SYNCHRONOUS DIAGNOSIS OF TESTICULAR AND THYROID CANCER IN A YOUNG MALE

Testicular cancer is the most common neoplasm in young males. The early diagnosis and the appropriate treatment make it a curable malignancy in over 90% of the patients, but 6% of the patients with testicular cancer develop a second, mostly treatment-related, malignancy in another primary site many years after the first diagnosis. The simultaneous appearance of a testicular tumor with another primary neoplasm is rarely described in the literature. Here is presented an interesting case of a coexisting non-seminomatous germ cell testicular tumor with a papillary thyroid carcinoma, which was detected early during post-treatment restaging of the testicular tumor. The synchronous presence of these two neoplasms might indicate a probable common pathogenetic background. As treatment-related oncogenesis is highly improbable in this case and the common environmental factors are not known yet, the interest is focused on genetic predisposition. Recent discoveries in molecular genetics show that the two neoplasms share common genetic alterations in the \( RAS \) and \( BRAF \) genes, which affect the significant signaling pathways. Interestingly, \( BRAF-V600E \) was positive in both primary malignancies in our individual.

**Keywords:** testicular cancer, papillary thyroid carcinoma, synchronous diagnosis.

Discovering a second primary tumor in an oncological patient is not a rare phenomenon [1]. The incidence of metachronous primary tumors can reach a percentage of 11.7% in such patients [2]. However, the synchronous appearance of two or more primaries in the same individual

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still remains a rare phenomenon. Billroth in 1889 was the first to reveal the co-existence of multiple independent neoplasms and to stimulate further research [3]. Since then, the literature has been enriched with several similar reports describing even cases with 6 different synchronous primaries [4]. Although many factors appear to play a role in this multiple carcinogenesis, genetic predisposition is probably the most crucial one [5].

Testicular cancer is the most common neoplasm in young males between 20 and 40 years old [6]. Non-seminomatous germ cell tumor with embryonal cell elements represents the most common histological type that often presents with painless testicular swelling and has an excellent 10-year survival of 95% when the appropriate treatment protocols are followed [7, 8]. While extra-testicular primary neoplasms can be developed years after radiation and chemotherapy, due to the treatment toxicity, the concomitant presence of a testicular tumor with other primary malignancies is an unusual phenomenon, as the patients are usually young and healthy individuals at the time of diagnosis [9]. Here is presented the fourth case so far of a rare coexistence of papillary thyroid carcinoma with a testicular primary tumor in a young adult. Simultaneously, an investigation is attempted of the possible genetic, environmental, or potential causes explaining this concurrency [10, 11].

Case report

A 26-year-old male patient presented with a short history of painful swelling of the left testis. Based on the suspicious ultrasound findings, the clinical examination and the significantly elevated tumor markers [alpha-fetoprotein (AFP), β-human chorionic gonadotropin (β-HCG), lactate dehydrogenase (LDH)], he underwent a left orchiectomy. The histological examination revealed a mixed non-seminoma from germ cells with >95% elements of the embryonic carcinoma. The staging scans revealed the metastatic foci in the para-aortic lymph nodes (>5 cm) and multiple distant metastases in the lungs (Fig. 1). The tumor markers after orchiectomy remained high and namely AFP = 28.4 ng/ml, β-HCG = 1.2 IU/ml, and LDH = 662 IU/ml. According to the TNM staging, the tumor was staged as pT3cN3M1aS2, and subsequently, the patient was treated with 4 cycles of BEP chemotherapy (bleomycin, etoposide, and cisplatin). The post-chemotherapy PET/CT scan suggested the complete response of the primary and the metastatic lesions, but additionally revealed a metabolically hyperactive right thyroid nodule (Fig. 2). The tumor markers returned to normal after the completion of chemotherapy, however the thyroglobulin was found relatively elevated (136.6 ng/ml). An ultrasound-guided fine-needle aspiration biopsy of the suspicious thyroid nodule was performed, revealing a 2.5 cm nodule without abnormally enlarged cervical lymph nodes, and the cytology was indicative of papillary

Fig. 1. Axial chest CT scan showing 3 micronodular lesions in both lungs sizing within 8—18 mm (metastatic foci)
thyroid carcinoma. Following a multidisciplinary team discussion, the patient underwent a total thyroidectomy, and the histological examination confirmed the presence of a classic papillary carcinoma (pT3b) with minimal extrathyroidal extension. The patient additionally received radioactive iodine (I¹³¹). Due to high scientific interest, we examined the two primary malignancies for mutated genes, and the BRAF-V600E was found positive in both cases. The patient has been under regular follow-up for the last three years and he is still disease-free.

**Discussion**

Testicular cancer represents only 1% of all solid tumors, but in young males its incidence can reach almost 60%, showing an increasing trend in the last decades [12]. The germ cell tumors are divided into seminomatous and non-seminomatous tumors based on the clinical and histological criteria, despite their common origin. The embryonic cell elements are found in 90% of the patients just as in our case. A painless testicular mass is the most common clinical sign, although metastatic symptoms such as headache or abdominal pain are frequently the main complaints [13]. Following the optimal treatment, combining surgery with radiation and chemotherapy according to the disease stage, testicular cancer turns out to be a curable neoplasm, with over 90% survival rate [14]. Although 6% of the cases are prone to develop a second extra-testicular neoplasm, which often presents years after the toxic cancer treatment, the synchronous appearance of a second unrelated primary neoplasm along with the germ cell tumor is a rare finding in the literature [15]. These primary tumors are renal cell carcinomas in most of the cases or hematological malignancies [10]. Papillary carcinoma of the thyroid has been only three times presented to co-exist with embryonal testicular carcinoma by Ayoub et al. [10, 11], and here is presented the fourth case.

On the other hand, thyroid cancer is a quite common rapidly increasing endocrine neoplasm worldwide, with papillary thyroid cancer being the most prevalent histological type (80%) [16]. After the appropriate management depending on the neoplasm stage including hemi- or total thyroidectomy with or without modified neck dissection, adjuvant radioactive iodine ablation, and suppressive TSH therapy, the papillary thyroid carcinoma tends to have an excellent prognosis, with 90% of patients exceeding the 10-year survival [17]. The problem in this type of cancer remains a high recurrence rate, mainly in the advanced stages (almost 20%), which is associated with increased incurability and mortality. This is the reason why early detection is so important. According to the recorded

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**Fig. 2.** PET-CT scan after the completion of chemotherapy showing abnormal uptake in the right lower thyroid lobe
data, patients with thyroid malignancies have an 11% probability of developing a second primary neoplasm in the future, which is often located in another endocrine gland. Only 2.6% of this proportion accounts for the development of testicular cancer as a second malignancy later on in their life [18]. It is remarkable that in all three cases, synchronous with testicular cancer, the thyroid malignancy was always an incidental finding during re-staging scans right after chemotherapy.

The literature presents a plethora of reasons attempting to explain the synchronous appearance of these two primary neoplasms. Environmental, genetic, hormonal factors or chance alone may play an individual unique role in the simultaneous carcinogenesis at different sites [2]. First of all, in all three cases, the increased vigilance during re-staging and follow-up in individuals with germ cell tumors resulted in an earlier diagnosis of papillary thyroid carcinoma. Moreover, both neoplasms show a similar epidemiology by highly affecting young males between 20 and 40 [12, 16]. Those two factors are more compatible with the incidental co-existence of those histologically different tumors. Regarding the environmental factors, none of them has been associated so far with both malignancies, not even smoking, which is a well-known factor in the pathogenesis of numerous malignancies [19]. Thus, the attention is focused on the genetics, the probable genetic predisposition, and the chromosomal abnormalities that the two neoplasms may share [20].

The significant advancements in the field of genetics have allowed us to delineate the molecular underpinnings of testicular germ cell tumors and papillary thyroid carcinomas. The common signaling pathways leading to oncogenesis have been already identified for both neoplasms. Regarding papillary thyroid carcinoma, the \textit{BRAF-V600E} mutation is the most prevalent one [45%], followed by the \textit{RAS} mutations [21]. These ‘driver’ events in the MAPK/ERK signaling cascade are implicated in the dysregulation of cellular homeostasis leading to the characteristic hallmarks of cancer. \textit{KRAS}, \textit{NRAS}, and \textit{BRAF} (V599E and V600E) are the most commonly met mutated genes in the testicular tumors with the embryonic components, associated with tumor ontogenesis and apparently with chemoresistance [22]. These shared mutational signatures play a crucial role in the early stages of tumorigenesis via the MAPK and the PI3K-AKT pathway [20, 23]. In particular, the \textit{BRAF-V600E} mutation leads to the constitutive activation of the mitogen-activated protein kinase (MAPK) signaling pathway, resulting in uncontrolled cell proliferation, survival, and metastasis [21]. The above-mentioned data suggest a possible genetic predisposition for these two neoplasms, which can lead to synchronous oncogenesis with a possible additional effect of some unknown common environmental factors. Similarly, in our case, the concomitant presence of the \textit{BRAF-V600E} mutation in both tumors is probably coincidental and is most likely indicating a common pathogenetic background of oncogenesis.

In this case report, we described a rare coexistence of two primary malignancies in a young patient. This is the fourth case of synchronous appearance of a non-seminomatous testicular germ cell tumor with papillary thyroid carcinoma. Worth mentioning is the fact that in all four cases, only the testicular tumor had obvious clinical manifestations, and the incidental finding of the thyroid neoplasm was revealed due to the careful investigation and follow-up for the testicular malignancy. These data suggest that even in very young adults, the presence of two synchronous primaries is not impossible, and all the clinical and radiological findings should be meticulously investigated. Moreover, the precise therapeutic protocol should be followed for each neoplasm separately, according to the oncological principles.
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REFERENCES


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ОДНОЧАСНА ДІАГНОСТИКА РАКУ ЯЄЧКА ТА ЩИТОВИДНОЇ ЗАЛОЗИ У ЧОЛОВІКА МОЛОДОГО ВІКУ

Рак яєчка є найпоширенішим новоутворенням у чоловіків молодого віку. Рання діагностика та відповідне лікування приводять до одужання більш ніж у 90% пацієнтів. Варто зазначити, що у 6% пацієнтів з раком яєчка через тривалий час після першого діагнозу розвивається друге злоякісне новоутворення іншої первинної локалізації, здебільшого пов’язане з протираковою терапією. Одночасна поява пухлини яєчка з іншим первинним злоякісним новоутворенням рідко описується в літературі. У статті представлено цікавий випадок співіснуючої несеміноматозної гермінативної пухлини яєчка з папілярним раком щитоподібної залози, який був виявлений на ранній стадії під час повторного визначення стадії пухлини яєчка після лікування. Одночасна наявність цих двох новоутворень може свідчити про ймовірну спільну патогенетичну основу. Оскільки онкогенез, пов’язаний з лікуванням, у цьому випадку є дуже малоймовірним, а загальні фактори ризику навколишнього середовища ще невідомі, інтерес зосереджений на генетичній схильності. Недавні відкриття в молекулярній генетиці показують, що ці два новоутворення мають спільні генетичні зміни в генах RAS і BRAF, які впливають на важливі сигнальні шляхи. Цікаво, що BRAF-V600E був позитивним у клітинах обох первинних злоякісних новоутворень обстеженого пацієнта.

Ключові слова: рак яєчка, папілярний рак щитоподібної залози, синхронний діагноз.