Case Reports

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(4) 1–8

DOI: 10.1177/03000605211004702
journals.sagepub.com/home/imr
SAGE

Primary squamous cell carcinoma of the thyroid: a case report

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Abstract

Primary squamous cell carcinoma of the thyroid (PSCCT) is a rare and rapidly progressive malignancy that carries a poor prognosis. PSCCT is easily misdiagnosed as acute thyroiditis or as another thyroid malignancy. We have reported a 76-year-old woman who presented with progressive neck pain for 1 month. Thyroid function tests revealed subclinical thyrotoxicosis. Ultrasound disclosed a solid nodule with calcification in the right thyroid lobe. Laboratory findings included neutrophilic leukocytosis and an elevated erythrocyte sedimentation rate. The patient's condition was diagnosed as subacute thyroiditis, and she was treated with cefixime and ibuprofen. However, her treatment response was poor. She was then treated with oral prednisone. Her neck pain gradually resolved. The patient subsequently developed dysphagia, choking, dyspnea, and dysphonia with an insidious onset. Further examinations including computed tomography and painless gastroscopy revealed that the volume of the thyroid gland had increased significantly, extending to the anterior superior mediastinum. The trachea and esophagus were stenotic because of external compression. Partial thyroidectomy and tracheotomy were performed under extracorporeal membrane oxygenation. The diagnosis of PSCCT was established via histopathology and immunohistochemistry.

Keywords

Primary squamous cell carcinoma, thyroid, undifferentiated thyroid carcinoma, thyroiditis, molecular biomarker, case report

Date received: 20 February 2021; accepted: 23 February 2021

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Introduction

Primary squamous cell carcinoma of the thyroid (PSCCT) is a rare malignancy that comprises 1% of primary thyroid malignancies.[1] Fewer than 60 cases of PSCCT have been reported in the medical literature.[2] PSCCT has been characterized as an extremely aggressive tumor with a poor prognosis, and survival is often shorter than 1 year.[3] The low incidence of PSCCT has impeded clinical research and the development of evidence-based diagnostic algorithms and treatment guidelines. Although there are several recommended diagnostic procedures such as clinical evaluation, diagnostic imaging, and endoscopy, the early diagnosis of PSCCT remains difficult. PSCCT can be easily misdiagnosed as acute thyroiditis or as another thyroid malignancy, thus delaying treatment. Because preoperative determination regarding whether lesions are benign or malignant is not possible, new methods such as Fourier-transform infrared spectroscopy (FTIR) and Raman spectroscopy combined with multidimensional analysis are being explored to meet clinical needs.[4,5] We have reported a case of PSCCT in a patient presenting with neck pain as the initial clinical manifestation and reviewed the relevant medical literature. This case report is compliant with the consensus Surgical Case Report criteria.[6]

Case report

A 76-year-old woman presented to the Department of Endocrinology, Peking University International Hospital on June 26, 2019 with a 1-month history of progressive neck pain that was exacerbated by swallowing and a productive cough with yellow sputum. She denied fever and weight loss. Physical examination revealed II° thyroid enlargement with an indurated texture and no thyroid bruits. The lungs were clear to auscultation bilaterally without dry or wet rales. Pre-hospital thyroid function tests revealed a thyrotropin level of 0.04 μIU/mL, a free thyroxine level of 1.64 ng/dL, and a normal free triiodothyronine level. The peripheral blood leukocyte count was 11.58×10^9/L (78% neutrophils). The erythrocyte sedimentation rate (ESR) was 95 mm/hour. Ultrasound disclosed a solid nodule with intranodular calcifications in the right thyroid lobe. The outpatient diagnosis was subacute thyroiditis.

Treatment was initiated with cefixime 0.1 mg taken orally twice daily with ibuprofen 300 mg sustained-release capsules twice daily. However, the treatment response was poor. One month later, repeat thyroid function tests disclosed the following findings: thyrotropin, 0.02 μIU/mL (normal range, 0.27–4.2 μIU/mL); free thyroxine, 35.0 pmol/L (normal range, 12–22 pmol/L); free triiodothyronine, 5.3 pmol/L (normal range, 3.1–6.8 pmol/L); thyroglobulin 78.93 ng/mL (normal range, 3.5–77 ng/mL); and thyroxine receptor antibody, 0.46 IU/L (normal range, <1.75 IU/L). The patient's peripheral blood leukocyte count was 16.87×10^9/L, and it increased to 22.46×10^9/L (86.9% neutrophils). The ESR was 86 mm/hour. The neuron-specific enolase level was 16.6 ng/mL (normal range, <16.3 ng/mL). Her bone collagen CYFRA21-1 level was 11.16 ng/mL (normal range, <3.3 ng/mL). Ultrasound revealed diffuse thyroid disease suggestive of subacute thyroiditis, and a $1.7 \times 1.4 \times 1.3\,cm^3$ hypoechoic solid nodule with calcification was detected in the right thyroid lobe. The lesion featured an aspect ratio smaller than 1, a smooth edge, and ring enhancement. Ultrasound also disclosed polyglandular lymphadenopathy with cortical thickening involving bilateral cervical chains and the hilum (Figure 1). The patient's medical history was notable for Graves' disease complicated by hyperthyroidism that had been diagnosed more

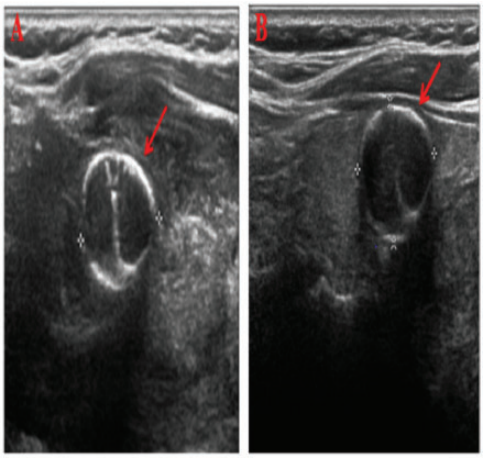

Figure 1. (A) Diffuse thyroid disease (possible subacute thyroiditis) and a hypoechoic solid nodule with annular calcification in the right thyroid lobe The lesion was approximately $1.7 \times 1.4 \times 1.3\ cm^3$ in size with an aspect ratio of less than 1, a smooth edge, and ring enhancement (July 1, 2019). (B) A hypoechoic solid nodule with annular calcification in the thyroid right lobe. The nodule was $1.71 \times 1.38\ cm^2$ in size with an aspect ratio of less than 1, a smooth edge, and a regular shape (November 27, 2017).

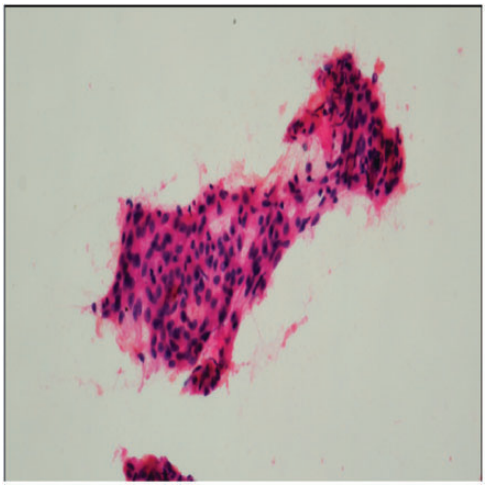

Figure 2. Fine-needle aspiration cytology of the thyroid nodules 2 years before the present illness disclosed adenomatoid nodules.

than 10 years earlier and that had responded to medical therapy. Adenomatoid thyroid nodules were diagnosed via fine-needle aspiration cytology (FNAC) 2 years before the present illness (Figure 2). She also experienced chronic pharyngitis for several years, type II diabetes mellitus, hypertension, outmoded cerebral infarction, and pre-excitation syndrome (after radiofrequency ablation). She denied radiation exposure and a family history of thyroid diseases or other malignancies. She was hospitalized and treated with oral prednisone acetate 10 mg twice daily, rapid-acting insulin subcutaneously thrice daily after meals, long-acting insulin subcutaneously at bedtime, oral metformin 0.5 g thrice daily, irbesartan 150 mg once daily, nifedipine controlled-release tablets 30 mg once daily, bisoprolol 5 mg once daily, rosuvastatin 5 mg once nightly, and aspirin 100 mg once daily. Prednisone was tapered to 10 mg daily on day 16 of hospitalization with the accompanying resolution of neck pain. Although neck pain did not recur, the patient experienced an insidious onset of dysphagia, choking cough, dyspnea, and dysphonia.

Chest radiography disclosed right-sided tracheal deviation (Figure 3). Computed tomography of the chest and neck revealed bilateral enlargement of the thyroid lobes and isthmus extending inferiorly to the anterior superior mediastinum with heterogeneity and indistinct boundaries. Other findings included tracheal stenosis and polyglandular lymphadenopathy involving the bilateral supraclavicular nodes and the perithyroid and carotid spaces. Stroboscopic laryngoscopy disclosed limited movement of right vocal cord and arytenoid cartilage with normal left-sided function. Both vocal cords were closed (Figure 4). Painless gastroscopy revealed a stenotic esophageal entrance (Figure 5). To relieve tracheal and esophageal stenoses, partial thyroidectomy and tracheotomy were performed

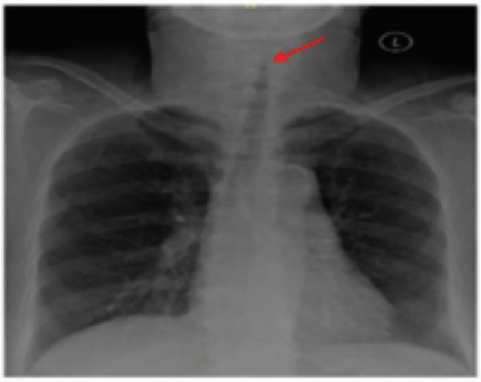

Figure 3. Chest radiography revealed tracheal stenosis and right-sided deviation.

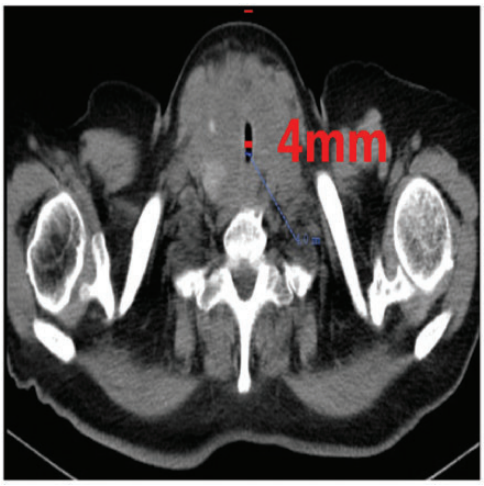

Figure 4. Computed tomography of the chest and neck revealed bilateral enlargement of the thyroid lobes and isthmus extending to the anterior superior mediastinum with heterogeneity and indistinct boundaries. Other findings included tracheal stenosis and polyglandular lymphadenopathy involving the bilateral supraclavicular nodes and perithyroid and carotid spaces.

under extracorporeal membrane oxygenation on August 15, 2019. The postoperative pathological examination disclosed a 4- × 3- × 2.5-cm^3 lesion with an eggshell-calcified nodule. Histopathologic evaluation revealed a poorly differentiated malignant

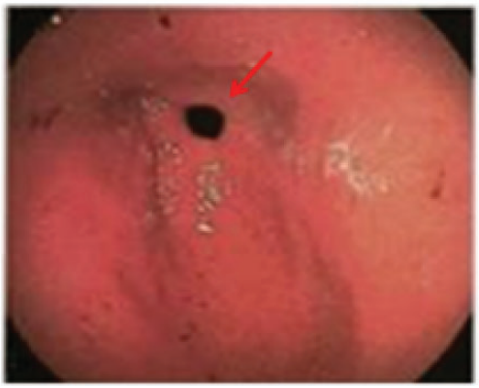

Figure 5. Painless gastroscopy disclosed a stenotic esophageal entrance.

tumor with features of squamous cell carcinoma (SCC), extensive necrosis with inflammatory reaction, and invasion of adjacent striated muscle, vasculature, and nerves. Immunohistochemistry revealed the following findings: galectin-3 (+), cytokeratin 19 (CK19; +), CD56 (−), Ki-67 (70% +), p53 (−), TTF-1 (minority +), TG (−), calcitonin (−), synuclein (−), CGA (−), Pax8 (+), and vimentin (scattered +) (Figure 6). The histopathologic and immunohistochemical findings confirmed a final diagnosis of PSCCT. The patient was admitted to the intensive care unit postoperatively. Unfortunately, the tumor gradually metastasized to the lungs, face, and other anatomic sites. Her course was further complicated by a surgical site infection and multiple organ failures that precluded antineoplastic therapy. The wound infection unfortunately progressed to sepsis that led to death on postoperative day 23 (September 7, 2019).

Discussion

SCC in thyroid tissue can result from either primary or secondary tumors, the latter of which are 10-fold more common.[7] The differential diagnosis of neck masses is broad, and it includes both malignant and benign

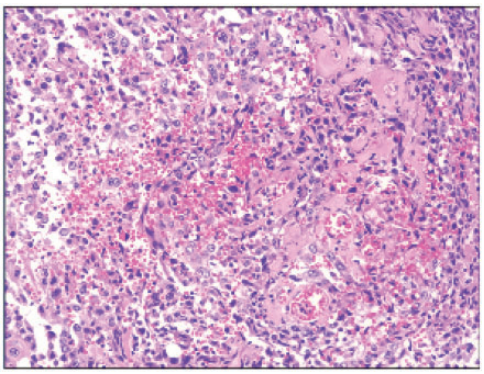

Figure 6. Histopathologic evaluation revealed a poorly differentiated malignant tumor with features of squamous cell carcinoma, extensive necrosis with inflammatory reaction, and invasion of adjacent striated muscle, vasculature, and nerves.

neoplasms. Accurate diagnosis of a neck mass is critical. Neck masses that result from metastatic disease are predominantly caused by SCCs arising from the aerodigestive tract. Because the lymphatic drainage patterns of the aerodigestive mucosae are highly consistent, the location of the mass may provide guidance concerning the site of the primary tumor. Lymphatic metastases in the posterior triangle are often related to nasopharyngeal carcinoma, whereas the nodes of the upper jugular chain drain the oral cavity, oropharynx, and larynx. Isolated supraclavicular lymphadenopathy should raise concern for tracheobronchial, distal esophageal, or gastric carcinomas. Although the overwhelming majority of cervical lymphatic metastases originate from SCCs of the aerodigestive tract, other primary cancers should be considered in the differential diagnosis. Cutaneous malignancies of the face and scalp are becoming increasingly common. Melanoma and aggressive SCCs, as well as uncommon cutaneous malignancies such as Merkel cell carcinoma, can metastasize to the neck. Other malignancies presenting as neck masses include paraganglioma and lymphoma. Despite their malignant histology, these masses are usually asymptomatic. However, symptoms related to the primary site of the tumor can often be elicited. Once the diagnosis of metastatic SCC is made, a search for the primary tumor must be performed. The probable primary site can often be identified via a review of the patient's history and physical examination, but panendoscopy and directed imaging may also be required.

Several proteins may serve as biomarkers to facilitate the differential diagnosis of neck masses. Pax8 is a transcription factor expressed in normal or neoplastic thyroid follicular epithelial cells, and it is present in >80% of anaplastic thyroid cancers (ATCs).[8] However, Pax8 is rarely expressed in lung, throat, thymus, or cutaneous SCCs. Vatsyayanet et al.[9] studied 32 cases of head and neck SCCs that had metastasized to the thyroid. In these cases, the histopathologic features were similar to those of PSCCT, but Pax8 was negative. Thus, Pax8 is a significant biomarker of PSCCT, and it can be used to distinguish PSCCT from other SCCs that are typically Pax8-negative.[10–13] Pax8 positivity usually indicates PSCCT, whereas a negative result in a thyroid tumor generally indicates metastatic SCC from another site. Lam et al.[14] found that thyroid cells do not express CK20. CK20-positive SCC of the thyroid is generally believed to represent metastatic tumors of either gastric, intestinal, or urinary tract epithelial origin. CK7 and CK19 are also expressed in PSCCT,[12,15] but at present, they are not considered to have diagnostic utility because of their low specificity.

The diagnosis of undifferentiated thyroid cancer depends primarily on FNAC. If FNAC is inconclusive, then hollow needle aspiration or excisional biopsy should be considered to teach a definitive diagnosis.[16] The histopathologic diagnosis of PSCCT requires the microscopic identification of keratin or intercellular bridge structures.[17]

Consequently, FNAC is prone to missed diagnoses and misdiagnoses of PSCCT. A meta-analysis concluded that the positive predictive value of FNAC for PSCCT may be less than 0.33, whereas FNAC yielded a misdiagnosis of papillary thyroid carcinoma or non-diagnostic lesions in more than 50% of patients with PSCCT.[17] The insensitivity of FNAC may be attributable to SCC cellular adhesion resulting from fibrosis and cytoplasmic interstitial reaction, leading to the failure of FNAC to obtain tumor cells. Another factor may be sampling errors caused by the cellular heterogeneity of SCC. Consequently, noninvasive tests to identify thyroid nodules have been studied. Depciuch et al.[4,5] demonstrated FTIR spectroscopy and Raman spectroscopy combined with multidimensional analysis can be used to distinguish benign (follicular adenoma) and cancerous lesions (follicular thyroid carcinoma) in thyroid tissue. However, current tests are limited in their ability to diagnose thyroid cancer. Preoperative determination of whether a lesion is benign or malignant is difficult. At present, the definitive diagnosis depends primarily on biopsy or postoperative histopathologic evaluation. In our case, the final diagnosis of PSCCT was established via postoperative histopathology.

PSCCT is a rare thyroid cancer that accounts for 0.2% to 1.1% of thyroid malignancies. Fewer than 60 cases have been reported in the medical literature. PSCCT can occur at any age, although it generally afflicts the elderly, with a peak incidence in the fifth and sixth decades. A female predominance is also observed, with a male to female ratio of approximately 1:2. Our current case was in line with these demographic trends. The biological behavior of PSCCT is similar to that of ATC. An enlarging anterior neck mass is the most common presenting symptom (60%), followed by dyspnea or dysphagia (20%) and dysphonia (15%). Late-stage disease features rapid growth and the progressive infiltration of surrounding structures. Infiltration rates may be as high as 77%, including invasion of the esophagus, trachea, and adjacent large blood vessels. At the time of diagnosis, our patient exhibited invasion of adjacent striated muscles, arteries, and nerves. The prognosis of PSCCT is generally poor with a low median survival time of 8 months, and the 1- and 2-year survival rates are 22.7% and 0%, respectively.[18] Because of the associated poor prognosis and low survival rate, it is particularly important to formulate an effective treatment plan for patients with PSCCT. However, there are no standardized evidence-based treatment guidelines.[19] Many authorities believe that improving the clinical outcome of radical tumor resection through a single treatment therapy will be difficult.

Cho et al.[17] concluded in a meta-analysis of 89 patients that complete resection was the only prognostic factor in multivariate analysis, and adjunctive therapies did not confer significant benefits. In the absence of distant metastases, local resection can be attempted. Local radiotherapy or neoadjuvant radiotherapy should be considered for non-resectable disease.[20] The role of postoperative adjuvant chemotherapy is controversial, and this treatment is often ineffective.[21] However, targeted treatment can be designed according to tumor genomics. For example, dabrafenib and trametinib can be selected for *BRAF* V600E-positive cases, and laratinib can be employed for patients who are *NTRK*-positive.[22] Our patient underwent partial thyroidectomy and tracheotomy to decompress the trachea and esophagus. Unfortunately, she developed metastases as well as a surgical site infection and multiple organ failures, which precluded antineoplastic treatment. The infection unfortunately progressed to sepsis and eventually claimed her life on postoperative day 23.

PSCCT is a highly invasive malignancy with a low incidence rate and poor prognosis. Early and accurate diagnosis is critical for designing rational treatment plans and improving survival rates. Clinicians should be aware of this rare and fatal disease to improve treatment outcomes. The lessons of this case are as follows: (1) new symptoms or abnormal auxiliary examination results that are inconsistent with a working diagnosis should trigger an expansion of the differential diagnosis and further investigations; (2) a significant increase in symptom severity or leukocyte counts in patients with subacute thyroiditis should prompt the exploration of other potential etiologies; (3) the possibility of tracheal obstruction must be eliminated in patients with thyroid nodules who develop dysphonia, cough, and choking; and (4) multidisciplinary approaches may improve the diagnostic timelines, treatment, and prognosis of this rare and aggressive malignancy.

Ethics statement

No ethical approval was required for this case report. Patient details were de-identified. Therefore, patient consent for publication was not required.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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References

1. Syed MI, Stewart M, Syed S, et al. Squamous cell carcinoma of the thyroid gland: primary or secondary disease? *J Laryngol Otol* 2011; 125: 3–9.
2. Raggio B, Barr J, Ghandour Z, et al. Primary squamous cell carcinoma of the thyroid. *Ochsner J* 2019; 19: 290–292.
3. Struller F, Senne M, Falch C, et al. Primary squamous cell carcinoma of the thyroid: case report and systematic review of the literature. *Inter J Surg* 2017; 37: 36–40.
4. Depciuch J, Stanek-Widera A, Lange D, et al. Spectroscopic analysis of normal and neoplastic (WI-FTC) thyroid tissue. *Spectrochim Acta A Mol Biomol Spectrosc* 2018; 204: 18–24.
5. Depciuch J, Stanek-Widera A, Skrzypiec D, et al. Spectroscopic identification of benign (follicular adenoma) and cancerous lesions (follicular thyroid carcinoma) in thyroid tissues. *J Pharm Biomed Anal* 2019; 170: 321–326.
6. Agha RA, Franchi T, Sohrabi C, et al. The SCARE 2020 guideline: updating consensus Surgical CAse REport (SCARE) guidelines. *Int J Surg* 2020; 84: 226–230.
7. Bolfi F, Domingues MA, Sobrinho-Simoes M, et al. Primary squamous cell carcinoma of the thyroid diagnosed as anaplastic carcinoma: failure in fine-needle aspiration cytology? *Case Rep Pathol* 2014; 2014: 301780.
8. Higgins SE and Barletta JA. Applications of immunohistochemistry to endocrine pathology. *Adv Anat Pathol* 2018; 25: 413–429.
9. Vatsyayan A, Mandlik D, Patel P, et al. Metastasis of squamous cell carcinoma of the head and neck to the thyroid: a single institution's experience with a review of relevant publications. *Br J Oral Maxillofac Surg* 2019; 57: 609–615.
10. Bishop JA, Sharma R and Westra WH. PAX8 immunostaining of anaplastic thyroid carcinoma: a reliable means of discerning thyroid origin for undifferentiated tumors of the head and neck. *Hum Pathol* 2011; 42: 1873–1877.
11. Bozorg-Ghalati F and Hedayati M. Molecular biomarkers of anaplastic thyroid carcinoma. *Curr Mol Med* 2017; 17: 181–188.
12. Suzuki A, Hirokawa M, Takada N, et al. Diagnostic significance of PAX8 in thyroid

squamous cell carcinoma. *Endocr J* 2015; 62: 991–995.
13. Ozcan A, Shen SS, Hamilton C, et al. PAX8 expression in non-neoplastic tissues, primary tumors, and metastatic tumors: a comprehensive immunohistochemical study. *Mod Pathol* 2011; 24: 751–764.
14. Lam KY, Lo CY, Liu MC, et al. Primary squamous cell carcinoma of the thyroid gland: an entity with aggressive clinical behaviour and distinctive cytokeratin expression profiles. *Histopathology* 2001; 39: 279–286.
15. Hu Z, Wang H, Wu B, et al. Clinical pathology analysis of primary squamous cell carcinoma of the thyroid. *Chinese J Cancer Prev Treat* 2010; 17: 1960–1962.
16. Smallridge RC, Ain KB, Asa SL, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. *Thyroid* 2012; 22: 1104–1139.
17. Cho JK, Woo SH, Park J, et al. Primary squamous cell carcinomas in the thyroid gland: an individual participant data meta-analysis. *Cancer Med* 2014; 3: 1396–1403.
18. Shrestha M, Sridhara SK, Leo LJ, et al. Primary squamous cell carcinoma of the thyroid gland: a case report and review. *Head Neck* 2013; 35: 299–303.
19. Au JK, Alonso J, Kuan EC, et al. Primary squamous cell carcinoma of the thyroid: a population-based analysis. *Otolaryngol Head Neck Surg* 2017; 157: 25–29.
20. Dumke AK, Pelz T, Vordermark D. Long term results of radio therapy in anaplastic thyroid cancer. *Radiat Oncol* 2014; 9: 90.
21. Batchelor NK. Primary squamous cell carcinoma of the thyroid: an unusual presentation. *J Bronchology Interv Pulmonol* 2011; 18: 168–170.
22. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med* 2018; 378: 731–739.