Breast Cancer in Cowden Syndrome: Manifestation of a Familial Cancer Syndrome

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Cowden syndrome is a familial cancer predisposition syndrome associated with an increased risk for breast, thyroid, and endometrial cancers and benign manifestations. With early detection and appropriate therapeutic treatment, many of its associated tumors and cancers are treatable. By better understanding mutations such as Cowden syndrome, additional targeted therapies can be developed and delivered.

Case Study

Mrs. O is 39 years old with stage II, multifocal ductal carcinoma in situ, hormone receptor-positive breast cancer. Her treatment has included mastectomy of the affected breast with prophylactic mastectomy of the second breast, followed by reconstructive surgery. She returned to the clinic to discuss additional evaluation and treatment.

Mrs. O is a college graduate with two children. She is employed part-time as a computer programmer. Her surgical history is significant for two prior procedures to remove lipomas and liver mass (benign). Mrs. O has had recurrent bronchitis and eczema. Mrs. O’s genogram revealed multiple, sporadic cancers in her family (see Figure 1). Her paternal grandfather died of colon cancer, as did many of his siblings. In addition, Mrs. O’s mother and maternal grandmother had breast cancer, a paternal uncle (deceased) had renal cancer, an uncle and a sibling (whose son has macrocephaly) have thyroid cancer, another sibling (whose son has autism, seizures, macrocephaly and café-au-lait spots) has breast cancer and lipomas, a brother has cutaneous lipomas, and two cousins have lipomas. The live generations represent ages ranging from 60–70 years; the next generation ranges from 30–40 years, and the youngest generation ranges from infancy to 30 years.

Focused physical examination found Mrs. O to be alert with no acute distress. She is 5’2” and weighs 120 lbs, with 120/62 blood pressure and a heart rate of 72 beats per minute. She has multiple simple and filiform papular lesions on the center of her face. Her neck has no thyromegaly or palpable nodules. Mrs. O’s surgical incisions are well healed without overgrowth of tissue at incision sites. Her abdomen is soft and nontender.

Treatment Options

To date, few specific treatment options exist for Cowden syndrome. The main goal is the treatment of the presenting tumor, benign or cancerous, through recognized therapies that target the specific pathologic and clinical features of the primary tumor. With early detection and appropriate therapeutic treatment, many associated tumors and cancers are treatable. However, one must be vigilant and continue surveillance for signs and symptoms of additional growths because at least 40% of Cowden syndrome cases, meaning that cowden syndrome or variants of the same gene exist for Cowden syndrome. The main goal is the treatment of the presenting tumor, benign or cancerous, through recognized therapies that target the specific pathologic and clinical features of the primary tumor. With early detection and appropriate therapeutic treatment, many associated tumors and cancers are treatable. However, one must be vigilant and continue surveillance for signs and symptoms of additional growths because at least 40% of Cowden syndrome cases, meaning that cowden syndrome or variants of the same gene exist for Cowden syndrome. The main goal is the treatment of the presenting tumor, benign or cancerous, through recognized therapies that target the specific pathologic and clinical features of the primary tumor. With early detection and appropriate therapeutic treatment, many associated tumors and cancers are treatable. However, one must be vigilant and continue surveillance for signs and symptoms of additional growths because at least 40%...
of affected individuals will have more than one primary tumor (Miller, 2007). The National Comprehensive Cancer Network (NCCN) guidelines for Cowden syndrome management are listed in Figure 3.

**Family Surveillance**

In a family with a member who has documented Cowden syndrome, detailed physical examination should be started at five years prior to the age at which diagnosis of an established cancer was made in another family member. Genetic screening and counseling should be recommended for all immediate family members of patients with Cowden syndrome (Eng, 2000). Of note, 20% of individuals meeting criteria for Cowden syndrome may test negative for the genetic PTEN mutation; however, additional testing such as clinical deletion and promoter-mutation analysis (blood work for DNA analysis) should be performed because about 10% of individuals who test negative for Cowden syndrome will have mutations located in PTEN promoter regions (Eng, 2003; Pilarski & Eng, 2004; Zhou et al., 2003).

In addition to genetic screening of family members, a structured protocol for regular health screenings should be implemented, with the goal of early identification in family members at risk (NCCN, 2010). Services should be extended to individuals who display specific characteristics related to either Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome but may not meet all established criteria for diagnosis. Additional services such as referrals and resources should be discussed with individuals and their families. Mental health counseling is important to assist with potential emotional distress for people diagnosed with Cowden syndrome as well as family members at genetic risk for hamartoma.

**Follow-Up**

Breast cancer in patients with Cowden syndrome has a 50% chance of bilateral occurrence at 10 years (Lalloo & Evans, 1999; Litton & Hunt, 2009). Therefore, Mrs. O opted to have bilateral mastectomies.

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**Figure 1. Breast Cancer Risks**


**Figure 2. Family Health Portrait**

BrC—breast cancer; CAN—other cancer; ColC—colon cancer; Gl—gastrointestinal disorder; HemAS—hemangiomas; KiC—kidney cancer; LipAS—lipomas; LuC—lung cancer; MacLY—macrocephaly; ThC—thyroid cancer; UtC—uterine cancer

*Note.* Arrow points to patient.
Women
- Breast self-examination (BSE) training and education and regular monthly BSE starting at age 18
- Clinical breast examination semiannually, starting at age 25 or 5–10 years before the earliest known breast cancer in the family
- Annual mammography and breast magnetic resonance imaging screening starting at age 30–35 years or 5–10 years before the earliest known breast cancer in the family (whichever is earlier)
- For endometrial cancer screening, consider participation in a clinical trial to determine the effectiveness and necessity of screening modalities.
- Discuss option of risk-reducing mastectomy on case-by-case basis and counsel regarding degree of protection, extent of cancer risk, and reconstruction options.

Men and Women
- Annual comprehensive physical examination starting at age 18 or five years before the youngest age of diagnosis of a component cancer in the family (whichever comes first), with particular attention to breast and thyroid examination
- Baseline thyroid ultrasound at age 18 and consider annually thereafter
- Consider annual dermato logic examination.
- Education regarding the signs and symptoms of cancer

Risk to Relatives
- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives.

Figure 3. Cowden Syndrome Management


Mrs. O is considering additional reconstructive and cosmetic surgery; however, she is concerned that the reconstruction, new tissue, and nipple and areola sparing techniques may impact visualization of the breasts in future diagnostic screenings (Miglioretti et al., 2004; Miller, 2007; Uppal, Mistry, & Coatesworth, 2007). She also decided to have six weeks of adjuvant radiation therapy. Mrs. O will see the clinic social worker to discuss her feelings about having a hereditary cancer syndrome and the implications for her family.

Conclusion

Research is examining ways to identify additional disorders that may have PTEN mutations. By better understanding mutations that occur, more targeted therapies can be developed and delivered. Participation in clinical trials is encouraged for these rare disorders. Affected individuals can list their interest in participating in clinical trials at www.nccn.org. People with Cowden sometimes are misdiagnosed, and family members are not made aware of resources and methods they can take to prevent or screen for associated issues. Mrs. O is at high risk for other cancers in the future; emphasizing recommendations for future screenings for Mrs. O and her family members is the most important aspect of follow-up treatment.

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References

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