MEDULLARY CARCINOMA OF THYROID PRESENTING AS MILIARY MOTTLING OF THE LUNG

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ABSTRACT

Medullary carcinoma of thyroid gland (MTC) is a rare disease and presenting as miliary shadows in the lung is an even rarer entity. In about 75 % of MTC presents as a sporadic and the rest as inherited, with common associations with (multiple endocrine neoplasia) MEN 2A , MEN2B, Non MEN is familial. It is extremely uncommon to document this condition in the lung. We present a case report of a 36yr old female, a known case of treated pulmonary tuberculosis and hypothyroidism who presented with acute onset respiratory symptoms of 1 week duration for which she was provisionally diagnosed as miliary tuberculosis elsewhere and was put on antitubercular agents. A complete and extensive work-up done on her at our centre revealed medullary carcinoma of thyroid (MTC) with metastasis to lung.

Key Words : *Medullary thyroid cancer, military tubercles, calcitonin.*

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INTRODUCTION:

Medullary thyroid carcinoma (MTC) is a distinct thyroid carcinoma that originates from the parafollicular C cells of the thyroid gland which produce calcitonin. Sporadic, or isolated MTC accounts for 75% of cases and inherited MTC constitutes the rest. Familial MTC constitutes 4% of thyroid cancers.[1] Mutations in the *RET* (Rearranged during Transfection) proto-oncogene is the core problem. This disease usually presents as a solitary thyroid nodule with metastases. Locally advanced disease can present as hoarseness, dysphagia, dyspnoea.

In this case study, we document a patient who presented with fever and acute onset respiratory symptoms for 1 week. Investigations showed anemia and urinary tract infection. Fine needle aspiration cytology (FNAC) of thyroid, breast lump and lymph node tissue revealed similar features suggestive of neuroendocrine tumour. The diagnosis of metastatic medullary carcinoma was clinched with grossly elevated Serum (Sr) Calcitonin.

CASE HISTORY

A 36 yr old female presented with intermittent fever, cough producing mucopurulent sputum, breathlessness at rest and retrosternal right sided chest pain of 1 week duration. She complained of loss of weight and appetite, recurrent episodes of loose stools and generalized myalgia. She was a known hypothyroid patient being treated elsewhere with eltroxin 75μgm/day and 1 year back was put on carbimazole for hyperthyroidism. She also gave history of receiving complete treatment for pulmonary tuberculosis few years back.

On examination she was emaciated, pale and had generalised lymphadenopathy with multiple, discrete, firm and tender lymph nodes. A firm, 2 by 2cm tender swelling was present in the right upper quadrant of the right breast. On local examination of neck, a firm diffuse thyroid swelling measuring 6x2 cms was felt. Her pulse rate was 123/min, respiratory rate was 30/min and blood pressure was 90/60 mm Hg. Cardiovascular system examination was unremarkable except for tachycardia. Respiratory system examination was normal. Laboratory investigations showed anaemia, leucocytosis and raised calcitonin levels while other parameters were within normal limits. (Table 1) In addition, urine culture grew pseudomonal aeruginosa colonies. During the investigations for her present respiratory illness, a thyroid function test was repeated at our centre which showed raised T3 level and carbimazole was stopped immediately.

Table 1: Details of laboratory tests done

LAB TESTS	OBSERVED VALUE	NORMAL RANGE
Haemoglobin	6.5 gm/dL	12- 14 gm/dL
Total Count cells/	16000 cells/ cu.mm	4000-11000 cu.mm
ESR	45 mm/hr	5-12 mm/hr
Urine Examination	Pus cells, trace protein	
Liver Function Test	Normal	
Renal Function Test	Normal	
TSH	4.004	0.4-4.5 mIU/L
Free T4	0.80	0.8- 1.5 ng/dL
T3	2.36	87-180 ng/dL
Blood Culture	No Growth	No Growth
Urine Culture	*Pseudomonas aeruginosa*	No growth
Peripheral Smear	Microcytic hypochromic red blood cells, neutrophilia, adequate platelets	Normochromic normocytic RBC, normal WBC, adequate platelets.
Serum Calcium	9.8	8.4-10.2 meq/dL
Serum Phosphorus	3.4	3-4.5 mg/dL
Serum Calcitonin	1873 pg/ml	0.2- 17 pg/ml

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An ultrasound of the thyroid gland showed multiple nodules in the right lobe of thyroid and soft tissue lesion in the prevertebral region, Echocardiogram revealed a mitral valve prolapse, bicuspid aortic valve, dilated right atrium and ventricle, no vegetations and normal left ventricular function. The chest x-ray showed multiple miliary shadows in bilateral lung fields.(Fig 1a),

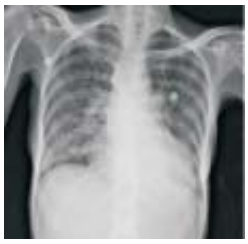

Fig 1 a: Chest x-ray which shows tree in bud appearance(which is classical of a reticulonodular pattern).

Following this a Pulmonologist opinion was sought to rule out reactivated tuberculosis. Biopsies were sent from the breast lump, thyroid and lymph node for histopathological examination. During the course the patient complained of left hip pain for which an orthopaedics opinion was sought. As per advice an x- ray spine (lateral view) was taken which showed a wedge compression fracture at D7-D8 level (Fig 1b).

Fig 1b : X-ray spine (lateral view)which showed a wedge compression fracture at D7-D8 level.

The x-ray pelvis with bilateral hips (AP view) showed a hyperdense lesion in the left femur. (Fig 1c).

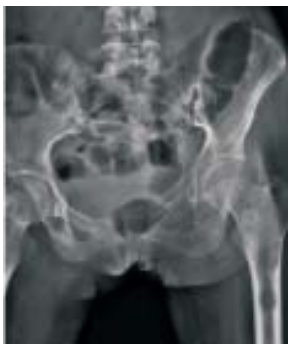

Fig 1c : represents x-ray pelvis with bilateral hips (AP view) showing a hyperdense lesion in the left femur.

CT- chest (Fig 2a and 2b) revealed tree in bud appearance(which is classical of a reticulonodular pattern), multiple nodular opacity, hilar lymphadenopathy and bilateral pleural effusion. The findings on x-rays and CT scans heightened our suspicion on the probability of a metastatic disease.

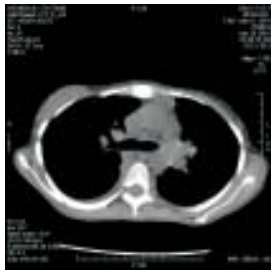

Fig 2(a)

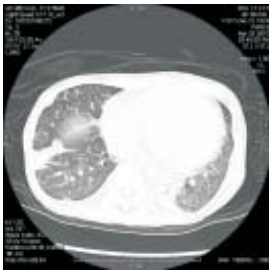

Fig 2(b)

Fig 2a and 2b represent CT chest showing multiple nodular opacity, hilar lymphadenopathy and bilateral pleural effusion.

FNAC OF breast (Fig 3a),thyroid (Fig 3b)and lymph node (Fig 3c) all showed plasmacytoid cells with features suggestive of a common origin of a neuroendocrine tumour. With a provisional diagnosis of metastatic medullary carcinoma, a serum calcitonin level was done which was grossly elevated confirming a medullary carcinoma of the thyroid gland with metastasis to lung,lymph node, breast and bone. Tissue sections studied from breast lump, thyroid and lymph node showed features of medullary carcinoma thyroid.

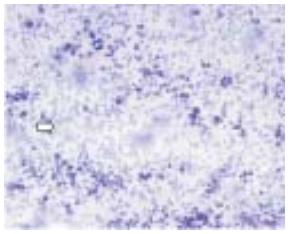

Fig 3(a)

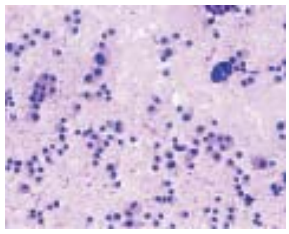

Fig 3(b)

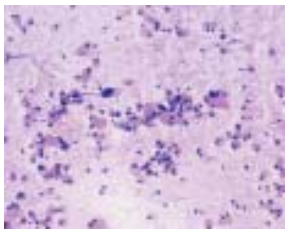

Fig 3(b)

(Fig 3a) FNAC of thyroid, (Fig 3b)breast and (Fig 3c) lymph node all showing plasmacytoid cells in cytological smears.

A final diagnosis of medullary carcinoma of thyroid with multiple metastasis was made. Outcome of the patient could not be assessed as the patient expressed desire to undergo treatment elsewhere for personal reasons.

DISCUSSION

Medullary carcinoma of the thyroid (MTC) is a distinct thyroid carcinoma that originates in the parafollicular C cells of the thyroid gland which produce calcitonin.[1]

Sporadic, or isolated, MTC accounts for 75% of cases, and inherited MTC constitutes the rest. Familial MTC constitutes 4% of thyroid cancers and most commonly associated with MEN 2A, MEN2B, Non MEN familial.[2]

Sr. calcitonin will be grossly elevated (>100 pg/ml)). Hence it can be used as a screening tool. Calcitonin levels crucial for diagnosis as in it is used as a biochemical marker, diagnostic tool, stage assessor, a guide to postoperative management and prognostic marker. Calcitonin is over 95% sensitive for detection of MTC when high.

The pathology lies in mutations in the *RET* (REarranged during Transfection) proto-oncogene, a receptor protein tyrosine kinase encoded on chromosome 10 Risk Stratification based on the subtype is also possible. Clinical Features usually are solitary thyroid nodule with metastases. Locally advanced disease can present as hoarseness, dysphagia, dyspnoea. Increased calcitonin causes diarrhoea by increased intestinal electrolyte secretion. It may be associated with paraneoplastic syndromes like pheochromocytoma, hyperparathyroidism,Cushings, carcinoid syndrome which should always be treated prior to the primary carcinoma. This cancer usually follows an indolent course and does not spread from the cervical lymph node system for months though lymph node involvement occurs early. Systemic metastases when present occur in the bones, liver, lung and brain.

Age above 50 yrs, metastasis, MEN 2B associaton and higher postoperative plasma Calcitonin levels are associated with poor prognosis.[3]

Diagnostic evaluation includes Calcitonin levels[4] (> 100 pg/ml), RET gene study with subtype in patient and family members for missense mutation if required, 24 hr urine catecholamine test to R/O MEN (Pheochromocytoma must always be treated before MTC). A diagnostic workup of such a case includes Pentagastrin Induced Raise in Calcitonin[5] (need not be done if genetic assay available), Ultrasound thyroid with cervical lymph nodes and FNAC to confirm the tumour, CT neck, chest and abdomen for evaluating metastasis.

Medical treatment includes Tyrosine Inhibitors targeted at the RET gene, but these drugs are in clinical trial phases. Motesanib a VEGF (Vascular Endothelial Growth Factor) inhibitor has shown encouraging results in its efficacy in maintaining a stable disease in clinical trials.Other drugs are sorafenib, sunitinib.[6,7]

Surgical measures are total thyroidectomy with central neck dissection. For positive surgical margins and mediastinal disease, adjuvant radiotherapy may be used.[3,5] Follow up after surgery includes serial measuremental of calcitonin every 6 months. A higher post surgical calcitonin doubling time is associated with poor prognosis[8]. For metastatic thyroid cancers, surgery cannot be performed. Chemotherpay with Adriamycin is the best agent in this scenario, but has a very poor success rate (.20%). External beam radiotherapy may be useful.

Prevention is by family screening programmes and doing prophylactic thyroidectomy in those having cancer induced RET gene[9]. The future in treatment lies in gene therapy in the form of corrective, immunomodulatory and cytoreductive gene therapy.

In conclusion this case is presented to heighten the clinical awareness of medullary carcinoma of thyroid masquerading as miliary tuberculosis.

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