MEN 2A WITH PRIMARY HYPERPARATHYROIDISM AND INTRATHYROIDAL PARATHYROID TISSUE: A RARE CASE REPORT

PRİMER HİPERPARATIROİDİZM VE İNTRATİROİDAL PARATİROİD DOKUYLA SEYREDEN MEN 2A: NADİR BİR OLGU SUNUMU

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Abstract

Multiple endocrine neoplasia type 2 (MEN Type 2) syndrome (Sipple syndrome) is a syndrome associated with mutations in the autosomal dominant inherited RET protooncogene. MEN Type 2 syndrome, which has three clinical subtypes, the clinical findings of the MEN 2A subtype are medullary thyroid carcinoma, primary hyperparathyroidism, and pheochromocytoma. In the literature, patients diagnosed with MEN 2A are often first presented with medullary thyroid carcinoma. Cases of MEN 2A presenting with parathyroid adenoma firstly are rare. In this case, an 18-year-old female patient who came to the internal medicine outpatient clinic with complaints of flank pain lasting for four years, nausea and headache for a month, was hospitalized to the internal medicine endocrinology clinic for further examinations. The patient was consulted to the otorhinolaryngology clinic because the patient's parathormone and blood calcium levels were high in the examinations and parathyroid adenoma was observed in the scintigraphy. Frozen tissue sample of operated patient's was compatible with parathyroid adenoma. The patient, whose blood calcium and parathormone levels were high after the operation, was rehospitalized to the endocrinology clinic. Pheochromocytoma diet was applied to the patient whose genetic test result was reported as multiple endocrine neoplasia type 2A. Thyroid nodule was observed in the neck ultrasonography. As a result of this, fine needle aspiration biopsy was performed on the patient. After total thyroidectomy was performed to the patient whose fine needle aspiration biopsy was reported as medullary thyroid carcinoma, the patient's clinical and laboratory findings regressed.

Keywords: Multiple endocrine neoplasia, parathyroid adenoma, pheochromocytoma, primary hyperparathyroidism, thyroid medullary carcinoma

Özet

Multiple endokrin neoplazi tip 2 (MEN Tip 2) sendromu (Sipple sendromu), otozomal dominant kalıtılan RET protoonkogenindeki mutasyonlarla ilişkili bir sendromdur. Üç klinik subtipi bulunan bu sendromdan MEN 2A subtipinin klinik bulguları medüller tiroid karsinomu, primer hiperparatiroidizm ve feokromositomadır. Literatürde MEN 2A tanısı alan hastalar sıklıkla medüller tiroid karsinomu ile presente olmaktadır. Paratiroid adenomu ile presente olan MEN 2A olguları daha nadirdir. Bu olguda da dört yıldır devam eden yan ağrısı, bir aydır devam eden bulantı ve baş ağrısı şikayetleriyle dahiliye polikliniğine başvuran 18 yaşındaki kadın hastada hiperkalsemi saptanması üzerine hasta ileri tetkik ve incelemeler için dahiliye endokrinoloji kliniğine yatırılmıştır. Hastaya yapılan tetkiklerde hastanın parathormon ve kan kalsiyumu seviyelerinin yüksek olması ve yapılan sintigrafide hastada paratiroid adenomu görülmesi nedeniyle hasta kulak burun boğaz kliniğine danışılmıştır. Frozen için gönderilen doku örneği paratiroid adenomuyla uyumluydu. Operasyon sonrası kan kalsiyumu ve parathormon düzeyleri yüksek seyreden hasta tekrar endokrinoloji kliniğine yatırıldı. Genetik test sonucu multiple endokrin neoplazi tip 2A olarak raporlanan hastaya feokromositoma diyeti uygulandı. Yapılan boyun ultrasonografide tiroid nodülü izlenmesi üzerine hastaya ince iğne aspirasyon biyopsisi yapıldı. İnce iğne aspirasyon biyopsisi medüller tiroid karsinomu olarak raporlanan hastaya total tiroidektomi uygulanması üzerine hastanın klinik ve laboratuvar bulguları düzelmiştir.

Anahtar kelimeler: Feokromositoma, multiple endokrin neoplazi, paratiroid adenomu, primer hiperparatiroidizm, tiroid medüller karsinomu

1. INTRODUCTION

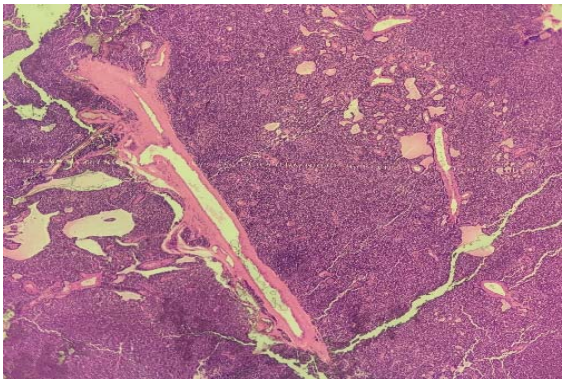
Multiple endocrine neoplasia type 2 (MEN Type 2) syndrome (Sipple syndrome) is a syndrome associated with mutations in the autosomal dominant inherited RET protooncogene. There are three subtypes of this syndrome: MEN 2A, MEN 2B, and familial medullary thyroid carcinoma. The clinical diagnostic criteria of MEN 2A are medullary thyroid carcinoma (MTC), primary hyperparathyroidism, and pheochromocytoma (1). Almost all patients with MEN 2A develop MTC. In addition, the risk of pheochromocytoma development is 50%, and primary hyperparathyroidism is 10-30% (2). Among the components of MEN 2A, MTC is the highest cause of morbidity and mortality (3). Therefore, total thyroidectomy is preferred in prophylactic treatment and curative treatment. The current recommendation in patients with MEN 2A is prophylactic total thyroidectomy before the age of 5 (4). In this study, an 18-year-old MEN 2A case presenting with primary hyperparathyroidism is presented.

2. CASE REPORT

An 18-year-old female patient was came to the internal medicine outpatient clinic with complaints of flank pain lasting for about four years, nausea and headache for one month. The patient has a known history of urolithiasis. A double J catheter was performed to the patient who had a history of stone removal one year ago. Patient's father and one sibling also had thyroid nodules. No other additional pathology was found in the patient and patient's family history. The patient was hospitalized to the endocrinology clinic for further examinations and treatment. Hypercalcemia detected in blood tests, so IV hydration was performed to the patient with isotonic fluid.

With the preliminary diagnosis of multiple endocrine neoplasia (MEN), a sample was taken from the patient for genetic analysis. Anterior pituitary (adenohypophysis) hormones, parathyroid ultrasonography and scintigraphy were also performed. Parathormone levels was (PTH): 223 pg/ml (15-65), Calcium levels was (Ca): 12.74 mg/dl (8.4-10). Patient's parathyroid scintigraphy showed activity consistent with parathyroid adenoma in the left lobe inferoposterior neighborhood. Patient was consulted to the otorhinolaryngology clinic service for the operation. Frozen material taken from the operated patient was compatible with parathyroid adenoma (Figure 1).

Figure 1: Histomorphological view of parathyroid adenoma



No decrease was observed in PTH values after the operation. The patient was followed up monthly. The PTH value in the follow-ups was 110.7 pg/ml, the Ca value was 11.37 mg/dl. Thereupon, the patient was re-hospitalized to the endocrinology clinic. The genetic test result of the patient was reported as MEN 2A. The patient was taken a three-day pheochromocytoma diet. After the diet, 24-hour urine was collected. Tumor markers were also sent. Metanephrine in urine: 51.8 µg/24 hours (0-180), normetanephrine: 17.7 µg/24 hours (0-451), vanilmandelic acid: 4.1 mg/24 hours (0-8), serum calcitonin: 88 pg/ml (0-18), CEA (carcinoembryonic antigen): 1.09 ng/ml (0-2.5). The patient's neck USG was repeated. On USG, several solid nodules with irregular borders were observed in the right thyroid lobe, the largest nodule was 9x7 mm in size. Thereupon, fine needle aspiration biopsy (FNAB) was performed and the biopsy result of the patient was reported as medullary thyroid carcinoma. Reactivity with chromogranin, synaptophysin and calcitonin was observed in immunohistochemical studies performed on this FNAB biopsy material (Figure 2). The patient was consulted to the otorhinolaryngology clinic, and total thyroidectomy was performed.

During the total thyroidectomy operation, two frozen preliminary studies were performed with the preliminary diagnosis of parathyroid adenoma. Materials sent for frozen were evaluated as compatible with thymus tissue. Histomorphology associated with parathyroid tissue or parathyroid adenoma was not observed.

In the pathological evaluation of total thyroidectomy material, histomorphology and immunophenotypic data consistent with medullary thyroid carcinoma measuring 7 mm in the right lobe were obtained (Figure 3). Ki 67 proliferation index was evaluated as 10%, necrosis, perineural invasion and capsule invasion were not observed.

Figure 2: A- FNAB Cytology H&E, B- Chromogranin Positivity, C-Synaptophysin Positivity, D- Calcitonin Positivity

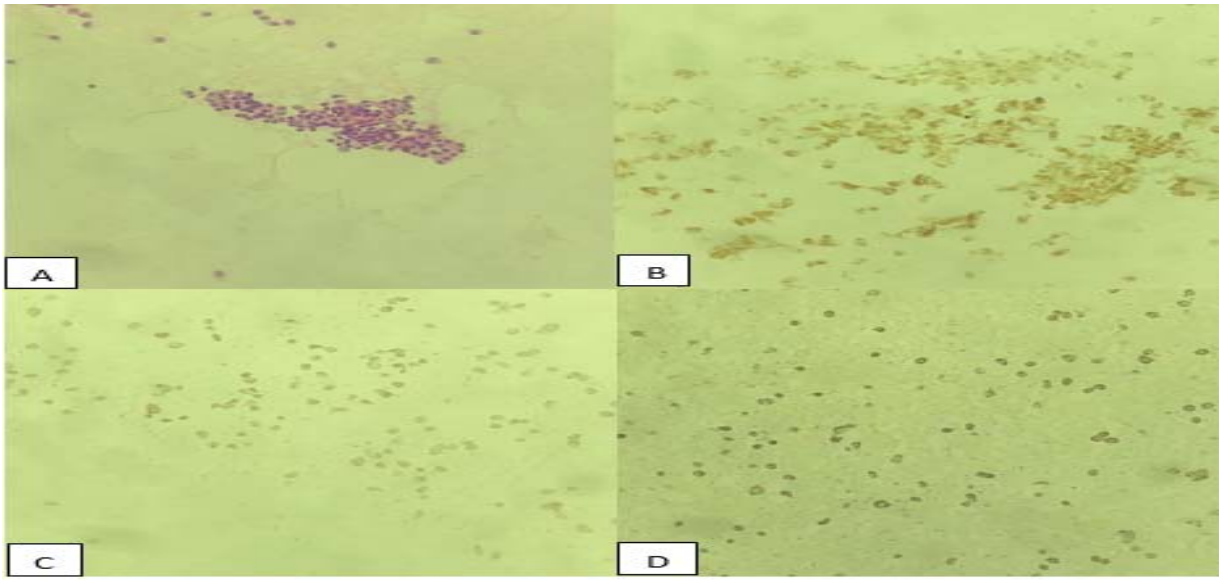


Figure 3: A-Medullary thyroid carcinoma, H&E, B- Chromogranin positivity, C- Synaptophysin positivity

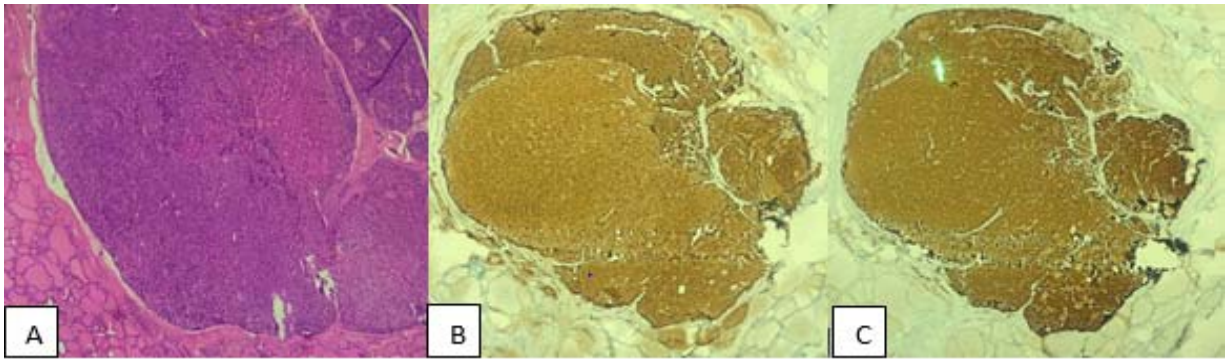
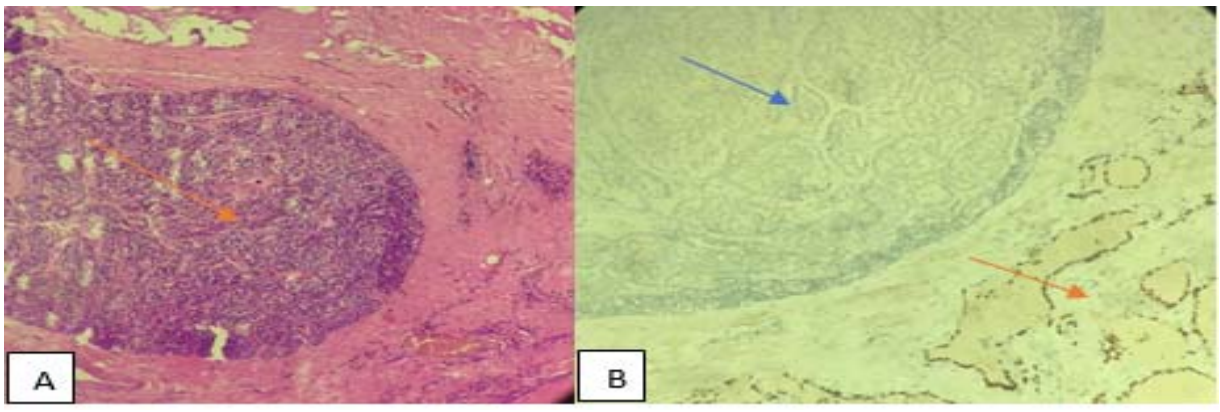


Figure 4: A-intrathyroidally located parathyroid tissue (red arrrow), B- TTF-1 negative parathyroid adenoma (blue arrow), TTF-1 positive thyroid tissue (red arrow)



In the sections of the thyroid tissue, there was an intrathyroidally located parathyroid adenoma with a diameter of 3 mm in the right lobe and 5 mm in the left lobe. In the immunohistochemical study, no positivity with TTF-1 was observed in parathyroid adenomas in the thyroid tissue containing TTF-1 positivity. (Figure 4). The lack of regressment in the laboratory and clinical findings of the patient and the absence of parathyroid adenomas in the frozen material are related to this condition.

No metastatic lymph node was observed in the lymph node dissection.

3. DISCUSSION

Histopathologically, medullary thyroid carcinoma is a malignant tumor with differentiation of parafollicular C cells. Therefore, immunohistochemical identification with calcitonin antibodies is essential. Increased calcitonin and carcinoembryonic antigen (CEA) levels are significant in the laboratory (1). Pheochromocytoma usually originates from the adrenal medulla, and pheochromocytoma seen in MEN 2 patients is histopathologically similar to sporadic pheochromocytoma cases (1). Although primary hyperparathyroidism originates from hyperplasia, it overlaps with non-familial parathyroid hyperplasia. Hyperparathyroidism rarely occurs in MEN 2A and its treatment is parathyroidectomy. If pheochromocytoma is detected before hyperparathyroidism and medullary thyroid carcinoma in MEN 2A syndrome, adrenalectomy should be performed before other operations planned. Because there is a risk of intraoperative catecholamine release in pheochromocytoma (5). In this case, pheochromocytoma was eliminated in the preoperative period.

Hyperparathyroidism is less likely to be detected as the first reason for admission in MEN 2A syndrome. Usually, medullary thyroid carcinoma is detected first. However, the first clinicopathological finding in this case was parathyroid adenoma. Oishi et al. (6) reported a 59-year-old female patient diagnosed with MEN 2A, whose disease relapsed 23 years later. Giacomelli et al. (7) reported a case of MEN 2A accompanied by papillary microcarcinoma in a 50-year-old female patient. Okada et al. (8) reported a case of a 30-year-old male patient whose first reason for admission was pheochromocytoma. Sim et al. (9) reported a 4-year-old boy who was diagnosed with MEN 2A with a strong family history of MEN and underwent prophylactic total thyroidectomy. Raue et al. (10) showed that the median age at the diagnosis of primary hyperparathyroidism in patients with MEN 2A was 38 years. Larsen et al. (11) in a multicenter retrospective study, it was found that primary hyperparathyroidism was the first component of only 0.9% of 1085 cases diagnosed with MEN 2A. Many cases of MEN 2A have been reported in the literature. However, most of these reported cases are older than this case, and the first component leading to the diagnosis is medullary thyroid cancer. In addition, total thyroidectomy was performed for medullary thyroid cancer for both prophylactic and curative treatment. As a result, hypothyroidism and hypocalcemia are expected in patients. Therefore, calcium and thyroxine treatment is applied in the postoperative period.

Even at micro level, thyroid medullary carcinoma can metastasize to lymph nodes. Therefore, a certain number of lymph node dissections are also performed together with total thyroidectomy. Skinner et al. (4) recommends neck lymph node dissection to MEN 2A patients over 8 years of age. In our case, 19 reactive lymph nodes were also dissected.

4. CONCLUSION

Before clinical manifestation in MEN syndrome, the disease can be diagnosed by genetic testing (12). In this case, the diagnosis of MEN 2A was confirmed by the genetic test result, and the first reason for admission was primary hyperparathyroidism. The patient, who was found to be pathologically compatible with parathyroid adenoma, did not present a clinical diagnosis of pheochromocytoma and medullary thyroid carcinoma at the first admission. However, after the patient's clinical and laboratory values did not regress after parathyroidectomy, the patient was re-evaluated. The patient, who was diagnosed as MEN 2A in the follow-ups, was provided with the necessary postoperative treatment. Primary hyperparathyroidism is not usually the first reason for admission in MEN 2A syndrome. In addition, despite the resection of the parathyroid adenoma in this case, the patient's clinical and laboratory findings did not regress. The presence of intrathyroidal parathyroid adenoma in the thyroidectomy material explains the reason for this condition, but also makes the case rare. Holm et al. (13) showed that the frequency of primary hyperparathyroidism was 8% in 204 patients diagnosed with MEN 2A between 1930 and 2021. In this case, the patient underwent total thyroidectomy and was followed up due to the risk of pheochromocytoma.

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