SPECIAL ARTICLE

Cowden Syndrome: Case Report, Update and Proposed Diagnostic and Surveillance Routines

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Abstract

Cowden syndrome (CS) is an infrequent autosomal dominant multisystem genodermatosis, generally involving the skin, oral mucosa, thyroid, breast and gastrointestinal tract. It is characterized by a late onset in the 2nd or 3rd decade of life, an extraordinary potential for malignant transformation, especially of breast and thyroid, and an identifiable germline mutation. In 80% cases, the human tumor suppressor gene, phosphatase and tensin homolog (PTEN) is mutated; mutations involving KILLIN, SDH B/D, PIK3CA and AKT1 genes account for the rest of the cases. Its clinical signs are not only the "essential pearls" for early and accurate diagnosis of CS but also help timely detection of neoplasia as they precede development of cancer by several years. We describe the first Indian and the third world report of polydactyly with CS, review this entity highlighting on recent clinical developments and emphasize on regular and thorough screening for prompt identification and management of the potentially malignant growths. We have also designed a baseline workup routine as well as a detailed screening program for these patients.

Key Words: *Genodermatosis, multiple hamartoma syndrome, phosphatase and tensin homolog, KLLN (Killin), hereditary cancer predisposition syndrome*

What was known?
- Cowden syndrome (CS) is a rare autosomal dominant multisystem complex genodermatosis, mostly due to PTEN mutations
- It has notable malignant associations which require aggressive screening.

Introduction

Cowden syndrome (CS), documented since 1963,[1] is a rare autosomal dominant multisystem hamartomatous, cancer predisposition syndrome with incomplete penetrance, variable expressivity and PTEN (phosphatase and tensin homolog) gene mutation[2] whose mucocutaneous manifestations, virtually universal, evolve slowly and may be followed by myriad afflictions of any/many organ/systems—frequent ones being thyroid, breast, skeleton and gastrointestinal tract—[3] eventuating in the development of cancer, at least one, in 40% patients.[4] Herein, reported is a case of CS with characteristic mucocutaneous papules, goiter, syndactyly and rare association of polydactyly, documented only twice earlier.[5] Salient features and recent advances of CS are briefly reviewed and a baseline workup and surveillance routine proposed.

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Case Report

A 41-year-old female presented with numerous raised solid lesions over neck, axillae, groins and forehead since 5 years. She was born with an extra digit each on right hand and left foot, the former amputated surgically two decades back. She had underwent subtotal thyroidectomy for multinodular goiter 2 years ago. Physical examination revealed pallor, macrocephaly, syndactyly (right 2nd and 3rd toes; left middle and ring fingers) and polydactyly [Figure 1] of left foot and a post-amputation stump adjacent to the right little finger. Dermatological examination revealed multiple, forehead papules [Figure 2]; skin tags over neck [Figure 3], axillae and groin; one verrucous nodule each over dorsa of left middle and right ring fingers; a midline, cervical scar (of thyroidectomy) and "cobblestone" tongue with coalesced papules [Figure 4]. Diagnosed as a case of CS she was investigated: Hemotological workup was normal except hemoglobin (9 gm%); biopsy of an acral nodule: Marked hyperkeratosis, acanthosis and papillomatosis; imaging studies (ultrasound abdomen and pelvis, chest x-ray, ECG, MRI brain and echocardiography) and certain special tests (upper GI endoscopy, colonoscopy and mammography): Normal. Testing for PTEN gene mutation was not possible. Acrochordons and facial

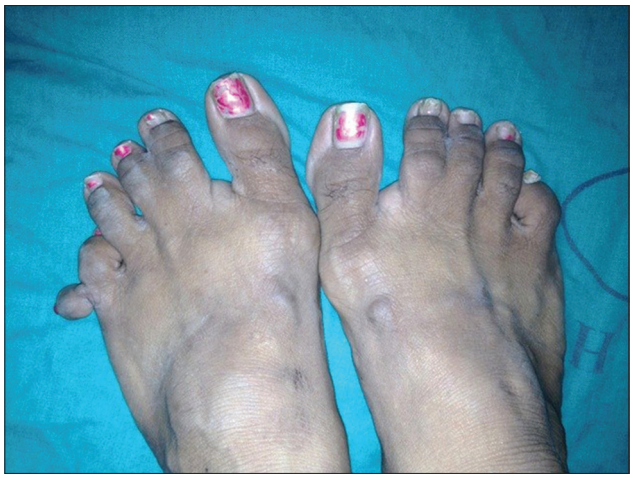

Figure 1: Bilateral syndactyly (2nd and 3rd toes) and unilateral polydactyly (left foot)

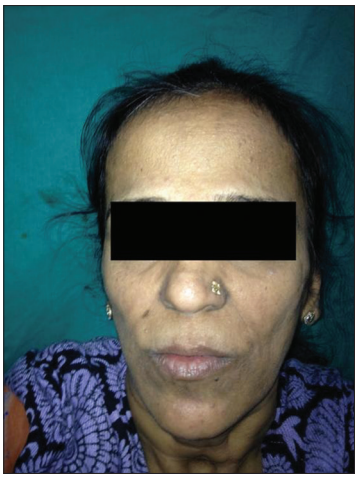

Figure 2: Numerous skin-colored papules over the forehead

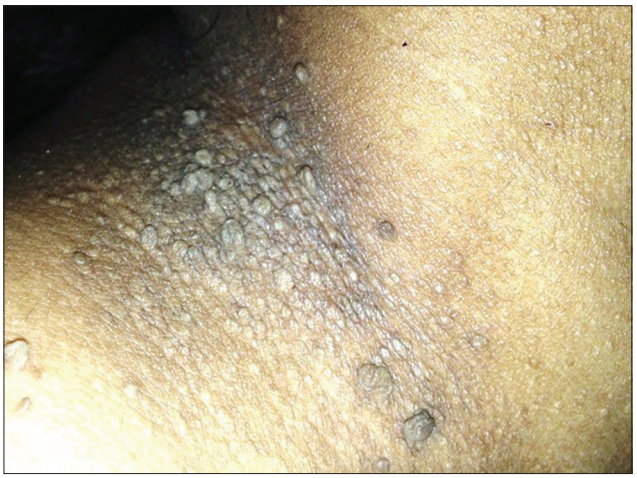

Figure 3: Multiple hyperpigmented skin tags over the neck

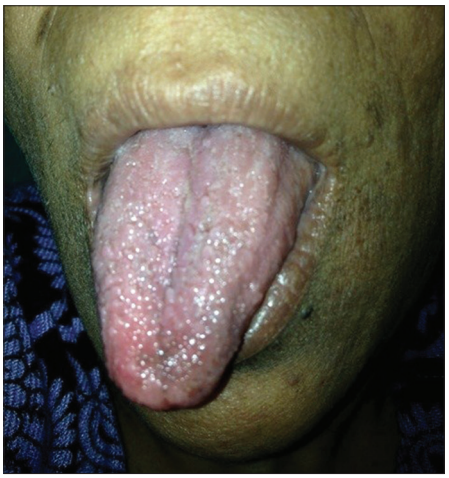

Figure 4: "Cobblestone appearance" of the tongue

papules were electrocauterized, acral nodules were excised and yearly surveillance was advised.

Discussion

Though originally described by Costello, Lloyd and Dennis defined this entity, christening it after Rachel Cowden, their patient who died of breast cancer.[1]

Detectable germline mutation of PTEN tumor suppressor present on chromosome 10q23.3, and loss of function of the resultant protein causing uncontrolled cell growth via the phosphoinositol-3-kinase/AKT pathway occur in 80% of the patients who meet the diagnostic criteria for CS. Succinate dehydrogenase B/D (SDHB/D) gene is involved in ~ 10% of patients.[6] Underexpression of PTEN or KILLIN—latter a TP_{53}-regulated novel tumor suppressor gene, co-located with and functioning similar to the PTEN gene but transcribed in the opposite direction—genes due to loss of function, by other mechanisms such as hypermethylation, may account for the majority of remaining CS cases.[6] With the recent discovery of phosphatidylinositol 4,5-bisphosphate-3 kinase catalytic subunit alpha (*PIK3CA)* and *AKT1* genes, the CS-susceptibility genes are presently six in number; however, PTEN, KILLIN and SDHB/D account for 92% of the cases.[6,7]

Diagnostic criteria for CS were initially proposed by Salem and Steck in 1983.[3] International Cowden Consortium (1995) recommended a revised classification to ascertain CS families, to which were added endometrial and renal cell carcinoma in 2000.[8]

The plethora of lesions, particularly mucocutaneous which evolve slowly, described ahead enjoins upon the dermatologist to suspect this syndrome and initiate timely workup and aggressive screening.[1]

Mucocutaneous manifestations, apparent in 99-100% of patients,[8] range from *facial papules*, customarily trichilemmomas,[2] *acral keratoses* (70%), pinpoint *palmoplantar pits* (40%)[4,9] and acrochordons (15%)[9] to subcutaneous lipomas; less characteristic dyspigmentory-, atrophic-, cystic- and nail dystrophic lesions, as also benign tumors occur.[2,3,10] Linear Cowden nevus,

a non-organoid epidermal nevus characteristically associated with Type 2 segmental CS was recently (2007) established as a distinct entity.[4] Basal cell, Merkel cell and squamous cell carcinoma occur.[10] *Oral lesions* (in 83%)[7] generally occur as coalesced white lingual papules giving a "cobblestone appearance."[10]

Extracutaneous manifestations occur in approximately 90%, most frequently (67%) involving *thyroid gland*[11] in colloid goiter, thyroglossal duct cyst, thyroiditis (3%), hypo-/hyperthyroidism, adenoma, and carcinoma (12%).[1,3,9,11]

Skeletal abnormalities manifest in one-third patients; macrocephaly, most widespread (80%) and polydactyly, unusual reported just twice previously;[5,11] others being high arched palate (15%), adenoid facies, kyphoscoliosis, bone cyst and syndactyly.[1,2]

Breast afflictions have been reported in 50-76%;[1,2,11] mostly fibroadenoma (80%) and fibrocystic disease (60%), latter usually pre-cancerous eventuated in 36% of affected females as tumors.[9] High (85%) lifetime risk of acquisition at young (mean, forty years) age and frequently bilateral (25%) occurrence of breast

Table 1: Proposed baseline workup for Cowden syndrome

Investigation	To rule out
Hematological/Biochemical	
Complete blood count	Anemia due to GI blood loss or malignancy Lymphoproliferative disorders
Urine analysis (urine cytology if h/o RCC in family)	Proteinuria/hematuria in renal or bladder neoplasia
Stool analysis	Occult blood in colon polyps or cancer
Thyroid function test	Thyroid disease/malignancy
Renal function test	Renal cell carcinoma
Liver function test	Hepatocellular carcinoma
S. calcium	Parathyroid disease
Imaging studies	
Mammography (also in males if clinically indicated)	Breast cancer
Thyroid scan	Thyroid disease
Colonoscopy	polyps, esophageal glycogenesis
Upper GI endoscopy	
USG abdomen and pelvis	Lesions in uterus, ovaries, kidney, etc
USG testes (in men)	Lipomas etc.
MRI brain	Lhermitte–Duclos disease and other CNS lesions
PET scan (if h/o headache and cerebellar dysfunction)	Lhermitte–Duclos disease
Chest x-ray	Pulmonary hamartoma, lipoma, cyst
Echocardiography	Valvular abnormalities
Intravenous pyelography (if abnormal urine analysis)	Renal cancer, nephrolithiasis
Histopathological	
Biopsy from mucoctaneous lesions (e.g., colon polyps, trichilemmoma)	Confirm diagnosis
Biopsy/FNAC from thyroid nodules	Benign/malignant thyroid lesions
Endometrial biopsy (if required)	Endometrial cancer
References	
Psychiatry	Mental retardation by IQ test
Orthopedic	Skeletal abnormalities (e.g., macrocephaly, syndactyly, bone cyst)
Ophthalmology	Cataract, glaucoma, vascular anomalies
ENT	Oral and laryngeal lesions
Genetic studies	
MLPA (multiple ligation dependent probe amplification) Southern blot RT-PCR Semiquantitative multiplex PCR Monochromosomal hybrid analysis	PTEN, KILLIN, SDH, etc., gene defect in patient and first degree relatives. (Serum/plasma samples in EDTA at 4°C, following an informed consent, can be sent to *Institute of Genomics and Integrative Biology*, New Delhi for evaluation)

RCC: Renal cell carcinoma, GI: Gastrointestinal, PTEn: Phosphatase and tensin homolog, KILLIN: Killin, SDH: Succinate dehydrogenase, USG: Ultrasonography, FNAC: Fine needle aspiration cytology, ENT: Ear, nose, throat, MLPA: Multiplex ligation-dependent probe amplification, RT-PCR: Reverse transcription - polymerase chain reaction, CNS: Central nervous system

Table 2: Proposed screening routine for Cowden syndrome

Organ	Schedule
General physical exam	Begin at 18 years of age or 5 years before diagnosis of thyroid/breast malignancy in family (whichever is first)
Skin	Annual dermatological examination
Breast	Monthly breast self examination, training and education 18 years onward
	Half-yearly clinical breast examination 25 years onward or 5-10 years before earliest known breast cancer in family (whichever is first)
	Mammography and MRI annually beginning at 21 years[12]
	Prophylactic mastectomy (case-by-case basis, even in males)
Thyroid	Physical thyroid examination after 18 years of age
	USG thyroid annually 10 years onward[12]
	Biopsy of suspicious lesions if any
	Prophylactic thyroidectomy (case-by-case basis)[16]
Colorectum	Colonoscopy 35 years onward and then every 5-10 years (or ↑ frequently if patient is symptomatic, occult blood in stool analysis or polyps present)
Endometrium	Encourage patient education, prompt response to symptoms and participation in clinical trials
	Annual endometrial examination by endometrial blind repel biopsies of suspicious lesions, 35-40 years onward or 5-10 years younger than age of diagnosis of endometrial cancer in family member
	Annual transvaginal USG in post-menopausal women
	Risk reducing hysterectomy (case-by-case basis)[8]
Renal	Annual urine analysis
	Annual urine cytology and renal USG if family h/o renal cancer[8]
Education	Signs and symptoms of Cowden's disease, risk and extent of cancer and treatment options
	Genetic counseling and testing to be advised to patient and first degree relatives

MRI: Magnetic resonance imaging, USG:Ultrasonography

cancer mandates strict surveillance and prophylactic mastectomy, if required.[1,11]

Gastrointestinal (GI) endoscopy visualizes polyps (in 85%), more frequently colorectal;[10] pathologically: Predominantly hamartomatous[9,10] but with a 16% lifetime risk of acquiring colorectal carcinoma.[12]

Management can only be symptomatic or aesthetic after a high index of suspicion and thorough work up (proposed in Table 1) enables an early diagnosis of CS. Mucocutaneous lesions respond promptly to systemic acitretin but recur on discontinuation.[2] Facial papules have been tried with all modalities of treatment for warts. Future treatment options aim to restore PTEN-associated molecular pathways. An early targeting of mammalian target of rapamycin (mTOR) protein[13] and suppression of the exaggerated PI3K/Akt pathway by a timely administration of rapamycin may be salutary as per a study, completed in October 2012, by the U.S. National Cancer Institute.[2] The role of vitamin E as an anti-cancer adjunct and preventive agent in CS patients with SDH mutations has been established.[14]

As the mucocutaneous manifestations of CS precede cancer development by several years, dermatological counseling can provide these patients with an opportunity for expert screening for cancer prevention.[3] We propose [Table 2] a screening routine adapted from the National Comprehensive Cancer Network (NCCN) guidelines (updated 2010),[15] modified by an earlier—at 21 years—commencement of annual mammography/MRI breast, USG thyroid from 10 years onward in agreement with the recommendations by Reigert-Johnson *et al.*,[12] and prophylactic hysterectomy[4] and thyroidectomy.[16]

Genetic testing for gene aberrations will help cancer management, e.g. patients with KILLIN hypermethylation, in whom exists higher rate of cancer breast (3-fold) and renal (>2-fold) than those with PTEN mutations, can make informed decisions to the patients about when they should start cancer surveillance and whether they should consider prophylactic surgeries.[6] Those with SDH mutations can potentially benefit by adjunctive vitamin E.[14] Despite a high incidence of sporadic mutations in CS—as also in our case—first degree relatives should also be advised genetic testing.

Conclusion

Like our patient, most of them present merely for aesthetic management of their mucocutaneous lesions providing the dermatologist with a window of opportunity. Hence, raising our suspicion, appropriate workup and aggressive screening as proposed will help arrive at a timely diagnosis, thereby facilitating successful management.

What is new?
- Following the discovery of new CS-susceptibility genes, their number has been raised to six, now including PTEN, KILLIN , SDHB/D,*PIK3CA* and *AKT1*
- The unfolding of novel genes in the pathogenesis of CS has lead the path to new treatment modalities like vitamin E and will help point out patients suitable for genetic counseling
- Sirolimus for treatment of hamartomas in CS
- Baseline workup routine for newly diagnosed CS patients
- Aggressive screening routine based on recent incidences of various cancers in CS
- The first Indian and the third world report of polydactyly with CS.

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