CASE REPORT

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SYNCHRONOUS PRESENTATION OF PAPILLARY THYROID CARCINOMA AND HODGKIN LYMPHOMA – A CASE REPORT

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Summary

Multiple primary malignancies are increasingly detected due to advanced imaging modalities and comprehensive diagnostic protocols. Papillary thyroid carcinoma (PTC) is the most frequent type of thyroid neoplasm with ever-rising incidence. Hodgkin lymphoma (HL) is a lymphoid neoplasm more common in young adults and usually involves cervical lymph nodes. PTC is known to be radiation-induced in previously treated lymphoma patients but the synchronous appearance of these two malignancies in patients without a history of radiation exposure is very rare. We present a case of a 42-year-old male patient who was incidentally diagnosed with HL during the workup for a lump in the right lobe of the thyroid gland. Contrast-enhanced CT of the neck demonstrated a large heterogeneous nodal mass in the right thyroid lobe suggesting thyroid neoplasm. Lymphadenopathy was present on the opposite left side of the neck and bilaterally in the mediastinum with enlarged homogeneous nodes atypical for thyroid metastases. Fine needle aspiration and histopathological analysis of samples received after thyroidectomy and neck dissection confirmed PTC and classical HL. The patient was referred to treatment of HL which showed signs of primary refractory disease with response and complete remission on the second-line chemotherapy regimen. Radio-iodine ablation of remnant thyroid tissue is planned after hematological stabilization. This paper aims to describe a rare condition of concomitant occurrence of primary thyroid and hematological malignancies and to discuss the challenges in the diagnosis and management of synchronous tumors.

KEYWORDS: *multiple primary malignancies, papillary thyroid carcinoma, Hodgkin lymphoma*

INTRODUCTION

Patients presenting with thyroid lump and cervical lymphadenopathy may cause diagnostic dilemmas. In the case of proven thyroid carcinoma, it is important to distinguish enlarged lymph nodes that belong to lymphatic metastasis from much rarer concomitant lymphoproliferative disease. Diagnosis may be assumed by radiological features of pathologically changed nodes and is confirmed after analysis of pathological specimens.

Although both papillary thyroid carcinoma (PTC) and Hodgkin lymphoma (HL) are frequently diagnosed malignancies, their joint appearance in an individual patient is rare and alters the course of the treatment. The development of PTC as the second malignancy after irradiation of the neck used to treat patients with lymphoma has been well-known(1). On the other hand, the coexistence of PTC and HL in patients with no history

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of radiotherapy is very unusual and has been described in only several cases(2-6).

CASE REPORT

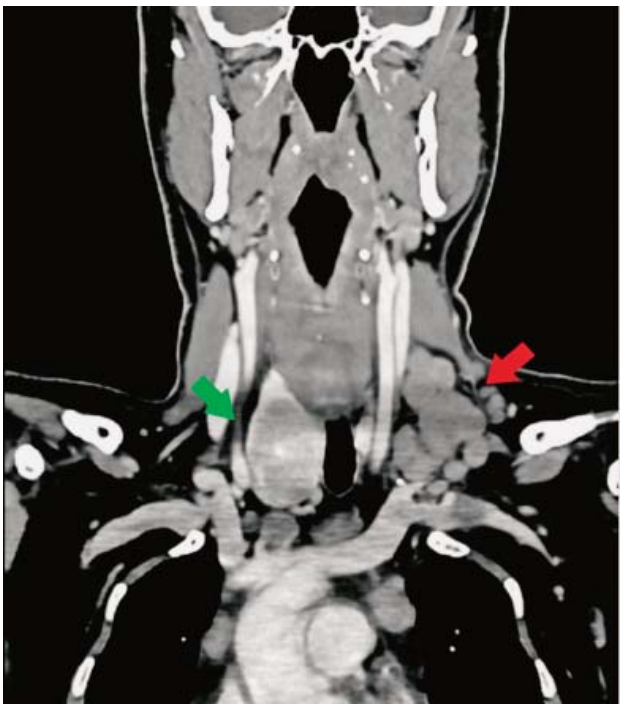
We present a 42-year-old male patient with a neck lump and cervical lymphadenopathy. The patient did not report B symptoms, significant past medical history, or history of radiation exposure.

Laboratory tests revealed a slightly increased percentage of neutrophils (77.6%; normal = 44-72%) with a decreased percentage of lymphocytes (12.4%; normal = 20-46%). Levels of total proteins (85 g/L; normal = 66-81 g/L) and C-reactive peptide (12.7 mg/L; normal < 5.0 mg/L) were also above normal values. Erythrocyte Sedimentation Rate (ESR) was increased (20 mm/h; normal 2-13 mm/h).

Contrast-enhanced computed tomography (CE-CT) of the neck showed a heterogeneous nodule in the right lobe of the thyroid. On the left side of the neck, in regions III, IV, and V, round lymph nodes of homogeneous structure were seen which were continuously followed into the upper mediastinum on both sides. On the right side of the neck, there was no pathological lymphadenopathy (Figures 1 and 2).

Fine needle aspiration biopsy of the thyroid lump suggested PTC (Bethesda V) but findings in the enlarged lymph nodes on the left side indicated lymphoproliferative disease with elements of granulomatous inflammation. The patient underwent total thyroidectomy, right-sided neck dissection, and biopsy of the lymph nodes on the left side of the neck. Pathological analysis proved conventional PTC without metastases in the lymph nodes on the right side. Enlarged lymph nodes on the left side were diagnosed as classical HL, subtype nodular sclerosis. After PET-CT, the patient was classified as stage III.

The patient was referred for further hematological treatment. First-line chemotherapy included 4 cycles of escalated BEACOPP (escalated dose of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone). Since re-evaluation PET-CT showed signs of primary refractory disease, treatment was continued with second-line ICE regimen (fosfamide, carboplatin, etoposide), BEAM (carmustine, etoposide, cytarabine, and melphalan) conditioning and autologous stem cell transplantation. After 2 cycles of ICE protocol, PET-CT showed complete remission of the disease. An adjuvant radio-iodine treatment is planned after a course of chemotherapy is completed.



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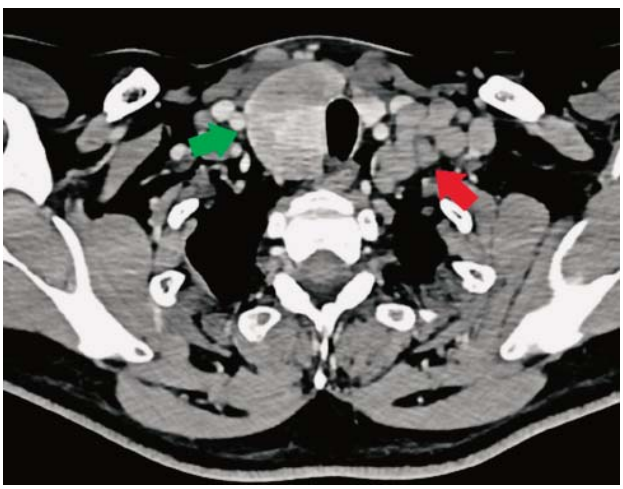

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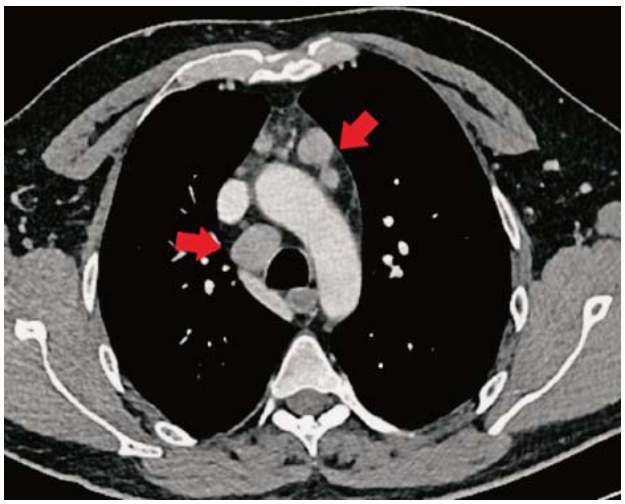
Figure 1. Contrast-enhanced CT in coronal (a) and axial (b) plane: a heterogeneous nodule in the right lobe of the thyroid (green arrow) and pathological lymphadenopathy on the left side of the neck (red arrow).



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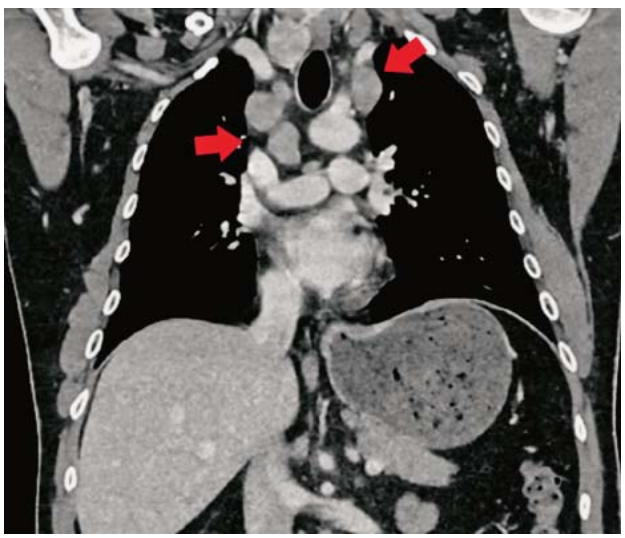

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Figure 2. Contrast-enhanced CT in axial (a) and coronal (b) plane: pathological lymphadenopathy in the mediastinum (red arrows).

DISCUSSION

Multiple primary malignancies (MPM) were first described in 1869 and since then the incidence has progressively increased over time. Today the frequency of MPM in the same or different organ systems ranges from 2% to 17%. Tumors are defined as synchronous if they appear at the same time or metachronous if the second tumor is detected 6 months afterwards(7). The synchronous category is considered a less common and synchronous association of solid tumors with a hematological malignancy such as Hodgkin's disease is considered one of the rarest among synchronous MPMs(8).

Detection of concomitant tumors often occurs incidentally when computed tomography (CT) is performed to stage a patient with a known malignancy and it is usually noted first by a radiologist when a new lesion atypical for metastases is detected(7). If the clinical and radiological findings are not typical for the primary malignancy, re-biopsy is the only option to confirm the possibility of MPMs(8).

PTC is the most frequent thyroid neoplasm accounting for 80 to 85% of all thyroid cancer cases. Besides a clear association between PTC and radiation exposure, chromosomal rearrangements including the RET protooncogene, NTRK1, and MET gene and mutations in the BRAF gene have been identified in the pathophysiology of PTC(9).

CT features of PTC are very similar to the nodular goiter. Some of the findings that help diagnose thyroid nodules as PTC are irregular rings, marginal defects, and enhanced blurring(10). PTC tends to metastasize rather early to local lymph nodes and approximately 50% of patients have cervical lymph node metastases at the time of their initial presentation(11). Thyroid nodal metastases commonly occur in the central compartment (level VI) and the ipsilateral mid or lower jugular chain nodal groups (levels III and IV). The highest lymph node in the central compartment is the Delphian node or prelaryngeal lymph node and involvement of this group in PTC is predictive of advanced nodal disease. Other nodal sites are the lower paratracheal nodes in the superior mediastinum (level VII), the retropharyngeal, and the gastroesophageal groups(12).

Approximately 40% of all lymph node metastases from PTC tend to completely cavitate a lymph node by cystic degeneration(11). Apart from cystic components, other CT findings from a nodal mass that suggest a primary thyroid origin include calcification, intense enhancement, or hyperdensity from proteinaceous or hemorrhagic content(12).

Patients with PTC were at elevated risk for secondary primary tumor and the risk is stronger in the first year after the first malignancy(13).

HL is a rare monoclonal lymphoid neoplasm with a bimodal age distribution that usually arises in cervical lymph nodes. Patients with HL frequently report painless supra-diaphragmatic

lymphadenopathy and so-called B symptoms (profound weight loss, high fevers, and drenching night sweats). Fine-needle aspiration frequently shows non-specific findings and definitive diagnosis is through excision biopsy from a lymph node. Classical HL accounts for approximately 95% of all HL, and it is further subdivided into four subgroups: nodular sclerosis (NSHL), lymphocyte-rich (LRHL), mixed cellularity (MCHL), and lymphocyte-depleted (LDHL)(14).

Imaging studies cannot differentiate various subtypes of HL but radiological signs could help suggest the diagnosis and thus lead to biopsy samples being taken to confirm it. The most well-known form of lymphoma is the lymph node form. Any lymph node area can be affected but HL is most commonly located in the lymph nodes of the neck and mediastinum. A lymph node with a short axis of more than 1 cm is considered to be pathological(15,16). Involved nodes show the characteristic features of malignant adenopathy(17).

Many studies have reported the association of thyroid malignancy with lymphoma in those treated with radiotherapy. However, not more than 10 cases of synchronous PTC and HL with no history of radiation exposure had been reported in the literature(4). There is no clear link between HL and PTC regarding genetical or environmental risk factors but the most plausible explanation is the presence of yet unidentified molecular link or general vulnerability carrying a higher risk for malignant transformation(2,5).

Management of patients with synchronous malignancies differs from individual tumor treatment strategies. Several factors that should be considered by a multi-disciplinary team include pathological types, biological behavior, and stage of tumor as well as age, risk factors, and clinical symptoms of a patient. As a general rule, treatment of cancer with the most aggressive malignancy potential and worse prognosis is prioritized(18). Because of its rarity and lack of experience, there are no standardized treatment guidelines in cases of concomitant lymphoma and thyroid cancer. The most accepted is the *lymphoma first* approach in which thyroid treatment is performed only after hematological stabilization. There are several reasons supporting this method: the prognosis of most lymphomas is worse than that of differentiated thyroid carcinoma, the therapeutical time interval before treating the PTC does not affect morbidity or mortality, and finally administration of chemotherapy for lymphoma before cervical dissection reduces lymphadenopathy which decreases the risk of surgical complications(19). However, in our case, this approach wasn't applicable since HL was diagnosed after the workup for PTC had already been started. This scenario appears to be more common in patients without presenting B symptoms in which cervical lymphadenopathy is more likely to be linked with metastatic thyroid carcinoma(4). Treatment of HL is based on chemotherapy alone, most commonly using ABVD or BEACOPP regimen, or chemotherapy followed by involved-site radiation therapy. The recommended treatment of PTC is surgical excision, usually with total thyroidectomy that can be followed by radioiodine therapy for ablation of residual thyroid tissue. All patients require long-term levothyroxine therapy(4,20).

CONCLUSION

Although in patients with cervical lymphadenopathy and PTC the most common diagnosis is lymphatic metastasis, the possibility of synchronous thyroid cancer and lymphoma should not be ignored.

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Sažetak

SINKRONA PREZENTACIJA PAPILARNOG KARCINOMA ŠTITNJAČE I HODGKINOVOG LIMFOMA – PRIKAZ SLUČAJA

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Višestruki primarni zloćudni tumori (Multiple primary malignancies, MPM) sve se češće otkrivaju zahvaljujući naprednim načinima snimanja i sveobuhvatnim dijagnostičkim protokolima. Papilarni karcinom štitnjače (Papillary thyroid carcinoma, PTC) najčešća je vrsta neoplazme štitnjače sa stalno rastućom incidencijom. Hodgkinov limfom (Hodgkin lymphoma, HL) je limfoidna neoplazma koja je češća u mladih odraslih osoba i najčešće zahvaća cervikalne limfne čvorove. Poznato je da je PTC induciran zračenjem u prethodno liječenih pacijenata s limfomom, ali istodobna pojava ove dvije zloćudne bolesti u bolesnika bez povijesti izloženosti zračenju vrlo je rijetka. Prikazujemo slučaj 42-godišnjeg pacijenta kojemu je slučajno dijagnosticiran HL tijekom obrade čvora u desnom režnju štitnjače. CT vrata s kontrastom pokazao je veliku heterogenu nodalnu masu u desnom režnju štitnjače što ukazuje na neoplazmu štitnjače. Limfadenopatija je bila prisutna na suprotnoj lijevoj strani vrata i bilateralno u medijastinumu s povećanim homogenim čvorovima atipičnim za metastaze tumora štitnjače. Aspiracija tankom iglom i histopatološka analiza uzoraka dobivenih nakon tireoidektomije i disekcije vrata potvrdili su PTC i klasični HL. Pacijent je upućen na liječenje HL-a koji je pokazao znakove primarne refraktorne bolesti s odgovorom i potpunom remisijom na drugu liniju kemoterapije. Radiojodna ablacija ostatnog tkiva štitnjače planira se nakon hematološke stabilizacije. Cilj ovog rada je opisati rijetko stanje istodobne pojave primarnih zloćudnih bolesti štitnjače i hematoloških tumora te raspraviti izazove u dijagnostici i liječenju sinkronih tumora.

KLJUČNE RIJEČI: *višestruki primarni zloćudni tumori, papilarni karcinom štitnjače, Hodgkinov limfom*