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RESEARCH ARTICLE

MANAGEMENT OF MEDULLARY THYROID CARCINOMA

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Abstract

Medullary thyroid carcinoma (MTC) compromises 3–10% of all thyroid cancers and arises from parafollicular C cells.This study reviews the current management of medullary thyroid carcinoma emphasizing the current practice in the preoperative diagnosis and evaluation of patients with MTC, and surgical treatment options for managing the thyroid and neck lymph nodes.

Introduction:-

Thyroid cancer is the most common endocrine malignancy and accounts for approximately 1% of all human malignancies. Carcinoma of the thyroid gland is considered to be an indolent disease; many affected individuals die of other causes. An estimated 1,500 patients die of this disease each year (Gilliland et al., 1997).

Four tumor types account for more than 90% of thyroid malignancies: papillary thyroid carcinoma [PTC], follicular thyroid carcinoma [FTC], medullary thyroid carcinoma [MTC], and anaplastic thyroid carcinoma (Gulben et al., 2006).

Medullary thyroid carcinoma (MTC) compromises 3–10% of all thyroid cancers and arises from parafollicular or calcitonin-producing C cells. In contrast to papillary and follicular thyroid carcinomas, no difference in distribution between females and males is observed (Jason et al., 1999).

Histologically, MTC is characterized by uniform polygonal cells with finely granular eosinophilic cytoplasm and central nuclei. C cell hyperplasia is associated with MTC, being the precursor lesion in malignant transformation to MTC. MTC is usually a slow growing tumor with an indolent clinical course, with the overall 10-year survival being reported to be around 50% (Bergholm et al., 1997).

MTC may be sporadic (75% of cases), or may occur as a manifestation of either the hereditary syndrome Multiple Endocrine Neoplasia type 2 (MEN 2A or MEN 2B) (25% of cases), or rarely as an isolated familial syndrome (FMTC). In familial forms, tumors are usually bilateral and multifocal (Catharina et al., 2007).

The most common clinical presentation of sporadic medullary thyroid carcinoma is a solitary thyroid nodule. Patients with bulky disease, local or metastatic disease, with extremely high levels of calcitonin may have severe secretory diarrhoea as a principal symptom. Patients with familial MTC who are identified by screening with stimulation tests or with molecular analysis (detection of RET gene mutation) are usually identified before the development of macroscopic disease (Evans et al., 1999).

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Before the availability of genetic testing for familial MTC, basal and stimulated serum calcitonin levels were used to screen patients. Sequential calcitonin and carcinoembryonic antigen (CEA) measurements are still important as a tumor marker for surveillance of patients with MTC.

Various nuclear imaging studies have been evaluated in patients with MTC to identify gross and occult metastases. 131I thyroid scans are of no utility since MTC does not concentrate iodine. Similarly, thallium as well as technetium scans have been used with minimal efficacy. Several studies used somatostatin receptor scintigraphy in the setting of MTC. The results are promising for this imaging technique, but occult lesions smaller than 1 cm as well as liver lesions are still missed with this technique. Although not specific, ultrasound, MRI, CT, PET, and PET/CT imaging are increasingly being used in the management of patients with MTC (Moley et al., 2003).

Chemotherapy and external beam radiotherapy (EBRT) are, for the most part, ineffective against MTC, rendering surgical resection the only definitive therapy. For patients with sporadic MTC who are not identified by biochemical or genetic screening, the appropriate operation in most cases is total thyroidectomy, central node dissection, and ipsilateral modified radical neck dissection. Total thyroidectomy is indicated in this sporadic setting because a small proportion of lesions may be multifocal and because it may not be clear at the time of operation whether a patient is an index case of familial disease or the disorder is a true sporadic case. Because all familial syndromes have a high propensity for multifocal tumors, total thyroidectomy is always indicated. Combined with thyroid resection, a central lymph node dissection should be performed, removing lymphoid tissue from the level of the hyoid bone superiorly to the innominate vessels inferiorly and laterally to the jugular veins (Feig et al., 2006).

Pathology of Thyroid Cancer

Risk Factors:

Approximately 9% of thyroid cancers are associated with prior radiation exposure. The risk of cancer from radiation increases linearly with doses up to 20 Gy, with thyroid ablation occurring at higher dose levels. The risk of developing thyroid cancer is inversely related to age at exposure. A history of exposure to ionizing radiation in childhood is a major risk factor for thyroid malignancy, almost always of the papillary type.

Aside from radiation exposure, few environmental risk factors have been confirmed for thyroid carcinoma. Hormonal factors and dietary intake of iodine, retinol, vitamin C, and vitamin E have been suggested to play a role in the etiology of thyroid cancer that has yet to be defined.

Associations have been described between thyroid cancer and several other inherited syndromes, including familial polyposis, Gardner syndrome, and Cowden disease (familial goiter and skin hamartoma). In addition, papillary thyroid cancer may occur with increased frequency in some families with breast, ovarian, renal, or central nervous system malignancies.

Medullary thyroid cancer occurs with a higher frequency in patients who have Hashimoto thyroiditis. The mechanism underlying these associations is not well understood (Gagel et al., 1996).

Molecular genetics of the thyroid cancer:

Over the past ten years, significant progress has been made in the identification of genes linked to the pathogenesis of thyroid cancer. Studies of the patterns of genetic alterations present in thyroid tumors suggest that there are differences in the pathogenesis of the different thyroid tumor types, which most likely account for the range in biological behavior observed among thyroid cancers.

The RET proto-oncogene, which is located on chromosome 10 and encodes a tyrosine kinase receptor, is believed to play a role in the pathogenesis of both hereditary and sporadic medullary thyroid

carcinomas (MTCs) and papillary thyroid carcinomas (PTCs). Activating point mutations in the RET proto-oncogene of parafollicular C cells have been detected in virtually all hereditary forms of MTC, including familial MTC, multiple endocrine neoplasia 2A (MEN 2A), and MEN 2B, which account for approximately 25% of MTCs. Mutations in the RET proto-oncogene have also been found in sporadic MTC, although different codons of the RET proto-oncogene are affected. Rearrangements of the RET proto-oncogene in thyroid follicular cells are considered to be an early event in the development of Pecs. Nearly all patients with autosomal dominant MEN 2A or MEN 2B will develop MTC; screening for germline RET mutations has been invaluable in the early identification of patients who have a genetic basis for their disease. The discovery of the RET proto-oncogene has had significant clinical impact, affecting the screening and prophylactic treatment of patients who are members of the MEN kindreds. Somatic mutations in the Ras oncogene have been found in both benign and malignant thyroid tumors, and thus also seem to be an early event in thyroid tumorigenesis, although some reports suggest that Ras mutations are more prevalent in follicular thyroid carcinomas (FTCs).

Medullary thyroid carcinomas represent 5% of all thyroid cancers. 75% of tumors are sporadic, and 25% occur as part of an autosomal dominant hereditary syndrome. Sporadic MTC often presents in the fifth decade as a unilateral solitary nodule. Patients with familial MTC more commonly present in the fourth decade with multifocal nodules in the upper poles of both thyroid lobes, where there is the greatest concentration of C cells. Bilateral C-cell hyperplasia is believed to be a precursor to the development of hereditary MTC. Histologically, MTC is an intermediate-defined, nonencapsulated, invasive mass composed of spindle-shaped or rounded cells separated by fibrous septa and amyloid deposits. Positive immunohistochemical staining for calcitonin, carcinoembryonic antigen, and amyloid aids in the diagnosis of MTC. Medullary carcinomas are slow growing but have a propensity to metastasize early, usually before the primary tumor reaches 2 cm. Fifty percent of patients have regional metastases at the time of diagnosis. Cervical and upper mediastinal lymph nodes are the usual sites involved. Ten-year survival rates for MTC depend on the extent of disease at presentation and are 90% when disease is confined to the thyroid gland, 70% when cervical metastases are present, and 20% when distant metastases are present. The prognosis for patients with MTC falls between that of patients with undifferentiated tumors and patients with well-differentiated tumors. Poor prognostic factors include age greater than 50 years at diagnosis, metastases at the time of diagnosis, and association with MEN 2B. Seventy percent of patients with MEN 2B have metastases at the time of diagnosis of MTC and of these patients, fewer than 50% survive 5 years.

Histopathology of Medullary Thyroid Carcinoma:

Under macroscopic examination, medullary thyroid carcinoma shows a hard and firm consistency and is either chalky white or red in color on cross-section.

Histologically, medullary thyroid carcinoma is pleomorphic with spindleshaped or rounded cells characteristically organized in a nested

pattern. Mitoses are not very frequent, nuclei are usually uniform, and the eosinophilic cytoplasm is characterized by the presence of secretory granules. Deposits of amyloid substance are frequently (60–80%) observed between tumoral cells (Sletten et al., 1976).

Discussion:-

Medullary thyroid cancer (MTC) currently accounts for5%–10% of all thyroid cancers. The clinical course of MTC varies from an extremely indolent tumor that can go unchanged for years to an aggressive variant that is associated with a high mortality rate. The majority of MTCs are sporadic, but approximately 20% of MTCs are hereditary (Rebecca et al., 2015).

KaptanGullben et al. (2006) stated that approximately 84% of cases are sporadic.

Pellegriti et al. (2003) found in their study that about 70% of cases were sporadic.

According to the review, no difference in distribution between females and males is observed. The clinical appearance is mainly in the fourth and fifth decades, but a wide range of age at onset is present (Bhattacharyya, 2003).

According to the review, the most common clinical presentation of sporadic medullary thyroid carcinoma is a thyroid nodule, either single or belonging to a series of nodules configuring the clinical picture of amultinodular goiter (Gharib et al., 1992).

Sophie Leboulleux et al. (2004) stated that Patients with sporadic MTC usually present with a palpable thyroid nodule.

Moley and Jeffrey stated that Respiratory complaints, hoarseness and dysphagia are observed in about 15% of patients at the time of initial presentation (Moley et al., 2010).

Moley& De Benedetti (1999) and Scollo et al. (2003) found that lymph node metastases are found in 20–30% of patients with an MTC of less than 1 cm in diameter, in 50% of patients with a tumour > 1–4 cm in diameter and in up to 90% of patients with a tumour> 4 cm in diameter.

Rebecca Sippel et al. (2008) stated that a neck ultrasound should be performed as part of the initial evaluation of any patient with a new diagnosis of MTC. The ultrasound can be used to look for additional thyroid tumors as well as the presence of suspicious neck lymphadenopathy. A contrast-enhanced computed tomography (CT) of the chest, mediastinum, and abdomen is also recommended as part of the metastatic evaluation of a patient with an initial diagnosis of MTC.

Tollin et al. (2000) stated that ultrasound guided fine-needle aspiration biopsy is the method of choice for determining the risk of malignancy.

Rosalinda Camargo et al. (2007) found that the overall accuracy of fine-needle aspiration biopsy (FNAB) was 85.8%. Therefore, they concluded that this methodology may improve the preoperative diagnosis of thyroid cancer.

Concerning the surgical treatment of MTC.

Catharina IhreLundgren et al., 2007) stated that total thyroidectomy and centrallymph node dissection is the minimum appropriate treatment. More extensive neck dissection is indicated for larger tumours, multicentric disease, or where central node involvement is demonstrated.

Concerning the operative and post operative complications,

Jason Fleming et al. (1999) found in their study that postoperative complications included seven cases (17%) of permanent

hypoparathyroidism . There were no iatrogenic recurrent laryngeal nerve injuries; one patient required recurrent nerve resection to achieve complete tumor extirpation.
Jason Fleming et al. (1999) reported in their study that the median follow-up of the patients was 35 months; local recurrencewas documented in 13% of patients.
Brierley et al. (2012) reported on the use of adjuvant cervical external beam radiation therapy (EBRT) in high-risk patients.
Jason B. Fleming et al. (1999) reported in their study that 62.5% of the patients received EBRT after surgery.
KaptanGullben et al. (2006) reported in their study that the 5 year survival rate was 51%; recurrence developed in 34% of patients during the follow-up period, 28% of patients had distant metastases.

Conclusion:-

Medullary thyroid carcinoma (MTC) is a rare form of thyroid cancers; females are more susceptible to MTC than males (F/M =2.3/1), the majority of female patients diagnosed in the fourth or fifth decades of life, but MTC occurs earlier in males in third or fourth decades (mean age is 38 years old). survival rate is 75%, mortality rate is 25%, 3 years survival is 80%, 5years survival is 60%, 8 years survival is 10%. 75% of the patients received.

Medullary Thyroid Carcinoma is a more aggressive disease that dosenot concentrate radioactive iodine; so aggressive surgery including total thyroidectomy and at least central neck dissection is the treatment of choice.

Adjuvant external radiotherapy; external beam radiation therapy and systemic chemotherapy have a role in treatment of metastatic MTC.

Recommendations:-

• All patients undergoing thyroidectomy for MTC should be followed with postoperative serial serum calcitonin levels to survey for persistent or recurrent disease.
• All family members of a patient with MTC should be screened for hypercalcitonaemia and ret proto-oncogene mutation.
• Good medical data registry and patients' files that facilitate follow up of the patients and medical researches.

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