Insular Thyroid Carcinoma In A Patient With Cowden Syndrome

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Abstract

Cowden syndrome is characterized hamartomatous lesions that can develop from all three germ cell derivatives. This disorder predisposes patients to develop malignant tumors of the breast, endometrium, and thyroid. We present a patient with clinically relevant manifestations of Cowden syndrome, with genetic verification, impacting by way of airway compromise due to hamartomas, urinary tract abnormalities, and insular thyroid cancer. This case illustrates the value of recognizing Cowden syndrome at an earlier stage to (1) permit early management to decrease the morbidity of untreated hamartomatous growths, and (2) perform an elective thyroidectomy to preempt the appearance of the thyroid malignancy. Through this case report, we provide further insight into management of this disorder.

Case Report

Patient was a 48 year old Caucasian male who developed swelling in the right neck over two months. He also reported a 24 lb weight loss, dysphagia, hoarseness, difficulty breathing, and a fluctuant mass along the left lower lip. He included the removal of multiple benign lesions from his back, hands and feet over the last 20 years. Family history included a fibrous growth on his mother’s hand, a sister with fibrous tumors in the uterus resulting in hysterectomy, and a second sister with an unspecified growth in her cheek.

PE revealed macrocephaly, with a head circumference of 69 cm, [above the 99th percentile] coupled with a small nose and mandible. Multiple subcutaneous lipomatous lesions were found about the body and the planter surface of his feet revealed palmpotral keratosis. A 12 cm mobile and nontender right lower neck mass displaced the trachea towards the left. A firm submucosal mass then distorted the left lateral wall. Flexible fiberoptic laryngoscopy revealed extensive papillary lesions extending from the nasopharynx, to the base of tongue, and into the supraglottic larynx, which obscured view of the vocal folds.

FNA of right lower neck mass demonstrated an epithelial neoplasm with cells showing granularity to focally clear cytoplasm. Thyroid function studies, calcitonin levels and CEA were normal. A PET/CT scan showed large hypermetabolic oropharyngeal and supraglottic mass, large right neck lymph mass, two small mildly hypermetabolic left level IIa lymph nodes, a small low attenuation nodule at the left thyroid, and mildly enhancing soft tissue enlargement at the left lower lip.

A cricothyrotomy was performed in the operating room under local anesthesia and then converted to a tracheotomy. Initial visualization of the oral cavity revealed prominent papillary proliferations on the base of tongue almost completely obliterating the airway. Multiple biopsies were taken and then 50% debulking of tumor mass was achieved. Micro-direct laser laryngoscopy with biopsy and resection of left lower lip mass was performed. After debulking the larynx was visualized. Rigid esophagoscopy revealed submucosal nodules in esophagus and stomach with an irregularity to the z-line at the GE junction. Biopsies demonstrated polyoid fibrovascular mucosal tissue with some squamous hyperplasia. The thyroid isthmus removed during tracheostomy showed thyroid adenoma. The left lower lip mass was a hemangioma.

The patient returned to the operating room for right thyroid lobectomy with tracheostomoplasty. Surgery was only complicated by failed attempts to catheterize the patient. A urology consult was obtained and flexible cystoscopy revealed an obliterated urethra with several small openings that were to small to cannulate with a Benson wire. A supracystic catheterization was placed. Pathology of the right thyroid mass revealed poorly differentiated (insular) carcinoma with capsular and lymphovascular space invasion. The sample was chromogranin, calretinin, and synaptophysin negative, while it was both thyroglobulin and thyroid transcription factor positive.

The patient was then performed and 1131 treatment was completed. Unrelated with cystodytis was unremarkable. Cerebral MRI, with gadolinium, showed developmental venous anomalies, small vessel ischemic changes and subtle focal asymmetry in right cerebellum. Genetic testing was performed and a heterozygous nonsense mutation in exon 5 of the PTEN gene was found, consistent with diagnosis of CS.

Discussion

Cowden Syndrome (CS), also known as multiple hamartoma syndrome, is an autosomal dominant disorder characterized by benign and malignant hamartomatous lesions that can develop from all three germ cell derivatives (ectodermal, endodermal, and mesodermal tissues). Tissues most commonly affected include breast, thyroid, uterus, brain, and mucocutaneous tissues4-6. Patients with CS also have a higher prevalence of malignant tumors of the breast, thyroid gland and endometrium as well as gastrointestinal tract conditions. CS demonstrates age related penetrance with average onset at 39 years3. However, 90% of patients manifest some form of CS by age 20, with 99% of patients demonstrating a sign by age 291. Incidence is estimated at 1 in 200,000. However, it may have a much higher prevalence than estimated due to variable expressivity, as many patients only possess subtle skin findings1,4,5.

First described in 1963, it was not until 1995 that operational diagnostic criteria for CS were first set forth4. During the following two years, CS was linked to a germline mutation in PTEN tumor suppressor gene located at 10q23.3. This mutation was found in 80% of CS patients, with 2/3 of the mutations located in exons 5 and 7.1,3,6 PTEN is a dual-specificity protein phosphatase and acts as a tumor suppressor. It plays a role in cell cycle arrest and apoptosis, and acts as an antagonist to PI3K/AKT pathway, thus negatively regulating cell cycle progression. Mutation of this gene thus allows unregulated growth resulting in hamartomas. This unregulated growth is exemplified in the high frequency of sporadic PTEN mutations associated within many sporadic malignancies1-3. Bannayan-Riley-Ruvalcaba Syndrome is a related disease, with PTEN mutations found in 60% of patients. The overlapping mutations suggest that CS and BRRS are allelic and that the syndromes may be part of a larger group, collectively named PTEN Hamartoma-Tumor Syndrome1,2. Proteus syndrome and Proteus-like syndrome may also lie in the continuum of PHTS1,2.

Conclusion

We present a patient with clinically relevant manifestations of Cowden syndrome impacting by way of airway compromise due to hamartomas, urinary tract abnormalities, and insular thyroid cancer. The delayed diagnosis - at age 48 - addressed abnormalities in their advanced stage. This case illustrates the value in recognizing this disorder at an earlier stage at which time an elective thyroidectomy would have been recommended along with appropriate management to decrease the morbidity untreated hamartomatous growths.

References