Simultaneous Hodgkin lymphoma and \textbf{BRAF}^{V600E}-positive papillary thyroid carcinoma

A case report

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Abstract
Rationale: Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy. However, the simultaneous occurrence of PTC and Hodgkin Lymphoma (HL) was rarely reported.

Patient concerns: We present a case of simultaneous BRAF\textsuperscript{V600E}-positive PTC and HL in a 17-year-old female.

Diagnosis: She was referred to our clinic with a painless lump in her left neck. A highly suspicious thyroid nodule and multiple enlarged lymph nodes in the neck were found by ultrasonography examination. The suspicious nodule was diagnosed as PTC by fine needle aspiration cytology.

Interventions: A total thyroidectomy with bilateral lymph node dissection was performed and the microscopic examination revealed a 2-cm PTC with BRAF\textsuperscript{V600E} mutation and HL (mixed cellularity) in the bilateral lymph nodes. PTC was postoperatively considered as T1bN0M0. Levothyroxine (125 μg/d) was administered to the patient for thyrotropin suppression therapy. Then the patient was referred to the Department of Hematology to receive 4 cycles of ABVD followed by 30 Gy involved-site radiotherapy and radioactive iodine (RAI) therapy for thyroid cancer.

Outcomes: After two cycles of ABVD, multiple enlarged lymph nodes showed a significant response to the chemotherapy in the patient.

Lessons: Simultaneous HL and BRAF\textsuperscript{V600E}-positive PTC is extremely rare. Biopsy of the suspicious lymph nodes should be performed to confirm malignancy metastasizing from PTC or other lesions. Similarly, in HL patients with suspicious thyroid nodule, ultrasound-guided fine needle aspiration of thyroid nodule should be performed to exclude thyroid malignancy.

Abbreviations: \textsuperscript{18}FDG-PET = \textsuperscript{18}fluorodeoxyglucose positron emission tomography, ABVD = doxorubicin/bleomycin/vindesine/dacarbazine, CT = computed tomography, EORTC = the European Organization for Research and Treatment of Cancer, ESMO = European Society for Medical Oncology, FNAC = fine needle aspiration cytology, HL = Hodgkin lymphoma, LYSA = Lymphoma Study Association, PTC = papillary thyroid cancer, RAI = radioactive iodine, TERT = telomerase reverse transcriptase, TSH = thyrotropin.

Keywords: BRAF mutation, Hodgkin lymphoma, papillary thyroid cancer, treatment

1. Introduction
Papillary thyroid cancer (PTC) represents more than 90% of all thyroid cancer cases and it is the most indolent form of the disease.\cite{1} Prognosis is excellent, with 20-year survival surpassing 90% when appropriate therapy is undertaken.\cite{2} Hodgkin lymphoma (HL) accounts for approximately 10% of cases of newly diagnosed lymphoma in the United States.\cite{3} HL is most frequently diagnosed in the group ages 20–34 years.\cite{3} Multiple studies have reported an increased risk for thyroid cancer as secondary neoplasms after treatment for HL patients.\cite{4–7} However, the synchronous PTC and HL is very rare. We found only two reports in the English literature reporting simultaneous PTC and HL.\cite{8}

Herein, we present a case of simultaneous \textit{BRAF}\textsuperscript{V600E}-positive PTC and HL in a teenager.

2. Case presentation
A 17-year-old teenager, who complained about a painless lump in her left neck for one week, was admitted to our clinic. The lump was approximately the size of 3 × 5 cm. During this period, the patient did not have fever, drenching night sweats, or weight loss. After the physical examination, a 2 × 3 cm thyroid nodule was incidentally palpated in the left lobe. Then the patient underwent ultrasonography examination revealing a highly suspicious nodule with a size of 2.24 × 2.0 × 3.25 cm in the left thyroid lobe. In addition, the ultrasound presented enlarged lymph nodes...
Regional lymph node metastases are present at the time of diagnosis in a majority of patients with PTC, approximately in 20%–50% of patients. The most common site of nodal metastases is in the central neck (level VI). Lymph nodes in the lateral neck, anterior mediastinum and rarely in level I may also be involved by thyroid cancer, whereas supradiaphragmatic painless lymphadenopathy, including mediastinal involvement, or left neck nodal enlargement, or right neck nodal enlargement, is also a common mode of presentation of HL. In this patient, there were multiple enlargement lymph nodes in the bilateral neck, supraclavicular fossa, and mediastinum, and even a few fusions of enlarged lymph nodes. FNA of the suspicious lymph nodes should be performed for cytology and washout for Tg measurement to confirm malignancy metastasizing from PTC or other lesions. Involvement of multiple supradiaphragmatic nodal areas, specifically with the presentation of a fusion of enlarged lymph nodes or B symptoms, may remind us of the possibility of lymphoma, and core needle biopsy or even excisional biopsy of involved lymph node instead of FNA is preferred to establish a definitive diagnosis. Similarly, in HL patients with suspicious thyroid nodule, ultrasound-guided FNA of thyroid nodule should be performed to exclude thyroid malignancy.

Multiple primary cancers are defined as the occurrence of two or more primary cancers in the same patient, either simultaneously or sequentially. The synchronous occurrence of PTC and lymphoma is extremely rare. We found only 2 cases reporting simultaneous PTC and non-Hodgkin lymphoma and 2 cases with simultaneous PTC and HL. Pianovski in 2004 reported HL was presented as a rapidly enlarging supraclavicular nodule 30 days after a total thyroidectomy in a teenager and Rizkallah et al in 2014 reported a case of HL presenting as typical B symptoms incidentally diagnosed with PTC by mediastinoscopy in a young man. Both of them had no molecular analysis of PTC and were little different from our case; the occurrence of PTC in HL was presented as a suspicious thyroid nodule and enlarged cervical lymphadenopathy.

Synchronous multiple primary cancers are difficult to manage because of lack of a standard approach. Surgery for thyroid cancer is an important element of a multifaceted treatment approach, and RAI therapy was considered after total thyroidectomy to improve the outcome of PTC.
disease-free survival by destroying residual disease or persistent disease in intermediate/high-risk level differentiated thyroid cancer patients, whereas chemotherapy and radiotherapy are the mainstays of HL treatment. With current treatment advancements, approximately 90% of all patients diagnosed with HL achieved an excellent disease control. The initial treatment of HL will be optimal when a patient was diagnosed with the HL and PTC. First, PTC is a most indolent form of thyroid cancer; second, enlarged lymph nodes involved by HL will diminish or disappear after HL treatment and thus will be helpful to preoperatively make a better surgery strategy for PTC to improve the completeness of surgery and decrease the injury and wound complication of regional lymph node dissection. For our patients, in fact, there was no need for the cervical lymph nodes dissection because the lymph nodes will respond to chemoradiotherapy. Hence, we agreed that the “lymphoma first approach” was recommended for the synchronized condition. In this patient, we started the chemotherapy of HL after total thyroidectomy. It is noted that patients received HL treatment are at increased risk of secondary neoplasms, specifically thyroid cancers. Chemo-radiotherapy has been proposed as a cause of this increased risk, especially radiation exposure of the thyroid gland increases the risk of a secondary thyroid malignancy at the younger ages. We suggest that a total thyroidectomy and RAI therapy are necessary to improve long-term survival of this synchronous condition.

**4. Conclusion**

Simultaneous HL and **BRAF** \textit{V600E}-positive PTC is extremely rare, which may pose significant diagnostic and treatment challenges. To date, although there is no standardized approach, we suggest “lymphoma first approach,” and total thyroidectomy and RAI therapy for thyroid cancer are necessary to improve the long-term survival of the synchronized condition. Further studies are still necessary to clarify the molecular mechanism of synchronous occurrence of 2 malignancies.

**Author contributions**

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References

[1] Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012;62:220–41.
[2] Davies L, Welch HG. Thyroid cancer survival in the United States: observational data from 1973 to 2005. Arch Otolaryngol Head Neck Surg 2010;136:440–4.
[3] Shanbhag S, Ambinder RF. Hodgkin lymphoma: a review and update on recent progress. CA Cancer J Clin 2018;68:116–32.
[4] Baras N, Dahm S, Haberland J, et al. Subsequent malignancies among long-term survivors of Hodgkin lymphoma and non-Hodgkin lymphoma: a pooled analysis of German cancer registry data (1990–2012). Br J Haematol 2017;177:226–42.
[5] Gözdăsoólu S, Pamir A, Ünal E, et al. Secondary neoplasms in children with Hodgkin’s lymphoma receiving C-MOPP and radiotherapy: presentation of four cases. Turk J Haematol 2016;33:66–70.
[6] Garaventa A, Haupt R, Panarello C, et al. Early occurrence of a secondary thyroid carcinoma in a child treated for Hodgkin disease. Med Pediatr Oncol 2001;36:396–7.
[7] Chowdhiy AK, Fung C, Chowdhiy VK, et al. A population-based study of prognosis and survival in patients with second primary thyroid cancer after Hodgkin lymphoma. Leuk Lymphoma 2018;59:1180–7.
[8] Dudeque Pianovski MA, de Lacerda Filho L. A teenager with simultaneous Hodgkin disease and thyroid carcinoma. Med Pediatr Oncol 2003;41:91–2.
[9] Eichenauer DA, Aleman BMP, André M, et al. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:v19–29.
[10] Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26:1–33.
[11] Park SL, Caberto CP, Lin Y, et al. Association of cancer susceptibility variants with risk of multiple primary cancers: the population architecture using genomics and epidemiology study. Cancer Epidemiol Biomarkers Prev 2014;23:2568–78.
[12] Popivanov GI, Bochev P, Hristoskova R, et al. Synchronous papillary thyroid cancer and non-Hodgkin lymphoma: case report. Medicine (Baltimore) 2018;97:e9831.
[13] Singh NJ, Tripathy N, Roy P, et al. Simultaneous triple primary head and neck malignancies: a rare case report. Head Neck Pathol 2016;10:233–6.
[14] Acosta-Ortega J, Montalbán-Romero S, García-Solano J, et al. Simultaneous medullary carcinoma of the thyroid gland and Hodgkin’s lymphoma in bilateral lymph nodes of the neck: a potential pitfall in fine-needle aspiration cytology. Diagn Cytopathol 2004;31:253–8.
[15] Rizkallah JJ, Jambrat SS, Maalouli GD. Synchronous diagnosis of a Hodgkin lymphoma and a papillary carcinoma of the thyroid. Case Rep Intern Med 2014;2014:123578.
[16] Liu S, Gao A, Zhang B, et al. Assessment of molecular testing in fine-needle aspiration biopsy samples: an experience in a Chinese population. Exp Mol Pathol 2014;97:292–7.
[17] Cucue C, Hempel WM, Sabater L, et al. Chromosomal instability in Hodgkin lymphoma: an in-depth review and perspectives. Cancers (Basel) 2018;10:91doi: 10.3390/cancers1004091.