Clinical Case Report

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Simultaneous Hodgkin lymphoma and *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*^{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*^{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*^{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: ^{18}FDG-PET = [18F]fluorodeoxyglucose positron emission tomography, ABVD = doxorubicin/bleomycin/vinblastine/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.[1] Prognosis is excellent, with 20-year survival surpassing 90% when appropriate therapy is undertaken.[2] Hodgkin lymphoma (HL) accounts for approximately 10% of cases of newly diagnosed lymphoma in the United States.[3] HL is most frequently diagnosed in the group ages 20–34 years.[3] Multiple studies have reported an increased risk for thyroid cancer as secondary neoplasms after treatment for HL patients.[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.[8]

Herein, we present a case of simultaneous *BRAF*^{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 × 2 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

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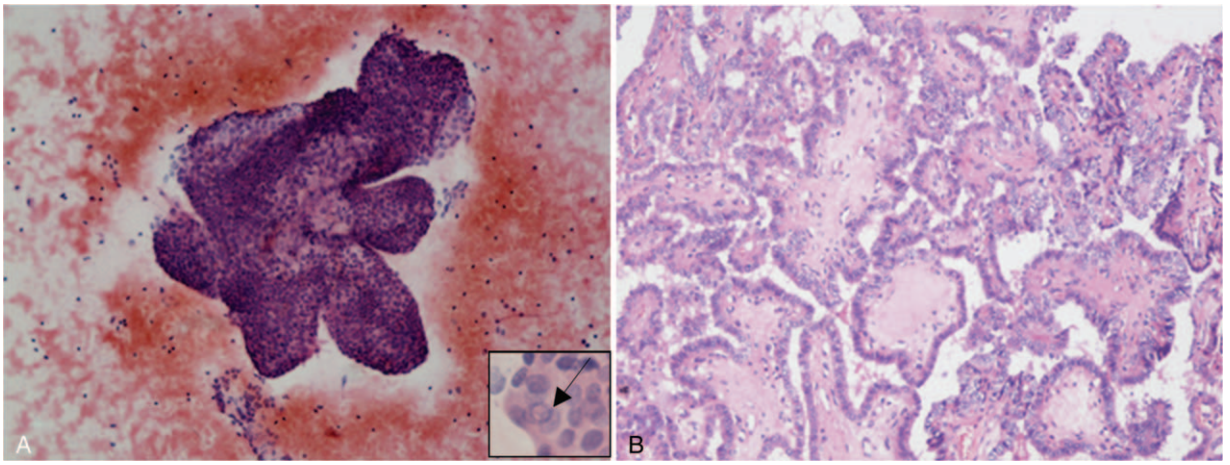

Figure 1. FNA and histological slides of papillary thyroid cancer. (A) Hematoxylin and eosin staining of FNA (magnification of main image, ×200; magnification of the smaller image, ×400), illustrating the papillary structures and intranuclear cytoplasmic pseudoinclusions (arrow). (B) Representative histological images of hematoxylin-eosin staining of sections from papillary thyroid cancer. FNA = fine needle aspiration.

in bilateral neck and supraclavicular regions, and their maximum size was 5.03 × 2.46 cm. The suspicious nodule was aspirated and PTC was diagnosed by fine needle aspiration cytology (FNAC) (Fig. 1A). The patient was referred to the Department of Otorhinolaryngology Head and Neck Surgery. After admission, we performed a contrast-enhanced computed tomography, which revealed a low-density shadow lesion in the left thyroid lobe and multiple enlarged lymph nodes, even a few fusions of enlarged lymph nodes in the neck, supraclavicular fossa, and mediastinum. The patient was preoperatively diagnosed as PTC and cervical lymph node metastasis. A total thyroidectomy with cervical lymph nodes dissection was performed at June 19, 2018. The microscopic examination of thyroid gland indicated PTC with a size of 2 × 1 × 1 cm and extracapsular invasion in the left lobe and goiter in the right lobe. Surprisingly, the cervical lymph nodes were engaged by classical HL (mixed cellularity type) by histological and immunohistochemical analysis (Fig. 2). The $BRAF^{V600E}$ mutation and TERT promoter mutation were also postoperatively analyzed. The PTC was only $BRAF^{V600E}$ mutated. The patient refused to take ^{18}FDG-PET scanning. Sixteen days later, we performed a whole body CT, which revealed multiple enlarged lymph nodes in the neck, submandibular, and mediastinum. No apparent sign of organ metastasis or bone marrow involvement was observed. According to the Ann Arbor classification and the European Organization for Research and Treatment of Cancer (EORTC)/Lymphoma Study Association (LYSA), this patient was subsequently diagnosed with Stage IIA HL (mixed cellularity type) and was further allocated to intermediate stage due to the elevated ESR (57 mm/h).[9] According to 2015 ATA guidelines, PTC was postoperatively considered as T1bN0M0, and Levothyroxine (125 μg/d) was administered for thyrotropin suppression therapy. After multidisciplinary discussion, the patient was referred to the department of Hematology to receive 4 cycles of ABVD followed by 30 Gy involved-site radiotherapy according to 2018 ESMO Clinical Practice Guidelines and radioactive iodine (RAI) therapy for thyroid cancer. After two cycles of ABVD, multiple enlarged lymph nodes showed a significant response to the chemotherapy. The Institutional Ethics Committee of our hospital approved the publication of the case. The patient has provided informed consent for publication of the case.

3. Discussion

Regional lymph node metastases are present at the time of diagnosis in a majority of patients with PTC, approximately in 20%–50% of patients.[10] 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.[10] 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.[3] 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.[11] 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.[12–15] Pianovski in 2004[14] reported HL was presented as a rapidly enlarging supraclavicular nodule 30 days after a total thyroidectomy in a teenager and Rizkallah et al[15] 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 an 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

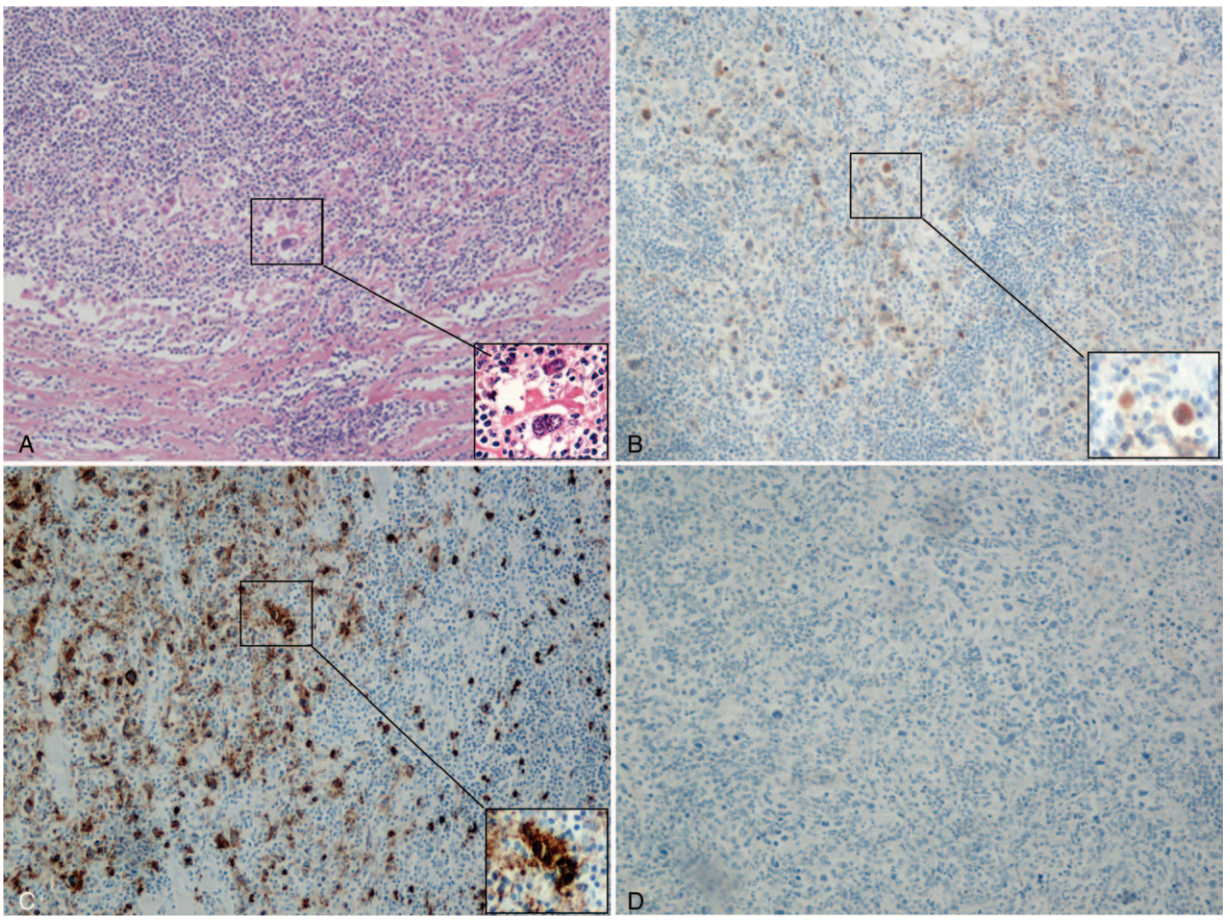

Figure 2. Histological and immunohistochemical analysis of the lymph node of the patient. (A) Hematoxylin and eosin staining of the tumor tissue (magnification of main image, ×200; magnification of the smaller image, ×400). Hodgkin and Reed-Sternberg cells were observed in a cellular background rich in lymphocytes, histiocytes, and eosinophils. Tumor cells were (B) CD30-positive, (C) CD15-positive, and (D) TTF-1 negative. The smaller image shows the magnified image of the area.

disease-free survival by destroying residual disease or persistent disease in intermediate/high-risk level differentiated thyroid cancer patients,[10] whereas chemotherapy and radiotherapy are the mainstays of HL treatment.[9] With current treatment advancements, approximately 90% of all patients diagnosed with HL achieved an excellent disease control.[3] 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[1]; 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.[8,12] 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.[4,7] Chemoradiotherapy 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.

$BRAF^{V600E}$ mutation plays an important role in the development of thyroid cancer.[16] In our case, *BRA*F mutation was positive in PTC. The malignant cells in HL have its unique microenvironment and are characterized by a highly altered genomic landscape.[17] Different molecular pathways may play a role in the transforming events in HRS cells. However, the potential molecular link between thyroid cancer and HL is yet unknown. Further studies are necessary to clarify the molecular mechanism of synchronous occurrence of 2 malignancies.

4. Conclusion

Simultaneous HL and $BRAF^{V600E}$-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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Writing – review & editing: Shu Liu, Huachao Zhu.

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