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MEDULLARY CARCINOMA OF THE THYROID AND RELATED SYNDROMES

CASE REPORT

CLINICAL SUMMARY:

This is the second [redacted] admission for this 33-year old [redacted] male geologist admitted through the emergency room on [redacted] with a chief complaint of fever, chills, and cough and died on [redacted] The patient was first seen at [redacted] in [redacted] 1972 with an acute upper G.I. bleed. He required a transfusion of 6 units of blood and was treated medically. An upper G.I. series revealed a duodenal ulcer and achalasia of the esophagus. Chest x-ray demonstrated prominent bilateral hilar adenopathy with right middle lobe collapse. Lab values on admission were hemoglobin 8.2, hematocrit 23, white blood cells 15.7, plasma glucose 264, BUN 34, total protein 5.9, albumin 3.2, sodium 133, potassium 4.2, bilirubin total 3.0, SGOT 27, and alkaline phosphatase 31. Upon discharge lab values were white blood cells 16, hematocrit 35, hemoglobin 11.8, BUN 7, SGOT 42, and alkaline phosphatase 64. The patient underwent a surgical procedure for achalasia and hilar lymph node biopsy. The hiatal hernia was repaired and the pathological report on the biopsy revealed metastatic adenocarcinoma of a subaortic lymph node but no involvement of the esophagogastric lymph node. Etiology of the primary tumor was unknown but thought to be either lung or pancreas. The patient began receiving cobalt therapy during [redacted], receiving 2,000 rads and another 2,000 rads in [redacted] to both hila, supraclavicular areas, and to the mediastinum. He did fairly well after radiation therapy and gained weight during this period. He noted no side effects or symptoms. The patient was seen in clinic on [redacted] and was thought to be doing well at that time. Four days prior to his last admission the patient noted the onset of malaise and a subjective low grade fever. He was seen in Thoracic Clinic 3 days prior to admission a chest x-ray showed a possible infiltrate in the right lower lobe. Two days later he began to feel much worse and was begun on antibiotics. The next morning he noticed that his fever was worse and he had a cough productive of a minimal amount of sputum. Physical exam on admission: Blood pressure 140/84, pulse 144, respiration 32, temperature 104; he was noted to be in acute distress, pale, and having coughing spasms. Several small cervical nodes were felt on examination of the neck. Increased breath sounds on the left base near the scar of the thoracotomy and rales over the right base were noted on chest exam. The heart rate was rapid with a hyperdynamic murmur grade II/VI and an S4 gallop. The guaiac test was negative. The nailbeds were cyanotic. Chest x-ray revealed hilar blurring and a right lower lobe infiltrate. Sputum showed a mixed flora with moderate polys and a rusty color. Past history revealed the patient sustained rib fractures in 1967 secondary to an automobile accident and subsequently developed bilateral bronchopneumonia while hospitalized. He has smoked a pack-a-day or less of cigarettes for the past 10 years. The patient stated that his father died of adenocarcinoma of the stomach, his mother died of breast cancer, and an uncle died of lung cancer. Following admission the patient was begun on 600,000 units of penicillin every 6 hours. On [redacted] he became progressively dyspneic and hypoxemic. Oxygen was increased 100% but the pO_2 only increased to 50. He became hypotensive, anuric, and deteriorated rapidly, dying at 4 P.M. on [redacted]. The clinical impression was 1) adenocarcinoma of the hilar lymph nodes--

primary unknown, 2) radiation pneumonitis with a large right-to-left shunt, 3) hepatomegaly, and 4) bacterial bronchopneumonia.

GROSS PATHOLOGY:

Lungs: Bilateral masses were noted, each near the hilum. A 2- 2.5 cm. grey-white lesion appeared to arise from one of the left lobar bronchi. The lesion in the right lung was slightly larger, 2.5 - 3 cm. in diameter contiguous with and slightly compressing the right middle lobe bronchus. Both tumor masses were firm and solid and neither contained gross areas of ossification nor hemorrhage. Several small hilar and mediastinal nodes were replaced by grey-white tumor tissue. Areas of the right middle lobe were atelectatic. From the small vessels of the right middle and right upper lobe, thick red to greyish-white thrombi could be expressed from the surface.

Adrenals: The adrenals were involved bilaterally with tumor. The left adrenal weighed 38 grams and contained a 4 x 3 cm. poorly defined, firm and greyish-white mass with an area of hemorrhage in the tumor. The right adrenal weighed 40 grams and contained a 1.5 x 1.5 cm. firm greyish-white node without obvious areas of necrosis and hemorrhage. Neither tumor completely obliterated the adrenals as areas of yellow cortex were noted in both glands.

Thyroid: The external surface of the thyroid appeared normal and the capsule remained intact. On cut surface a 1.5 cm. firm greyish-white well demarcated nodule was embedded within the left lateral lobe. Infiltration into surrounding tissue or cervical nodes was not apparent grossly.

MICROSCOPIC PATHOLOGY:

Thyroid: The uninvolved thyroid did not reveal a nodular change. In the sections of tumor tissue the cells were arranged in solid sheets or irregular groups separated by a hyaline amyloid containing stroma. The tumor cells were pleomorphic. Many were round or spindle shaped, all lacking a consistent form throughout the tumor. The nuclei were dark and hyperchromatic with a low nuclear to cytoplasmic ratio.

Adrenals: The pattern of cells in the tumor varied in arrangement. The stroma was loose and quite vascular. Some of the cells were grouped into irregular cords and others arranged in clusters and nests. The cytoplasm contained both coarse and fine granulation. The nuclei were small, round and darkly staining.

Lungs: A generalized pneumonitis was noted in all lung sections examined with interstitial fibrosis, thickened alveolar walls, and occasional hyaline membranes. Many of the alveolar cells were hyperplastic and desquamated. Bronchonpeumonia was seen in patchy areas of several sections. The alveolar capillaries were congested and the space filled with neutrophils and fibrin. Special stains demonstrated gram-negative rods in areas of tissue involved with bronchopneumonia. The area of neoplastic tissue revealed a pleomorphic pattern of solid nests or clusters of small,

uniformly staining cells and areas of a trabecular-like pattern. The stroma in several areas of the tumor tissue had undergone a hyaline change seen on routine staining. Both vascular and lymphatic invasion was demonstrated and tumor emboli were seen in several of the large vessels.

SUMMARY:

Initially, the patient presented with a gastrointestinal bleed. Upper GI series revealed a duodenal ulcer and further studies demonstrated bilateral hilar masses and achalasia of the esophagus. A thoracotomy was performed to correct the esophageal defect and to take a lymph node biopsy. Subsequent pathological examination of the biopsy revealed metastatic adenocarcinoma of a subaortic lymph node and either pancreas or lung was thought to be the primary site. The patient received 4,000 rads of irradiation tothe mediastinum over a 6-week period and apparently did well for several weeks up until 4 days prior to his final admission when he developed malaise and a low grade fever which progressed to include chills, a productive cough, and respiratory distress. Clinically the patient was thought to have radiation pneumonitis with a right to left shift. Microscopic examination confirmed the diagnoses of radiation pneumonitis. All lung sections revealed the characteristic interstitial fibrosis of alveoli, thickening of alveolar walls, and hyaline membrane formation. But, in addition to the changes induced by radiation the patient had a bacterial bronchopneumonia with sepsis. Chest film upon final admission showed a possible infiltrate in the right lower lobe. Sections of lung revealed patchy areas of bronchopneumonia and gram-negative rods in the alveolar lumens. Postmortem lung and blood cultures showed Enterobacter to be the etiologic agent responsible for both the bronchopneumonia and sepsis. In a review of radiation pneumonitis, J. Chandler Smith describes a late stage of penumonitis in which progressive fibrosis develops with a dry irritative cough and worsening in dyspnea.

Microscopic examination of the lesions noted grossly revealed a very interesting combination of tumors. Histologically the characteristics of the thyroid tumor were consistent with a type of solid, nonpapillary "medullary carcinoma" as described by Hazard et al. This tumor because of its undifferentiated nature is often grouped with the highly malignant tumors, yet the clinical behavior is that of a low grade malignancy. In a study of 21 cases classified as medullary carcinoma of the thyroid, the gross features were similar to this case. The neoplasms were hard, firm and greyish-white ranging in size from 1.5 - 8.0 cm. in diameter and did not disrupt the glandular nor invade surrounding tissue. Microscopically perhaps the most distinguishing feature was the atromal amyloïd present in all 21 cases.

Histologically the lung tumors resemble a bronchial carcinoid. The location at the hilum favors carcinoid. But the bilateral tumors are most probably metastases from the medullary carcinoma of the thyroid for several reasons. First, the association of a bronchial carcinoid, medullary thyroid tumor and bilateral pheochromocytoma is highly unlikely and review of the literature has failed to demonstrate a case of this nature. Second, the neoplasm in some instances may resemble other neoplasms but the finding of amyloid stroma is of special significance in assessing the nature of the tumor to be a metastatic lesion from a medullary carcinoma. Amyloid stroma was noted in the lung masses. Finally, electron micrographs of the lung lesions failed to demonstrate argentaffin granules which are commonly noted in carcinoids.

In summary, this patient died of bronchopneumonia superimposed on radiation pneumonitis secondary to irradiation for bilateral hilar masses thought to be adenocarcinoma. At autopsy the patient was found to have a medullary carcinoma of the thyroid with bilateral metastases to the lungs and a bilateral pheochromocytoma.

HISTORY OF MEDULLARY CARCINOMA OF THYROID (MCT)

1932 - Eisenberg and Wallerstein (Arch. Path. 14:818, 1932) note frequent thyroid carcinoma in patients with pheochromocytoma.

1959 - Hazard, Hawk, and Crile (J. Clin. Endocrinol. 19:152, 1959) define MCT as a clinicopathologic entity distinct from other thyroid neoplasms. Prior to 1959, this tumor was called "anaplastic" or "undifferentiated" carcinoma of thyroid, but Hazard et al were impressed with its less aggressive behavior and named it MCT.

1961 - Sipple identified a syndrome of thyroid carcinoma and pheochromocytoma with 6 cases (Am. J. Med. 31:163, 1961).

1965 - E.D. Williams finds 15 case reports, (J. Clin. Path. 18:288, 1965) adds 2 more and identifies the carcinoma as the medullary or solid type with amyloid stroma. Since then 265 cases have been reported.

1965 - Schimke identifies familial MCT as an autosomal dominant (Ann. Int. Med. 63:1027, 1965).

1966 - E.D. Williams adds neuromata to the syndrome (J. Pathol. Bacteriol. 91:71). So do Ruppert et al (Metab. 15:537).

1967 - E.D. Williams suggests that MCT might hypersecrete calcitonin (J. Clin. Path. 20:395), which had been discovered 6 years earlier by Copp et al (Proc. Can. Fed. Biol. Soc. 4:17, 1961).

1968 - Neher's group in Basel and McIntyre's in London jointly isolate calcitonin in astonishingly high amounts from MCT's (Nature, 200:984) and thus substantiate suspicions that MCT was a C-cell or parafollicular cell carcinoma.

1968 - Melvin et al add hyperparathyroidism to the syndrome (P.N.A.S. 59:1216).

1968 - Schimke et al (NEJM 279:1) add marfanoid habitus to the syndrome, a feature first noted by Mielke in 1965 (Gastroenterology, 48:379).

PARAFOLLICULAR OR C-CELLS OF THE NORMAL THYROID

Origin of the C-cells: They migrate to the lateral thyroid with the ultimolbranchial body when it joins the gland (Carvalleihra and Pearse Histochemie 8:175, 1967). But Pearse now theorizes that they originate from the neuroectodermal cells of the neural crest, migrate to the ultimobranchial body, and travel with it to the lateral thyroid (In Calcitonin 1969, Springer-Verlag, p. 36).

Morphology: Polyhedral epi-and parafollicular cells with characteristic round granules with electron-dense cores and a double membrane closely applied. These granules strongly suggest a secretory product, probably a polypeptide or protein, resembling granules of polypeptide secreting endocrine glands.

Function: Bauer and Teitelbaum (Lab. Invest. 15:323, 1966) isolated the secretory granules of thyroid homogenates, found them identical to parafollicular cells and demonstrated that they contain calcitonin activity.

Pearse found specific immunofluorescence of C-cells after incubation of thyroid with anticalcitonin antiserum (Pearse, Proc. Royal Soc. B. 164:476, 1966), proving them to be calcitonin secreting cells. Pearse emphasizes 3 cytochemical characteristics of C-cells which he says are common to all 8 cell types which secrete polypeptides of MW <8000 Amine (catechols 5-HT, other) and Precursor (of amines) Uptake and Decarboxylase (of amino acids) and calls these cells the "APUD series" and believes they are all of neuroectodermal origin.

Calcitonin M - Isolated from human MCT and thought to be the normal human hormone.

32 amino acids with entire molecule probably required for activity, though many substitutions possible.

Hypocalcemic action through specific inhibition of osteoclastic bone resorption (Reynolds and Minkin. Calcitonin 1969 p. 168). Precise mechanism uncertain.

Directly increases renal clearance of calcium (Pak et al, ibid).

THE TUMOR

I. Pathology

Gross - Firm, grayish, gritty 1-8 cm. nodules without a capsule. May be sharply demarcated from normal tissue, but often blend imperceptably into normal tissue. Multicentric.

Light Microscopic - 3 main cell types: Polyhedral, spindle-shaped cells (like an oat cell carcinoma), round cells, or plasmacytoid or mixtures of these neoplastic cells. Bi- or trinucleate cells are often present. Mitoses rare. Cells are arranged in sheets with fibrous septae dividing tumor into nests or compartments. Occasionally pseudofollicles filled with amyloid = diagnostic of MCT. Usually in the stroma or near the cells and may represent amorphous polymerized secretory product. Generally stains with Congo Red. Never seen outside the tumor. There is a 4th cell type, the stromal cell, probably a modified fibroblast. When spindle cells predominate, there is less amyloid. Calcification common. Ljungberg et al (Brit. M.J.: 1:279, 1967) found tinctorial characteristics of chromaffin tissue, in common with carcinoid and oat cell tumors. Bordi et al (Virchows Arch. Abt. A. Path. Anat. 359: 145, 1972) found a different cell type in their tumor, one resembling an ectopic ACTH-producing tumor. In other tumors ganglion cell-like cells with dendritic process are demonstrable by silver impregnation (Tateishi et al, Cancer: 30, 755, 1972).

Unique secretory granules in tumors seen electromicroscopically resembling those in parafollicular cells (Aoi: Okajima Folia Anat. Jap. 42: 63, 1966). Silver grains attach to granules as in other polypeptide producing cells. These authors note a close relationship between number of granules and the amyloid deposits, suggesting that the latter is secretory product accumulating in pseudofollicles. However, it could be degenerated cell debris. Granules are polarized, facing pseudofollicles. They have electron-dense cores, and a double membrane closely applied or separated by a thin halo (Bordi et al, 1972).

II. Clinical Features

A. Vital MCT Statistics

Sex Distribution - 58% in females, well below the female preponderance characteristic of other thyroid neoplasms.

Percent of Thyroid Neoplasms - 3.5 - 9.4% but Williams believes >10%. Hill et al (Medicine 52:141, 1973) find MCT in 12.6% of all males with thyroid Ca and 7.5% of females.

Racial Distribution - No racial or ethnic differences from cancer in general.

Age Distribution - 10 to 82 years with a mean age of 47.2 years (Hill et al, ibid; Fletcher, Arch. Surg. 100:257, 1970).

Familial vs. Sporadic - No good statistics. Hill found familial MCT in only 3 of 67 cases of MCT. However, he did not screen with serum calcitonin levels so this is certainly an underestimate of familial incidence. Melvin found hypercalcitoninemia in 27% of members of an MCT family.

B. Local Manifestations of MCT

Symptoms - Usually none. Patient may discover an anterior neck mass (most common chief complaint). 7% have symptoms of distant metastases, e.g., bone pain, etc. Metastases may be discovered before a primary thyroid tumor is detectable.

Signs - Single or multiple thyroid nodules or diffuse enlargement of gland or cervical nodes - Euthyroid.

Lab - "Cold nodule(s)" on scan. Mediastinal adenopathy and fibrosis not uncommon. Needle biopsy or open biopsy of gland is diagnostic if amyloid is found (Ljungberg, Acta. Cytol. 16:253, 1972). Not a recommended procedure, however.

Radiologic Findings of Tumor - Homogeneous conglomerate calcification on one of both sides of trachea - very dense and irregular resembling inflammatory calcification. Calcified metastatic lymph nodes look tuberculous. Calcification of hepatic metastases. Such calcification is pathognomonic and was found in the thyroid in 35% of MCT's examined for this. Bone metastases, usually lytic, sometimes sclerotic in 10%. Superior mediastinal masses, diffuse interstitial lung metastases, resembling sarcoidosis. Also fibrosis in lungs and mediastinum due to desmoplastic tendency of tumor.

C. Endocrine Manifestations of Appropriate Secretory Products of the Tumor

1) Hypercalcitoninemia - No manifestations. Only 3 cases of hypocalcemia has been reported in MCT. Calcium usually is normal or high. Calcium tolerance is slightly increased in MCT (Melvin, Rec. Prog. Horm. Res. 28, 399, 1972).

2) Humoral GI tract stimulant - 32% of MCT patients have diarrhea, the most common single early symptom! 3-30 watery stools per day containing undigested food but no blood, mucus, or fat. Sudden irresistible urge to defecate. Diarrhea may precede diagnosis of MCT by months and MCT should be in the differential diagnosis of unexplained diarrheal disease. Rapid

transit rate and excessive water and electrolyte loss demonstrated and these disappear with complete removal of tumor. Williams (Lancet 1:22, 1968) reports increased plasma prostaglandins E_2 and $F_{2\alpha}$ in blood of 2 MCT patients with diarrhea and in 4 of 7 tumors; they increase intestinal motility and might cause diarrhea. Diarrhea is equally common in familial and sporadic cases. Controlled by small doses of antispasmodics and opiates and is, therefore, probably a motility disturbance.

3) Hyperhistaminasemia - No symptoms but histamine flare after intracutaneous injection may be absent (Baum and Adler, Arch. Optical. 87:574, 1972).

D. Endocrine Manifestations of Ectopic Hormone Production by the Tumor

1) Serotonin - The carcinoid syndrome is relatively rare in MCT, (Moertel et al, 1965), but probably will not explain frequent flushing and diarrhea. Hill found one classical carcinoid syndrome but the tumor tissue contained low levels of serotonin, but MCT is a definite source of ectopic serotonin production.

2) ACTH - Cushing's syndrome occurs in 2 - 4% of MCT cases. Melvin et al (Metab. 19:831, 1970) reported 7 cases and Williams has seen 10 such cases. (Since pheochromocytoma may also produce Cushing's, the MCT is not necessarily the source of the ACTH.) MCT is the only thyroid tumor known to cause Cushing's. High plasma ACTH and cortisol return to normal after thyroidectomy unless ACTH-secreting metastases or pheo is present.

3) MSH - Could explain pigmentation in Cunliffe's case.

E. Special Laboratory Tests Relating to Secretory Products of Tumor

1) Calcitonin -

a) Basal serum calcitonin - Radioimmunoassay or bioassay showing increased calcitonin in plasma or tumor (1000-8000 x normal thyroid concentration) is diagnostic. Basal hypercalcitoninemia present in 75% of MCT patients. 11 of 12 MCT patients reported by Keiser et al at NIH (Ann. Int. Med. 78:561, 1973) had an elevated basal serum calcitonin level by radioimmunoassay (>1.0 ng/ml). Normals are always <0.38 ng/ml.

b) 4-Hour Calcium - (0.01 mg/kg/hr) or glucagon infusion test; both stimulate calcitonin secretion normally and can be used as provocative tests in suspected cases of MCT with a normal basal level. Calcium is much better than glucagon, and induced marked rises in 12 of 55 members of an MCT kindred who had normal basal calcitonin levels (Melvin et al -1972). to more than 2 ng/ml. Normals rise to <0.6 ng/ml.

c) Urinary Calcitonin (bioassay or immunoassay) - Normals have <1 ng/ml, all MCT's have >1 ng/ml.

d) Screening for MCT: Basal calcitonin assay of plasma is an excellent screening test for MCT! In 14 of 48 members of 2 MCT kindreds basal serum calcitonin was elevated; 13 were operated on; MCT not detectable by any other means, was found in 7 (Black et al, Arch. Surg. 104:579, 1972). All family members of an MCT patient should have a serum calcitonin assay yearly. Anyone with basal hypercalcitoninemia should probably have a total thyroidectomy.

2) Serum Histaminase - Serum histaminase, a normal C-cell product, is elevated (> 3.5 units/ml) in 50% of MCT patients (0.8 - 150 units/ml) and was highest with metastases. In parallel calcitonin histaminase determinations in MCT patients, only 30% had ↑ histamine while 75% had ↑calcitonin. No difference between histaminase levels of familial and sporadic MCT. A good marker of the disease if positive and an index of course of the disease. It falls with Rx, and thus reveals presence of residual tumor or recurrence. False positive in pregnancy and after heparin injection. In tumor it ranges from 260-13,000 units/g, compared to 6-14 units/g in normal tissues (Baylin et al, NEJM 283:123g, 1970).

3) DOPA Decarboxylase - Tumor contains 20-90 times as much as adjacent thyroid. Not yet measured in serum and not a clinical test as yet. (Beaven, Ann. Int. Med. 78:561, 1973).

4) Hypercorticotropinemia - Not different from other ectopic ACTH production, but it may suppress with dexamethazone. This should not exclude the diagnosis.

5) Prostaglandins - Immunoassay for prostaglandins (Levine and Van Vanakis, BBRC 41:1171, 1970) in serum of 6 familial MCT cases (Melvin, 1972), all without diarrhea, and 6 sporadic MCT cases, 3 of whom had diarrhea. None of the 6 familial cases had high prostaglandins of the A B E series. Of the sporadic cases one of the diarrhea group had an elevated serum prostaglandin (8-12 ng/ml) in the ABE series. F_2^{α} was not elevated.

F. Natural History of the Tumor -

Difficult to ascertain due to rarity of untreated diagnosed cases. Probably intermediate in malignancy in the spectrum of thyroid carcinoma. There are 3 histologic types (Wells, Ann. Int. Med. 78:572, 1973) and one has the impression that the more cellular type is most malignant:

Histology	No. of Patients	No. with Metastases	Age at Surgery (Yrs)	Interval Dx - Surgery (Yrs)
Cellular	4 (17%)	0	17-27	0
Intermediate	9 (39%)	4 (44%)	15-53	0-8
Fibrotic	10 (44%)	4 (44%)	17-64	0-9
TOTAL	23	8 (36%)		

Often very indolent with one report of 36 year survival after initial diagnosis of thyroid disease. Another untreated patient lived 12 years after detection of neck mass (Wells). Hill et al observed a brother of an MCT patient who refused Bx of a neck mass growing steadily for 30 years. Finally when his nephew and niece developed MCT he had it removed and MCT of thyroid and cervical node was found. 18 year survivals after discovery of metastases has been described more than once. Williams (J. Clin. Path. 19:114, 1966) has suggested the existence of benign C-cell adenomas which may explain the long course of some patients. At the other extreme, a 15-year old girl (Hill et al) noted a neck mass in December 1963; in August 1964 she died of widespread metastases.

Early regional lymph node metastases are the rule; 6 of 11 patients of Melvin et al (NEJM, 285: 1115, 1971) had lymph node involvement before clinically detectable thyroid disease was noted (they had been found to have hypercalcitoninemia and were explored for this reason).

Multicentric. Earliest lesions seem to appear first in upper posterior pole of gland, where C-cells are most common. Only 29% unilateral. Spreads throughout thyroid and in 60-75% to cervical lymph nodes (Freeman and Lindsey- AMA Arch. Path. 80:575, 1965), 38% to mediastinal nodes (Ibanez et al: Cancer, 20: 706, 1957). Later lungs, liver, adrenals, bones, heart, pleura, and brain in decreasing order of frequency (Kaplan and Peskin - Surg. Clin. Of North America 51:125, 1971).

G. Treatment of Tumor:

a. Surgery: Wells now advocates total thyroidectomy with routine resection of the central cervical lymph nodes and lateral cervical nodes if involved. Wells favors an ipsilateral radical or modified neck dissection, but Crile and Melvin both feel that a radical neck does not help. Melvin recommends clearing of mediastinal lymph nodes through a split sternum

whenever cervical nodes are involved. NEVER permit a subtotal for MCT because bilateral involvement is probably always present; even when thyroid appears grossly normal microscopic tumor nests are likely to be present. 6 of 6 subtotals had a recurrence (WELLS). Always take out central nodes. Even when complete removal of a tumor is impossible take out as much as you can because patients seem to improve.

NOTE: Always exclude pheochromocytoma and hypercortisolism before neck surgery for MCT to avoid hypertensive crisis or shock during surgery.

b. Irradiation: No good data as yet. Certainly indicated in inoperable cases and when complete removal of tumor is not certain. Probably not effective; 3 of Melvin's 4 cases did poorly.

c. Thyroid hormone Rx - Useless

d. Chemotherapy - Aminoguanidine reduces serum histaminase in all MCT patients but fails to shrink tumor or even reduce serum calcitonin (Melvin, 1972). Bleomycin under study.

DISORDERS ASSOCIATED WITH MCT

A. Classification of the MCT Syndrome Complex

1. MCT or functioning C-cell of carcinoma of thyroid alone.

2. MCT calcitonin hypersecretion plus "ectopic" hyperproduction of one or more of the following:

Serotonin, ACTH, MSH

3. MCT with or without #2 but with hyperparathyroidism due to parathyroid hyperplasia or adenoma.

4. MCT with or without 2 and/or 3 but with pheochromocytoma.

5. MCT with or without any or all of the above but with mucosal neuromata.

6. Other features: a. Marfanoid habitus

b. Diverticula

c. Megacolon

d. Desmoplasia

e. Peptic ulceration

f. Myopathy

g. Pigmentation

7. Any of the above features alone or in any combinations but without MCT.

B. Disorders Associated with MCT

1. Hyperparathyroidism

a. Incidence - Only 21 cases reported with MCT as of 1972 but there were 16 of 25 cases of familial MCT with parathyroid disease in the remarkable "W. kindred" of Keiser et al and of those 12 had hyperplasia which accounts for only 10% of non-familial hyperparathyroidism. True prevalence of hyperparathyroidism in MCT is uncertain, but it occurs in both familial and non-familial cases, although Hill has seen it only in

familial. It is less common with MCT than in Type I multiple endocrine adenomastosis. Five of 15 cases of Kaplan and Peskin had hypercalcemia and 1 had nephrolithiasis.

Hyperplasia may involve 1 or more glands --involvement of all 4 is rare, and the histology resembles pseudoadenomatous hyperplasia of Black and Haff (Am. J. Clin. Path. 53:565, 1970) more than classical chief cell hyperplasia. Calcium may be consistently normal despite hyperplasia and ↑PTH (? biologically inactive immunoreactive secretory product).

Association of Parathyroid Disease with MCT

No. of Patients	↑ Se Ca^{++}	Hypercellularity	Hyperplasia*	Adenoma(s)
45	19	4	27	14

* only 10% of ordinary non-familial hyperparathyroidism

b. Treatment - At the time of thyroidectomy remove only grossly abnormal parathyroid tissue, unless patient is hypercalcemic, in which case all abnormal glands can be removed. NOTE: But beware of hypercalcemia resulting from boney metastases and Gelhorn-Plimpton.

(Tell surgeon to mark parathyroid glands that remain with a suture because he may be back in because of recurrent hyperparathyroidism or MCT.)

NOTE: MCT should be considered whenever a diagnosis of hyperparathyroidism is made. A serum calcitonin should be obtained after surgery when calcium is normal, even if thyroid looked normal. Always ask surgeon to examine the thyroid for tumor.

c. Cause of Parathyroid Disease:

Probably not secondary to hypercalcitoninemia because parathyroid hyperplasia has been found in a patient in the NIH kindred in whom serum calcitonin was normal. Melvin et al (Rec. Prog. Horm. Res. 28:399, 1972) reports PTH was<0.6 ng/ml in 177 normals. In Melvin's J-kindred without basal or calcium-induced hypercalcitoninemia PTH exceeded 0.6 ng/ml in 40%. In 15 patients with nonfamilial MCT serum PTH was normal. Melvin and Keiser both conclude that this is an inherent component of the syndrome, the result a defect in a single gene affecting the neural crest.

2. Pheochromocytoma

a. Incidence - 17% of Hill's MCT group had pheo; 23% of Steiner's familial pheo group had MCT. Only coexist in familial MCT, according to Hill, who believes sporadic cases with Pheo and MCT represent new mutations

of the MCT gene (Knudsen et al, Clin. J. Hum. Gen. 24:514, 1972). True incidence uncertain because either lesion may appear first, and, when it appears first, MCT can kill before the pheo appears. It usually precedes pheo.

b. Character - Bilateral in 46% --same as familial pheo without MCT (Nourok, Ann. Int. Med. 60:1028, 1964) which could be same disease and makes up 33% of all pheos (Hermann and Mornex-Human Tumors Secreting Catecholes - MacMillan Co., N.Y. p. 1). Only 5% bilaterality of spontaneous pheo (Graham, Int. Abstr. Surg. 92:105, 1951). Melvin states it's bilateral in 75% (Rec. Prog. Horm. Res. 28:399, 1972). Always ask surgeon to check both sides.

Less often symptomatic (only 37%) when associated with MCT than when alone. Only 6% have hypertension (Kaplan) suggesting less norepinephrine secretion; but 50% of Steiner's cases had sustained or paroxysmal hypertension. 7 of 11 in NIH kindred had classic pheo symptoms. Malignant pheo reported although histologic evidence without metastases is questioned. [Remember: A pheo can also secrete ACTH and cause Cushing's syndrome.] MCT-associated pheos respond poorly to provocative testing with tyramine.

c. Rx: Always remove pheo before MCT. Never do neck surgery without careful exclusion of pheo by usual methods.

NOTE: Always suspect MCT in a pheo patient and do a calcitonin level after the pheo is removed.

Mucosal Neuromata

a. Small polypoid neuromas, consisting of nerve fiber bundles are often found on the conjunctivae and buccal and lingual mucosa (Williams (J. Path. Sect. 91:71, 1966). Lip and tongue tumors usually before age 20--reported at birth and in first decade. These nodules had been recognized independently of associated disease since 1927. ("Bumpy lip" disease; "barnacle tongue"). Thickened lid margin with elevated cilia.

b. White cords, probably visible myelinated nerves, radiate from the cornea 360° like a sunburst (Baum, Arch. Opth. 87:574, 1972). In sporadic as well as familial MCT.

c. True neurofibromata very rare in MCT.

d. GI ganglioneuromatosis with myenteric and submucosal plexus disease, megacolon, diverticulosis reported. (Cf achalasia of the Parkland case).

Marfanoid Appearance without Marfan's Syndrome - (5%) Arachnodactyly, marfanoid body, pectus excavatus, pes cavus, poorly developed muscles.

Typical Facies - Acromegaloid but not coarse. Unrelated MCT patients resemble each other and suggest family relationship.

Desmoblastosis - Mediastinal and pulmonary fibrosis around metastases. ? humoral factor. Could fibrosis in the thyroid be due to this?

Myopathy - Single case report by Cunliffe et al (Am. J. Med. 48:120, 1970) of 19 year old girl with bumpy lips and tongue, flushing, sweaty, and "floppiness" since age 6 months, weakness. EMG=myopathy. Segmental muscle fiber necrosis, increased interfibrillary granular material shown to be glycogen, enclosed in vacuoles (lysosomes), as in muscle glycogenosis due to acid maltase deficiency. Many mitochondria, some degenerated.

Gynecomastia - 2 cases (Aach and Kissane, Am. J. Med. 46, 961, 1969; Melvin 1972). Ectopic gonadotropins not as yet demonstrated.

RELATIONSHIP BETWEEN MCT COMPLEX AND OTHER POLYPEPTIDE (APUD) PRODUCING ENDOCRINE TISSUE

APUD and other C-cell cytochemical characteristics are shared by many polypeptide-producing cells, G-cells, (gastrin), corticotrophs (ACTH), melanotrophs (MSH), B-cells, (insulin), G-cells (Gastrin), A_2-cells (glucagon), S-cells (secretin), L-cells (pancreozymin), (?) EG cells (GLI), enterochromaffin cells (5-HT, Kinins (?)). Pearse proposes the "unifying hypothesis" that all these endocrine glands, plus parathyroids, thymus, adrenal medulla and paraganglia, and hypothalamus are related through a common, neuroectodermal stem cell in the foregut mucosa. This cell migrated from the neural crest (cf MEA) to the primitive gut, in which they form the enterochromaffin system and the developing endocrine glands which bud off from the foregut, as well as the chromaffin system, including the adrenal medulla. This theory would explain the following observations:

1. Remarkable potential of carcinoid tissue for ectopic production of peptide hormones. A bronchial carcinoid has even been reported to produce calcitonin (Milhaud et al. C.R. Acad. Sci. Ser. D 270:2159, 1970).

2. Argentaffin and chromaffin cells in MCT together with serotonin and catecholamines, and serotonin excess in MCT.

3. Presence of calcitonin in adrenal medulla, thymus, parathyroids.

COMPARISON OF MULTIPLE ENDOCRINE ADENOMA SYNDROME (MEA) I AND MCT COMPLEX ("MEA TYPE 2")

1. Transmission of MEA Type I - Same as Type II:

Familial - Autosomal dominant usually (Case of Mauer et al with negative family history and parents who were cousins only one suggesting recessive inheritance).

Sporadic - not uncommon.

2. Syndromes in MEA I - Differ from Type II.

a. Pituitary adenomas in 55 of 85 cases of MEA I (Ballard)

(1) 42% chromophobe (85% of non-MEA tumors)

(2) 27% eosinophilic with acromegaly (10-14% of non-MEA tumors).

b. Parathyroid Adenomas (85%) or Hyperplasia (different stages of same genetic defect) - Similar to Type II, though hyperplasia more common.

c. Islet cell adenoma or adenocarcinomas.

(1) Multicentric and mixed α- and β-cell types nesidioblastosis-Vance et al).

(2) Hyperinsulinism, hypergastrinism, hyperglucagonemia. Vance suggests that islet hormones cause 2^{O} adrenocortical, parathyroid and pituitary secretion.

d. Adrenal cortical hyperplasia, adenomas, or adenocarcinoma.

(1) Hypercortisolemia with Cushing's most common.

(2) Aldosteronomas rarely (Sutherland et al, 1966)

e. Carcinoid of bronchus (Williams and Celestin, 1962) or intestine (Anderson, 1966; Eschbach, 1962).

f. Thyroid adenomas, nodular hyperplasia colloid goiters, Hashimoto's. These are rare.

g. Pheochromocytoma - Not reported in Type I.