

TP53 gene mutation in lymphoepithelioma-like carcinoma of the breast with thyroid cancer: A case report

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Abstract. Globally, breast cancer is the most common malignancy among women and thyroid cancer is also one of the common cancer types among women. Patients with breast cancer exhibit a higher incidence of thyroid cancer than that noted in the general population. The exact mechanism of multiple tumors remains elusive. In the present study, the case of a patient with multiple tumors harboring gene mutation is reported. Specifically, a patient with lymphoepithelioma-like carcinoma of the breast (LELC-B) and thyroid cancer is described. It was hypothesized that the short interval between the onset of these two types of malignant tumor may be related to the TP53 gene mutation status of the patient. To date, a specific relationship between gene mutations and multiple tumors is yet to be determined. Therefore, additional studies are required to address this topic.

Introduction

Globally, breast cancer is the most common malignancy among women, and thyroid cancer is also one of the common cancer types among women (1). When one disease arises, the risk of developing the other disease increases (2). This bidirectional relationship has been reported; however, the underlying reasons for this co-occurrence remain unclear (3). A study has suggested that these cancer types may share some common etiologies, including gene levels, hormonal factors and environmental and therapy-related factors (4). The present study mainly focused on the gene mutation field.

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Lymphoepithelioma-like carcinoma (LELC) is a rare malignant epithelial neoplasm that often occurs in the nasopharynx (5). LELC of the breast (LELC-B) is very specific with regard to its clinical setting. LELC-B is characterized by notable lymphatic proliferation, infiltration and undifferentiated carcinoma tissue. Since this disease is rare in the breast and thus few cases have been reported, follow-up and summary are particularly important. In the present study, the case of a patient who had LELC-B along with thyroid cancer is reported. A full series of genetic testing was performed to explore the root cause of the disease. The following case is presented in accordance with the CARE reporting checklist.

Case report

A 56-year-old postmenopausal woman who had a left breast tumor was admitted to The Department of Breast Surgery at The Second Hospital of Dalian Medical University (Dalian, China) in May, 2020. Ultrasound, molybdenum target and magnetic resonance imaging examinations revealed the presence of a tumor at the aforementioned location, which was 1.0x0.8 cm in size (Fig. 1). The tumor was graded Breast Imaging Reporting and Data System 4B according to the common diagnostic grading system for breast imaging, developed by the American Society of Radiology (6). Subsequent thyroid ultrasound examination indicated a 0.43x0.46 cm mass in the middle and lower poles of the left thyroid (Fig. 2). Computed tomography of the thorax and abdomen indicated a lack of distant metastases (Fig. 3). The patient exhibited no notable previous medical history or family history. Crude needle biopsy of the left breast tumor indicated LELC-B. The thyroid tumor fine needle biopsy revealed papillary carcinoma. Since each disease develops differently, after full communication with the patient, breast tumor surgery was selected as the first treatment step. Therefore, the patient underwent left breast mastectomy and sentinel lymph node biopsy. Based on the histopathological and immunohistochemical findings (based on experiments performed by The Department of Pathology at The Second Hospital of Dalian Medical University), which were negative for estrogen receptor, progesterone receptor and receptor tyrosine-protein kinase erbB-2 (Fig. 4), the patient was diagnosed with LELC-B (triple negative), staged as pT1N0M0. In large areas of hematoxylin-eosin-stained tissue, the tumor cells were scattered in the dense lymphocyte background with a large cell volume, rich cytoplasm, vesicular

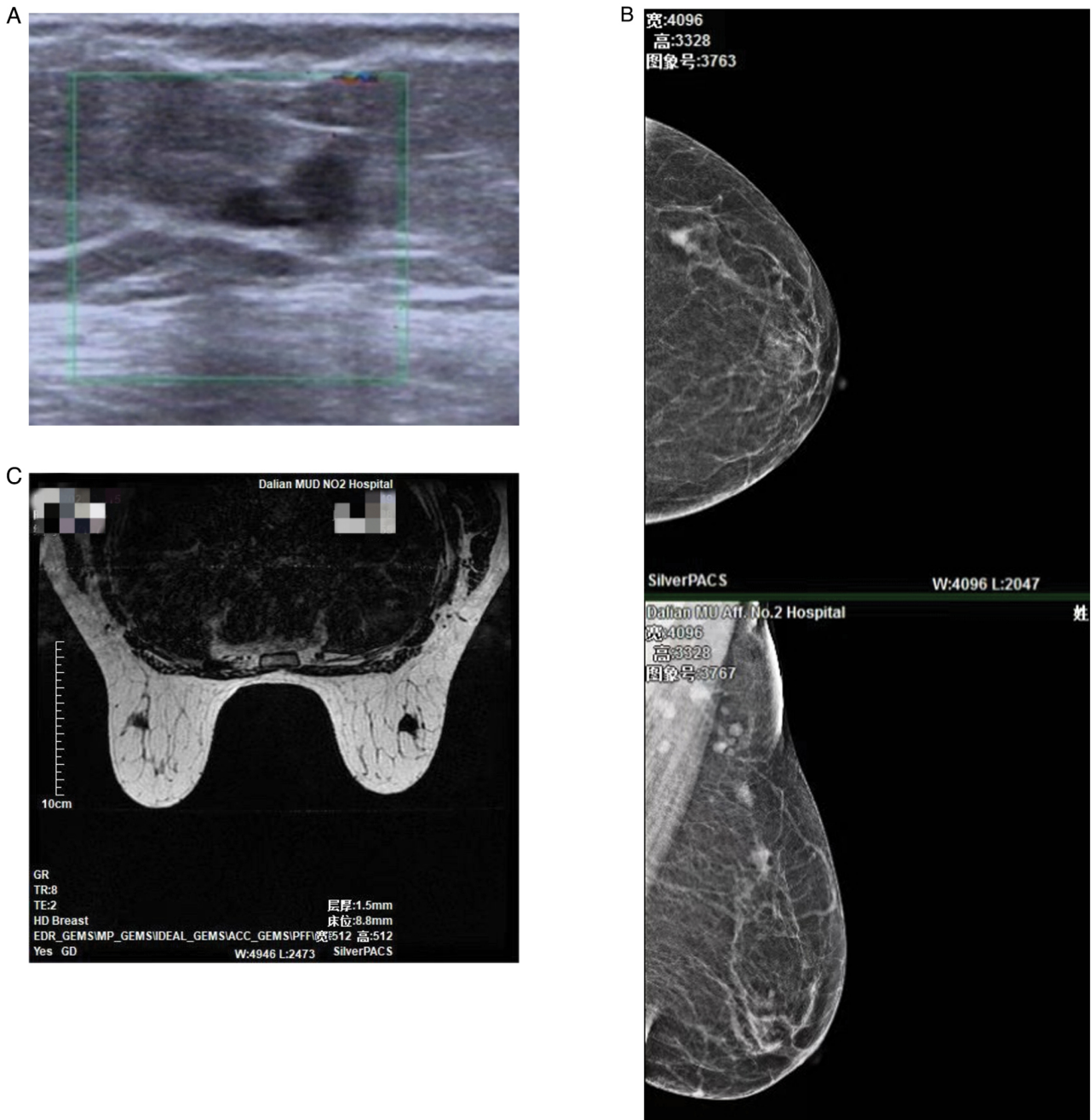


Figure 1. (A) Ultrasound image of the breast. (B) Molybdenum target image. (C) Magnetic resonance imaging examinations of the breast.

nucleus and apparent nucleolus (Fig. 5). Pathological staging was defined according to the tumor staging criteria established by the American Joint Committee on Cancer (AJCC) (7).

After 3 weeks, radical resection of the left thyroid cancer was performed. According to the postoperative pathological report of the thyroid tumor, the tumor was 0.4 cm in diameter and had metastasis in the central cervical lymph nodes. According to the AJCC guidelines (8), the clinical diagnosis was papillary carcinoma of the left thyroid (pT1N1M0). Postoperatively, the patient received 8 cycles of adjuvant chemotherapy based on the pharmorubicin combined with cyclophosphamide (EC)-Taxol (T) regimen. This regimen consisted of 4 cycles of pharmorubicin (90 mg/m²) and cyclophosphamide (600 mg/m²) administered successively with 4 cycles of docetaxel (90 mg/m²) administered

intravenously every 21 days. The surface area of the patient was 1.607 mg/m², so the specific dosing of pharmorubicin was 145 mg, of cyclophosphamide was 1 g and of docetaxel was 145 mg. By November 2024, no disease was noted in the follow-up after initial diagnosis and surgical treatment, and the patient still had a good prognosis. The timeline of the case presentation is presented in Fig. 6.

Due to the short interval between the onset of the two types of malignant tumors, a full range of genetic testing was performed, including germline and somatic mutations. Breast tumor paraffin sections and blood samples were used for genetic testing. The test used probe hybridization capture and Illumina high-throughput sequencing to detect all exonic and some intronic regions of 830 genes. The gDNA was

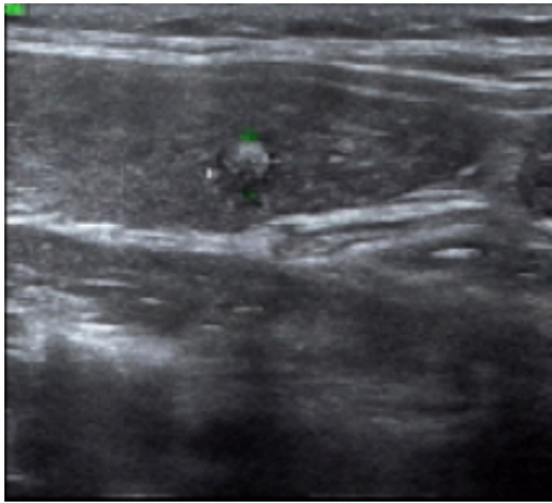


Figure 2. Ultrasound image of the thyroid.

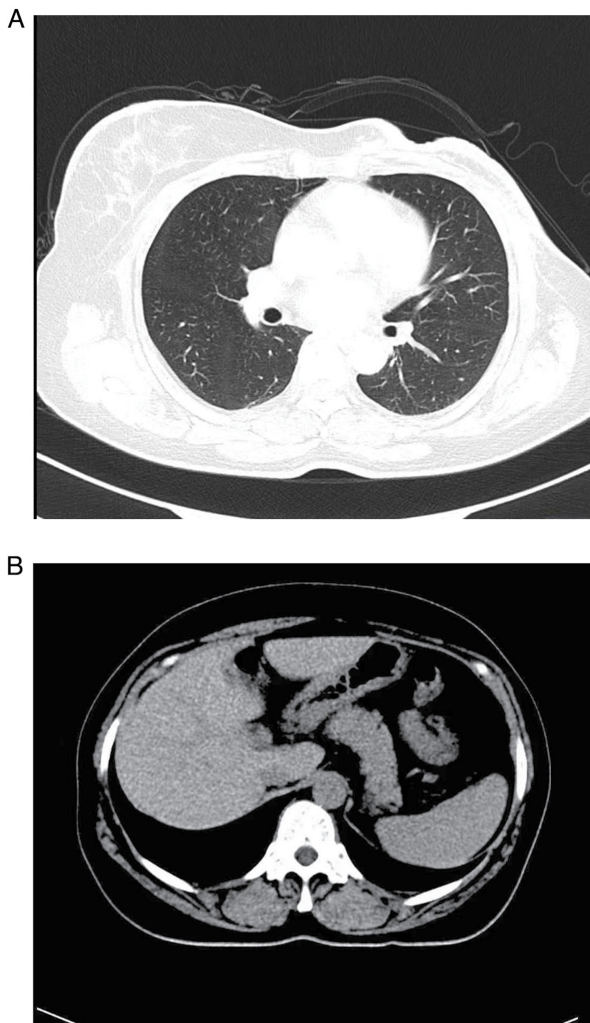


Figure 3. (A) Computed tomography of the thorax. (B) Computed tomography of the abdomen.

extracted from the tissue samples and blood using the AllPrep DNA/RNA mini kit (Qiagen, Inc.; cat. no. 80204). The gDNA was tested for fragment size, quality and total concentration

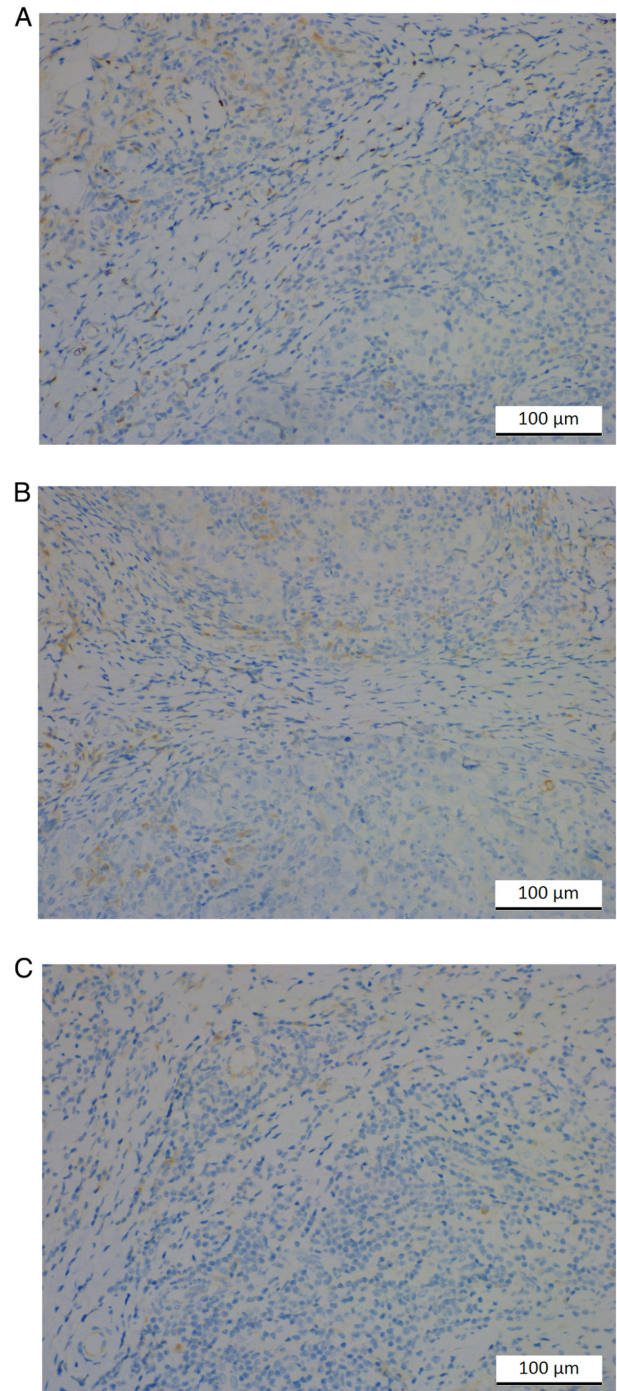


Figure 4. Pathology detecting the expression of (A) the estrogen receptor, (B) the progesterone receptor and (C) the receptor tyrosine-protein kinase erbB-2 (magnification, x20).

using a 2200 Bioanalyzer (Agilent Technologies, Inc.). The gDNA library was constructed using the KAPA Hyper kit (KAPA Biosystems; Roche Diagnostics). The concentrations of the libraries were measured using the Qubit 3 (Thermo Fisher Scientific, Inc.). The capture probes were designed using a tiling method and were custom-synthesized by Agilent Technologies, Inc.. The gDNA library was enriched for the target regions using the designed capture probes. The enriched libraries were amplified with the P5/P7 primers. After quality control with the 2200 Bioanalyzer,

Table I. Results of gene mutation analysis.

Gene	Mutation type	Nucleotide change	Amino acid change	Frequency (%)	Chromosome	Exon	Transcript accession no.
TP53	Missense mutation	c.844C>T	p.Arg282Trp	4.5	17	8/11	NM_001126112.2
MET	Missense mutation	c.1592C>G	p.Ser531Cys	7.4	7	5/21	NM_001127500.2
FAT3	Missense mutation	c.5382C>A	p.Ser1794Arg	7.1	11	9/25	NM_001008781.2
ATR	Missense mutation	c.3227A>G	p.His1076Arg	6.5	3	16/47	NM_001184.3
ABCB4	Missense mutation	c.2057A>G	p.Asp686Gly	5.3	7	16/28	NM_018849.2

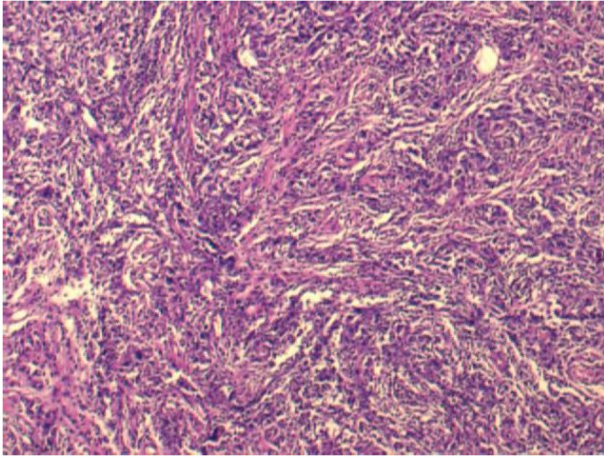


Figure 5. Hematoxylin-eosin staining of lymphoepithelioma-like carcinoma of the breast. In large areas, the tumor cells are scattered in the dense lymphocyte background with a large cell volume, rich cytoplasm, vesicular nucleus and apparent nucleolus (magnification, x20).

quantification was performed using Qubit 3 and the qPCR NGS library quantification kit (Agilent Technologies, Inc.). All libraries were diluted according to the manufacturer's instructions (the starting concentration was 1.5 nM and the final loading concentration was 200 pM) and were mounted on the Illumina NovaSeq 6000 platform (NovaSeq 6000 S1 Flow Cell; lot no. 20911202) for high-throughput sequencing using the NovaSeq 6000 S1 Reagent Kit v1.5 (lot no. 20028317; Illumina, Inc.), and the sequencing strategy was PairEnd150. Tissues were sequenced at a 500X depth. Sequencing data in the FASTQ format were aligned to the human reference genome (hg19) using the BWA v.0.7.10 software (<https://github.com/lh3/bwa>). Single nucleotide variants (SNVs) were detected using the Mutect v3.1 software (<https://gatk.broadinstitute.org/hc/en-us/articles/360037593851-Mutect2>). Insertions and deletions of short fragments were detected using strelka2 v2.0.17 software (indel) (<https://github.com/Illumina/strelka>). All detected SNV and indels were confirmed by Integrative Genomics Viewer v2.3.34 (<https://igv.org>) to obtain a final list of SNVs and indel mutations. SNVs and indels were annotated using Variant Effect Predictor v92.4 (<https://grch37.ensembl.org/info/docs/tools/vep/index.html>). Structural variant testing was performed using an internally improved version of CREST (9). Copy number variation detection was performed using Control Free-C version 8.0 (<https://github.com/BoevaLab/FREEC>). This testing detected

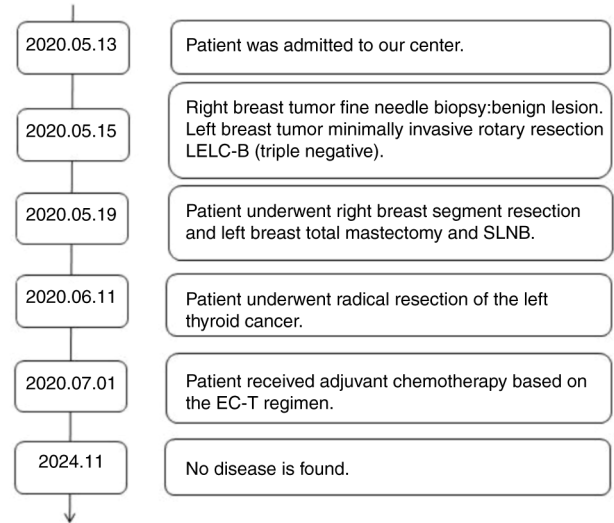


Figure 6. Timeline of the case presentation. LELC-B, lymphoepithelioma-like carcinoma of the breast; SLNB, sentinel lymph node biopsy; EC-T, pharmacologic treatment with epirubicin and cyclophosphamide-Taxol.

TP53, MET, FAT3, ATR and ABCB4 missense mutations and the absence of germline mutations (Table I).

Discussion

The case of a special type of breast cancer (LELC-B) along with thyroid cancer is reported in the present study. LELC is an undifferentiated carcinoma composed of malignant epithelial cells with a large lymphocyte background. LELC can occur in various organs such as the stomach, skin, uterine cervix, skin, trachea, lung and urinary bladder (10). Although LELC-B was initially described in 1994 by Kumar and Kumar (11), to the best of our knowledge, <40 cases have been reported to date (12). Moreover, no clear guideline has been reported to define the optimal oncological treatment for this cancer type. Therefore, the treatment of LELC-B is generally based on published case reports as well as clinical experience. Based on the cases reported in the literature and the present case, it can be deduced that the clinical manifestations of LELC-B are similar to those of common invasive breast cancer (13). Considering the possibility of the local spread and lymph node metastasis in LELC-B, it is recommended that measures should be implemented to control potential distant spread and to ensure that surgery combined with systemic therapy is performed. In the present study, the patient underwent an EC-T

regimen for adjuvant chemotherapy. To date, the patient has not developed a new disease and has an optimal prognosis.

Breast and thyroid cancer have been shown to occur as multiple primary tumors more frequently than is expected in women. Specifically, epidemiological studies have found an increased incidence of breast cancer in women with thyroid cancer, as well as an increased incidence of thyroid cancer in women with breast cancer (14). Certain studies have suggested that the simultaneous occurrence of these cancer types may share some etiologies, including gene level, hormonal factors, environmental and therapy-related factors (4,15). However, the specific risk factors have not been determined for the coexistence of these two cancer types. Both breast and thyroid glands are endocrine organs and are regulated by the hormone hypothalamic-pituitary axis. Therefore, a study has shown that increased estrogen or other female hormone levels may increase the risk of thyroid cancer (16). Similar hormonal mechanisms affect the risk of both cancer types (17). In addition, gene mutations may also lead to the co-occurrence of these cancer types. The breast and thyroid glands may share common gene mutations that are responsible for the development of both diseases. This could also explain why the time interval between these two malignancies was very short in the present study. A previous clinical study has demonstrated that the subsequent treatment of breast cancer does not result in an increased risk of thyroid cancer and vice versa (3).

According to the case reported in the present study, it is suggested that thyroid tissue examinations should be regularly performed on patients with breast cancer due to generally higher prevalence of thyroid cancer. This is very beneficial to patients and it is always prudent to detect and treat diseases as early as possible. In addition, in the present case report, the type of LELC-B was triple negative and the axillary lymph nodes had not metastasized; therefore, the patient did not receive hormonal therapy and radiotherapy. It has been shown that the majority of triple-negative breast cancer cases have a family history of breast cancer. The patient reported in the present study exhibited the triple-negative pathological type and had no family history of malignancy; therefore, it was concluded that the occurrence of LELC-B and thyroid cancer in this patient was due to the gene mutations. A published study has shown that multiple tumors are unique and their clinical features, treatment strategies and prognosis are notably different from those of single tumors, and the majority of multiple tumors exhibit genetic differences (18). Therefore, patients with multiple tumors may possess gene mutations. It is suggested that gene detection in patients with multiple tumors should be improved. This can aid the understanding of the pathogenesis of the disease and the selection of the appropriate treatment for patients.

Gene testing on the patient reported in the present study indicated TP53 gene mutation. Mutations in MET, FAT3, ATR and ABCB4 were also noted; however, the effect of these mutations on protein function is not yet clear. TP53, encoding the tumor suppressor protein p53, is the most frequently mutated gene across all cancer types and its mutation or deletion can cause genomic instability and cell proliferation (19). A previous report has suggested that TP53 mutations are found in up to 40% of papillary thyroid cancer cases, and in 30% of breast cancer cases (20). Typically, TP53 point mutations are located in the region between exons 5

and 8. Gene mutation is one of the key factors leading to tumorigenesis. In triple-negative breast cancer, the mutation rate of TP53 gene is high and the common type of mutation is the missense mutation (21). This leads to the loss of function of the p53 protein, which in turn causes cancer cells to grow and metastasize. TP53 mutations are associated with poor prognosis in patients with breast cancer; however, LELC-B exhibits an improved prognosis compared with breast cancer and close follow-up of these patients is particularly important. In addition, TP53 gene mutations also occur frequently in aggressive thyroid cancer. TP53 gene mutations provide a favorable environment for tumor occurrence and development and aid the ability of tumor cells to escape surveillance and promote proliferation and invasion (22).

In the present study, the TP53-p.Arg282Trp mutation in the patient sample was located in the LSH2 region of the DNA binding domain (DBD) of the p53 protein. It has been reported that this mutation changes the conformation of the DNA binding surface of the p53 protein and reduces the DNA-binding ability of this protein, which loses its transcriptional activation function (23). TP53 gene mutations may be a causal agent linking synchronous breast and thyroid tumors. It has been shown that TP53 mutations and hypoxia-mediated metabolic alterations can lead to the acidification of the tumor microenvironment and to the reshaping of their immune pattern, which promotes cancer cell proliferation (24). This could be a potential therapeutic target for cancer. The genetic test results from the present case did not indicate that gene mutations were negatively associated with immunity; therefore, immunotherapy may be considered if recurrence occurs in the follow-up period.

In conclusion, LBLC-B complicated with thyroid cancer is very rare. Furthermore, a significant TP53 gene mutation occurred in the patient reported in the present study. Whether the mutation of the TP53 gene in this patient sample will cause other diseases is not currently known; it should be further monitored via follow-up. At present, there is no clear specific relationship between these gene mutations and multiple tumors, which requires further research.

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Availability of data and materials

The data generated in the present study may be found in the BioProject database under accession number PRJNA1212304 or at the following URL: <https://www.ncbi.nlm.nih.gov/bioproject/?term=PRJNA1212304>.

Authors' contributions

JS, JG, JL and HZ confirm the authenticity of all the raw data. JS, JG, JL and HZ participated in treating the patient. JS and

JG were responsible for the manuscript writing. HZ gave the financial support. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the Declaration of Helsinki (as revised in 2013).

Patient consent for publication

Written informed consent was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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References

- Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 74: 229-263, 2024.
- Li J, Liu Y, Jin J, Shi Q, Ji Y, Zhang B and Hu P: Study on clinicopathological features and risk factors of patients with multiple primary breast cancers and thyroid disease. *Mediators Inflamm* 2023: 3133554, 2023.
- Bolf EL, Sprague BL and Carr FE: A linkage between thyroid and breast cancer: A common etiology? *Cancer Epidemiol Biomarkers Prev* 28: 643-649, 2019.
- Huang NS, Chen XX, Wei WJ, Mo M, Chen JY, Ma B, Yang SW, Xu WB, Wu J, Ji QH, *et al*: Association between breast cancer and thyroid cancer: A study based on 13 978 patients with breast cancer. *Cancer Med* 7: 6393-6400, 2018.
- Abdou AG and Asaad NY: Lymphoepithelioma-like carcinoma of the breast: Cytological, histological, and immunohistochemical characteristics. *Diagn Cytopathol* 43: 210-213, 2015.
- Rao AA, Feneis J, Lalonde C and Ojeda-Fournier H: A pictorial review of changes in the BI-RADS fifth edition. *Radiographics* 36: 623-639, 2016.
- Giuliano AE, Connolly JL, Edge SB, Mittendorf EA, Rugo HS, Solin LJ, Weaver DL, Winchester DJ and Hortobagyi GN: Breast cancer-major changes in the American joint committee on cancer eighth edition cancer staging manual. *CA Cancer J Clin* 67: 290-303, 2017.
- Perrier ND, Brierley JD and Tuttle RM: Differentiated and anaplastic thyroid carcinoma: Major changes in the American joint committee on cancer eighth edition cancer staging manual. *CA Cancer J Clin* 68: 55-63, 2018.
- Wang J, Mullighan CG, Easton J, Roberts S, Heatley SL, Ma J, Rusch MC, Chen K, Harris CC, Ding L, *et al*: CREST maps somatic structural variation in cancer genomes with base-pair resolution. *Nat Methods* 8: 652-654, 2011.
- Nanev V, Naneva S, Yordanov A, Strashilov S, Konsoulova A, Vasileva-Slaveva M, Betova T and Ivanov I: Lymphoepithelioma-like carcinoma of the breast synchronous with a high-grade invasive ductal carcinoma and ductal carcinoma in situ in a different quadrant of the same breast: A case report. *Medicina (Kaunas)* 58: 1146, 2022.
- Kumar S and Kumar D: Lymphoepithelioma-like carcinoma of the breast. *Mod Pathol* 7: 129-131, 1994.
- Nieto-Coronel MT, Perez-Sanchez VM, Salazar-Campos JE, Diaz-Molina R and Arce-Salinas CH: Lymphoepithelioma-like carcinoma of breast: A case report and review of the literature. *Indian J Pathol Microbiol* 62: 125-128, 2019.
- Koufopoulos N, Syrios J, Papanikolaou A, Misitzis I, Kapatou KA, Dimas D and Khaldi L: Lymphoepithelioma-like breast carcinoma. *Pol J Pathol* 69: 98-104, 2018.
- Liu J and Liang L: The association between thyroid and breast cancers: A bidirectional mendelian randomization study. *Front Endocrinol (Lausanne)* 14: 1185497, 2023.
- Kohler C, Chang M, Allemann-Su YY, Vetter M, Jung M, Jung M, Conley Y, Paul S, Kober KM, Cooper BA, *et al*: Changes in attentional function in patients from before through 12 months after breast cancer surgery. *J Pain Symptom Manage* 59: 1172-1185, 2020.
- Diao Y, Wang R, Cui J, Jin C, Chen Y and Li X: Risk factors for secondary thyroid cancer in patients with breast cancer: A propensity-matched SEER analysis. *Sci Rep* 14: 12679, 2024.
- Halada S, Casado-Medrano V, Baran JA, Baran JA, Lee J, Chinmay P, Bauer AJ and Franco AT: Hormonal crosstalk between thyroid and breast cancer. *Endocrinology* 163: bqac075, 2022.
- Cybulski C, Nazarali S and Narod SA: Multiple primary cancers as a guide to heritability. *Int J Cancer* 135: 1756-1763, 2014.
- Sabapathy K and Lane DP: Therapeutic targeting of p53: All mutants are equal, but some mutants are more equal than others. *Nat Rev Clin Oncol* 15: 13-30, 2018.
- Manzella L, Stella S, Pennisi MS, Tirrò E, Massimino M, Romano C, Puma A, Tavarelli M and Vigneri P: New insights in thyroid cancer and p53 family proteins. *Int J Mol Sci* 18: 1325, 2017.
- Yi D, Xu L, Luo J, You X, Huang T, Zi Y, Li X, Wang R, Zhong Z, Tang X, *et al*: Germline TP53 and MSH6 mutations implicated in sporadic triple-negative breast cancer (TNBC): A preliminary study. *Hum Genomics* 13: 4, 2019.
- Grawenda AM, Møller EK, Lam S, Repapi E, Teunisse AF, Alnæs GI, Børresen-Dale AL, Kristensen VN, Goding CR, Jochemsen AG, *et al*: Interaction between p53 mutation and a somatic HDMX biomarker better defines metastatic potential in breast cancer. *Cancer Res* 75: 698-708, 2015.
- Ragu ME, Lim JMC, Ng PS, Yip CH, Rajadurai P, Teo SH and Pan JW: TP53 somatic mutations in Asian breast cancer are associated with subtype-specific effects. *Breast Cancer Res* 25: 48, 2023.
- Luo K, Qian Z, Jiang Y, Lv D, Zhu K, Shao J, Hu Y, Lv C, Huang Q, Gao Y, *et al*: Characterization of the metabolic alteration-modulated tumor microenvironment mediated by TP53 mutation and hypoxia. *Comput Biol Med* 163: 107078, 2023.



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