

Multiple Endocrine Neoplasia Type 4 (MEN4) Syndrome

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Multiple endocrine neoplasia type 4 (MEN4) is a recently defined endocrine tumor syndrome which is inherited in an autosomal dominant way. It has been identified late because its clinical characteristics resemble a lot to MEN1 syndrome. It occurs due to an inactivating mutation on the cyclin-dependent kinase inhibitor (*CDKN1B*) gene (which normally controls the cell cycle).

40-year-old female patient applied to the emergency department with confusion, tremor, and cold sweats. Her blood glucose level was 44 mg/dL and Ca⁺⁺ was 11.5 mg/dL. Due to her hypoglycemia and hypercalcaemia, she was admitted to our clinic with a preliminary diagnosis of MEN1. In the follow-up, blood sugar was 14 mg/dL, insulin 20.5 mIU/mL, C-peptide 11 ng/mL, 24-hour urine Ca⁺⁺ was 664 mg/day, and parathyroid hormone was found as 140.8 pg/mL. During the systemic investigation, we figured out that she had nephrolithiasis and hypoglycemia story and she had experienced an increase in her shoe size. When compared to the old photographs, it was seen that her facial features

got more rough characteristics. The case, which had 407 ng/mL insulin-like growth factor-1, did not show any GH suppression to glucose. There was not any adenoma in the pituitary magnetic resonance imaging (MRI) which was performed for suspected acromegaly. In neck US, a lesion consistent with parathyroid adenoma was found close to the inferomedial part of the thyroid gland. In the abdominal MRI performed with preliminary diagnosis of insulinoma, there were tumor lesions of 36x32 cm and 26x21 mm in the pancreas head and neck, respectively, 3x6 cm in the right suprarenal and 6.5x1.2 cm in the left suprarenal gland.

Due to the life-threatening risks of hypoglycemia, a pancreatectomy was planned first, but since the adrenal tumor sizes were in the surgical margins, bilateral surrenalectomy was necessary. After the simultaneous pancreatectomy and bilateral surrenalectomy, patient's acromegaly was cured and secondary diabetes occurred. The parathyroid surgery will be performed in January, and the patient is under follow-up with medical treatment.

The patient whose pancreas and parathyroid neoplasms were consistent with MEN1 syndrome was negative in terms of *MEN1* (*MEN1N*) gene mutation on chromosome 11. After the pancreatectomy and bilateral surrenalectomy, the acromegaly features regressed in our patient who was biochemically and clinically diagnosed with acromegaly but had a negative pituitary scanning. Pancreas and adrenals were histopathologically growth hormone (GH)-negative, but GH-releasing hormone dyeing is still in progress. The patient needs to be studied for *CDKN1B* mutation in terms of MEN4 syndrome which is the 1-2% of the MEN1N negative patients whose symptoms are concordant with MEN1 syndrome.

Key words: MEN4 syndrome, MEN1, *CDKN1B*, MEN1N, acromegaly, insulinoma, parathyroid adenoma