Journal of
Clinical and Biomedical Investigation

Mini Review

Bajaj A, J Clin Biomed Invest 2021, 1:1

The Flowing Cellule-Medullary Thyroid Carcinoma

Anubha Bajaj *

Consultant Histopathologist, AB Diagnostics, India.

Correspondence to: Anubha Bajaj, Consultant Histopathologist, AB Diagnostics, India.

Received date: February 03, 2021; **Accepted date:** February 15, 2021; **Published date:** February 22, 2021

Citation: Bajaj A. (2021) The Flowing Cellule-Medullary Thyroid Carcinoma. J Clin Biomed Invest 1(1): pp. 1-4. doi: 10.52916/jcbi21404

ABSTRACT

Medullary thyroid carcinoma is a malignant neuroendocrine neoplasm engendered from calcitonin secreting C cells or para-follicular cells of ultimobranchial body situated upon neural crest. Majority of hereditary medullary carcinomas are engendered by gain of function germline mutations within RET proto-oncogene. Medullary carcinoma demonstrates variable morphology and configures cellular nests, cords or follicles with spherical, plasmacytoid, polygonal or spindle-shaped tumour cells incorporated with granular, eosinophilic to amphophilic cytoplasm with secretory granules, spherical nuclei with finely stippled or coarsely clumped nuclear chromatin with indistinct nucleoli. Medullary thyroid carcinoma is immune reactive to calcitonin, CEA, TTF1, PAX8, calcitonin gene related peptide, ACTH, somatostatin, gastrin releasing peptide, neurotensin, low molecular weight keratin, chromogranin A and B, synaptophysin, neuron specific enolase or progesterone receptors. Medullary thyroid carcinoma requires segregation from neoplasms such as Hürthle cell carcinoma, metastatic neuroendocrine carcinoma, anaplastic or poorly differentiated thyroid carcinoma or paraganglioma-like variant, De Quervain's thyroiditis, follicular thyroid carcinoma, Graves' disease, intestinal carcinoid tumour, Multiple Endocrine Neoplasia (MEN) type II, papillary thyroid carcinoma, thyroid lymphoma, solitary thyroid nodule, thyrotoxicosis or toxic nodular goitre. Medullary carcinoma can be appropriately managed with total thyroidectomy and cervical lymphadenectomy for regional lymph node metastasis. Tumour progression or reoccurrence can be monitored with evaluation of serum calcitonin and CEA.

Keywords:

Thyroid carcinoma, Tumour, Graves' disease, Thyroidectomy.

Introduction

Medullary thyroid carcinoma is a malignant neuroendocrine neoplasm engendered from calcitonin secreting C cells or para-follicular cells of ultimobranchial body situated upon neural crest. Certain small cell carcinomas manifest as variants of medullary thyroid carcinoma. Paraganglioma -like variant is an exceptional subtype associated with deposition of melanin pigment. Additionally designated as C cell carcinoma, solid carcinoma with amyloid stroma or parafollicular cell carcinoma, medullary thyroid carcinoma may concur with C cell differentiation and emerge as a sporadic tumefaction or familial neoplasm. Medullary carcinoma is frequently situated upon junction of upper and middle segment of thyroid lobes. Sporadic or non hereditary medullary carcinoma is a solitary lesion manifesting an obscure aetiology and is commonly discerned between 40 years to 60 years. Few sporadic neoplasms may display gain of function germline mutations within RET proto-oncogene. Familial or hereditary medullary carcinoma is frequently bilateral, multi-centric and accompanied by C cell hyperplasia. Young subjects are commonly incriminated with mean age of disease emergence at 35 years [1,2].

Familial neoplasms may configure as a component of MEN IIA or MEN IIB syndrome, Familial Medullary Thyroid Carcinoma (FMTC) syndrome, von Hippel-Lindau disease or neurofibromatosis. Majority of hereditary medullary carcinomas are engendered by gain of function germline mutations within RET proto-oncogene. Commonly, exon 6/M918T genetic mutation ensues. Tumefaction is generally detected upon screening for serum calcitonin levels or mutational analysis of RET oncogene upon peripheral blood. Genomic mutations of HRAS and KRAS occur in neoplasms devoid of RET mutation.

Genetic fusion MYH13-RET is infrequent in neoplasms devoid of RET/RAS chromosomal mutation. Besides, genetic fusions as GFPT1-ALK and EML4-ALK may be discerned. Medullary micro-carcinoma is incidentally discovered, frequently bilateral and exhibits a magnitude of ≤ one centimetre. Regional lymph node metastasis is infrequent. Medullary micro-carcinoma is commonly associated with prophylactic thyroidectomy. Tubular (follicular) variant is composed of neoplastic cells configuring follicular structures typically layered with neoplastic cells, resembling solid tumour segments. Lumina of various neoplastic follicles may be imbued with colloid-like substance or appear vacant. Tumefaction may simulate follicular thyroid carcinoma. Medullary carcinoma represents as a painless thyroid tumefaction. Upon thyroid scan with radioactive iodine tracer, neoplasm manifests as a 'cold' nodule. Regional lymph node metastases are frequent. Commonly, lymph nodes of central compartment and ipsilateral or contralateral jugulo-carotid lymph node chains are implicated. Distant metastasis may ensue. Serum calcitonin levels appear concurrent with tumour burden. Subjects demonstrating tumour metastases manifest severe diarrhoea or flushing. Certain neoplasms may secrete ACTH or corticotrophin-releasing hormone and induce Cushing's syndrome [1,2].

Upon gross examination, sporadic neoplasms characteristically

appear as singular, well circumscribed, grey to tan, non-encapsulated tumefaction. Familial neoplasms are commonly bilateral and represent as solid, firm, grey, tan or yellow, multiple, infiltrative tumour nodules. Enlarged lesions demonstrate foci of haemorrhage or necrosis. Tumefaction is generally confined to middle or upper portion of thyroid gland, segments associated with elevated density of C cells. Micro-carcinoma is a neoplasm <1 centimetre magnitude. Besides, tumefaction <0.5 centimetre magnitude associated with absence of clinically detectable metastatic disease can be designated as micro-carcinoma [1,2]. Cytological examination exhibits a cellular aspirate composed of spherical, elliptical, plasmacytoid or spindle-shaped cells disseminated singularly or configuring miniature clusters. Tumour cells enunciate abundant cytoplasm, eccentric nuclei and 'salt and pepper' nuclear chromatin. Pink, azurophilic, intracytoplasmic granules or intra-nuclear pseudo-inclusions may be discerned. Amyloid deposits are occasional.

Paraganglioma-like variant is predominantly constituted of elliptical to spindle-shaped epithelial cells manifesting cohesive, well circumscribed, three dimensional cellular clusters. Isolated, individual or bizarre tumour cells are exceptional. Stromal amyloid or colloid aggregates are absent. Tumour cells depict an inconspicuous cytoplasm, nuclear grooves, intra-nuclear inclusions, significant nuclear atypia, bi-nucleation and coarse, granular nuclear chromatin [1,2].

Upon microscopy, medullary carcinoma demonstrates variable morphology or may simulate diverse malignant thyroid neoplasms. Commonly, tumefaction configures cellular nests, cords or follicles or an admixture of aforesaid patterns. Tumour cells appear spherical, plasmacytoid, polygonal or spindle-shaped and are incorporated with granular, eosinophilic to amphophilic cytoplasm with secretory granules. Tumour nuclei are spherical and demonstrate finely stippled or coarsely clumped nuclear chromatin with indistinct nucleoli. Nuclear pseudo-inclusions are occasional. Mitotic figures are minimal. Intervening stroma enunciates calcitonin or amyloid deposits, coarse calcification or occasional psammoma-like bodies and appears significantly vascular with glomeruloid configurations or elongated cords of vascular articulations. Intra-tumour mucin pools may be discerned. Foci of angio-lymphatic tumour invasion are frequent. Features such as significant neutrophilic infiltrate, oncocytic tumour cells or papillary tumour configuration are infrequent. Uninvolved thyroid follicles may appear entrapped within tumour periphery [1,2].

Familial medullary carcinoma is associated with C cell hyperplasia whereas sporadic tumefaction appears devoid of aforesaid hyperplasia. Medullary micro-carcinoma delineates complex microarchitecture with solid tumour configuration, desmoplastic stroma and focal amyloid deposits. Tumour cells appear spheroidal, polygonal, spindle-shaped or plasmacytoid. Concurrent C cell hyperplasia is frequent [1,2].

Diverse subtypes of medullary carcinoma appear devoid of prognostic significance and mandate differentiation as

- Amphicrine variant is composed of tumour cells imbued with mucin and intra-tumour calcitonin
- Angiosarcoma-like variant demonstrates cleft-like spaces and focal haemorrhage
- Follicular variant is constituted of neoplastic follicles incorporating eosinophilic secretion
- Giant cell variant is an aggressive tumefaction comprised of enlarged cells imbued with bizarre tumour nuclei [1,2]
- Melanotic variant exemplifies focal deposits of melanin pigment.
- Oncocytic variant simulates Hürthle cell adenoma or carcinoma. Tumefaction is traversed by prominent fibro-vascular septa [1,2]
- Paraganglioma-like variant exhibits nested tumour cells or nest-like tumour configuration accompanied with pigmented dendritic cells akin to sustentacular cells
- Small cell variant is an aggressive neoplasm simulating small cell pulmonary carcinoma.
- Spindle cell variant is exclusively constituted of spindle-shaped tumour cells
- Squamous cell variant may exhibit foci of squamous differentiation

Besides, clear cell variant, papillary variant, pseudo-papillary variant or encapsulated variant may be discerned. Ultrastructural examination exhibits a singular, membrane bound electron dense, intracytoplasmic granule. Tubular (follicular) variant enunciates secretory granules, apical microvilli and well configured desmosomes adjacent to luminal poles. Secretory granules of magnitude 130 nm or 280 nm demonstrate calcitonin [1,2].

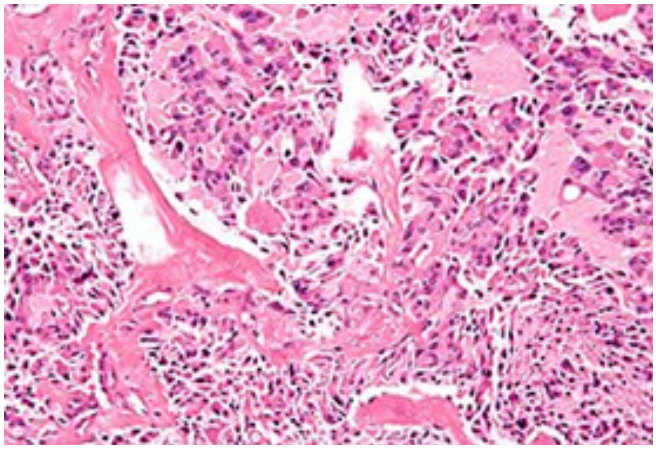

Figure 1: Medullary carcinoma depicting nests and aggregates of enlarged tumour cells with abundant, eosinophilic cytoplasm, uniform to hyperchromatic nuclei, broad fibrotic bands and lack of mitosis.

TNM staging of medullary thyroid carcinoma is denominated as:

Primary tumour

- TX: Primary tumour cannot be assessed
- T0: No evidence of primary tumour
- T1: Tumefaction ≤ 2 centimetres and confined to thyroid
- T1a: Tumefaction is ≤ 1 centimetre and confined to thyroid
- T1b: Tumefaction is between 1 centimetre to 2 centimetres and confined to thyroid
- T2: Tumefaction is between 2 centimetres to 4 centimetres and confined to thyroid

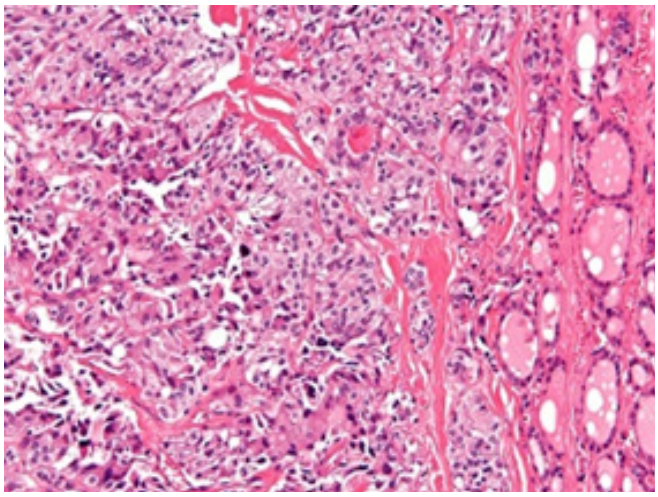

Figure 2: Medullary carcinoma depicting sheets, cords and miniature follicles of neoplastic cells with abundant eosinophilic cytoplasm, enlarged or uniform vesicular nuclei and bands of fibrous tissue traversing tumour parenchyma. Compressed, colloid filled follicles abut the tumour.

- T3: Tumefaction is >4 centimetres or extension beyond thyroid commences
- T4a: Tumefaction is moderately advanced, extends beyond thyroid and infiltrates adjacent tissues as larynx, trachea, oesophagus or vagus nerve
- T4b: Tumefaction is significantly advanced and infiltrates vertebral column or adjacent, enlarged blood vessels [2,3]

Regional lymph nodes

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis present
- N1a: Tumour extends to lymph nodes circumscribing thyroid gland as pretracheal, paratracheal or prelaryngeal nodes
- N1b: Tumefaction extends to cervical, retropharyngeal or superior mediastinal lymph nodes [2,3]

Distant metastasis

- MX: Distant metastasis cannot be assessed
- M0: Distant metastasis absent
- M1: Distant metastasis into diverse viscera, distant lymph nodes or bones may occur [2,3]

Staging of medullary carcinoma is designated as:

- Stage I (T1, N0, M0):
  Tumour is ≤ 2 centimetre magnitude and confined to thyroid. Regional lymph node or distant metastasis is absent [2,3].
- Stage II is composed of:
  ~T2, N0, M0: Tumour is between 2 centimetres to 4 centimetres and confined to thyroid. Regional lymph node or distant metastasis is absent [2,3].
  ~T3, N0, M0: Tumour is >4 centimetre magnitude with mild extension beyond thyroid. Regional lymph node or distant metastasis is absent [2,3].
- Stage III is comprised of:
  ~T1 to T3, N1a, M0: Tumour magnitude is variable with mild extension beyond thyroid. Metastasis to regional nodes as pretracheal, paratracheal or prelaryngeal lymph nodes is observed. Metastasis to distant lymph nodes or diverse organs is absent [2,3].
- Stage IV A is comprised of
  ~T4a, any N, M0: Tumour magnitude is variable with extension into adjacent soft tissues. Regional lymph node metastasis may or may not occur. Distant metastasis is absent [2,3].
- ~T1 to T3, N1b, M0: Tumour magnitude is variable with mild extension beyond thyroid. Metastasis into cervical, superior mediastinal or retropharyngeal lymph nodes is discerned. Distant metastasis is absent [2,3].
- Stage IVB exhibits
  ~T4b, any N, M0: Tumour magnitude is variable with tumour extension into vertebral column or adjacent, enlarged blood vessels. Regional lymph node metastasis may or may not occur. Distant metastasis is absent [2,3].
- Stage IVC enunciates:
  ~any T, any N, M1: Tumour magnitude is variable and extension beyond thyroid may or may not occur. Regional lymph node metastasis may or may not be discerned. Distant metastasis are present [2,3].

Medullary thyroid carcinoma is immune reactive to calcitonin, CEA, TTF1, PAX8, calcitonin gene related peptide, ACTH, somatostatin, gastrin releasing peptide, neurotensin, low molecular weight keratin, chromogranin A and B, synaptophysin, neuron specific enolase or progesterone receptors. Congo red stain can be employed to discern intra-tumour amyloid deposits. Immunocytochemistry for calcitonin, CEA or thyroglobulin can be adopted with thin layer cytology. Paraganglioma-like variant is immune reactive to calcitonin or S100 protein. Fontana-Masson stain can be utilized to ascertain melanin deposits. Small cell variant of medullary carcinoma is immune reactive to calcitonin. Tubular (follicular) variant appears immune reactive to calcitonin or calcitonin gene related peptide. Luminal substance is variably immune reactive to calcitonin. Medullary thyroid carcinoma is immune non reactive to thyroglobulin or oestrogen receptors. Paraganglioma-like variant is immune non reactive to HMB45. Tubular (follicular) variant is immune non reactive to thyroglobulin [3,4].

Medullary thyroid carcinoma requires segregation from neoplasms such as Hürthle cell carcinoma, metastatic neuroendocrine carcinoma, anaplastic or poorly differentiated thyroid carcinoma or paraganglioma-like variant, De Quervain's thyroiditis, follicular thyroid carcinoma, Graves' disease, intestinal carcinoid tumour, Multiple Endocrine Neoplasia (MEN) type II, papillary thyroid carcinoma, thyroid lymphoma, solitary thyroid nodule, thyrotoxicosis or toxic nodular goitre. Medullary thyroid carcinoma demonstrates elevated levels of serum calcitonin and CEA. Tumour progression or reoccurrence can be monitored with evaluation of serum calcitonin and CEA. Exceptionally, serum calcitonin may be normal. Medullary carcinoma can be appropriately managed with total thyroidectomy and cervical lymphadenectomy for regional lymph node metastasis. Total thyroidectomy is particularly suitable for treating familial medullary carcinoma [3,4].

Medullary micro-carcinoma is amenable to thyroidectomy and dissection of lymph nodes confined to central or lateral neck, contingent to serum calcitonin levels. Factors associated with inferior prognostic outcomes are sporadic medullary carcinoma, advanced tumour stage, incriminated elderly males, enhanced mitotic activity, cervical lymph node metastases or vascular tumour invasion. In contract to MEN II A, individuals with medullary carcinoma concurrent with MEN II B demonstrate an aggressive clinical course. Neoplasms exhibiting RET/m918T genetic mutation display an unfavourable clinical outcome. Tumefaction with RAS chromosomal mutation expounds minimally aggressive clinical course. Factors delineating favourable prognostic outcomes emerge as tumour incrimination within young females, familial medullary carcinoma or medullary micro-carcinoma. Medullary micro-carcinoma exhibiting adverse outcomes is accompanied by systemic symptoms, metastatic disease upon initial tumour discernment, desmoplastic stroma or deposition of amyloid [3,4].

References

1. Master SR, Burns B. Medullary Thyroid Cancer. Stat Pearls International 2021 Treasure Island, Florida.

2. Guo QQ, Zhang SH, Niu LJ, et al. (2019) Comprehensive evaluation of medullary thyroid carcinoma before surgery. Chin Med J (Engl) 132(7): pp. 834-841.

3. Opsahl EM, Akslen LA, Schlichting E, et al. (2019) Trends in Diagnostics, Surgical Treatment, and Prognostic Factors for Outcomes in Medullary Thyroid Carcinoma in Norway: A Nationwide Population-Based Study. Eur Thyroid J 8(1): pp. 31-40.

4. Kaliszewski K, Ludwig M, Ludwig B, et al. (2021) Update on the Diagnosis and Management of Medullary Thyroid Cancer: What Has Changed in Recent Years? Cancers (Basel) 14(15): p. 3643.