC is characterised by permanent activation of the Wnt/ β -catenin signalling pathway through transcription factor CDX2, activates small intestine gene expression at low levels and colonic gene expression at higher levels [21]. These mechanisms of embryonic intestinal induction would explain both the blockage in the terminal/follicular differentiation of follicular cells (or their precursor cells) in CMTC, as well as its phenotype [22].

Due to distinct clinicopathological, IHC profile and genetics, CMTC is no longer considered as a subtype of PTC in the 2022 WHO classification of thyroid tumours.

Histomorphological differentials of CMTC includes columnar cell subtype, tall cell subtype and diffuse sclerosing subtype; former two subtype run an aggressive course. Columnar cell subtype is typically hypercellular neoplasm showing thin papillae or glandular spaces lined by pseudostratified epithelium, with supra and subnuclear vacuolisation and lack typical nuclear features of PTC [5,23]. Tall cell subtype of PTC is usually a highly papilliferous tumour composed of tall cells, whose height is three times their width, abundant eosinophilic (oncocyctic like) cytoplasm and with typical nuclear features of PTC. Follicles are stretched and elongated with tram-track appearance [5,23,24].

In a background of young patients with PTC, diffuse sclerosing subtype of PTC is the closest differential diagnosis for CMTC. Diffuse sclerosing subtype of papillary carcinoma has prominent squamous areas which could simulate morules of CMTC. Nevertheless, diffuse sclerosing subtype is characterised by the presence of dense sclerosis, with patchy to dense lymphocytic inflammation, and extensive lymph vascular invasion and numerous psammoma bodies [3,24,25]. CMTC has rare or absent psammoma bodies. All three variants are always immunoreactive for thyroglobulin [5,23].

Poorly Differentiated Carcinoma (PDC) with a solid-trabecular-insular pattern of growth pattern can mimic CMTC. However, PDC have high mitotic index (≥ 3 mitotic figures per 2 mm²) and lack of nuclear features of PTC against a cribriform pattern of growth with CD10 positive morules and negativity for thyroglobulin in CMTC [26].

The CMTC can mimic metastatic breast carcinoma because of its cribriform pattern of growth and positivity for oestrogen and PRs [27]. Clinical correlation with imaging findings is essential as both tumours show positivity for oestrogen and PRs. PTC is positive for thyroglobulin, TTF1, PAX8, Hectort Battifora Mesothelial-1 (HBME1) and BRAF V600E [28]. It can also mimic metastatic colon cancer. But the immunoprofile of TTF-1 positivity in the CMTC facilitates the diagnosis of CMTC over metastatic colon cancer. It can also mimic other thyroid tumours like hyalinising trabecular tumour, PTC, poorly differentiated thyroid carcinoma.

When psammoma bodies are inconspicuous in a tumour with nuclear features mimicking PTC along with cribriform and morular growth patterns warrants a diagnosis of CMTC [29]. A high Ki-67 labelling index usually indicates aggressive behaviour, high-grade malignancy, and/or poor prognosis. Ki-67 labelling indices are significantly higher in aggressive-type PTCs than in conventional-type PTCs [30]. Hirokawa M et al., reported a case of CMTC that had a high Ki-67 labelling index (15%), despite its excellent prognosis [30]. In our study, aggressive histological features like necrosis and mitosis were absent. Hence, Ki67 and apoptosis were not counted. The absence of mitosis and necrosis in our cases may be due to the indolent course in our cases with no aggressive behaviour, although two of our cases had late recurrence as regional lymphnodal metastasis.

The CMTC is generally associated with a relatively indolent clinical course and good prognosis. Cases with high proliferative index and/or poorly differentiated features can be particularly aggressive [17,23]. Rare cases with multiple lymph node, lung, brain and bone metastases have been reported in the literature [6,19,31]. None of the cases in our study had extra thyroidal organ metastases. Presence of TERT promoter mutations indicate clinical aggressiveness [31]. Management of CMTC typically follows a similar approach to that of PTC. Total thyroidectomy is usually considered sufficient with or without lymph node dissection. Locally advanced cases are managed with external beam radiotherapy [3,32]. RAI with 131I has occasionally been used [18]. All the five cases in our study were also being treated with the same. Owing to the indolent nature, the reported recurrence rate is approximately 8.5%, which is lower than the 16.1% recurrence rate observed in classical PTC and the disease related mortality in these cases was 2%, which is similar to the 2.5% reported in classical PTC cases [3,27].

CONCLUSION(S)

The CMTC is a unique thyroid carcinoma with distinct cytomorphological, IHC and molecular characteristics. CMTC is frequently misdiagnosed as tall cell or columnar subtype of PTC. Pathologist need to be alert when there is a mixture of patterns and nuclear features are not typical; it is recommended to perform panel of IHCs including TTF1 and thyroglobulin. The clinical implication in recognising this entity is that CMTC is said to have an indolent course compared to PTC and might not always require radioactive iodine therapy. This unique diagnosis warrants screening for FAP, particularly if the patient has multifocal disease. Through systematic screening, colon cancer can be detected in its incipient stages, before clinical symptoms become apparent.

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