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RESEARCH ARTICLE

WHEN A LARGE PNEUMO-MEDIASTINALNEUROENDOCRINE CARCINOMAREVEALS A FAMILIAL MULTIPLE ENDOCRINE NEOPLASIA TYPE 1: A CASE REPORT

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Abstract

Multiple endocrine neoplasia type 1 (MEN1) is an uncommon hereditary condition transmitted in an autosomal dominant pattern, notable for its wide variability in clinical presentation. Neuroendocrine tumors of the bronchi and lungs (bpNETs) usually remain clinically silent and are most frequently identified incidentally on imaging examinations. We report the case of a 43-year-old patient with a history of recurrent renal colic with emission of stone in urine, infertility and family history of tumors in 1st and 2nd degree. He has been followed-up in oncology for a bulky high grade mediastino pulmonary neuroend ocrine carcinoma measuring 13 cm in long axis, undergoing chemo-radiotherapy and he has been referred to our department for diagnostic work-up of hypercalcemia, parathyroid in origin, which was discovered by chance during a pre-chemotherapy work-up.Conventional and functional imaging confirmed a right parathyroid adenoma, then the patient benefited from parathyroidectomy. On hypothalamic-pituitary MRI, he had a pituitary macroadenoma measuring 15 mm long. Genetic testing for mutation of the MEN1 gene is in progress. Familial MEN1 is diagnosed when an individual exhibit one of the major clinical features of the syndrome and has a first-degree relative already confirmed with MEN1. Affected patients often face a diminished quality of life and a markedly shorter life expectancy than that of the general population.

Introduction:-

Multiple endocrine neoplasia type 1 (MEN1) is an uncommon hereditary tumor syndrome with autosomal dominant transmission, notable for its wide variability in clinical presentation. It results from heterozygous germline mutations in the MEN1 gene situated on chromosome 11q13.MEN1 is a tumor suppressor gene that encodes the menin protein,

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which plays a role in the regulation of gene transcription[1,2,3].Classically defined by the presence of tumors in the 'three Ps' [4]: parathyroid glands, pituitary gland, and pancreatic neuroendocrine tissues. MEN1 may also manifest with additional endocrine tumors, such as adrenocortical neoplasms, foregut-derived neuroendocrine tumors outside the pancreas, and, rarely, pheochromocytomas.

The prevalence of multiple endocrine neoplasia type 1 (MEN1) is estimated to range from 3 to 10 cases per 100,000 individuals, highlighting its status as a rare hereditary tumor syndrome. In MEN1, neuroendocrine tumors most commonly arise in the parathyroid glands, with subsequent involvement of the duodenum, pancreas, adrenal, pituitary glands, thymus, and lungs. The penetrance of MEN1 mutations is age-dependent, typically manifesting from approximately 10 years of age and progressively increasing to nearly complete penetrance by 60 years, with almost all mutation carriers exhibiting clinical manifestations by this age. Penetrance varies depending on the affected organ, with parathyroid involvement being the most pronounced, nearly complete, and typically the earliest to manifest. A diagnosis of familial MEN1 [6] is established when a patient presents with one of the primary clinical manifestations of MEN1 and has a first-degree relative with a confirmed MEN1 diagnosis.

Case presentation:

The patient was 43 years old and had a medical history of recurrent renal colic with emission of stone in urine, infertility, gastric cancer in the maternal grandmother which led to her death 15 years ago, liver cancer in the mother which led to her death seven years ago and his sister suffering from lung cancer. He was followed-upwith oncology team for a bulky, poorly differentiated, high-grade mediastino-pulmonary tumor, 13 cm long **(figure 1)**, and underwent chemo-radiotherapy.

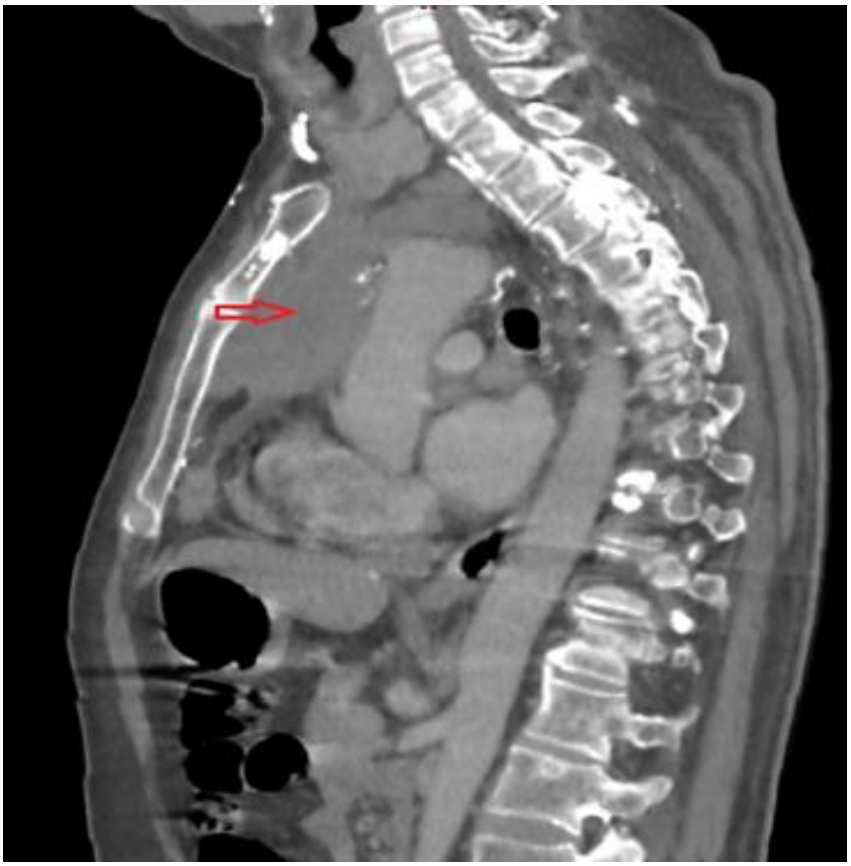
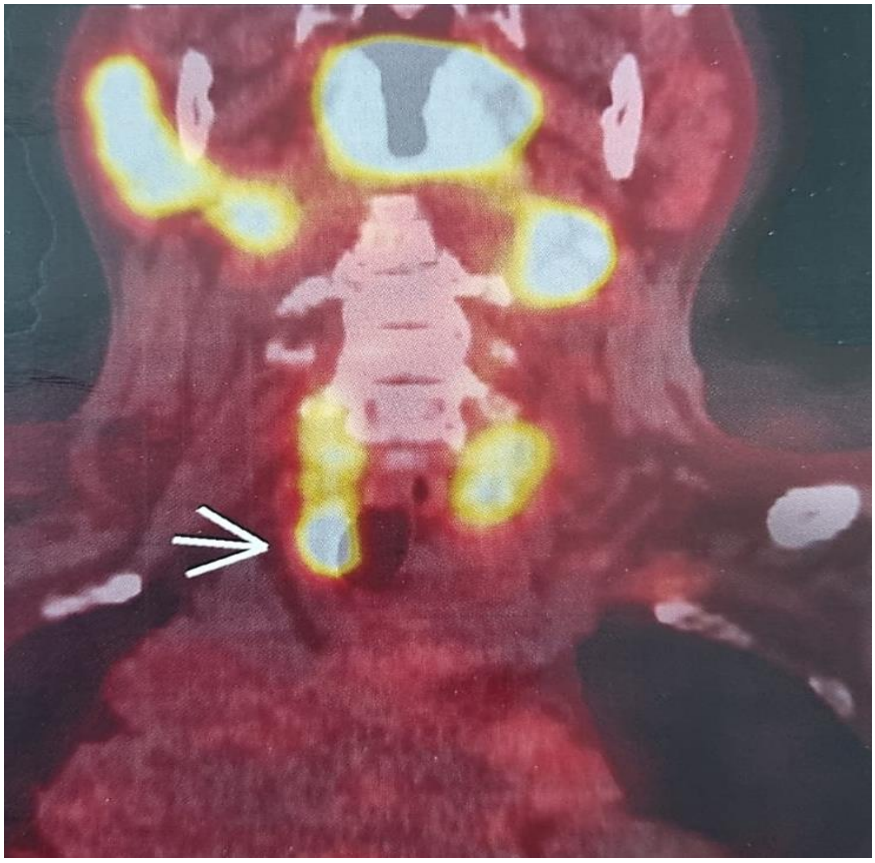


Figure 1Sagittal thoracic CT scan showing a bulky mediastino-pulmonary tumor measuring 13 cm in greatest diameter (arrow).

He presented with hypercalcemia, incidentally discovered during a pre-chemotherapy work-up. Clinical examination showed a stable patient in good general condition (WHO performance status 0), with stable hemodynamic, respiratory, and neurological parameters. Multiple punctiform lentigines were noted on the face, trunk, and back. The remainder of the clinical examination was unremarkable. Biologically, her initial calcium level was 113 with a PTH(parathyroid hormone) of 178ng/ml (4×N) and a normal 24-hour urinary calcium of 279mg/24h.Cervical ultrasound showed a nodule opposite the inferior pole of the right lobe of the thyroid, measuring 20 mm in height and 12x10 mm in transverse diameter.MIBI scintigraphy showed a focus of fixation below the inferior pole of the right lobe, suggestive of a parathyroid adenoma **(Figure 2).**

Figure 2 Parathyroid uptake below the inferior pole of the right thyroid lobe on MIBI scintigraphy.



Although the patient has received parenteral rehydration at a rate of threeliters per day and oral rehydration (twoliters per day), calcium levels were still rising, reaching 131mg/L, which is why cinacalcet 30mg daily was introduced. Blood calcium levels fell to 108mg/L 48 hours after the introduction of cinacalcet. The patient was referred to the otorhinolaryngology-head and neck surgery department for a right parathyroidectomy. The anatomical examinationof the specimen revealed a parathyroid adenoma.

Both the immediate recovery and long-term follow-up were satisfactory, and no recurrence was observed.Assessment of the impact of the hypercalcemia revealed correct renal function with creatinine at 6.46mg/l, and on renal ultrasound multi-lithiasis of the kidneys, more marked on the right, with no impact on the excretory cavities. Vitamin D was 26ng/ml, and osteodensitometry (ODM) showed osteoporosis. Cardiac electrocardiograms and trans-thoracic echocardiography revealed no abnormalities. The ophthalmological assessment was normal.For the diagnosis of MEN1, the hypothalamic-pituitary MRI revealed a pituitary macroadenoma measuring 15×7.7×9mm**(figure3).**

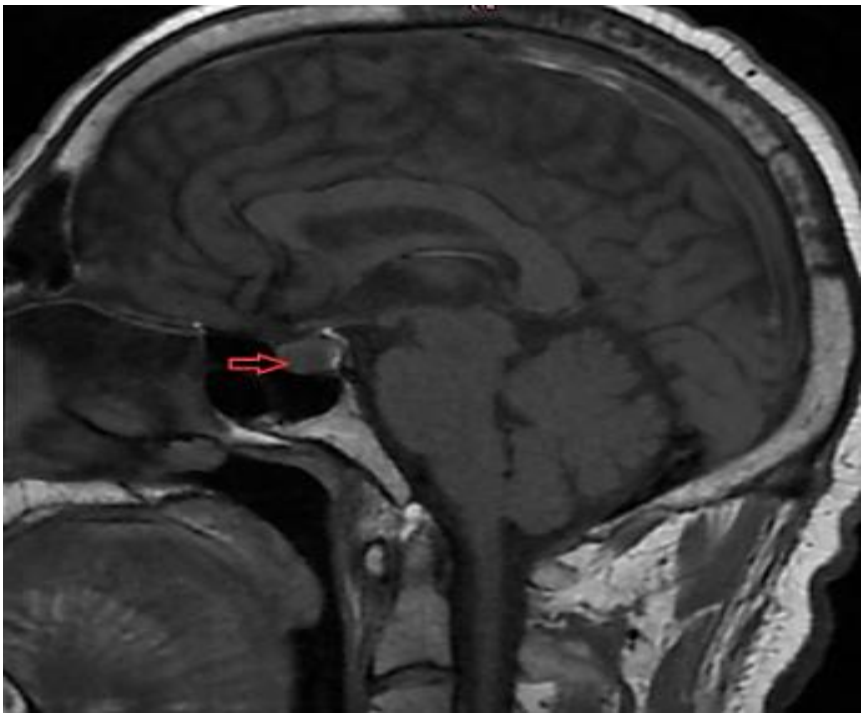


Figure 3Sagittal brain MRI of the sellar region demonstrating a pituitary macroadenoma (15×7.7×9mm) (arrow).

Upper endoscopy was done searching for other neuroendocrine tumor of gastrointestinal tract, the results were normal. Examination of the mammary glands was normal.As for intracranial effect of pituitary macroadenoma, there were no signs of intracranial hypertension, no visual disturbances, no vomiting, and no cerebrospinal fluid leakage from the nose, neither headache.

Hormonal evaluation of the endocrine axes revealed 8-hour cortisol levels at 124.7ng/ml, 24h urinary free cortisol is normal at 59nmol/24h, normal FT4 at 11.9pmol/l, hyperprolactinemiathat result from pituitary stalk compression, with prolactin level at 89.3ng/ml, IGF1 (Insulin-like Growth Factor 1) at 498ng/ml (1.8×N), normal testosterone level at 5.66ng/ml and normal gonadotropins (FSH 7.37mIU/ml and LH 5.51mIU/ml).Genetic testing for mutations in the MEN1 gene stillin progress.

Discussion:-

The diagnosis of MEN1 may be confirmed through clinical findings, family history, or genetic evidence. A clinical diagnosis is made when an individual develops at least two tumors linked to MEN1. A familial diagnosis applies when a patient presents with a single MEN1-associated tumor but has a first-degree relative affected by MEN1. A genetic diagnosis is established when a germline mutation in the MEN1 gene is identified.[7].The primary endocrine tumors associated with MEN1 include parathyroid adenomas or hyperplasia, gastroenteropancreatic neuroendocrine tumors, and pituitary adenomas.

In addition to the most common manifestations, adrenal tumors, bronchial carcinoids (BC), thymic carcinoids (TC), and skin tumors may also develop. Bronchial and thymic carcinoids [8] are reported in 3.6–8.4% of patients with MEN1. Primary hyperparathyroidism (HPT) is typically the first clinical manifestation in patients with MEN1, occurring in 90% to 100% of cases. This is commonly followed by the development of pancreatic neuroendocrine tumors (pNETs), which may be functional (20%–70%), with gastrinomas being the most frequent, or nonfunctional (80%–100%). Pituitary adenomas are also observed in approximately 20%–65% of patients[9].The way in which MEN1 is discovered in our patient is extremely unusual, starting from pneumo-mediastinal neuroendocrine tumor followed by hypercalcemia revealing primary hyperparathyroidism.

Bronchopulmonary neuroendocrine tumors (bpNETs) are frequently silent and usually discovered incidentally on imaging studies. Their penetrance is estimated at about 1.3% by the age of 40. When symptomatic, they may manifest with clinical features such as cough, shortness of breath, or hemoptysis.Diagnosis is preferably confirmed histologically via bronchial endoscopy following radiological detection; however, in cases of small bpNETs, particularly when multiple lesions are present, diagnosis may rely solely on radiological criteria without histological confirmation[5,10]. Current guidelines recommend periodic screening of patients with MEN1 for both thymic and bronchial carcinoid tumors every 1 to 2 years using CT or MRI, as these neoplasms may be associated with significant morbidity and mortality [8].

Primary hyperparathyroidism[11]is a common condition, with a global prevalence ranging from 0.2% to 1.3% in studied populations. It represents the most frequent endocrine manifestation in patients with MEN1 with penetrance approaching 100% by the age of 50. HPT is typically the initial manifestation of MEN1, with an average age of onset between 20 and 25 years. Patients with MEN1-associated HPT often present with multiglandular involvement, with tumors that are asymmetric in size and are considered independent clonal adenomas. Severe hypercalcemia and atypical parathyroid tumors, including parathyroid carcinoma, are infrequently observed in MEN1 patients [1,9,10].

The diagnostic criteria are consistent with those established for sporadic primary hyperparathyroidism.Multiple imaging modalities, including cervical ultrasound, 99mTc-sestamibi scintigraphy, and 18F-fluorocholine positron emission tomography (PET), are available for tumor localization and confirmation of parathyroid origin. The selection of the imaging technique typically depends on the preferences and expertise of the surgical team managing the patient [5,12]. Calcimimetics can be used to reduce parathyroid hormone (PTH) levels and normalize blood calcium concentrations, with calcium levels guiding dose titration.In patients with MEN1, some clinicians advocate for minimally invasive parathyroidectomy involving selective excision of only the enlarged glands, while others recommend subtotal parathyroidectomy (removal of three and a half glands) or total parathyroidectomy with autotransplantation[5,9].

Pituitary disease [10]constitutes the initial clinical manifestation in approximately 20% of MEN1 cases and may present as early as five years of age. The prevalence of pituitary carcinoma does not appear to be increased in this population.Functional pituitary adenomas are more prevalent in MEN1, with prolactinomas accounting for approximately 60-65% of cases, growth hormone-secreting tumors for about 25%, and corticotrope adenomas causing Cushing disease for around 5%[10,13].The management of MEN1-associated pituitary adenomas follows the same principles and treatment protocols as those used for sporadic pituitary adenomas [10].

Pancreaticoduodenal and gastric neuroendocrine tumors represent the initial clinical manifestation of MEN1 in approximately 20% of patients [5]. Functioning duodenopancreatic neuroendocrine tumors are often diagnosed based on elevated plasma biochemical markers and the presence of clinical syndromes associated with hormone hypersecretion [5,7]. Gastrinomas are present in approximately 30% of patients with MEN1. These tumors secrete gastrin, which stimulates excessive gastric acid production, potentially resulting in severe peptic ulceration and gastrointestinal bleeding, a clinical condition known as Zollinger–Ellison syndrome [7].

MEN1-associated gastrinomas often follow a malignant course, with metastasis to regional lymph nodes and the liver occurring in approximately 50% of cases, frequently prior to diagnosis [9,13]. Insulinomas are the most common functioning pancreatic neuroendocrine tumors (pNETs) in patients with MEN1, with an incidence of up to 15%. In approximately 10% of cases, insulinoma represents the initial clinical manifestation of the syndrome[7,13]. Due to their high malignant potential, these tumors constitute the primary contributors to morbidity and mortality in MEN1 patients[3]. Less commonly occurring pancreatic neuroendocrine tumors (pNETs), such as glucagonomas, VIPomas, and GHRH-secreting tumors, also cause clinical symptoms due to hormonal hypersecretion and may be associated with poor prognosis [7].

Nonfunctioning pancreatic neuroendocrine tumors (NF-pNETs) are the most prevalent pNET subtype and represent the leading cause of excess mortality in MEN1 patients [5]. These tumors represent the most frequent cause of death in MEN1 patients, with delayed diagnosis contributing to increased mortality[13].For radiological evaluation, MRI remains the most reliable diagnostic modality[7].Patients with MEN1 may develop a variety of tumors, including lipomas, collagenomas, facial angiofibromas, central nervous system tumors such as meningiomas and ependymomas, as well as smooth muscle tumors like leiomyomas. Cutaneous tumors are often multiple and frequently precede the onset of hormone-dependent clinical manifestations, thereby facilitating early diagnosis of

MEN1 [13].For fertility, the limited data suggest that MEN1 itself does not adversely affect fertility, associated pituitary disease in MEN1 patients may compromise reproductive potential[7].

Genetic screening in MEN1 is valuable for confirming clinical diagnosis, identifying mutation carriers, and enabling early tumor surveillance, thereby contributing to the reduction of morbidity and mortality associated with these neoplasms [7,13].Patients identified as carriers of the familial MEN1 mutation should be referred to a specialized medical team for ongoing surveillance and management.

Conversely, individuals without the familial MEN1 variant are not considered at risk for developing the syndrome and therefore do not require routine monitoring [5].Patients with MEN1 face an increased risk of premature mortality, with a reported 50% mortality rate before the age of 50 [2]. This underscores the importance of genetic screening and regular prospective monitoring for individuals carrying MEN1 mutations [10].

Conclusion:-

MEN1 is a rare disorder characterized by diverse clinical phenotypes. Tumors arising in atypical sites, such as the lung or thymus, are often overlooked, posing diagnostic challenges. In multiple endocrine neoplasia type 1 (MEN1), primary hyperparathyroidism usually represents the first and most frequent clinical feature.

Affected individuals tend to have a diminished quality of life and a notably shorter life expectancy than that of the general population.The prognosis is primarily determined by the metastatic potential of pancreatic and thymic tumors, as well as complications arising from hormonal hypersecretion. Consequently, early multidisciplinary management by specialized teams is essential to improve survival outcomes and quality of life.

Ethics Statement:
Consent was obtained from the patient for publication of this case report and any accompanying images.

Author Contributions
All authors contributed equally to the conception, preparation, writing, and revision of this article.

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Conflicts of Interest
The authors declare no conflict of interest.

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