Available online at www.elixirpublishers.com (Elixir International Journal)

Medical Oncology

Elixir Medical Oncology 157(2021) 55549-55552

ISSN: 2229-712X

Multiple Primary Malignant Neoplasms Involving the Thyroid, Lung and Adrenal Gland: A Case Report with Review of the Literature

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ARTICLE INFO

Article history:
Received: 29 June 2021;
Received in revised form:
1 August 2021;
Accepted: 10 August 2021;

Keywords
Papillary Thyroid Carcinoma,
Parathyroid Adenoma,
Pulmonary Adenocarcinoma.

ABSTRACT

To present an unusual case of Multiple primary malignant neoplasms and to describe the steps we followed to evoke each diagnosis trying to reveal an underlying genetic disorder and to discuss the best strategy of treatment of our patient. We describe the work-up, diagnosis, and treatment course of a 50-year-old woman who presented with papillary thyroid carcinoma, parathyroid adenoma, pulmonary adenocarcinoma and pheochromocytoma. The tumor involvement of the parathyroid and the adrenal gland led us to think about NEM2 syndrome. Instead of medullary thyroid cancer which is invariably present in NEM2 syndromes, our patient presented a papillary thyroid cancer. We could think that the total thyroidectomy that have been performed in our patient could have prevented the appearance of a medullary thyroid carcinoma. The possibility of carrying out a DNA sequencing with research of germline RET mutation could have been very interesting to determine if this case can be considered as an unusual MEN 2A syndrome. Tumor DNA sequencing has a major role to determine molecular characteristics in different tumors and research eventual common biomolecular abnormalities, which can provide a genetic counseling.

Introduction

The incidence rate for multiple primary malignant neoplasms (MPMNs) is estimated to be between 0.73 and 11.7% [1]. MPMNs are defined as two or more unassociated primary malignant tumors that occur in the body synchronously or metachronously [2]. Each tumor originates from different tissues and organs, presents as a distinct pathological type and excludes lesions that are secondary or metastatic to other tumors[3]. MPMNs can be divided into two categories: i) Synchronous, defined as malignancies that occur within 6 months of the diagnosis of a previous malignant neoplasm; and ii) metachronous, defined as malignancies that occur >6 months apart. In a recent study, the risks of developing second primary cancers were higher in cancer survivors compared with the general population with a 3.8% higher incidence of metachronous second primary cancers within a median follow-up time of 2.5 years; furthermore, the estimated 10-year cumulative risk of second primary cancers for patients who were firstly diagnosed with cancer aged between 60 and 69 was as high as 13%[4]. Compared with a single primary tumor, MPMNs have increased malignant behavior and a worse prognosis[5].

Case Report

A 50-year-old Moroccan woman presented to a clinic in Rabat, Morocco on February 2016 for mild abdominal pain and fatigue that had lasted 2 months. She had no prior medical history, a family history of cancer was found in the siblings, the father and paternal uncle and aunt as showed in her medical family tree (Fig. 1.). Her maternal family history was negative for malignancy. She denied tobacco usage or alcohol consumption.

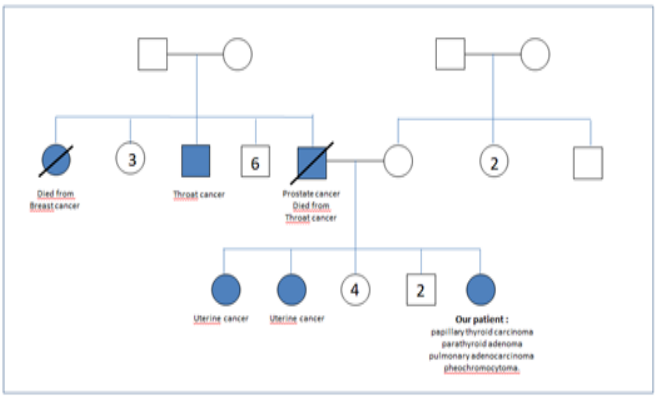

Fig 1. Medical family tree of our patient.

Blood and radiological examinations were performed and led to the diagnosis of a primary hyperparathyroidism, chemistry panel was normal except for ionized calcium level of 58mg/L and serum PTH level of 145 pg/ml. Cervical ultrasound showed inferior polar parathyroid nodule, it has also detected an incidental suspicious thyroid nodule on the lower pole of right lobe of thyroid gland, classified as TI-RADS 4A. On March, 2016, the patient underwent a right lobectomy + isthmusectomy with parathyroid adenoma excision. Histopathology revealed papillary thyroid carcinoma measuring 0.5 x 0.3 cm without capsular invasion, and an intrathymic ectopic parathyroid adenoma which was the cause of the primary hyperparathyroidism. Five weeks later, thyroid totalization was performed, the tissues were sent for pathologic evaluation, and it was free of tumor according to pathology lab report. Postoperative use of radioactive iodine (RAI) was not indicated in our patient.

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At 20 months follow-up, the appearance of an infectious-looking nodule in left lower lobe on the thoracic CT scan was observed and was closely monitored by thoracic CT every 3 months.

As the pulmonary nodule did not disappear despite the use of antibiotic treatment, a pet scan was performed and showed abnormal focal hypermetabolic activity in the lower lobe of the left lung corresponding to a primary tumor; it also revealed an incidental focal hyperfixation in the left adrenal gland.

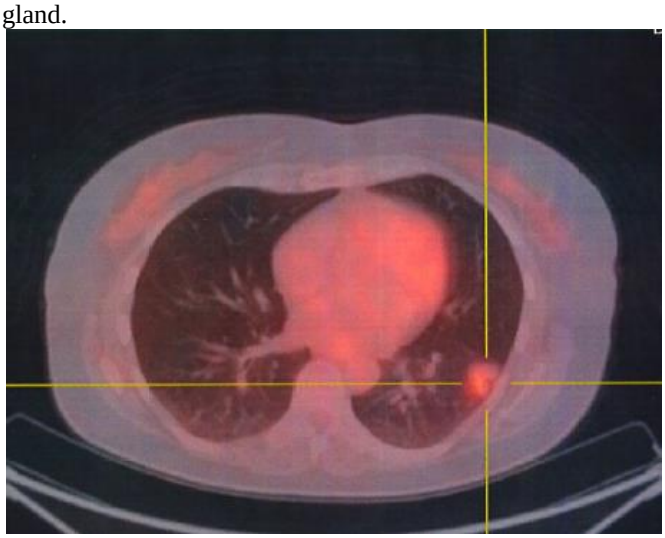

Fig 2. Pet scan showing abnormal focal hypermetabolic activity in the lower lobe of the left lung

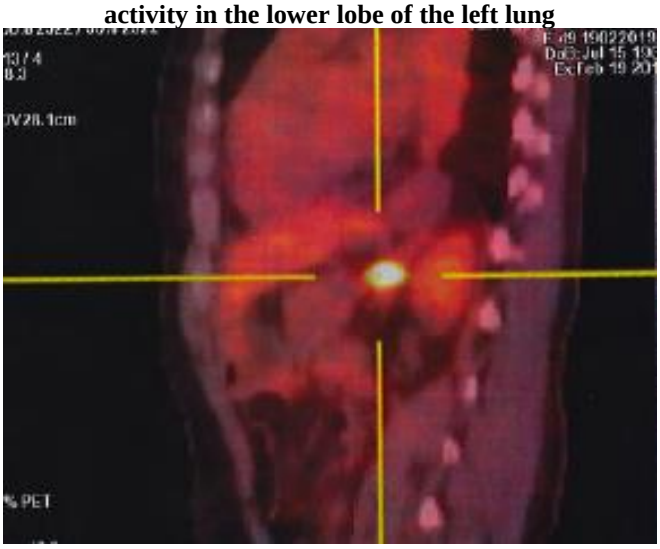

Fig 3. Pet scan showing an incidental focal hyperfixation in the left adrenal gland

Lung biopsy was done and revealed a primitive *lung lepidic adenocarcinoma*. The bone scintigraphy and brain scan did not reveal any metastatic lesions. On September 18, 2018, *lower right lobe segmental resection* was performed and histopathology showed complete resection of the adenocarcinoma that measured 3 cm in diameter with no lymph node involvement, margins negative, with vascular invasion and mediastinal pleural involvement. The tumor staging was pT2 N0, stage IB . No EGFR mutation or *ALK* translocation were detected, and the *PD-L1* expression level was low (2%)

The patient received 3 cycles of adjuvant platinum-based chemotherapy (cisplatin-pemetrexed)

Regarding the adrenal mass, the patient underwent an F-FDG PET/CT scan that showed increased FDG uptake of the adrenal lesion that looked wrongly like a single secondary lesion

The patient was submitted to laparoscopic left adrenalectomy from a retroperitoneal approach on March 23, 2019.

A 10x8mm tumor was removed and the pathological report confirmed the diagnosis of pheochromocytoma

The patient has since returned back home and is being followed in our department.

Discussion

The malignancies in our patient were all completely asymptomatic and were accidentally discovered. Papillary carcinoma of the thyroid was accidentally discovered during the surgery for the primary hyperparathyroidism. Thereby, it was diagnosed at a very early stage and was classify as ”low risk” for recurrence and the patient had been followed up. When the lung nodule appeared 20 months after thyroid lobectomy, we first thought about a pulmonary infection. After ruling out pulmonary tuberculosis, she was treated by probabilistic broad spectrum antibiotherapy. As the nodule did not disappear, the diagnosis of pulmonary metastasis was very plausible. Stimulated Tg was <2 ng/mL with negative antithyroglobulin antibodies, RAI imaging was also negative. Lung biopsy was then indicated. As the histopathology report showed that it was rather a Primary pulmonary adenocarcinoma, and since the patient had no risk factors for developing lung cancer, we asked for a re-reading of the biopsy slide in another histology laboratory. The diagnosis was confirmed and once again, the tumor was at an early stage and the resection was complete. Adjuvant chemotherapy in stage IB of lung cancer is not usual, but it was indicated in this case because the tumor had vascular invasion and visceral pleural involvement.

According to the PET scan results concerning the adrenal mass, we evoked a possible distant metastasis of the lung cancer. As it was a single lesion, left adrenalectomy was performed and the diagnosis of pheochromocytoma was made. The patient did not have any symptoms due to excessive catecholamine secretion as palpitation, headache or sweating. Once again, it was a stage I tumor.

In this case, the coexistence of Papillary Thyroid Carcinoma, NSCLC and pheochromocytoma in a patient with a family history of cancer reflects the fact that there is a genetic predisposition.

Multiple primary malignant neoplasms (MPMN) were first described by Billroth in 1889 [6].

Until the extremely detailed compilation study of 1,259 case reports by Warren and Gates in 1932, MPMN were considered merely medical curiosities[7].

MPMs in a single patient are relatively rare but have increase in frequency in recent decades. Among those with multiple primary malignancies, double cancer is commonly seen, while triple cancers occur in 0.5% of patients, and quadruple or quintuple cancers occur in only less than 0.1% of the population[8].

Multiple mechanisms have been implicated in the pathogenesis of this entity, including hereditary, immune and environmental factors such as chemicals, viruses, chemotherapeutic regimens and ionizing radiation[9].

Furthermore, increased survival of cancer patients, the growing life expectancy and the development of improved diagnostic techniques, have all contributed to the increased frequency of MPMs[9].

The criteria later enunciated by warren and gates are now generally accepted: 1) each of the tumors must present a definite picture of malignancy; 2) each must be distinct; and

3) the probability that one was a metastatic lesion from the other must be excluded.

The study of multiple primary malignant tumors is of paramount importance since it could unravel clinical associations of certain malignancies, uncover various germ-line and genetic mutations and help tailor follow-up and screening in these patients [10,11].

This report describes a rare case of a patient that after she was cured from a papillary thyroid carcinoma and ectopic parathyroid adenoma, presented 20 months later two synchronous malignancies: lung lepidic adenocarcinoma and pheochromocytoma.

Patients diagnosed with early stage lung cancer have an increased risk for second primaries compared with the general population without a prior cancer diagnosis. Many second malignancies are related to smoking. The rate of second primaries is slightly lower in first primary adenocarcinoma with a rate of 3.36 per 100 person-years than in squamous cell carcinoma with a rate of 3.77 per 100 person-years. It is highest in small cell lung cancer (SCLC) with 4.46 cases per 100 person-years. There is no significant association with radiotherapy[12].

The most common second cancers are in the lung, especially if the first primary was a SCLC. The most common second lung malignancies are adenocarcinomas (29.9%) followed by squamous cell carcinomas (27.1%). SCLCs represent only 7.9% of the second pulmonary malignancies after a first lung cancer [13].

In the other hand, the presence of parathyroid adenoma, thyroid and adrenal malignancy led us to think about Multiple Endocrine Neoplasia.

MEN 2 is characterized by medullary thyroid carcinoma, pheochromocytoma and primary parathyroid hyperplasia and is suspected when there are at least 2 of these 3 common tumors. It is subclassified into three distinct syndromes: MEN 2A, MEN 2B and familial medullary thyroid carcinoma (FMTC).

FMTC is suspected in families with 2 or more cases of medullary thyroid cancer and no evidence of parathyroid or adrenal gland problems.

MEN2A is suspected when there are at least 2 of the 3 common tumors, such as medullary thyroid cancer, pheochromocytoma, or parathyroid adenoma, in 1 person or a close relative. Close relatives are generally considered to be parents, siblings, and children. Medullary thyroid carcinoma has been reported in children as young as 2 years of age, although it more commonly develops between the ages of 5 and 18 years.

MEN2B is suspected in children with mucosal neuromas, meaning lumps on the tip of the tongue, and typical facial features, such as thickened lips. Medullary thyroid cancer can occur very early in childhood.

MEN 2 is caused by germline activation of an oncogene, RET (Rearranged in Transfection)[14] that encodes a receptor tyrosine kinase which is required for the normal growth and maturation of cells derived from the neural crest [15,16].

In patients with only one or two clinical features, identification of a germline RET (Rearranged in Transfection) mutation or the identification of the clinical features of MEN 2A in other first degree relatives is required to make the diagnosis [17].

It is estimated that about 1 in 30,000 people has MEN2. Most people with MEN2B do not have any family history of the condition. They have a de novo mutation in the RET gene. Fewer than 5% of people with MEN2A are thought to have a de novo mutation in the RET gene.

Early diagnosis by screening of family members in MEN 2 kindred is essential because medullary thyroid cancer is a life-threatening disease that can be cured or prevented by early thyroidectomy [18].

Pheochromocytoma occurs in approximately 40% of patients with MEN 2A [19], it usually appear about 10 years later than C cell hyperplasia or MTC [20] and it is identified either by screening or through heightened vigilance for symptoms (paroxysm of anxiety,headache, diaphoresis, palpitations or tachycardia). It may be cured by unilateral adrenalectomy in patients who have unilateral disease with a normally appearing controlateral gland [21].

Outcome of the Study Patient

Our patient did not have a medullary thyroid carcinoma, but a papillary carcinoma, and it is unusual for pheochromocytoma to precede the development of MTC, however, it has already been described in the literature that rarely pheochromocytoma may be the first manifestations of MEN 2 [22].

In our patient, we couldn't have a mutational analysis of the RET, but as RET mutation is highly suspected, we can say that MTC could develop later if total thyroidectomy was not performed before, and that this surgery maybe prevented the development of MTC.

Tumor DNA sequencing would have been interesting to determine molecular characteristics of these tumors and research eventual common biomolecular abnormalities, but genetic screening in our case were not feasible.

In a MEN 2A family, a sample from one subject already known to be affected should be tested in order to determine the specific RET mutation for that family. All subjects of unknown status in that family should then be definitively genotyped for detecting RET mutations carriers.

Conclusion

Tumor DNA sequencing has a major role to determine molecular characteristics in different tumors and research eventual common biomolecular abnormalities, which can provide a genetic counseling.

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