Medullary Thyroid Cancer

Overview and case study of a rare cancer

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BACKGROUND: Medullary thyroid cancer (MTC) is a rare cancer that has historically been managed by endocrinologists. In 2011, the first of several multi-targeted tyrosine kinase inhibitors was approved as treatment for MTC. These drugs have changed the management of MTC to teams that include oncologists and oncology nurses.

OBJECTIVES: This article illustrates MTC diagnostics, surveillance, management of adverse drug reactions, and disease progression through a case study.

METHODS: An overview of MTC is offered, followed by an in-depth case study that examines MTC from the patient’s perspective.

FINDINGS: Oncology nurses can influence patient outcomes through the provision of patient education, support, and management of disease and treatment complications.

KEYWORDS
medullary thyroid cancer; tyrosine kinase inhibitor; oncology nurse

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Medullary Thyroid Cancer Background

There are four types of thyroid cancer: papillary, follicular, medullary, and anaplastic. MTC accounts for only 1%–2% of thyroid cancers, as compared to 84% for papillary, 11% for follicular, and less than 1% for anaplastic (Cabanillas, McFadden, & Durante, 2016; Lim, Devesa, Sosa, Check, & Kitahara, 2017; Wells et al., 2015). However, MTC is responsible for about 13% of all thyroid cancer–related deaths (Gilliland, Hunt, Morris, & Key, 1997; Kebebew, Ituarte, Siperstein, Duh, & Clark, 2000). The number of MTC cases is on the rise, with a 2.3% average annual increase in incidence from 1992–2012 (Lai, 2010; Mao & Xing, 2016; Randle et al., 2017). Affected individuals are usually diagnosed in the fourth decade of life (Hu, Ying, & Jimenez, 2014). Seventy-five percent of cases are sporadic, or random, whereas the remaining cases are familial, or hereditary (Hedayati, Zarif Yeganeh, Sheikholeslami, & Afsari, 2016). Women with sporadic MTC are affected more often than men, at a ratio of 3:2 (Roman, Lin, & Sosa, 2006). Sporadic and familial cases may have similar presentations; therefore, patients with isolated MTC should be offered germline testing (Romei, Ciampi, & Elisei, 2016).

Pathophysiology

MTC tumors are neuroendocrine tumors; they are derived from neural crest parafollicular cells (C cells) in the thyroid gland (Matias-Guiu & De Lellis, 2014). Their primary function is to secrete a hormone, calcitonin (CTN), which helps to regulate serum calcium homeostasis (Cote, Grubbs, & Hofmann, 2015). CTN levels serve as a useful biomarker for MTC because
abnormally high levels can aid in diagnosis and postsurgical surveillance (Jameson, 2013). C cells do not take up iodine or radiation, which differentiates them from other cells found in the thyroid (Jameson, 2013); consequently, MTC treatments are limited.

The majority of MTC tumors stem from a RET (rearranged during transfection) proto-oncogene mutation on chromosome 10q11.21 (Carlomagno, 2012). This gene encodes a tyrosine receptor protein involved in growth, differentiation, and migration of developing tissues (Rowland & Moley, 2015). The RET oncogene is composed of 21 exons that encode the RET protein (Mohammadi & Hedayati, 2017). The various presentations of MTC cases may result from mutations in the different exons (Hedayati et al., 2016). In MTC, 25%–33% of RET proto-oncogene mutations have been identified in codon 918 (Mohammadi & Hedayati, 2017) and tend to have a more aggressive clinical course (Oczko-Wojciechowska et al., 2017).

Initial Presentation and Diagnostic Evaluation
The most common initial presentation of MTC, as well as other thyroid malignancies, is a palpable neck mass, typically a solitary thyroid nodule or enlarged lymph node (Saad et al., 1984). Symptoms of hoarseness, dysphagia, and/or respiratory difficulty can occur if the tumor has invaded surrounding structures (Roy, Chen, & Sippel, 2013). High CTN levels may also cause flushing and diarrhea.

A CTN level should be drawn because CTN is the primary biochemical marker used for detection and staging of MTC. Carcinoembryonic antigen (CEA) levels should also be drawn; a high CEA level at the time of diagnosis is a poor prognostic marker. For patients with confirmed or suspected MTC, ultrasound and computed tomography of the chest and neck are ordered as a standard clinical workup to further visualize malignancy in the neck and determine metastatic spread (Hu et al., 2014).

Treatment
Surgery is the only curative treatment for MTC (Matias-Guiu & De Lellis, 2014). If a cure is not possible, treatment options are based on disease progression, which is monitored with sequential imaging studies and with determination of tumor marker doubling time (Raue & Frank-Raue, 2015).

Systemic treatment for progressive MTC has been limited to dacarbazine-based chemotherapy; however, this treatment has a high toxicity profile and resulted in reduction of tumor size in only 25% of patients treated (Hu et al., 2014). Another systemic treatment, somatostatin analog therapy, has been used in tumors that reveal positive uptake of octreotide, which is a growth hormone inhibitor involved in tumor genesis (Diez & Iglesias, 2002). For localized metastatic disease, radioimmunotherapy (Kraebner-Bodéré et al., 2010) and chemoembolization (Griebeler, Gharib, & Thompson, 2013) have been used with limited effectiveness.

Multitargeted TKIs were approved for use with MTC beginning with vandetanib (Oncology Times, 2011), followed by cabozantinib (Oncology Times, 2012) and sorafenib in 2013 (National Cancer Institute, 2013). These drugs block some of the actions of the RET tyrosine kinase receptor (Puxeddu, Romagnoli, & Dottorini, 2011), as well as other growth receptors involved in tumor proliferation, such as the epidermal growth factor receptor and the vascular endothelial growth factor receptor (Santoro & Carlomagno, 2013).

The side effects of TKIs result from the particular receptor that is blocked. For example, in addition to RET, cabozantinib inhibits vascular endothelial growth factor, which can lead to gastrointestinal fistulas, perforations, and hemorrhage, as well as systemic hypertension and venous thrombosis (Hoy, 2014). Figure 1 lists the side effects reported for TKIs used in the treatment of MTC.

Prognosis
The stage of disease at the time of diagnosis is the major factor in determining prognosis. Seventy percent of patients with MTC have cervical lymph node metastasis at the time of diagnosis; 10% of these patients also have distant metastasis (Quayle & Moley, 2005; Scollo et al., 2003). The most common sites for distant metastasis are the mediastinum, liver, lungs, and bone (Roy et al., 2013). The overall 10-year survival rate of patients with distant metastases is 40% (Roman et al., 2006).

Sporadic Medullary Thyroid Cancer Case Study
Initial Diagnosis
In March 2011, Karyn, a 32-year-old mother of five, presented to a walk-in clinic complaining of a severe sore throat and difficulty swallowing. Her examination revealed a deviated trachea and a large mass on the left side of her neck; a computed tomography

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(CT) scan confirmed the clinical findings (see Figure 2). Three weeks later, a fine needle biopsy pathology report confirmed MTC. At the time biopsy results were reported, blood tests revealed a CTN level of 4,999 (normal range = 7–14) and a CEA level of 153.9 (normal range = 0–2.5). A whole-body CT scan showed no sign of distant metastasis. Karyn was referred to a major cancer center for urgent surgery to prevent airway compromise.

**Thyroidectomy**

Six days after her biopsy results confirmed the MTC diagnosis, Karyn underwent a total thyroidectomy with central compartment neck dissection, left modified radical neck dissection, and a right select neck dissection. Pathology results from her surgery reported three masses measuring 2.9 cm x 2.1 cm x 1.8 cm, 2.5 cm x 2.1 cm x 1.7 cm, and 2.6 cm x 1.4 cm x 1.2 cm; MTC was confirmed in each mass. Pathology results also identified 9 of 37 lymph nodes on the left side of her neck as being MTC positive and 4 of 8 lymph nodes on the right side of her neck as being MTC positive.

Genetic testing was negative for the specific RET mutations involved in familial MTC; however, because the testing is not 100% accurate, Karyn was advised that her children should undergo ultrasound screening of the thyroid as they enter puberty and again when they are aged about 18 years.

Karyn’s postoperative course was uneventful. Her voice was not affected by the surgery or the malignancy. Her pain was well managed, and her CTN levels were stable at 296. She was discharged six days after the surgery and scheduled for follow-up every three months for the first year (see Figure 3).

**First Postoperative Year**

At Karyn’s three-month follow-up, a CT scan of the neck revealed no residual tumor in the thyroid bed; however, three 6 mm supraclavicular lymph nodes had developed in the right side of her neck. Although her CTN levels indicated residual tumor, nothing on the scans warranted surgical exploration, and she was scheduled for repeat scans in three months.

Six months after the surgery, Karyn’s CTN level had risen slightly to 337, but her CEA level had decreased to 5.5. The nodule in the thyroid bed was no longer visible on the CT scan. Karyn was scheduled for repeat scanning at six-month intervals.

**Disease Progression**

One year later, Karyn felt enlarged lymph nodes on the left side of her neck. A CT scan of the neck revealed a 1.5-cm left cervical lymph node, and her CTN and CEA levels were elevated. With her medical team deeply suspicious that the lymphadenopathy represented persistent MTC, Karyn underwent an exploratory surgery to remove the residual disease. Her postoperative course was uneventful, with no residual pain or paresthesias.

During her three-month postoperative visit, Karyn was advised that she had persistent (noncurable) MTC and that the nodules noted on her chest CT scan likely indicated metastatic disease. Medical treatment options, including TKI therapy, were discussed but would proceed only if her CEA and CTN levels began doubling over a six-month period. A watchful waiting approach was agreed on by Karyn and her medical team.

In January 2013, nearly two years since her initial surgery, Karyn’s CEA levels had risen from 9.4 at her prior visit to 17.9. Magnetic resonance imaging (MRI) revealed multiple hepatic lesions consistent with metastasis (see Figure 4). Resection of the liver was not an option because the lesions were scattered through all lobes of the liver. Ablation also was not an option because the lesions were so small that ablation would destroy too much healthy...
tissue. Karyn was referred to a world-renowned oncologist, who specialized in MTC, to discuss systemic treatment.

At the time of her initial oncology evaluation, Karyn was asymptomatic, and the cancer was not interfering with her daily activities, which included homeschooling her children. TKI therapy carried a 14% risk of death during the first year of use; as a result, the oncologist recommended a watch-and-wait approach. The following timeline represents events that occurred during Karyn’s third, fourth, and fifth years of her journey with MTC.

**SUMMER 2013:** Karyn’s CTN level had doubled from her post-surgical baseline to nearly 10,000, whereas her CEA level had risen to almost 700. Karyn was still asymptomatic from her disease, with no disruption to her daily activities. She underwent an octreotide scan to determine if the tumors would take up the drug and, therefore, be amenable to sandostatin analog therapy. Karyn’s scan was negative; consequently, additional treatment options were discussed, including TKI therapy and clinical trials using a CEA vaccine and viral therapeutic treatments. One month later, Karyn and her family moved closer to extended family. She was referred to another regional cancer center where her disease progression was followed by oncologists who ordered sequential ultrasounds of the liver. The sample from Karyn’s primary tumor was mapped in preparation for TKI therapy; results of the mapping would guide the selection of the agent. Results revealed a \textit{RET} 918 mutation.

**SUMMER 2014:** Karyn explored alternative therapies, including following a vegan diet, with the hopes of slowing the progression of her disease. For six months, her CTN levels stabilized, but she became anemic and was weak and fatigued.

**SUMMER 2015:** Karyn and her husband traveled to Mexico to pursue alternative therapies. She felt well for another two months.

**FALL 2015:** Karyn developed diarrhea and flushing of the palmar aspects of her hands. In the years since her diagnosis, her initial (and most trusted) endocrinologist had moved to another cancer center. Through contacts at the Thyroid Cancer Survivors’ Association (ThyCa), Karyn reconnected with him and began the first of many trips to a cancer center across the country. Initiation of cabozantinib was planned; however, given the side effect profile of TKIs, Karyn wanted to explore the option of a clinical trial or possible surgery beforehand. At the suggestion of her endocrinologist, Karyn sought out clinical trials for medical treatment of MTC. Unfortunately, every physician she consulted advised her that enrolling in clinical trials held less hope of tumor regression than TKI therapy. Karyn also developed palmar-plantar erythrodysesthesia, causing blistering on the bottom of her feet. Her TKI dosage was slowly increased to 60 mg per day. In late December, Karyn developed slurred speech and numbness on the left side of her body. Her
MRI scan was negative for stroke, and her symptoms resolved within three days. Karyn’s symptoms were attributed to a medication side effect; consequently, her TKI dose was reduced to 40 mg per day.

**JANUARY 2016:** About three months after initiation of TKI therapy, scans revealed some tumor necrosis. Karyn was still struggling with diarrhea and was losing muscle mass. She was receiving IV hydration as much as three times weekly at a local infusion center. When her BMI dropped to 17, she received a peripherally inserted central catheter and nightly parenteral feeding for two weeks.

**JULY 2016:** Karyn developed severe abdominal pain with distention and was hospitalized locally. Her liver tumors had grown significantly, and the liver was compressing the gallbladder. She was managed medically with steroids and discharged one week later.

**AUGUST 2016:** Karyn was admitted to the cancer center for chemoembolization with the hope of shrinking her largest liver tumor. Her bilirubin was initially too high for the procedure; therefore, a biliary drain was placed, and parenteral steroid therapy was initiated. Five days later, the procedure was completed when her bilirubin levels allowed. Karyn had now failed the first TKI therapy; initiation of vandetanib was planned.

**SEPTEMBER 2016:** Five days after starting vandetanib, Karyn was admitted to the local hospital with severe weakness and abdominal pain. CT scans indicated some necrosis of the chemoembolization-treated tumor; however, new tumors were noted outside of the liver. Palliative care was advised, and Karyn was discharged to her home with hospice care.

**OCTOBER 2016:** Three weeks after discharge from the hospital, Karyn died peacefully at home.

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**FIGURE 4.**
**METASTATIC NODULES IN LIVER**

![Image](image.png)

*Note.* Image shows magnetic resonance imaging scan of abdomen, axial view.

*Note.* Used with permission of Mayo Foundation for Medical Education and Research.

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**IMPLICATIONS FOR PRACTICE**
- Increase awareness of medullary thyroid cancer and the need for early detection.
- Provide support and education as patients weigh treatment options, and become knowledgeable regarding tyrosine kinase inhibitor therapy and the management of treatment complications.
- Identify signs and symptoms of disease progression.

**Discussion**

MTC is a rare cancer, and this case represents an aggressive form. Karyn felt pressure from family, friends, and even other patients with thyroid cancer to start treatment early. However, no studies support early treatment. Initial clinical trial data for cabozantinib show a four-month period of progression-free survival, with no significant difference in overall survival time compared to no drug treatment (Nagilla, Brown, & Cohen, 2012). Karyn’s case, involving the most aggressive RET mutation, supports these data.

The most pervasive and significant symptom Karyn experienced was diarrhea. She tried several treatment options, including the use of food logs, the elimination of foods that worsened the problem, and various drugs (e.g., loperamide, diphenoxylate/atropine, octreotide, codeine sulfate, cannabis oil); nothing provided relief. Karyn did experience mild relief with the use of metoclopramide, which is normally used to stimulate gastrointestinal motility. Ultimately, it was the inability to control this symptom that interfered with Karyn’s activities of daily living and decreased her quality of life. A clinical trial using a natural clay, calcium aluminosilicate, has shown reduction of diarrhea in a small group of patients with MTC (Dadu et al., 2015); however, this option was not discussed by any of the physicians Karyn consulted.

**Patient Education**

Because of MTC’s slow progression, patient education can be provided gradually, when the patient is ready to accept it. During the first two years of her disease, Karyn was in the shock and denial phases of illness. She needed to hear, and did hear, messages of encouragement and hope, along with appropriate amounts of education. Although computer screens are now in most examination rooms, Karyn was never able to look at the scans of her tumors; her medical team was sensitive to this and kept the screens turned away from her view.

Karyn’s initial reluctance to learn about her disease was not because of health illiteracy. She was a valedictorian and received a scholarship to a prestigious university where she minored in sports medicine and graduated with honors. As Karyn adjusted to her new normal, living with incurable cancer, she gradually began to research treatment options and clinical trials. Karyn’s medical team recognized this attitudinal shift and provided educational and research resources that she used to help weigh her treatment options. She was able to work with her medical team and start systemic treatment as a well-informed patient.

**Patient Support**

Patients with MTC may live with incurable cancer for 10 years or longer. The key is to live as full a life as possible. During Karyn’s
initial visit to the cancer center, her medical team emphasized this issue. She was advised that, between visits, she should try to forget about the cancer and focus on her family, career, and hobbies.

As their cancer progresses, patients with MTC may need individual and family counseling to cope with the lifestyle changes and the uncertainty that accompanies disease progression. Oncology nurses can offer patients suggestions to relieve stress, such as exercise, meditation, and mindfulness practices. Nurses can also provide resource information for counseling. Support groups can be beneficial; however, there are very few patients with MTC. Karyn experienced this as the only patient with MTC in her thyroid cancer support group. She was also referred to a general cancer support group, Pink Heals (www.pinkfiretrucks.org), which provided her with a tremendous amount of encouragement and support.

**Implications for Practice**

Oncology nurses need to become familiar with TKIs and their possible adverse reactions. Karyn experienced diarrhea as a complication of her disease and later as a side effect of treatment. Nurses can do the following:

- Help patients eliminate food triggers.
- Provide information regarding scheduling and dosing of anti-diarrheal medications.
- Offer education concerning skin breakdown prevention and treatment, as well as palliation of rectal pain.
- Medication education should include the following:
  - Preventive skin care and treatments for palmar-plantar erythrodysesthesia
  - Anticipatory guidance regarding possible severe or life-threatening complications
  - Blood pressure monitoring
  - Stroke education awareness
  - Signs of gastrointestinal bleeding

**Conclusion**

Oncology nurses are now involved in the care and management of patients with MTC. They need to be aware of the specifics of this rare cancer, including the disease process, genetic implications, types of mutations, treatment options, management of disease, and treatment complications.

To date, there are no specific protocols for the timing of treatment initiation. New TKIs and treatment options are being approved, but none come without the possibility of severe adverse reactions. Therefore, it is vital that patients with MTC be managed by a team that is familiar with the latest treatment options.

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