Case Reports in Oncology

Case Rep Oncol 2018;11:399–403

DOI: 10.1159/000490238
Published online: June 22, 2018

Case Report

Genomic Profiling Reveals Medullary Thyroid Cancer Misdiagnosed as Lung Cancer

Eva J. Gordon[a] David Parker[a] Kelly Barth[a] Jennifer Pena[a]
Julia A. Elvin[b] Thomas DeLeon[c] Nina J. Karlin[c]

[a]Private Health Management, Inc., Los Angeles, CA, USA; [b]Foundation Medicine, Inc., Cambridge, MA, USA; [c]Division of Hematology and Oncology, Mayo Clinic Hospital, Phoenix, AZ, USA

Keywords
Genomic profiling · Medullary thyroid cancer · Non-small cell lung cancer · *RET* mutation · Misdiagnosis

Abstract
Mutations or other alterations in the *RET* gene have been implicated in a variety of malignancies – most commonly thyroid, but also chronic myelomonocytic leukemia, acute myeloid leukemia, and lung, breast, pancreatic, and colon cancers. Here we present a case of a gentlemen initially diagnosed with and treated for non-small cell lung adenocarcinoma. Genomic profiling of his tumor specimen revealed a *RET* point mutation with a known association with medullary thyroid cancer (MTC). Further pathological and molecular diagnostic evaluation confirmed a diagnosis of MTC, leading to a change in treatment from standard chemotherapy for non-small cell lung cancer to targeted therapy against RET and potential implications regarding inherited cancer risk for his offspring. The patient experienced a clinical response to treatment and several months of improved quality of life. This case illustrates the capacity of genomic profiling to uncover molecular drivers of disease and help ensure proper diagnosis and management of cancer.

KARGER

Eva J. Gordon, PhD
Private Health Management, Inc.
1880 Century Park East, Suite 425
Los Angeles, CA 90067 (USA)
E-Mail egordon@privatehealth.com

Case Report

A 70-year-old man presented in April 2015 with pain in the left shoulder, neck, and lower back. Computed tomography (CT) of the thorax without contrast revealed mediastinal lymphadenopathy and numerous bilateral, ill-defined, noncalcified nodules in the lungs. Magnetic resonance imaging (MRI) of the cervical and lumbar spine showed extensive marrow-replacing lesions, concerning for widespread osseous metastatic disease. Positron emission tomography/CT demonstrated hypermetabolic activity in the right thyroid, lungs, mediastinal and hilar lymph nodes, and throughout the axial and appendicular skeleton. Thyroid ultrasound revealed a dominant, hypoechoic 3.3-cm solid nodule in the right lobe and multiple other smaller nodules. Differential diagnosis included lung cancer, thyroid cancer, and lymphoma.

In June 2015, CT-guided lung and bone biopsy, along with fine-needle aspirate (FNA) of the right thyroid, were performed. Although napsin A was negative, the diagnosis was initially determined to be poorly differentiated adenocarcinoma consistent with lung primary. Tissue from the bone biopsy otherwise stained positive for TTF-1 and CAM 5.2, and negative for PAX-8 and CD57. Cytology from the thyroid FNA showed morphology identical to the tumor in the lung and bone biopsies, consistent with non-small cell lung cancer. Treatment with carboplatin and pemetrexed was initiated, but the patient experienced severe adverse effects and thereafter declined further treatment.

However, in July 2015, tissue from the lung biopsy underwent comprehensive genomic profiling (CGP) of 315 genes (FoundationOne; Foundation Medicine) [1]. This analysis revealed a single point mutation in the tyrosine kinase "*rearranged during transfection*" (*RET*) proto-oncogene gene, C630R; no alterations commonly associated with lung cancer (e.g., EGFR, ALK) were detected. Given the documented association of point mutations in *RET* with medullary thyroid cancer (MTC) [2], complete workup for metastatic MTC was initiated. In addition, to gain further insight into the origin and clinical significance of the *RET* mutation, genomic profiling of circulating tumor DNA (ctDNA) (Guardant360; Guardant Health) [3] and germline sequencing of *RET* (Multiple Endocrine Neoplasia Type 2 assay; Ambry Genetics) [4] were also performed. Initially, the ctDNA analysis was reported as no alterations detected. However, upon further inquiry, it was discovered that the *RET* C630R mutation was actually present at an allele frequency of 29.9%; this level of the *RET* variant in the ctDNA was initially interpreted to be a germline alteration and thus not reported as a somatic alteration. Notably, the results of the germline testing did not reveal any alterations in *RET*.

In September 2015, the patient transferred care to another institution, where pathology confirmed neuroendocrine origin of the tissue (consistent with MTC). Chest CT with contrast showed no significant change in pulmonary nodules, lymph nodes, osseous lesions, and thyroid nodules when compared with all available prior imaging, with the exception of a slight increase in size in one of the liver lesions. Repeat MRI analysis also favored neuroendocrine malignancy due to the T2 hyperintense lesions in the liver, adrenal involvement, sclerotic osseous metastases, and restricted diffusion in the pancreas. Based on this information, the diagnosis was officially changed to metastatic MTC. As guidelines for MTC recommend no treatment in the absence of progression and symptoms, observation with repeat imaging in 2 months was recommended, though denosumab was continued to manage osseous disease.

Imaging at the end of October 2015 showed no interval change in the thyroid lesions but slight worsening in the pulmonary nodules, bilateral hilar and mediastinal lymphadenopathy, and concern for lymphangitic carcinomatosis, suggesting sufficient disease progression to begin treatment with the RET-targeting agent vandetanib. Over the next 6 months, the patient experienced increasingly improved symptoms, energy, mood, and appetite, with an improved

quality of life. However, in April 2016, he started experiencing a decline in function, and clinical, radiological, and serological assessment suggested disease progression. Treatment was switched to cabozantinib, but the patient continued to deteriorate over the next several weeks and ultimately passed away from his disease in July 2016.

Discussion

Molecular profiling, including genomic, transcriptomic, proteomic, and immunomic analysis, is increasingly important for the efficient identification and prioritization of treatment strategies for cancer patients [5]. Technologies are rapidly emerging to characterize the molecular properties and behavior of cancer cells, ranging from identification of genomic mutations in tumor cells or ctDNA, to quantification of protein levels in tumor tissue, to drug sensitivity testing in patient-derived organoids or xenografts. Collectively, this information can facilitate the diagnostic process and inform treatment options, including FDA approved and off-label therapies, as well as clinical trials selection.

MTC is a rare, aggressive subtype of thyroid cancer, comprising ~3–10% of all thyroid cancers [2, 6]. MTC originates in the parafollicular, or C cells, of the thyroid, which are responsible for producing the hormone calcitonin. Approximately 75% of MTC develops sporadically; the remaining 25% is hereditary, manifesting in patients with the type 2 multiple endocrine neoplasia syndromes or the related syndrome, familial MTC. Alterations in the *RET* gene have been implicated in a variety of malignancies – most commonly thyroid, but also chronic myelomonocytic leukemia, acute myeloid leukemia, and lung, breast, pancreatic, and colon cancers [7]. *RET* mutations are found in ~95% of familial MTC and in ~50% of sporadic forms of the disease [8]. Whether MTC is inherited or acquired, gain of function alterations in RET are causative and targetable by RET-targeting therapies such as vandetanib and cabozantinib [6].

Though numerous alterations spanning the *RET* gene have been identified, point mutations at positions 634 and 918 are the most common [2]. Notably however, a 2005 report describes a family of 29 members in four generations in which 6 were diagnosed with MTC, all positive for a germline C630R mutation in *RET* [9]. Missense mutations at codons affecting such highly conserved cysteine residues are believed to affect the region between extracellular and transmembrane domains, which is integral to disulfide bond formation needed for receptor dimerization.

A few clinical aspects of this case could have raised suspicions that the original diagnosis of lung adenocarcinoma was incorrect. First, the thyroid mass (~3 cm) was significantly larger than the lung lesions (each ~1 cm). In addition, though the incidence of lung cancer is approximately 4 times that of thyroid cancer [10], metastasis of any primary tumor to the thyroid is rare. Thyroid metastases represent less than 4% of all thyroid malignancies and have an overall incidence of 1.4–3% (but range from ~4 to 25% in autopsy studies) [11]. In addition, there have been only 9 reported cases originating from the lung [12]. In contrast, metastasis to the lung from differentiated thyroid cancer (papillary and follicular) and from MTC occurs at a rate of 4–23 and 33%, respectively [13]. Though the presence of TTF-1 supports either a lung or a thyroid primary, the absence of PAX-8, CD57, and calcitonin erroneously led to the conclusion that tumor cells were not of thyroid origin; and since napsin A is positive in 50–60% of lung adenocarcinomas, its absence did not rule out a lung origin. In retrospect, the poor differentiation of the tumor cells, decalcification of the bone specimen, and variability of PAX-8 and calcitonin in MTC may have contributed to the absence of these thyroid markers in this

case. While *RET* can be altered in both thyroid and lung cancers, the specific *RET* point mutation (as opposed to *RET* fusions identified in ~1% of lung cancers [14] and approximately 20% of papillary thyroid cancers [8]) identified by CGP of the tumor tissue prompted further clinicopathological workup (immunostaining for neuroendocrine markers chromogranin and synaptophysin; expert pathology consultation; serum calcitonin, elevated at 1,102 pg/mL; and serum calcitonin/carcinoembryonic antigen ratio of 225.5 ng/mL) and ultimately re-diagnosis as MTC.

This case demonstrates the utility of tumor CGP for both establishing and confirming the correct diagnosis and ensuring appropriate therapy for cancer patients. In this patient, given the initial diagnosis of lung cancer, single gene tumor testing would likely have resulted in assessment only of a subset of mutations in a few select genes associated with lung cancer (e.g., *EGFR, BRAF, ALK, ROS,* and possibly *RET* fusions), all of which would have been negative and would not have called the initial diagnosis into question. Moreover, this approach would also have failed to identify the targetable driver mutation (*RET*) and instead directed the patient towards a standard lung adenocarcinoma chemotherapy regimen – which is known to be ineffective against MTC while still subjecting the patient to the side effects of chemotherapy. Targeting the *RET* oncogene allowed this patient to derive 6 months of dramatically improved quality of life and stable disease. It is interesting to note a 2011 report, which describes another case of lung and thyroid lesions presenting simultaneously, where genomic profiling was also the key factor in determining the correct diagnosis [15]. However, in that case, it was the presence of an EGFR mutation that led to a correct diagnosis of lung cancer and initiation of appropriate targeted therapy with erlotinib. Cases like these strongly support the earlier use of comprehensive molecular diagnostics to ensure proper diagnosis and treatment for patients with clinically advanced malignancies.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

1 Frampton GM, Fichtenholtz A, Otto GA, Wang K, Downing SR, He J, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol. 2013 Nov;31(11):1023–31.
2 Hedayati M, Zarif Yeganeh M, Sheikholeslami S, Afsari F. Diversity of mutations in the RET proto-oncogene and its oncogenic mechanism in medullary thyroid cancer. Crit Rev Clin Lab Sci. 2016 Aug;53(4):217–27.
3 Lanman RB, Mortimer SA, Zill OA, Sebisanovic D, Lopez R, Blau S, et al. Analytical and clinical validation of a digital sequencing panel for quantitative, highly accurate evaluation of cell-free circulating tumor DNA. PLoS One. 2015 Oct;10(10):e0140712.
4 Mu W, Lu HM, Chen J, Li S, Elliott AM. Sanger Confirmation Is Required to Achieve Optimal Sensitivity and Specificity in Next-Generation Sequencing Panel Testing. J Mol Diagn. 2016 Nov;18(6):923–32.
5 Schmidt KT, Chau CH, Price DK, Figg WD. Precision Oncology Medicine: The Clinical Relevance of Patient-Specific Biomarkers Used to Optimize Cancer Treatment. J Clin Pharmacol. 2016 Dec;56(12):1484–99.
6 Romei C, Ciampi R, Elisei R. A comprehensive overview of the role of the RET proto-oncogene in thyroid carcinoma. Nat Rev Endocrinol. 2016 Apr;12(4):192–202.

7 Mulligan LM. RET revisited: expanding the oncogenic portfolio. Nat Rev Cancer. 2014 Mar;14(3):173–86.
8 Nikiforov YE. Thyroid carcinoma: molecular pathways and therapeutic targets. Mod Pathol. 2008 May;21(S2 Suppl 2):S37–43.
9 Dourisboure RJ, Belli S, Domenichini E, Podesta EJ, Eng C, Solano AR. Penetrance and clinical manifestations of non-hotspot germline RET mutation, C630R, in a family with medullary thyroid carcinoma. Thyroid. 2005 Jul;15(7):668–71.
10 Howlader NN, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Cronin KA et al (eds). SEER Cancer Statistics Review, 1975-2013. National Cancer Institute Bethesda, MD, based on November 2015 SEER data submission, posted to the SEER web site, April 2016.
11 Disibio G, French SW. Metastatic patterns of cancers: results from a large autopsy study. Arch Pathol Lab Med. 2008 Jun;132(6):931–9.
12 Wey SL, Chang KM. Tumor-to-Tumor Metastasis: Lung Carcinoma Metastasizing to Thyroid Neoplasms. Case Rep Pathol. 2015;2015:153932.
13 Chopra S, Garg A, Ballal S, Bal CS. Lung metastases from differentiated thyroid carcinoma: prognostic factors related to remission and disease-free survival. Clin Endocrinol (Oxf). 2015 Mar;82(3):445–52.
14 Bos M, Gardizi M, Schildhaus HU, Buettner R, Wolf J. Activated RET and ROS: two new driver mutations in lung adenocarcinoma. Transl Lung Cancer Res. 2013 Apr;2(2):112–21.
15 Albany C, Jain A, Ulbright TM, Einhorn LH. Lung cancer, thyroid cancer or both: an unusual case presentation. J Thorac Dis. 2011 Dec;3(4):271–3.