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The Report of KRAS Mutation and NRAS Wild Type in a Patient with Thyroid Metastasis from Colon Cancer: a Rare Case Report

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ABSTRACT

Colorectal cancer (CRC) metastasis to the thyroid gland is rare. Here we report a 45 yr-old man in western Iran referred to Hematology Clinic, Kermanshah City, Iran in March 2014 with complaint of exertional dyspnea, multi-nodular goiter as well as complaint of exertional dyspnea, and multi-nodular goiter. His history included a low anterior resection of rectum in 9 months ago for a high-risk stage II rectal adenocarcinoma. He did not show clinical signs of hyperthyroidism other than thyroid enlargement. In thyroid nodule the FNA cytology, pathology reported anaplastic thyroid malignancy. Pathologists reported final diagnosis of colorectal metastasis of thyroid gland. Then due to metastatic pattern of disease, his pathology was evaluated for RAS molecular assay. In the patients of metastatic CRC, RAS testing is the first step to identify those patients that could benefit from anti-EGFR monoclonal antibodies treatment.

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Introduction

The most common sites of metastasis from colon cancer are the regional lymph nodes, the liver, the lung, and the peritoneum. Colon cancer metastasis to the thyroid gland is rare (1). The incidence of thyroid metastasis postmortem, from all tumor types, ranges between 1.9% and 9.5% (2), possibly due to a high oxygen and iodine environment which may impair the ability of metastatic cells to settle and develop (3) or due to vascular or lymphatic spread (4). Three closely related RAS oncogenes, HRAS, NRAS, and KRAS, have been identified in mammals and a role for wild-type H-Ras and N-Ras proteins in mediating RTK signaling and proliferation of cancer cells that harbor mutant K-Ras has also been demonstrated (5).

Here we present a case where lung metastasis and thyroid gland metastasis occurred around one year following primary CRC.

Case Report

A 54-year old man was presented to to Hematology Clinic, Kermanshah City, Iran in

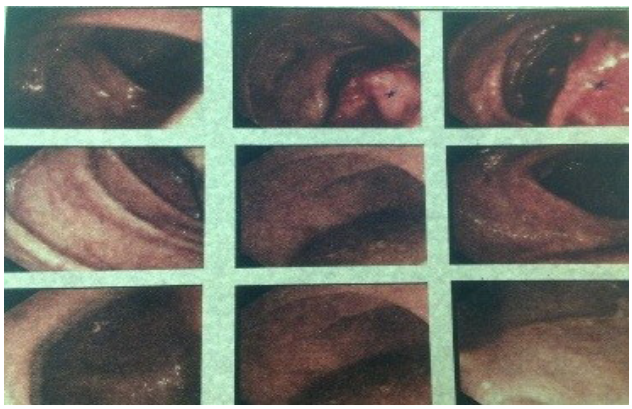

Fig. 1
In colonoscopy sigmoidal mass lesion can be seen

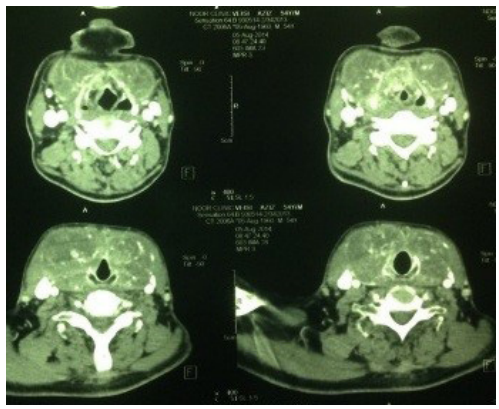

Fig. 2
In coronal CT scan section shows that enlargement bilateral thyroid mass that encased laryngo-tracheal lumen

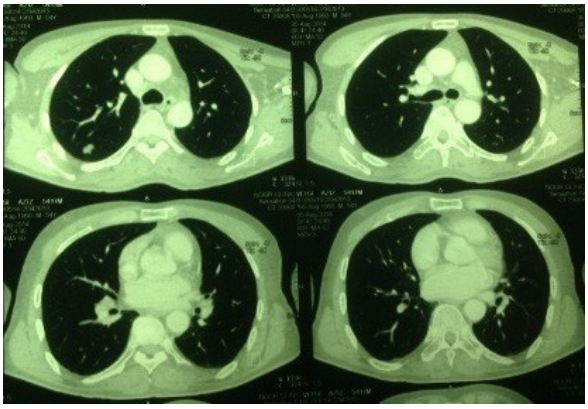

Fig. 3
In CT scan of the lung, multiple nodular lesions can be seen

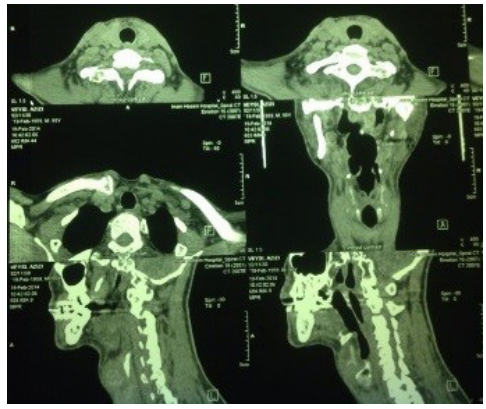

Fig. 4
In direct laryngoscopy narrowing of airway in trachea can be seen

March 2014 in March 2014 with complaint of exertional dyspnea, multi-nodular goiter. His history was included a low anterior resection of rectum in 9 months ago (July 2013) for a high-risk stage II rectal adenocarcinoma with a normal CEA proportion on that time (Fig. 1). He did not hold clinical signs of hyperthyroidism other than thyroid enlargement. CT scan and ultrasonography showed multinodular goiter with compression effect on trachea. Thyroid isotopic scan showed multiple cold nodules uptake. In thyroid nodule the FNA cytology, pathology reported anaplastic thyroid malignancy. Whole body scintigraphy was normal. He referred for total bilateral thyroid thyroidectomy that was done (Fig. 2). In imaging staging study, abdominal CT scan was normal. In chest CT scan that a few multiple small bilateral nodules in both side of lung were seen (Fig. 3).

After total successful bilateral thyroidectomy (Fig. 4 and Fig. 5) and immunohistochemical (IHC) (CK7 was positive (Fig. 6) but cytokeratin (CK) 20, CDX-II, thyroid transcription factor-1 (TFF-1) were negative). Pathologists reported final diagnosis of colon metastasis of thyroid gland. Then due to metastatic pattern of disease, his pathology was evaluated for KRAS and NRAS molecular assay that NRAS was wild type but KRAS codon12-mutation (p Gly12Asp (c.35G>A). Therefore, he was not eligible for the epidermal growth factor receptor (EGFR)

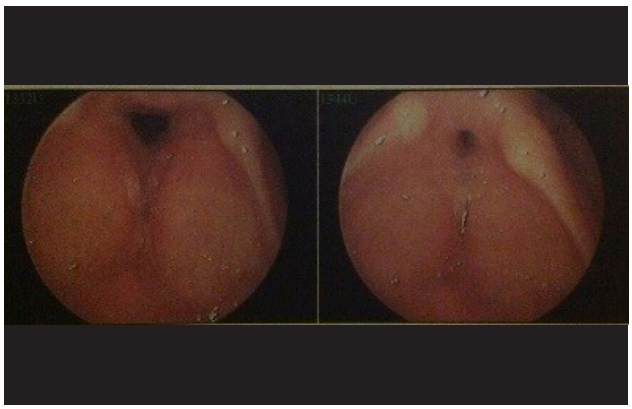

Fig. 5
In sagital and coronal CT scan section after surgery, without pressure on airway lumen

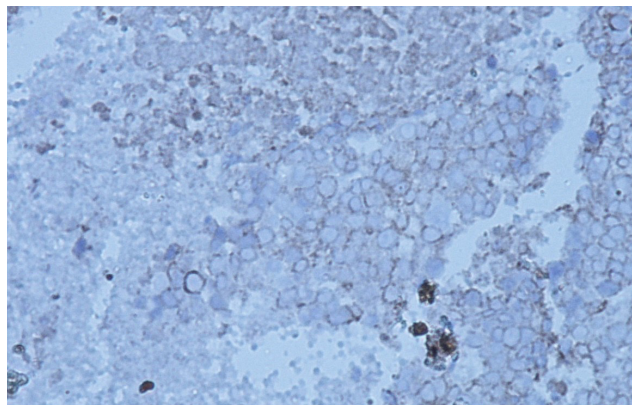

Fig. 6
CK7 staining showing a positive reaction

inhibitor, erbitux (cetuximab) therapy. At this time (Jun 2014) he was candidate for policy of metastatic colon cancer therapy with combination at chemotherapy and anti-angiogenesis of avastin (bevacizumab).

After recent 6 months of these events, he is alive and his complaints reduced with this new treatment. We decided to continue this protocol that consists of xeloda (capecitabine) in combination with avastin for 12 months and re-evaluated patient during this period.

Discussion

"Metastatic lesions to the thyroid gland are generally considered rare, possibly due to a high oxygen and iodine environment, which may impair the ability of metastatic cells to settle and develop" (3). Upon histological examination of autopsy cases, thyroid metastases were observed in 1.9% to 9.5% of cases (6). The timing of diagnosis of metastases to the thyroid is variable from time of initial diagnosis until years after treatment and can present as a single nodule or as multiple foci within the gland (4). A number of studies (1, 2, 3, 4, 6, 7) and our study show that patients with thyroid metastasis from colon cancer have upper than 50 years.

KRAS codon 12/13 mutations frequently occur in colon cancer, whereas they are extremely uncommon in thyroid tumors, DNA was extracted from the aspirated cells, and KRAS mutational analysis was carried out. In fact, CRC patients with tumors harboring a KRAS gene mutation do not derive benefit from this treatment (7). Primary and metastatic tumor tissues from the same patient can give different results on KRAS mutation status. However, the real discordance in KRAS genotyping results between primary and metastatic tumor tissues is not known yet (8).

Two studies (7, 9) and our study showed that there was a high KRAS mutational status concordance between primary and metastatic CRC specimens.

In our case with KRAS mutation, location of tumors was rectum in stage II but a study (10) reported that there was no significant difference in KRAS mutation with respect to tumor location (colon vs. rectum) and clinicopathological stage. The NRAS gene codes for a protein, N-ras, which is an alternate effector to KRAS (11) and NRAS regulate the DNA Damage Response in KRAS mutation Tumors (12). The KRAS mutations are predictive markers for the poor efficacy of anti-EGFR antibody therapies in patients with metastatic colorectal cancer (13). Effective targeting of oncogenic KRAS-driven tumors has remained a major challenge in cancer therapy (5).

A functional dependence of KRAS-driven tumors was defined on wild-type H- and NRAS

for the DNA damage response and reveals a promising therapeutic strategy for the treatment of mutant KRAS tumors and also demonstrated that mutant KRAS cancer cells require wild-type HRAS and NRAS for the activation of the ATR-Chk1-mediated DNA damage checkpoint and that this dependence can be exploited to specifically sensitize KRAS-driven cancers to DNA damageinducing agents (5). Herein, in a patient with CRC that has metastasis to lung and thyroid, KRAS and NRAS were mutation and wild-type, respectively, and this shows metastasis CRC with more severity.

In patients with occult primary tumors, immunohistochemical studies are useful for the characterization of poorly differentiated or undifferentiated tumors and for cell-type determination and pathologic diagnosis. However, because immunohistochemistry markers for unknown primary cancers are not uniformly specific or sensitive and because immunohistochemical analysis has not improved patient outcomes, a large series of marker studies should be avoided. Immunohistochemical studies should be used in conjunction with imaging studies to select the best possible treatment options for patients with occult primary tumors. Cytokeratins 7 and 20 Cytokeratins are useful for cell-type determination in primary and metastatic carcinomas and are the 2 most common immunostains used in occult primary tumors to define subsets of carcinomas (14). The use of TTF-1 staining distinguishes lung and thyroid primary tumors from other CK7-positive tumors, because most lung and thyroid carcinomas are positive for TTF-1(15) and in this case TTF is strongly is negative.

Metastasis to thyroid from CRC is more in age of upper than 50 years. Cytokeratins 7 and 20 cytokeratins are very helpful in occult primary tumors to define subsets of carcinomas. In the patients of metastatic CRC, KRAS and NRAS testing are the first step to identify which patients could benefit from anti-EGFR monoclonal antibodies treatment.

Acknowledgements

The authors declare that there is no conflict of interest.

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