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Case Report

A Case of Multiple Endocrine Neoplasia Type 1: A Rare Clinical Entity

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Abstract

Background and purpose: Multiple endocrine neoplasia is a rare clinical entity which comprises a group of patients who has primary hyperparathyroidism. **Case report**: A 44-year-old male came with the complaints of generalized aches and pains in different parts of body with predominant involvement of small joints of hand associated with fatigue specially more pronounced in the early morning and usually it was relieved by taking repeated sugar containing drinks leading to weight gain. He has features suggestive of acromegaly as evidenced by prognathism, prominent heal pad thickness, and coarse spade like fingers. He has hyperparathyroidism as evidenced by raised serum calcium and parathormone level and acromegaly as evidenced by raised serum growth hormone and insulin-like growth factor-1 level. His PET-CT whole body showed pituitary macroadenoma, tumour involving the tail of pancreas (insulinoma). So these multiple endocrine tumour in a single patient with a positive family history of primary hyperparathyroidism strongly suggests a genetic predisposition of the condition which convincingly can be attributed to multiple endocrine neoplasia type 1. MEN 2A and 2B and Familial Medullary Thyroid Cancer (FMTC) is being excluded by absence of medullary thyroid Cancer as evidenced by absence of thyroid mass on PET-CT. **Conclusion:** Multiple endocrine neoplasia, although a rare clinical entity, should be kept in mind in cases of hypercalacemia due to primary hyper parathyroidism.
Key words: Multiple endocrine neoplasia Type 1, 2A, 2B; Primary hyperparathyroidism (PHPT).

INTRODUCTION

The term multiple endocrine neoplasia (MEN) encompasses several distinct syndromes featuring tumors of endocrine glands, each with its own characteristic pattern. In some cases, the tumours are malignant, in others, benign. Benign or malignant tumours of non-endocrine tissues occur as components of some of these tumour syndromes. MEN syndromes are inherited as autosomal dominant disorders.

CASE REPORT

A 44-year-old male working in a local bank came from Chittagong presented to me with the complaints of generalized aches and pains in different parts of body with predominant involvement of small joints of hand and not associated with any degree of morning stiffness. He also complaints of fatigue especially more

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pronounced in the early morning and usually it was relieved by tea since 2010. He has also gained 5 kg weight in the last 3 months after taking repeated sugar containing drinks to get relieve of his weakness. He also has history of headache on and off since 2009. His headache was not associated with photophobia, phonophobia and was not preceded by aura or associated with visual disturbance. He also has dyspepsia, burning sensation in epigastric region associated with intermittent episodes of watery diarrhoea several times a day which used to be relieved by taking omeprazole. He was also having coarsening of facial muscle and lips with increasing the size of hands and feet and increasing shoe size. He has premature ejaculation associated with erectile dysfunction. He has multiple pedunculated skin lesion of variable size and shape in abdomen which was biopsied and found to be lipomas. He does not have cold intolerance or constipation nor has muscle weakness affecting the activities of daily living.

On past history he had no history of urinary stones. He is non-diabetic but borderline hypertensive (average blood pressure measuring 140/90 mm Hg for which he refused to take anti-hypertensive despite the advice of doctors as it deteriorates his performance and currently on lifestyle changes alone. He does not have any previous history of rheumatoid arthritis, gout, hyperuricaemia, or any other connective tissue disease. He does not have any history of tuberculosis but has hypercholesterolaemia for which he is on atorvastatin. He has family history of primary hyperparathyroidism (PHPT) in two brothers and one sister and no other functioning tumour in them till now. On examination he has coarse lips, prognathism, spade-like fingers, and increased heal pad thickness with mild bilateral proptosis. His locomotor system examination reveals joint tenderness on pressure without obvious features of synovitis. There is no raised temperature of articular or periarticular structure.

He was diagnosed as a case of PHPT initially on the basis of raised serum calcium and parathormone level by an endocrinologist .The patient then consulted me and on the basis of his features suggestive of acromegaly and recurrent episodes of hypoglycaemia as evidenced by his persistently low blood sugar level I had offered him to have testing for growth hormone and insulin level where both were found to be increased. Later, the case as multiple endocrine neoplasia type 1 (MEN1) was diagnosed. For further evaluation he had been to abroad where he was further evaluated and confirmed as a case of MEN1 and he had undergone parathyroidectomy. By removing three out of four parathyroid glands his serum calcium level is now under good control and progression of his parathyroid bone disease is halted to some extent. He aslo has pituitary macroadenoma and insulinoma along with vitamin D deficiency and secondary osteoporosis. His current medication includes diazoxide for controlling hypoglycaemia and octreotide for growth hormone hypersecretion and high dose vitamin D supplementation for his vitamin D deficiency.

DISCUSSION

MEN1, also known as Wermer's syndrome, is a rare hereditary endocrine cancer syndrome characterized primarily by tumours of the parathyroid glands (95% of cases), endocrine gastroenteropancreatic tract, e.g., gastrinomas, insulinomas and carcinoid tumours (30–80% of cases) and anterior pituitary, e.g., prolactinomas (15–90% of cases).[1] MEN1 has autosomal dominant inheritance with a high degree of penetrance. Cutaneous tumours are common in MEN1 and include multiple angiofibromas (previously considered pathognomonic for tuberous sclerosis), collagenomas, and lipomas. Recognizing these benign tumours is important because they can serve as markers for this tumour syndrome.

MEN 1is inherited as an autosomal dominant trait with an estimated prevalence of 2–20 per 100,000 in the general population. Approximately 10% of MEN 1 mutations arise de novo. The term "sporadic MEN 1" has been applied to this group.

The MEN1 gene: The MEN1 gene consists of 10 exons, spanning about 10 kb, and encodes a 610 amino acid protein named *menin*. The first exon and the last part of exon 10 are not translated. A main transcript of 2.8 kb has been described in a large variety of human tissues (pancreas, thymus, adrenal glands, thyroid, testis, leukocytes, heart, brain, lung, muscle, small intestine, liver, and kidney); an additional transcript of approximately 4 kb has been detected in pancreas and thymus, suggesting a tissue-specific alternative splicing.

The menin protein: Menin is a 610 amino acid (67 Kda) nuclear protein, highly conserved from mouse (98%), rat (97%) and, more distantly, zebrafish (75%) and drosophila (47%) (47–51). Human and mouse MEN1 amino acid sequences 95.8% identity and 98.4% similarity. Analysis of menin amino acid sequence did not reveal homologies to any other known human or mammalian protein, sequence motif, or signal peptide. The absence of significant homology to any other protein complicates efforts to elucidate the functions of menin.

Related conditions: Although not officially categorized as MEN syndromes, Von Hippel-Lindau disease[1] and Carney

complex[2] are two other autosomal dominant endocrine tumour syndromes with features that overlap the clinical features of the MEN syndromes. Although not transmitted in the germline, McCune-Albright syndrome is a genetic syndrome characterized by endocrine neoplastic features involving endocrine glands that overlap with those involved in MEN1 or MEN2.

Clinical features: The age of onset of endocrine tumours is usually in the teenage years, but symptoms from these tumours may not appear for several years, and the diagnosis is frequently delayed until the fourth decade of life. Cutaneous tumours may develop prior to the manifestation of overt clinical symptoms resulting from endocrine tumours. The earliest cutaneous tumours appear in the teenage years. Tumours may hypersecrete hormone, causing hypercalcaemia and recurrent nephrolithiasis (hyperparathyroidism), Zollinger-Ellison syndrome (hypergastrinaemia), hypoglycaemia (hyperinsulinaemia), amenorrhoea (hyperprolactinaemia), or acromegaly (excess growth hormone). Tumours of the pituitary gland may cause symptoms by mass effects. Angiofibromas, collagenomas, and lipomas do not typically cause symptoms, and they are mostly of cosmetic concern.

Parathyroid hyperplasia and adenomas: Hyperparathyroidism is the presenting feature of MEN1 in about 80% of patients. Patients present either with asymptomatic hypercalcaemia on biochemical screening or with the features of sporadic hyperparathyroidism. All four glands are diffusely hyperplastic and there may be nodule formation.

Pancratic endocrine tumours duodenal tumours: These occur in about 70% of patients with MEN1 and usually present between the ages of 15 and 50 if not identified by screening. Over 60% of tumours are gastrinomas and produce the Zollinger-Ellison syndrome and about 30% are insulinomas. Peptic ulcers account for most of the morbidity and mortality of the MEN1 syndrome and occur in about 10% of cases. As well as peptic ulcer, gastrinoma produces oesophagitis and diarrhoea. VIPoma (= vasoactive intestinal peptide and pancreatic polypeptide-secreting tumour), also known as Verner Morrison syndrome, have rarely been described and there are only isolated reports of glucagonoma, but non-functioning tumours may occur frequently. Diffuse hyperplasia of the pancreas is usually seen and is similar to the parathyroid. In the majority of cases there are multiple adenomata, most of which are less than 1 cm in diameter. Duodenal microgastrinoma is very common and probably accounts for almost half of all MEN1-associated gastrinomas. They are usually multiple, with up to 15 separate tumours.

Pituitary adenomas: This may be detected by screening in 30% of patients, but is found at post-mortem in 50%. Unlike the pancreas and parathyroid, there does not appear to be diffuse pituitary hyperplasia. Prolactinoma-producing hyperprolactinaemia is the most common tumour, and occurs in about 30% of cases. They tend to be more aggressive than sporadic cases.[3] Acromegaly, due to excessive production of human growth hormone (hGH) occurs in about 30%. Adrenocorticotrophic hormone (ACTH) may produce Cushing's syndrome but other functioning tumours are rare.

Skin lesions: These are common and occur in nearly 90% of patients, but they can be easily overlooked because of their subtle appearance. Benign tumours include multiple angiofibromas that were previously considered pathognomonic for tuberous sclerosis, collagenomas, and lipomas.[3] They should be sought because they can act as markers for this syndrome.

Other lesions: Lesions in other tissues have been reported, but their relationship to the syndrome remains controversial. Carcinoid tumours of the foregut, midgut, and thymus occur in about 10%, and are often found in the pancreas, but they are rarely symptomatic.

Diagnosis: Many people may also be diagnosed because of screening of first- and second-degree relatives of patients with MEN1. Diagnosis of MEN1 depends on having a high level of suspicion in patients who present with multiple facial angiofibromas, collagenomas, and lipomas, or other features such as hyperparathyroidism or increased gastric acid secretion. Investigations include hormone hypersecretion blood tests (e,g., serum parathormone, serum prolactin, growth hormone, serum gastrin, fasting insulin, and C-peptide assay); imaging studies (Sestamibi parathyroid scan, PET-CT scan of whole body, if appropriate) to look for the presence of tumours. DNA testing is available and identifies a mutation in about 80% of patients with familial MEN1. Mutation analysis may be used to confirm the clinical diagnosis, provide a genetic diagnosis, and screen asymptomatic family members. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing mutation in a family is known.[4]

Screening: The screening of first- and second-degree relatives of patients with MEN1 is aimed at early detection of parathyroid, pancreatic, or pituitary lesions in gene carriers, to reduce the associated morbidity. There is no evidence that screening reduces mortality, although the identification of affected individuals in 'malignant kindred' with aggressive pancreatic disease may allow curative surgery which would be expected to prolong survival. Screening lowers the age of

detection of the syndrome by about 20 years. The most useful screening investigations are serum calcium, fasting gastrin, and prolactin, although in practice a full gut hormone screen is usually performed. It has been suggested that the most sensitive markers of pancreatic disease are basal and test-meal stimulated pancreatic polypeptide and gastrin, and basal insulin and proinsulin, identifying lesions at least three years before imaging studies. As pancreatic tumours are the only life-threatening aspect of the syndrome, such a screening protocol has merit. The MEN1 syndrome rarely develops before the age of 5 or after the age of 70, and so screening should be performed annually from 5 to 65, and at longer intervals thereafter. Eighty percentage of affected individuals will have been identified by the 5th decade. Screening of patients with apparently sporadic pancreatic endocrine tumours for evidence of MEN1 is probably justified, especially in those with gastrinomas or insulinomas. There is little evidence to support screening in those with sporadic pituitary tumours. MEN1 is present in 15% of all patients with hyperparathyroidism, but hypercalcaemia per se may be associated with elevated fasting gastrin and pancreatic polypeptide. In those at risk of MEN1 this would be highly significant, but in those with sporadic hyperparathyroidism, this very rarely indicates pancreatic disease. Hence, screening of all patients with hypercalcaemia is not warranted. Routine germline MEN1 mutation testing of all cases of 'classical' MEN1, familial hyperparathyroidism, and sporadic hyperparathyroidism with one other MEN1-related condition is justified by national testing services, and testing should be considered for patients under 30 years old with sporadic hyperparathyroidism and multigland hyperplasia.[5] Genetic linkage analysis has greater than 95% predictive accuracy, and in most families a haplotype associated with the mutant allele can be found. If three markers can be identified, the accuracy improves to greater than 99%.

REFERENCES

1. Carney JA. Familial multiple endocrine neoplasia syndromes: components, classification, and nomenclature. J Intern Med. 1998;243(6):425–32.
2. Callender GG, Rich TA, Perrier ND. Multiple endocrine neoplasia syndromes. Surg Clin North Am. 2008;88(4):863–95.
3. Asgharian B, Turner ML, Gibril F, et al. Cutaneous tumors in patients with multiple endocrine neoplasm type 1 (MEN1). J Clin Endocrinol Metab. 2004;89(11):5328–36.
4. Falchetti A, Marini F, Luzi E, Giusti F, Cavalli L, Cavalli T, Brandi ML. Multiple endocrine neoplasia type 1 (MEN1): not only inherited endocrine tumors. Genet Med. 2009;11(12):825-35.
5. Cardinal JW, Bergman L, Hayward N, et al. A report of a national mutation testing service for the MEN1 gene: clinical presentations and implications for mutation testing. J Med Genet. 2005;42(1):69–74.