

Case Report

Running Title: Sipple Syndrome

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Sipple Syndrome: From Diagnosis to Management - A Case Report

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Abstract

Multiple endocrine neoplasia (MEN) is a rare inherited disease caused by multiple complex mutations in the RET gene. It is characterized by the occurrence of tumors involving more than two endocrine glands in the same patient. MEN is classified into two types: MEN type 1 (Wermer syndrome) and MEN type 2, which is further subclassified into two phenotypes: MEN 2A (Sipple syndrome) and MEN 2B (Shimcke syndrome). Sipple syndrome is the most common type of MEN type 2. It is characterized by the presence of medullary thyroid carcinoma (MTC), unilateral or bilateral pheochromocytoma, and primary hyperparathyroidism due to parathyroid cell hyperplasia or adenoma. In this article, the authors report a case of a 34-year-old Libyan woman with Rh positive B blood group who presented with an enlarged neck mass. Based on clinical, radiological, biochemical, and cytological assessments, the mass was diagnosed as MTC. Two weeks apart, the patient underwent right adrenalectomy and total thyroidectomy, while the parathyroid glands were found to be normal and preserved. In cases where a neck mass is the only symptom manifestation, it is crucial to carefully investigate for other MEN 2A findings, especially if there is a family history of MTC, to ensure a good prognosis. Patients with MEN 2A should undergo regular screening and be managed by a multidisciplinary team.

Keywords: Multiple endocrine neoplasia type 2a, Pheochromocytoma, Fluorodeoxyglucose, Calcitonin, Carcinoembryonic antigen

Introduction

Multiple endocrine neoplasia (MEN) 2A, also known as Sipple syndrome, is a rare

autosomal-dominant disorder with an incidence of about 1 in 30,000.¹ It is caused by mutations in the rearranged during

transfection (RET) gene, located on chromosome 10q11.2, which leads to damage of the C cells derived from the neural crest.² This syndrome was first reported by Sipple in 1961. According to the Revised American Thyroid Association Guidelines for the Management of medullary thyroid carcinoma (MTC) issued by the American Thyroid Association, it is further classified based on the presence of associated conditions: classic MEN2A, MEN2A with pruritic cutaneous lichen amyloidosis (CLA), MEN2A with Hirschsprung disease (HSCR), and familial thyroid medullary carcinoma (FTMC).^{3,4} Sipple syndrome is characterized by synchronous and/or metachronous polyglandular neoplasia that affects the thyroid gland, suprarenal gland, and parathyroid gland, leading to MTC (in 80%–100% of cases), uni- or bilateral pheochromocytoma (PCC) (in over 50% of cases), and primary hyperparathyroidism (15%–30% of cases), respectively.⁵ Almost all patients with MEN 2A have MTC, and it is typically detected before PCC is identified. Rarely, patients with MEN 2A may have an extra-adrenal catecholamine-secreting paraganglioma. MEN 2A is usually diagnosed based on history, clinical manifestations, biochemical tests, and imaging examinations when genetic testing is not available.^{5,6}

Surgical excision is the primary management approach, with pheochromocytoma being excised first when PCC and MTC occur simultaneously. Regular monitoring of serum calcitonin is crucial for follow-up. In this report, we present the case of a Libyan patient exhibiting synchronous double cancers, namely MTC and right pheochromocytoma, who presented only with a lump in the front of the neck without any other complaints.

Case Presentation

A 34-year-old married female patient presented to the hospital for evaluation of a

painless, enlarging neck mass that she noticed had started four months ago. The patient denied experiencing any secondary compressive symptoms or general symptoms of malignancy. She had no history of chronic illness or past medical conditions until recently. In the family history, her sister and first-degree cousin underwent total thyroidectomy for MTC a few years ago. In December 2020, she was referred to the Oncology Section of the Endocrine Unit at the National Cancer Institute, Sabratha Hospital, Libya, for suspected MTC based on the presence of thyroid nodules and elevated serum levels of calcitonin (Ct) and carcinoembryonic antigen (CEA), requiring further evaluation.

Her blood pressure was 100/60 mmHg, body temperature was 37°C, pulse rate was 72 beats per minute, and respiration rate was 20 breaths per minute. On physical examination, no abnormal findings were observed, except for a lateroventral neck mass measuring approximately 4 cm × 2 cm, which was not associated with palpable lymphadenopathy. Routine hematological and biochemical investigations revealed that she had Rh-positive blood type B. Complete blood cell count (CBC), thyroid function tests (TFTs), parathyroid hormone levels (PTH), calcium, alkaline phosphatase, norepinephrine, epinephrine, and dopamine were all within normal limits. Laboratory assessments confirmed high levels of calcitonin (1790 ng/L; normal value <10 ng/L) and CEA (6.8 ng/mL; normal value <2.5 ng/mL).

In January 2021, Ultrasonography (USG) of the thyroid gland revealed a slightly enlarged left lobe with multiple heterogeneous nodules present in both the left and right lobes. The largest nodule measured 1.5 cm × 1.5 cm and exhibited multiple calcifications and irregular borders (Figure 1). No cervical lymphadenopathy was observed.

A contrast-enhanced computed tomography (CT) scan of the entire body showed an

enlarged thyroid gland, particularly on the left lobe, with multiple mixed enhancing nodules in both lobes. The largest nodule measured 1.5 cm × 1.6 cm in the left lobe, with no evidence of local lymphadenopathy. The scan also revealed a 2.7 cm enhancing lesion in the right suprarenal region and a homogeneous contrasted (vascular) lesion measuring 2 cm in the left lobe of the liver. These results prompted the request for both a whole-body positron emission tomography (PET)-CT scan and fine needle aspiration (FNA).

FNA of the left thyroid nodule showed high suspicion for malignancy. The aspirate was highly cellular, with predominating thyrocytes of different sizes. Calcium particles, some resembling psammoma bodies, were also observed. The cells exhibited features consistent with papillary carcinoma.

The PET-CT scan revealed increased metabolic activity of fluorodeoxyglucose (FDG) in both thyroid lobes, indicating the possibility of MTC. The maximum standardized uptake value (SUV) was 4.3 on the right side and 7 on the left side. Additionally, increased FDG uptake was observed in the right suprarenal gland, suggesting a potential pheochromocytoma, with a maximum SUV of 5.8. Distant metastases were ruled out (Figure 2).

Based on these findings, a diagnosis of Sipple syndrome was made, and the patient was scheduled for total right adrenalectomy and total thyroidectomy, with a two-week interval between the procedures. After further diagnostic evaluation, the patient initiated α -adrenergic and then β -adrenergic blockade, along with intravenous fluid administration and regular blood pressure monitoring.

In May 2021, the patient underwent laparoscopic total right adrenalectomy without any associated complications. Macroscopic examination revealed a separate

gland measuring 5 × 3 × 2.5 cm, with a nodule of 3 × 2.5 × 2.5 cm. Histopathological examination described nests and sheets of large closely packed polyhedral cells arranged around stromal blood vessels. The cells exhibited a large amount of granular cytoplasm and round nuclei, consistent with predominantly alveolar pheochromocytoma (Figure 3A-C).

Two weeks later, in June 2021, the patient was admitted for the scheduled total thyroidectomy with central lymph node dissection. Surgery was performed without any postoperative complications. Macroscopic examination revealed a multinodular thyroid gland, with the isthmus measuring 2.5 × 1.5 × 0.5 cm and the right lobe measuring 5 × 2.5 × 3 cm, and the left lobe measuring 5.5 × 2.5 × 3 cm. Microscopic examination showed nodular lesions composed of sheets of compact cells with small nuclei and scant cytoplasm, along with a significant amount of amyloid (Figure 4). As regional lymphadenopathy was not detected preoperatively or intraoperatively, and the thyroid gland exhibited small nodules without capsule invasion, a neck lymph node dissection was performed. The parathyroid glands were preserved. Post-surgical evaluation confirmed the patient's clinical stability under replacement therapy. There was a progressive normalization of calcitonin and CEA levels.

The patient remained clinically stable after both surgical procedures, without immediate complications, and showed no signs of adrenal insufficiency or hypothyroidism. She continues to receive levothyroxine replacement therapy.

During follow-up examinations, the patient remained asymptomatic, with regular blood pressure. Three months later, metanephrines, calcitonin, CEA, PTH, and calcium levels indicated disease-free status for both pheochromocytomas and MTC. It is recommended to annually measure serum

calcitonin concentration to detect any residual or recurrent MTC after thyroidectomy.

This study received approval from the Ethics Committee of the National Cancer Institute in Sabratha, Libya (ethics code: 2023-404).

Discussion

The differential diagnosis of a neck mass is extensive and varies with age. This case describes a rare cause of a neck mass, hereditary MTC. An enlarging neck lump might be the only symptom of MEN disorder. Among the MEN variants, the rate of Sipple syndrome is approximately 80% of cases (Sipple, 1961).³

Although the pathogenesis of these combined polyglandular diseases has not yet been defined, it has been genetically found that numerous mutations throughout the rearranged during transfection (RET) proto-oncogene, located on chromosome 10q11.2 and encoding a receptor tyrosine kinase, have been documented in individuals with Sipple syndrome. Approximately 80% of all patients with MEN 2A variants were found to have mutations in codon 634.⁷ There has been a positive genotype-phenotype correlation in patients with MEN-2 complex, leading to improvements in earlier diagnosis, screening, and prognosis.⁵ Genetic testing is currently the main method of diagnosing MEN 2A in developed countries; however, it is not yet widely available in developing countries due to economic and technical limitations.

MTC is a neoplasia arising from the parafollicular or C-cells of neuroendocrine origin. It produces CEA. According to the literature, medullary thyroid cancer is described in 48-86% of patients as sporadic carcinomas and in 14-52% of patients with MTC as hereditary carcinomas (Engelbach et al., 2000).⁸

Metastasis of this neoplasia occurs in the cervical lymph nodes in 68%-80% of patients for both types. The prognosis of MTC

depends on age, gender, clinical presentation, TNM stage, distant metastases, and the extent of thyroidectomy (Clark et al., 2005).⁹

ABO blood groups and the Rh factor have been evaluated and considered as risk predictors in patients with thyroid cancer. Rh-positive patients with malignant disease have a significantly higher rate compared to patients with benign disease. On the other hand, thyroid cancer, extrathyroidal extension, and advanced stage are observed more frequently in patients with blood group B compared to non-B blood groups.¹⁰ The most effective method for early-stage MTC is to perform total thyroidectomy with central neck lymph node dissection (Kloos et al., 2009).¹¹ Thyroid hormone replacement is required after the operation. Prophylactic thyroidectomy is believed to be an effective treatment for patients with RET mutation carriers (Raue and Frank-Raue, 2012).⁷ In approximately 5% of these patients, serum calcitonin levels can rise again after surgery during follow-up (Leboulleux et al., 2004).¹² Therefore, it is crucial to regularly monitor serum calcitonin and CEA. These should be examined at 1, 3, 6, and 12 months after the initial thyroidectomy and twice a year thereafter, as well as an annual CT scan to detect the recurrence and metastasis of MTC. Pheochromocytoma is a neuroendocrine tumor that grows from specific cells known as chromaffin cells. These cells are characterized by the production of catecholamines and other neuropeptides. The majority of PCCs are benign and unilateral (Ungureanu et al., 2020).² Pheochromocytoma typically appears after the diagnosis of MTC (metachronous), frequently becoming evident about 10 years later in MEN2A patients, or simultaneously (synchronous). However, in 13%-27% of cases, it is reported as the initial manifestation (Romei et al., 2012).¹³ Clinical symptoms and signs of the disease occur in only 50% of patients and most commonly

affect individuals between the ages of 35 and 45, although children under 10 can also be affected (Thosani et al., 2013).¹⁴ According to previous literature, plasma and urinary normetanephrine and metanephrine levels have been shown to be more sensitive and specific in detecting PCC. Conversely, CT, magnetic resonance imaging (MRI), and PET are frequently used for evaluation. If a pheochromocytoma is detected, adrenalectomy should be performed before thyroidectomy to prevent intraoperative catecholamine release and bleeding. Long-term treatment with alpha and beta blockers should only be used in patients with unresectable tumors (Lei et al., 2016).⁵

Hyperparathyroidism rarely occurs in MEN 2A and results in excessive formation and release of parathyroid hormone (PTH). Primary hyperparathyroidism can be caused by solitary adenomas (80-85%), hyperplasia (10%), multiple adenomas (2%), and carcinomas (2-5%) (Prihantono et al., 2019).¹⁵ Since parathyroid endocrine glands play a significant role in calcium homeostasis, clinical manifestations include nephrolithiasis, osteopenia, or osteoporosis. Management involves subtotal or total parathyroidectomy with a subcutaneous autograft of a portion of a gland into the forearm (Ungureanu et al., 2020).²

Although this case has a family history of this syndrome, genetic testing was not available for the patient or her relatives. Therefore, the diagnosis of MEN 2A in our patient heavily relies on the patient's self-reported symptoms, biochemical tests, and imaging examinations.

Conclusion

We present a case of synchronous double cancers comprising MTC and pheochromocytoma as part of MEN 2A manifestations. These conditions can be diagnosed using biochemical tests and imaging examinations when genetic testing is not available. Our patient demonstrated an

asymptomatic PCC that was biochemically negative, as well as MTC with a single symptom of a gradually enlarging neck mass accompanied by high levels of calcitonin and CEA. This study highlights the importance of CT or MRI findings, which can alert healthcare providers to the presence of a pheochromocytoma, even in asymptomatic and biochemically negative patients. Considering the high probability of recurrence, we would like to emphasize the need for lifelong annual follow-up, including imaging check-ups and monitoring of calcitonin, CEA, and metanephrines in these patients. In the case of genetic syndromes, this approach not only facilitates the early detection of locally recurrent or metastatic disease but also enables the early diagnosis of other components of the syndrome in the patient or their first-degree relatives. This, in turn, allows for timely decisions regarding surgical intervention and the prevention of complications.

Informed Consent

Written informed consent was obtained from the patient for the publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Conflict of Interest

None declared.

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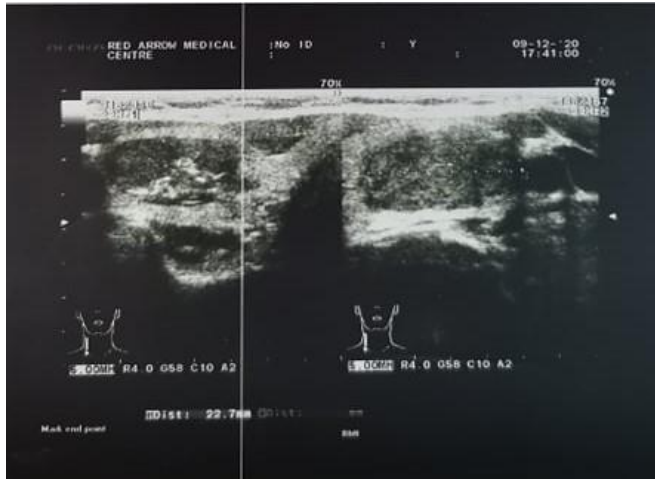


Figure 1. This figure shows the ultrasonography of the thyroid gland, depicting both lobes with multiple heterogeneous nodules and multiple calcifications.

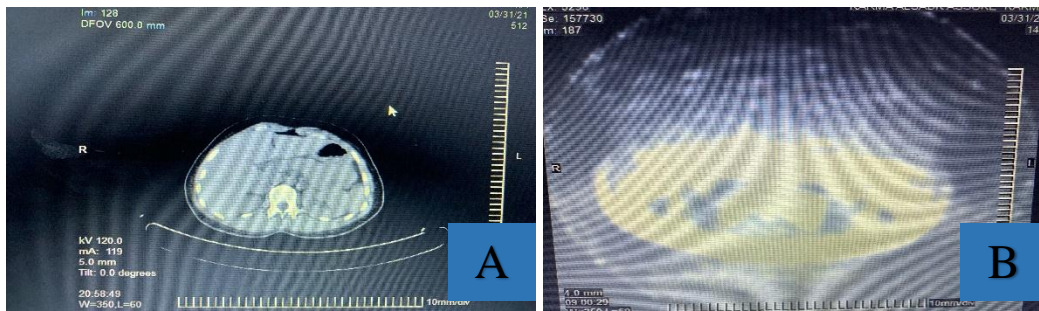
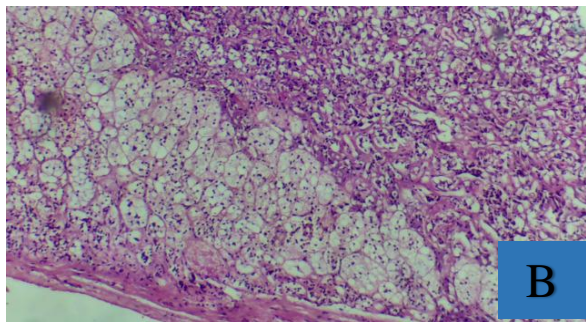
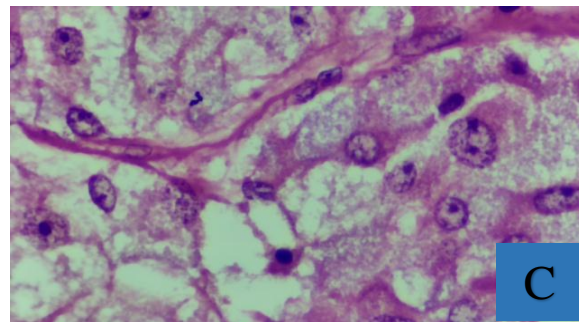


Figure 2. A and 2: PET-CT: These figures illustrate the increased metabolic activity of fluorodeoxyglucose at the level of a tumor in the right adrenal gland.

PET-CT: Positron emission tomography-computed tomography



b



c

Figure 3. A: This figure displays the gross specimen of the adrenal gland with a nodular solid adrenal tumor measuring 3×2.5×2.5 cm. B and C show microscopic views at different magnifications (hematoxylin-eosin stain; 20×, 40×, respectively), revealing a pheochromocytoma of the adrenal medulla with an alveolar pattern of growth and a rich vascular network using hematoxylin-eosin stain.

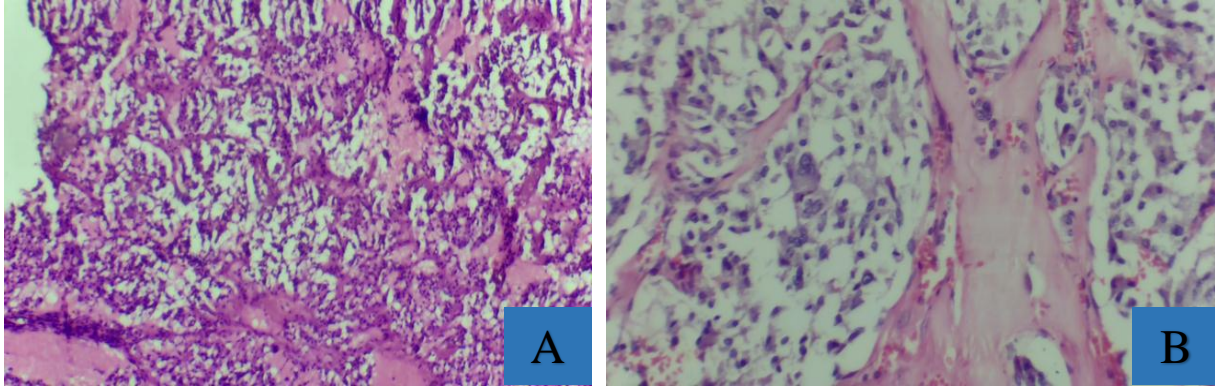


Figure 4: A and B: These figures show microscopic views at different magnifications (hematoxylin-eosin stain; 20 \times , 40 \times , respectively), displaying a medullary thyroid carcinoma with a trabecular pattern of growth, stromal amyloidosis, and tumoral cells with round nuclei using hematoxylin-eosin stain.