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**Thyroid RF11 | PSAT273**

**RET Gene Fusion In a Putative Case of Medullary Thyroid Cancer**

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**Background:** Oncogenic RET gene fusions have been identified in non-small cell lung cancer and non-medullary thyroid cancers, whereas RET point mutations are the key genetic finding in both inherited and sporadic medullary thyroid cancer (MTC). The presence of a RET gene fusion provides a target for selective RET inhibitor drugs. We describe an unusual patient with suspected MTC and a positive RET gene fusion, with excellent response to targeted therapy.

**Clinical Case:** A 50-year-old male presented to our institution with cough, fatigue, heat intolerance, and flushing. His only remarkable history was stage IIIBS Hodgkin lymphoma treated with chemotherapy, in remission for approximately 6 years. CT chest revealed new bulky mediastinal and hilar adenopathy with bulky cervical nodes.

VATS biopsy of a mediastinal node showed metastatic neuroendocrine neoplasm with plasmacytoid features that was immunoreactive for calcitonin, CEA and cytokeratin, but negative for TTF1 and PAX-8. The differential diagnosis included MTC or metastatic atypical carcinoid tumor.
Next Generation Sequencing was negative, including RET and RAS point mutations. Subsequent testing for re-arrangements showed a KIF5B-RET gene fusion, an onco-gene identified in lung adenocarcinoma. Biochemical findings showed a calcitonin level of 16,033 (normal < 10 pg/mL) and CEA 6.9 (normal < 4.7 ng/mL). Chromogranin A was 146.6 (normal < 101.16 ng/mL). ACTH and cortisol were normal. Neck US revealed a calcified 5 mm right upper pole thyroid nodule and extensive bilateral cervical nodes. A provisional diagnosis was made of MTC.

Vandetanib was started. Two months later, he reported worsening orthopnea, diarrhea, and weight loss. CT chest showed marked worsening with enlarging mediastinal hilar and supraclavicular adenopathy with new moderate sized pericardial and pleural effusion. Vandetanib was discontinued and Selpercatinib started, following FDA approval. He reported prompt resolution of dyspnea and diarrhea and improved weight and energy. Calcitonin declined to <2 pg/mL and CEA to 1.6 ng/mL four months into treatment. CT neck showed marked shrinkage of lymph nodes with a persistent calcified thyroid nodule. CT chest showed marked shrinkage of mediastinal and hilar masses, with resolution of bronchial narrowing and right pleural effusion.

Nine months after presentation, there were no chest symptoms and biochemical markers and imaging remained stable.

**Conclusion:** Approximately 25% of MTC tumors lack activating point mutations in RET or RAS genes. Analysis of actionable fusion mutations should be considered if there is metastatic disease. High serum calcitonin levels are not pathognomonic for MTC and tumor histology may overlap with neuroendocrine lung cancers, creating a diagnostic challenge. Depending on whether this patient’s tumor originated in the thyroid gland, it may represent an unusual case of RET gene fusion in MTC.

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