Hong Kong J. Dermatol. Venereol. (2018) **26**, 181-184

Views and Practice

Cowden syndrome: an under-recognised entity

SSW Cheng 鄭斯穎, IFM Lo 盧輝文, HM Luk 陸浩明

Introduction

It is estimated that 10% of cancers belong to inherited cancer syndromes due to mutation in cancer predisposition genes. Early recognition of inherited cancer syndromes is important for clinical care and genetic counselling. Through regular surveillance and risk reduction strategies, the morbidity and mortality associated with inherited cancer syndromes can be significantly reduced. Cowden syndrome (CS) is a rare autosomal dominant cancer-predisposing syndrome characterised by macrocephaly, multiple hamartomas and high risk of developing tumour. More than 90% affected individuals would develop the mucocutaneous stigmata, primarily trichilemmomas and papillomatous papules. However, it is often under-diagnosed. Here we have reported a case of Cowden syndrome that present as breast cancer and skin abnormalities. This highlights the importance of dermatological examination in recognising these cancer predisposition syndromes in clinical practice.

Clinical Genetic Service, Department of Health, Hong Kong

SSW Cheng, MB, ChB, FHKAM(Paediatrics)
IFM Lo, MB, ChB, FHKAM(Paediatrics)
HM Luk, MB, BS, FHKAM(Paediatrics)

Correspondence to: Dr. HM Luk
3/F, Cheung Sha Wan Jockey Club Clinic, 2 Kwong Lee Road, Kowloon, Hong Kong

Case report

A 51-year-old Chinese lady presented with bilateral breast cancer at the age of 44 years and had received total mastectomy and chemotherapy in Guangzhou. There was a past medical history of thyrotoxicosis and goitre at the age of 36 years with total thyroidectomy done in China in the same year. She had no family history of breast cancer or other cancers. She was referred to clinical genetic service in view of early onset of bilateral breast cancer.

Physical examination at initial consultation in 2015 revealed macrocephaly with a head circumference of 58.5 cm (2.5 cm >the 97th centile). She had a high forehead and darkened skin with multiple papillomatous lesions, particularly over the face, oral and perioral region (Figure 1). She had a thyroidectomy scar and bilateral mastectomy scars. Her intellectual level was normal and her cardiovascular, respiratory, abdominal examinations were unremarkable.

In view of her multiple papillomatous skin lesions, macrocephaly and history of bilateral breast cancer, a tumour predisposition syndrome, particularly PTEN hamartoma tumor syndrome was suspected. On review, she fulfilled the clinical diagnosis of Cowden syndrome as there were two major criteria (breast carcinoma and macrocephaly) and one pathognomonic mucocutaneous lesion (cutaneous facial papules and oral mucosal papillomatosis).[1]

Genetic testing on the *PTEN* gene was performed. A heterozygous pathogenic splice site variant PTEN {NM_000314.4}:c.[253+1G>A];[=] in exon 4 of *PTEN* gene was detected. This variant has been reported in the literature to be associated with Cowden syndrome.[1] Therefore, the molecular diagnosis of PTEN hamartoma tumour syndrome was substantiated. Family cascade screening showed it was a *de novo* change in family.

Discussion

Pathogenic Variants in the tumour suppressor gene (*PTEN*) leading to PTEN hamartoma tumour syndrome (PHTS), a spectrum of disorders that encompasses Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS) and Proteus-like syndrome. The *PTEN* tumor suppressor gene is located on 10q23.3 encoding a dual-specificity phosphatase that can dephosphorylate both protein and phospholipid substrates. Cowden syndrome is a rare autosomal dominant cancer-predisposing syndrome characterised by macrocephaly, multiple hamartomas and increased risk of developing several types of tumour particularly breast, thyroid and endometrial cancers, and also colorectal, renal cell carcinoma and melanoma. The penetrance of the condition is high as more than 90% affected individuals develop the mucocutaneous stigmata, primarily trichilemmomas and papillomatous papules by the third decade. Over 80% of patients with Cowden syndrome have the identifiable *PTEN* pathogenic variant.[1]

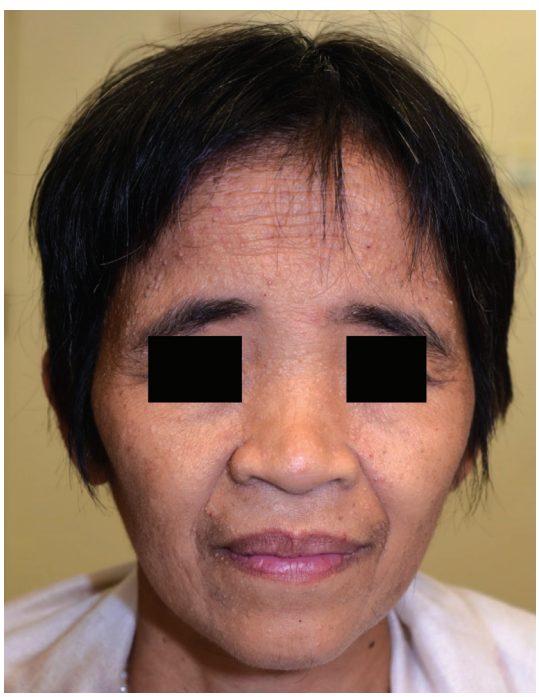

Figure 1. Patient with darkened skin and multiple papillomatous lesions over the face, oral and perioral region.

According to Hong Kong Cancer registry in 2015, breast cancer was the third most common cancer in Hong Kong with an incidence of over 3900 new cases reported.[2] The number of breast cancer cases has increased by nearly 70% since 2003 which is significantly higher than the overall average increase of 36%.[2] Around 5-10% breast cancer cases are thought to be hereditary. Apart from *BRCA1* (Breast Cancer gene 1) and *BRCA2* (Breast Cancer gene 2), some rarer inherited cancer syndromes may also present with a significantly increased risk of breast cancer. These include Cowden syndrome (due to mutations in *PTEN* gene as in our patient); Neurofibromatosis type 1 which is characterised by mutations in *NF1* gene; Li Fraumeni syndrome in which there are mutations in *TP53* gene; Peutz Jeghers syndrome which results from mutation in *STK11* gene; Hereditary diffuse gastric cancer which is caused by mutations in *CDH1* gene. These are tumour suppressor genes mutations of which can lead to uncontrolled cell and tumorigenesis. Cases of inherited cancer syndromes usually have a significant family history with positive findings on physical examination findings and presence of tumours. Early recognition of inherited cancer syndromes in the family members is important for clinical care and genetic counselling (Table 1).

Patients with Cowden syndrome have an increased risk of cancers including breast, thyroid, endometrial, and to a lesser extent, renal

Table 1. Specific physical features and tumour types associated with inherited cancer syndrome

Inherited cancer syndromes	Gene(s)	Tumour type(s)	Physical signs
Cowden syndrome	PTEN	• Thyroid cancer • Breast cancer • Colorectal cancer • Endometrial cancer • Renal tumour • Melanoma • Rare: dysplastic cerebellar gangliocytoma	• Macrocephaly • Mucocutaneous papillomatous lesions • Trichilemmomas • Penile freckling • Glycogenic acanthosis • Palmoplantar keratosis
Neurofibromatosis type 1	NF1	• Brainstem and cerebellar gliomas • Malignant peripheral nerve sheath tumours • Leukaemia • Gastrointestinal stromal tumours • Breast cancer • Retinal vasoproliferative tumours	• Café au laits macules • Neurofibromas • Macrocephaly • Hyperpigmentation • Hemihypertrophy • Axillary and/or groin frecklings • Osseous lesions • Lisch nodules
Li Fraumeni syndrome	TP53	• Osteosarcoma • Rhabdomyosacroma • Brain tumours e.g. glioblastoma multiforme and choroid plexus carcinoma • Breast cancer • Adrenocortical carcinoma (ACC) • Gastric cancer, gastrointestinal stroma tumours • Leukaemia	Nil
Peutz Jeghers syndrome	STK11	• Colorectal and gastric cancers • Small bowel cancer • Breast cancer • Ovarian cancers (mostly sex cord tumour with annular tubules), cervical cancer (adenoma malignum) and uterus cancer • Testicular cancer (sertoli cell tumour) • Lung cancer • Pancreatic cancer	• Mucocutaneous macules around the mouth, eyes, and nostrils and also in the perianal area, and buccal mucosa • Gynecomastia in males as a result of estrogen-producing Sertoli cell testicular tumours
Hereditary diffuse gastric cancer	CDH1	• Gastric cancer • Lobular breast cancer • Colorectal cancer	Nil

malignancy. In this regard, any individual with a *PTEN* pathogenic variant needs increased cancer surveillance for early tumour detection. According to NCCN guideline 2017,[3] annual comprehensive physical examination (including skin) and thyroid examination should be commenced at age of 18 or 5 years before the youngest age of diagnosis of a component cancer in the family (whichever comes first). For breast cancer screening, clinical breast examination and annual mammography (or breast MRI screening with contrast) are recommended to start at age of 25 and 30 respectively or 5 to 10 years before the earliest known breast cancer in the family (whichever comes first). For endometrial cancer screening, annual random endometrial biopsies and/or ultrasound should be considered at age of 30 years. Annual thyroid ultrasound should be started at the time of PHTS diagnosis. Colonoscopy and renal ultrasound are also needed starting from 35 years old and 40 years old respectively. Patient education and prompt response to symptoms (e.g. abnormal vaginal bleeding) are recommended. The estimated lifetime risk of breast cancer in patients with *PTEN* variants is around 85%.[1] The PTEN-related endometrial cancer risk starts at the age of 25 and rises to 30% by the age of 60 years.[1] Thus discussion about the option of hysterectomy and risk reducing mastectomy upon completion of child bearing and counselling regarding degree of protection, extent of cancer risk and reproductive desire and reconstruction options are advised.

References

1. Tan MH, Mester J, Peterson C, Yang Y, Chen JL, Rybicki LA, et al. A clinical scoring system for selection of patients for PTEN mutation testing is proposed on the basis of a prospective study of 3042 probands. Am J Hum Genet 2011;88:42-56.
2. Overview of 2015 HK Cancer statistics Cancer registration in Hong Kong http://www3.ha.org.hk/cancereg/pdf/top10/rank_2015.pdf. Assessed on 26 July 2018.
3. NCCN. Genetic/Familial High-Risk Assessment: Breast and Ovarian. Clinical Practice Guidelines in Oncology. 2017. Available online (registration required). http://www.jnccn.org/content/15/1/9.full. Assessed on 3 Jan 2017.