

Quiz Case 1

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AN ASYMPTOMATIC 9-year-old girl with normal childhood development was referred for DNA sequence analysis of the *RET* proto-oncogene on chromosome 10. She was the daughter of a woman with multiple endocrine neoplasia syndrome type 2A (MEN-2A). Genetic testing revealed a mutation involving codon 618 of the *RET* proto-oncogene that changed the wild-type TGC codon to a TCC codon. Her mother and 6-year-old sister carried the identical germline mutation of the *RET* proto-oncogene. Her serum calcitonin level was 40 ng/L (refer-

ence range, 0-4 ng/L). She underwent a total thyroidectomy with central lymph node dissection. Intraoperatively, there was no evidence of cervical lymphadenopathy, and the thyroid gland appeared normal.

The thyroid gland was grossly normal, without palpable or visible masses. The histopathologic findings of sections obtained from the right upper and middle poles of the thyroid are shown in **Figure 1** and **Figure 2**. Immunohistochemical studies for calcitonin (**Figure 3**) and thyroglobulin (**Figure 4**) were performed.

What is your diagnosis?

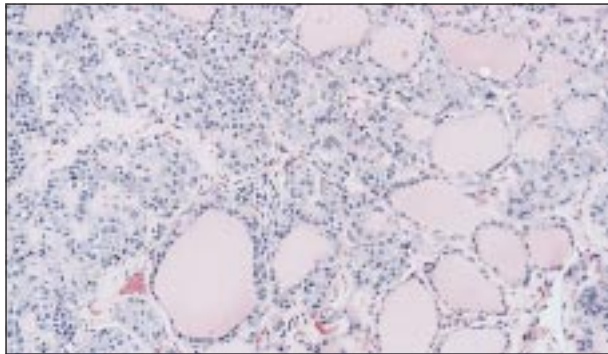


Figure 1.

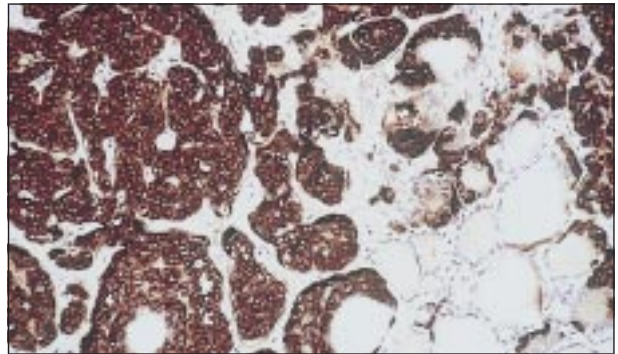


Figure 3.

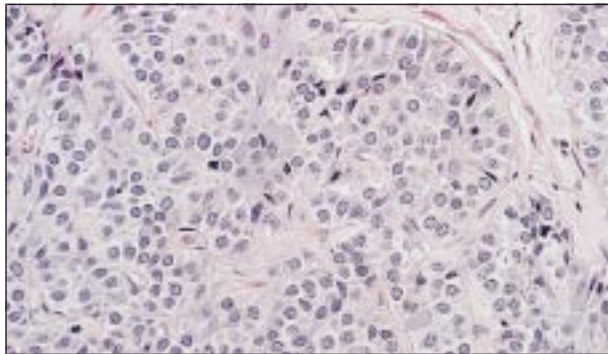


Figure 2.

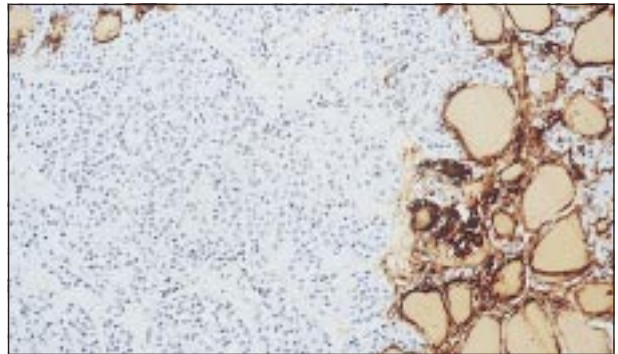


Figure 4.

Quiz Case 2

Joel H. Blumin, MD; Anthony A. Golsorkhi, BS; Gary M. Feinberg, MD; Gerald S. Berke, MD; Los Angeles (Drs Blumin and Berke and Mr Golsorkhi) and Riverside (Dr Feinberg), Calif

A 48-YEAR-OLD man presented with an 8-month history of a chronic cough. Examination revealed changes consistent with reflux laryngitis, and an aggressive antireflux regimen was initiated. The patient, who was otherwise healthy, did not have an appreciable response to medical therapy. Because of the persistent nature of his cough, he was taken to the operating room for evaluation with triple endoscopy, which revealed a pedunculated tracheal mass emanating from the right tracheal wall, approximately 2 cm distal to the cricoid cartilage (**Figure 1**). Because a vascular lesion was

considered, a biopsy specimen was not obtained. The patient was transferred to the University of California, Los Angeles, UCLA School of Medicine for further care.

Computed tomographic and magnetic resonance imaging scans were obtained to evaluate the extent of local disease and to determine whether there was locoregional metastasis (**Figure 2** and **Figure 3**). The patient was again taken to the operating room, where he underwent an en bloc resection of the mass through a transcervical approach. The histopathologic findings are shown in **Figure 4** (hematoxylin-eosin).

What is your diagnosis?

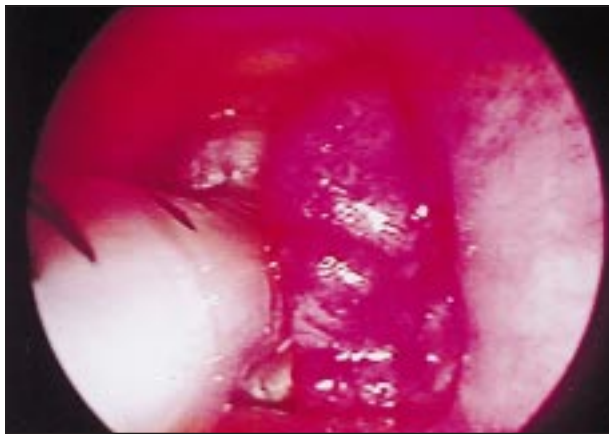


Figure 1.

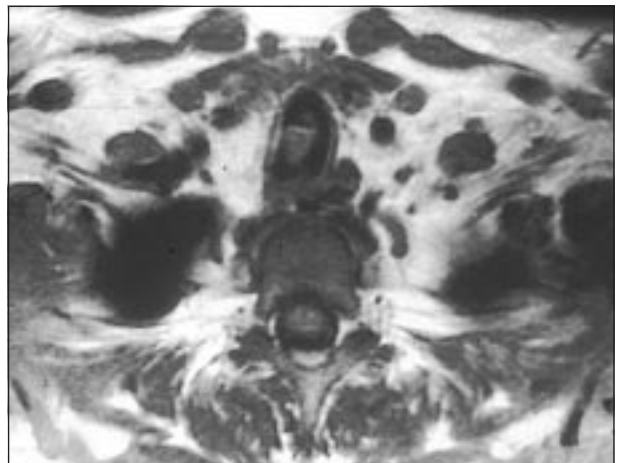


Figure 3.

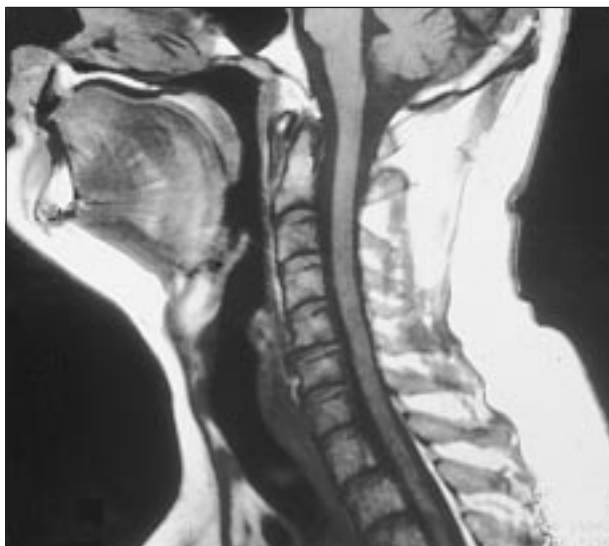


Figure 2.

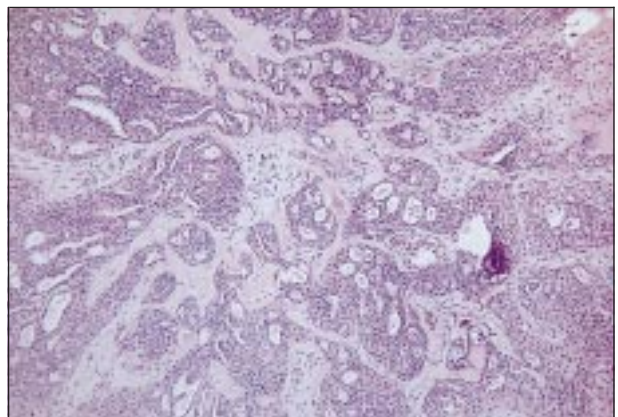


Figure 4.

Diagnosis Quiz Case 1

Diagnosis: Early medullary thyroid carcinoma (MTC), familial type, arising in a background of C-cell hyperplasia

Recent advances in molecular pathology have provided an increased understanding of the molecular genetics of MEN-2 syndromes and their association with mutations in the *RET* proto-oncogene.¹ These advances, in turn, have translated into more effective clinical treatment of patients with familial forms of MTC.^{1,2} Most familial cases of MTC can now be recognized and removed during their earliest stages, before they have metastasized. Testing for germline mutations of the *RET* proto-oncogene represents one of the greatest triumphs of molecular-genetic-based diagnostic medicine.¹⁻³

The MEN-2 syndromes are transmitted as autosomal dominant traits. They are subclassified as MEN-2A, MEN-2B, and familial MTC.^{1,4} MEN-2A is a triad of MTC, pheochromocytoma, and parathyroid hyperplasia and is the most common subtype.^{4,5} MEN-2B is also characterized by MTC and pheochromocytoma, but the occurrence of parathyroid hyperplasia is not common.⁵ In patients with MEN-2B, MTC tends to present earlier and runs a more aggressive course than its counterpart in patients with MEN-2A. Also, patients with MEN-2B may have developmental abnormalities, including marfanoid habitus, and failure to thrive owing to ganglioneuromatosis of the gastrointestinal tract.^{4,5} Whatever the subtype, MTC is clearly the most lethal component of the MEN-2 syndromes: more than 95% of the patients will develop this malignancy.^{1-3,5} Sometimes, MTC occurs in families but is not associated with other endocrine disorders. Familial MTC is defined by the presence of MTC in 4 or more family members with no evidence of pheochromocytoma or parathyroid disease.^{4,5} While MTC associated with MEN-2B is particularly aggressive, familial MTC is generally more indolent.⁵

Medullary thyroid carcinomas are relatively uncommon, accounting for 5% to 10% of all thyroid carcinomas, and can be separated into familial (MEN-associated) and sporadic forms.³⁻⁵ The more common sporadic form usually presents in adults, is usually unifocal, and is not associated with C-cell hyperplasia.^{4,6} In contrast, the familial form usually presents in younger patients, is often multifocal and bilateral, and is preceded by diffuse C-cell hyperplasia.^{4,5} On occasion, familial MTC may present as a single tumor in an adult. In these cases, the pathologist has traditionally played an important role in recognizing the familial nature of these MTCs by noting the presence of C-cell hyperplasia.^{4,6}

C-cell hyperplasia represents a multifocal proliferation of C cells within the thyroid gland, resulting in the progressive filling and obliteration of thyroid follicles. Aside from this single histologic feature, there are no other morphological findings that distinguish sporadic from familial forms of MTC.^{5,6} Medullary thyroid carcinoma of both types is histologically characterized by a nested or sheetlike pattern of growth (Figure 1 and Figure 2). The tumor cells tend to be round to spindle with eosino-

philic cytoplasm and a finely speckled chromatin pattern. The stroma often contains dense amorphous deposits of pink amyloid, a feature that can be highlighted with a Congo red stain for amyloid.⁵ Immunohistochemical stains are useful in discriminating MTC from other primary thyroid neoplasms.^{5,6} Unlike those tumors derived from the follicular epithelial cells, MTCs are consistently positive for calcitonin (Figure 3) and negative for thyroglobulin (Figure 4).

Medullary thyroid carcinomas are also relatively aggressive tumors, with an overall 10-year survival rate of 40% to 60%.^{2,4} By far, the most significant prognostic factor for patients with MTC is tumor stage.^{2,4,5} Tumors confined to the thyroid gland are usually cured by thyroidectomy. For those tumors that have spread beyond the thyroid to regional lymph nodes, the chance for survival is greatly diminished.^{2,4} Clearly, the best way to successfully manage MTC is to detect it in its earliest stages, before it has spread beyond the thyroid.

In the past, the primary method for screening individuals at risk for any of the familial forms of MTC was serum calcitonin measurements following pentagastrin and calcium stimulation. High serum calcitonin levels correlate with the presence of MTC.³ However, this stimulation approach has limitations.³⁻⁵ First, stimulation by pentagastrin and calcium is not completely sensitive: some patients with MTC will have a normal test result (false negative). Second, it is not completely specific: rarely, patients without MTC will have elevated stimulated calcitonin levels (false positive). Third, a normal test result provides no assurance that the individual will not develop MTC at some point in the future. Accordingly, affected and unaffected siblings alike are required to endure repeated surveillance testing and unremitting anxiety.³⁻⁵

The *RET* gene lies within chromosome 10q11.2. It codes for a cell-surface glycoprotein related to a family of receptor tyrosine kinases.⁷ *RET* messenger RNA is highly expressed in tissues and tumors derived from cells of embryonal neural crest, including thyroid, parathyroid, and adrenal medulla.^{7,8} Activating *RET* mutations are found in 97% of patients with MEN-2A and in 86% of patients with familial MTC.^{1,8} Importantly, in MEN-2A, the distribution of these mutations is largely restricted to 6 codons (609, 611, 618, 620, 630, and 634) in exons 10 and 11.^{1,7,9} Although somatic *RET* mutations have also been detected in sporadic MTCs, these mutations are not present in the patient's germline DNA.^{7,9}

RET gene testing for the detection of patients who are likely to have or to develop a familial form of MTC offers clear advantages over traditional testing.^{7,10,11} *RET* gene analysis is highly predictive.^{1,9,10} More than 90% of patients with a detected germline mutation will ultimately develop MTC.^{1,11} Thus, at-risk family members can be identified in early childhood, and their thyroid glands can be removed before their tumors can develop and progress. Conversely, the absence of a *RET* germline mutation provides the patient essentially a clean bill

of health and eliminates the need for ongoing surveillance. Also, *RET* testing of nontumoral tissue can be used to determine if an apparent sporadic case of MTC is in fact a MEN-2-associated cancer in an index patient.^{1,7,10,11}

Because the mutations associated with the MEN-2 syndromes are fairly limited, they are readily amenable to molecular detection.^{1,10} Investigators have performed direct mutation analysis of the *RET* gene using one of several rapid and simple molecular methods, including polymerase chain reaction to amplify the DNA and its analysis by restriction enzyme digest or direct sequencing.^{1,9-11} These methods have proved to be reliable, sensitive, and specific, and have led to prophylactic thyroidectomy and/or close follow-up of patients with *RET* germline mutations.^{1,9-11}

In conclusion, the early identification of *RET* mutation in the patient described herein led to an early intervention in the form of prophylactic thyroidectomy. Histopathologic findings of C-cell hyperplasia and microscopic foci of MTC confirmed the diagnosis of familial MTC and validated the use of prophylactic thyroidectomy. *RET* gene analysis is a powerful tool for the early detection of familial MTC.

Diagnosis Quiz Case 2

Diagnosis: Mucoepidermoid carcinoma (intermediate grade) of the trachea

Primary tumors of the cervical trachea are quite rare, with reports of fewer than 3 new cases per million per year.^{1,2} They represent a wide variety of histopathologic subtypes, among which adenoid cystic carcinoma and squamous cell carcinoma are the most common, representing approximately 76% of all tumors. Mucoepidermoid carcinoma of the trachea is quite rare, with only 18 cases recognized in a 40-year retrospective study of tracheobronchial tumors from Massachusetts General Hospital, Boston.³

Mucoepidermoid carcinoma of the trachea arises from the minor salivary glands that are abundant in the tracheal submucosa. It occurs in different age groups, ranging from pediatric to geriatric, and does not seem to be associated with tobacco use.³ The patient with mucoepidermoid carcinoma of the trachea typically presents with dyspnea, chronic cough, or hemoptysis. Occasionally, this type of tumor is found on a routine chest radiograph of an asymptomatic patient.

Diagnosis is made only after other tumors that are common to the trachea have been considered. Squamous cell carcinoma and adenoid cystic carcinoma represent the most and second most common primary tracheal tumors, respectively. Although less common, sarcomas and secondary neoplasms should also be considered when evaluating tracheal tumors. Workup of these lesions includes computed tomographic or magnetic resonance imaging to help evaluate the extent of disease and

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to aid in surgical planning. There are no specific laboratory values to monitor. Pulmonary function test results can help to predict surgical morbidity from the tumor extirpation. A history of significant chronic lung disease may make weaning the patient from the ventilator difficult, and a prophylactic tracheotomy should be considered.

The histopathologic appearance of tracheal mucoepidermoid carcinoma is similar to that of mucoepidermoid carcinoma in other regions of the head and neck. There is an admixture of 3 distinct cell types: atypical squamous cells, intermediate cuboidal to columnar cells, and tall and pyramidal mucinous cells. These tumors are thought to arise from salivary gland excretory duct cells. Mucoepidermoid carcinoma is commonly divided into 3 histologic grades based on architecture and resultant clinical course. Low-grade tumors are highly cystic and have a high ratio of mucinous cells to epidermoid cells. Necrosis and hemorrhage are generally absent or minimal. Cellular atypia and pleomorphism are minimal, and local invasion is generally not seen. High-grade tumors consist of solid sheets of atypical and pleomorphic epidermoid cells, with few mucinous cells and rare mucin. There is a high degree of necrosis and hemorrhage, and invasion is readily evident. Intermediate-grade tumors represent the bridge between low- and high-grade tumors: there are more epidermoid cells in intermediate-grade tumors than in low-grade tumors, but hemorrhage, necrosis, and cellular pleomorphism are not as fulminant as in high-grade tumors. The intermediate cuboidal to columnar type of cell is frequently found interspersed with

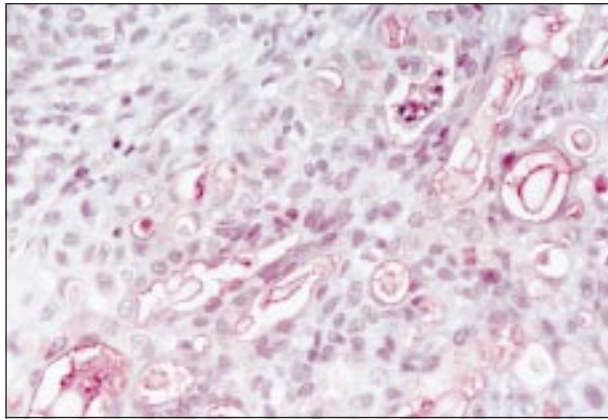


Figure 5.

mucoid cells, lining cystic spaces. Therefore, intermediate cells are associated with low- and intermediate-grade tumors. These cells may be found among solid sheets of squamous cells in high-grade tumors, however; thus, their presence does not exclude the diagnosis of high-grade mucoepidermoid carcinoma.⁴ Hematoxylin-eosin staining is generally adequate to make the pathologic diagnosis, but periodic acid-Schiff or mucicarmine staining can help to bring out the mucinous cells. To confirm the diagnosis in this case, the tumor was histopathologically examined with mucicarmine staining (**Figure 5**). Biologically, low-grade tumors are essentially benign, with local recurrence developing only after incomplete resection. Intermediate tumors tend to be more locally destructive and may be more likely to recur. The high-grade carcinomas readily metastasize and are associated with a poor prognosis.⁵

Treatment of tracheal mucoepidermoid carcinoma is primarily surgical, with complete en bloc resection recommended.^{2,3} Accurate surgical planning is required so that support from a thoracic surgeon is available if necessary. Often, direct laryngoscopy and tracheoscopy can be performed as a separate procedure for evaluation, diagnosis, and staging. Reports do not indicate that biopsy causes untoward bleeding; therefore, a preresection biopsy can be considered. The resection is generally approached through an apron incision low in the neck, but a sternotomy or thoracotomy may be required if the lesion is distally located. Tracheotomy may be necessary in individual cases, but can usually be avoided in resections for small-volume tumors where the trachea is reanastomosed over the indwelling endotracheal tube.

The most common procedure for an endotracheal tumor is tracheal resection with primary anastomosis of the cervical trachea. Mobilization of the trachea is necessary for a tension-free anastomosis. Maneuvers to obtain mobility of the cervical trachea include cervical flexion, pretracheal dissection, and hyoid release. A suprahyoid release is less associated with dysphagia than

is an infrahyoid release. Additional mobility can be obtained with the help of the thoracic surgeon through maneuvers within the chest, such as hilar release through a U-shaped incision of the pericardium, beneath the inferior pulmonary vein. Extraluminal extension of the tumor may require resection of the cervical esophagus, thyroid gland, or laryngeal nerves. If a recurrent laryngeal nerve is resected, immediate reinnervation with ipsilateral ansa cervicalis and arytenoid adduction is recommended.⁶ Lymphadenectomy is individualized in each case according to the extent and histologic features of the tumor. It would not be recommended for low- or intermediate-grade tumors.

The majority of patients (67%) in the series of Heitmiller et al³ had low-grade tumors, and none of them had a recurrence after resection. Two cases involved local extraluminal extension and were unresectable. Both tumors were high grade. Adjuvant radiotherapy has been used in patients with high-grade tumors, but the data are not sufficient to recommend its routine use.

Our patient underwent an en bloc resection of the pedunculated mass with the underlying tracheal wall. An ellipse of tracheal wall was taken as a margin. No invasion of the tumor stalk was noted at the time of surgery, and the tracheal wall was closed primarily after a prophylactic tracheotomy was performed. The tumor was classified as intermediate grade, and adjuvant external beam radiotherapy was recommended and performed. There was no evidence of tumor recurrence in our patient after approximately 1 year of follow-up.

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Submissions

Residents and fellows in otolaryngology are invited to submit quiz cases for this section and to write letters to the ARCHIVES commenting on cases presented. Quiz cases should follow the patterns established. See "Instructions for Authors."

Material for the PATHOLOGY FORUM should be mailed to the Editor.

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