

A Unique Case of Multiple Endocrine Neoplasm-1 (MEN-1) Syndrome satisfying all Six WHO Criteria

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ABSTRACT

Multiple Endocrine Neoplasia (MEN) syndromes are a group of genetically inherited diseases resulting in proliferative lesions (hyperplasia, adenomas and carcinomas) of the endocrine organs. MEN 1 syndrome principally includes tumors of parathyroid, pancreas and pituitary. Our case is a 45 year old male, previously operated for thymic carcinoma, subsequently presented with radiologically and pathologically confirmed neuroendocrine lesions involving pituitary, parathyroid, adrenal, pancreas, stomach and duodenum. This patient had a positive family history for MEN 1 syndrome thus satisfying all six WHO criteria for MEN 1 syndrome which is a rare observation with no previous published reports. Tumors in this syndrome are more aggressive and recur in higher proportion of cases than do similar tumors occurring sporadically in non-syndromic patients.

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Introduction

Multiple Endocrine Neoplasia (MEN) syndromes are a group of genetically inherited diseases resulting in proliferative lesions (hyperplasia, adenomas and carcinomas) of the endocrine organs. MEN1 syndrome (also known as *Wermer Syndrome*) is a rare inherited autosomal dominant disorder with an incidence of one in 30,000, seen in all age groups (ranging from 8 to 81 years) and an equal sex distribution. It is characterized by polyendocrinopathies usually presenting by the fifth decade. This syndrome exists in sporadic and familial forms.^[1] To label a case as MEN1 syndrome, two out of six WHO criteria need to be fulfilled.^[2] We report a unique case of 45 year old male satisfying all the criterias and with equally rare thymic involvement as the initial manifestation.

Case Report

A 45 year old male, operated for thymic carcinoma two years ago and treated with radiation, presented to our hospital in November 2013 with proximal muscle weakness, bone pains, weight loss, bilateral renal calculi and hydronephrosis. Patient was on proton pump inhibitors for peptic ulcer disease since nine years and oral hypoglycemics for type two diabetes mellitus since the past three years. On examination in the present admission, there were multiple whitish small nodular skin lesions like tags over neck, right elbow and popliteal fossa clinically suspected to be collagenomas (figure-fig. 1a) and a popliteal fossa lipoma. Vital parameters and systemic examination was unremarkable. Investigations showed raised serum glucose levels (fasting-214mg/dl), alkaline phosphatase (440U/L) and calcium (13.4mg %) and low serum phosphorus (1.6mg %). With the clinical suspicion of MEN 1 syndrome, he was further evaluated. Hormonal studies revealed elevated serum parathormone (319pg/ml) and prolactin (167ng/ml). Serum gastrin levels could not be carried out due to daily proton pump inhibitors therapy. Subsequent radiologic examination and octreoscan study showed multiple lesions - tumors in pituitary and parathyroid, nodules in stomach, duodenum, head of pancreas and adrenal, residual thymic lesion, sphenoid bone destruction and lytic, sclerotic foci in axial and appendicular skeleton (suspected as metastasis of thymic carcinoma). He underwent pituitary and parathyroid tumor resection. Pituitary gland showed histology of pituitary adenoma (fig.1b) with typical features like bone invasion and increased mitotic activity (fig.1c) and on immunohistochemistry (IHC) was positive for neuroendocrine markers (fig.1d). On studying the gross (fig.1e) and microscopy (fig.1f) of parathyroid resection specimens it revealed adenoma in one gland and hyperplasia in remaining three glands.

On reviewing the histology, previously operated thymic tumor was a neuroendocrine carcinoma (NEC) (fig.1g) confirmed immunohistochemically by chromogranin and synaptophysin positivity and negativity for TTF 1 and cytokeratin 5/6. Stomach biopsy was labelled as neuroendocrine tumor and was confirmed by IHC (fig.1h). On family screening (fig.2-family tree), patient's younger son had high serum levels of prolactin (1250ng/ml) and alkaline phosphatase (215 U/L) with pituitary macroadenoma and a thymic nodule thus suggesting presence of MEN 1 syndrome in him too. Based on these findings, we conclude our case as MEN 1 syndrome, with uniqueness of satisfying all the six WHO criteria.^[2] Post operatively in this patient, serum levels of prolactin, calcium and phosphorus started normalizing but bone pain persisted. On follow up after two months, he had severe diffuse bone pains in the back and extremities. Radiological examinations showed multiple nodules involving the sphenoid sinus, anterior mediastinum and axial skeleton with markedly elevated serum chromogranin levels (4530 ng/ml). Diagnosed to have neuroendocrine metastatic disease, he was put on palliative treatment with analgesics, dopamine receptor agonists and calcium and vitamin D supplements. Meanwhile genetic screening of both father (index case) and his son was carried out which did not reveal mutations in *MEN1* gene. At two and half year follow up, (April 2016) patient has improved symptomatically and is doing well till date.

Discussion

Usually MEN1 syndrome is characterized by three principle lesions viz. multiglandular parathyroid disease, enteropancreatic endocrine tumors, and anterior pituitary tumors.^[3] Clinical manifestations are related to tumor localizations and their secretory products. Spectrum of the lesions (endocrine and non-endocrine) and their incidence is elucidated in Table 1.^[1,4]

Hypercalcemia due to parathyroid hyperplasia (primary hyperparathyroidism) is the commonest and usually the first presenting manifestation of MEN 1.^[4] However this may not be always true, as in our case patient presented with thymic NEC. Thymic involvement is usually in form of thymic carcinoids seen in about 0-8% of patients with MEN 1. They are insidious tumor but can present in an aggressive fashion with poor prognosis if detected late.^[4] As our case presented well in time, despite having NEC,^[5] he had a relatively better outcome. After treatment for NEC, patient subsequently developed multiple endocrine tumors. So a clinical diagnosis of MEN 1 syndrome was suspected and confirmed by laboratory evaluation and histopathological examination there by making histopathological examination a helpful modality in MEN1

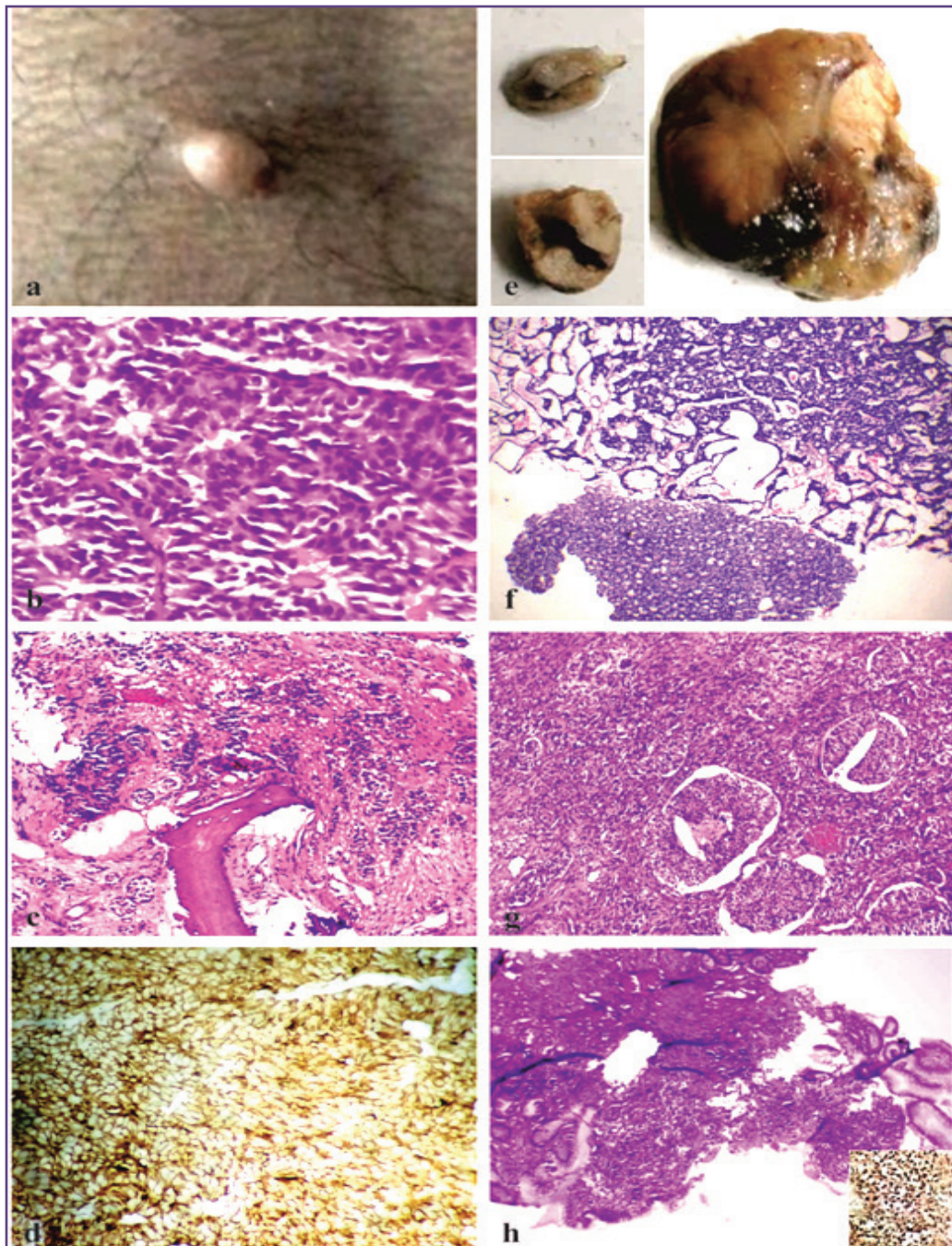


Fig. 1: a. Whitish small nodular skin lesions like tags - collagenomas
 b. Pituitary gland - tumor cells forming trabeculae, rosetoid and pseudopapillary architecture and cells are small, polyhedral to columnar with moderate eosinophilic cytoplasm, round to oval nuclei with finely dispersed chromatin (HE x 400)
 c. Pituitary tumor in nests and sheets reaching the bony tissue (HE x 100)
 d. Immunohistochemistry (IHC) - pituitary tumor cells are positive for synaptophysin (x400)
 e. Parathyroid glands- on left (above and below) showing hyperplasia, and on right is adenoma (grey brown with a few cystic and hemorrhagic areas)
 f. Parathyroid adenoma - multiple nodules containing many micro follicles with compressed parathyroid tissue at periphery (HE x 100)
 g. Thymus - tumor cells arranged in nests and cords showing nuclear atypia with foci of lymphovascular invasion (HE x 100)
 h. Stomach - antral biopsy showing nodules of round to polygonal monomorphic cells arranged in trabecular and insular pattern (HE x 40) (inset-IHC positive for synaptophysin)

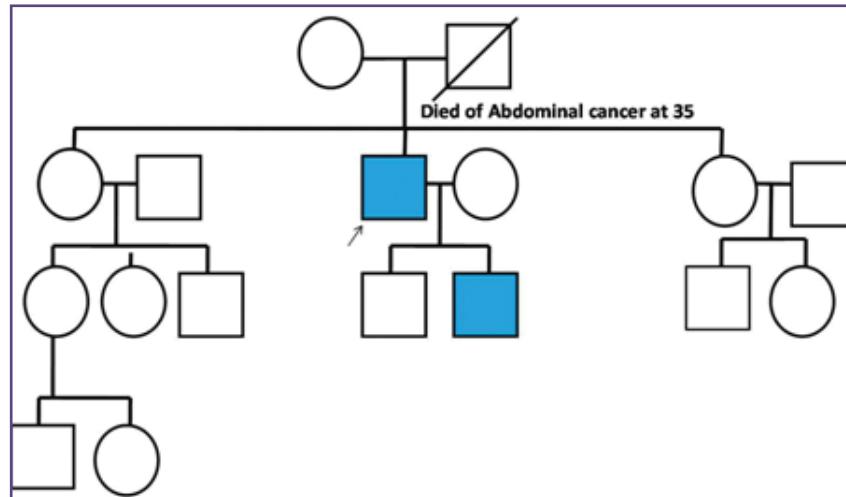


Fig. 2: Father of the index case died of abdominal cancer at 35 yrs and son has a thymic nodule and prolactinoma.

diagnosis. On studying the WHO diagnostic criteria for MEN 1 syndrome [2] we noticed that this case fulfills all of them which is tabulated below (Table 2) thus making it a unique scenario.

MEN1 syndrome is caused by inactivating mutations of the tumor suppressor gene, *MEN1*, located on chromosome 11q13. [6] It has been observed that 5% and 10% of MEN1 patients do not have mutations in the coding region but may involve the promoter or untranslated regions, which remains to be investigated. [7] This could be possible in our case too as this patient was not positive for commonly occurring MEN1 mutations.

Treatment results in MEN 1 are less successful due to tumor multiplicity, higher metastatic rate, and more aggressive

tumors than their sporadic non-syndromic counterparts. Untreated MEN 1 patients have decreased life expectancy and disease specific mortality is attributed to malignant pancreatic NET and thymic carcinoids. [8] Hence there is need for early diagnosis which is another key feature of the current case as this patient had dramatic clinical improvement and subsequently good prognosis as a result of timely diagnosis and aggressive treatment of different encountered lesions.

The incidence of MEN1 in the Indian population is unknown and reports highlighting the same were not available after literature search. [9] To the best of our knowledge, this is the first documented report of MEN-1 syndrome which fulfills all the criterias with a relatively rare presenting feature in the form of thymic tumor.

Table 1: Spectrum of lesions in MEN 1

| Lesion | Incidence | Clinical relevance |
|---|-----------|--|
| Commonest Endocrine Lesions | | |
| Parathyroid lesions | 95 % | Commonest presenting manifestation |
| Pancreatic islet cell/ neuro endocrine tumors | 30-80% | Commonest functional tumors - gastrinomas and insulinomas, overall about one third tumors are non-functional |
| Anterior pituitary tumors | 30-40% | Prolactinomas - commonest |
| Common skin lesions | | |
| Collagenomas | >70% | Represents genodermatosis, helps in presymptomatic diagnosis before hormone secreting tumors appear |
| Facial angiofibromas | 40-90% | |
| Lipomas | 20-30% | |
| Less Common lesions | | |
| Adrenocortical tumors | 20-30% | Majority non-functional adenomas, indolent behaviour, occurs late in disease course |
| Thyroid tumors | 25% | Incidental association noted |
| Carcinoids | 10% | Usually silent, asymptomatic, common locations- bronchi, thymus, gastrointestinal tract, pancreas |
| Meningiomas | 8% | Rare association, presents late |
| Pheochromocytomas | <1% | - |

Table 2: WHO Diagnostic Criteria for MEN 1 syndrome

| Sr. No | WHO criteria | Our Case |
|--------|---|--|
| 1 | Primary or recurrent primary hyperparathyroidism with multiglandular hyperplasia and/or adenoma | Parathyroid adenoma and hyperplasia |
| 2 | Duodenal and/or pancreatic endocrine tumor*- IHC proven, gastric enterochromaffin-like tumors | Gastric and pancreatic NET |
| 3 | Anterior pituitary adenoma*-IHC proven | Atypical pituitary adenoma |
| 4 | Adrenocortical tumors* | Adrenal adenoma |
| 5 | Thymic and/or bronchial endocrine tumors | Thymic NEC |
| 6 | First degree relative (parent, sibling, offspring) fulfilling MEN 1 syndrome criteria | Son with pituitary and thymic endocrine tumour |

* - functioning, non-functioning or multi-secreting; abbr: IHC-immunohistochemistry, NET- neuroendocrine tumors, NEC-neuroendocrine carcinoma

Conclusion

High index of suspicion is required for this syndrome when there are rarer presenting symptoms. Pathological examination of the lesions is beneficial for confirmation of MEN 1 cases. Routine surveillance of asymptomatic at-risk individuals by using all the available modalities for diagnosing multiple tumors occurring at a younger age, will help to reduce syndrome associated morbidity and mortality.

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Competing Interests

None Declared

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