

## PTEN Hamartoma Tumour Syndrome: Gastrointestinal Manifestations of Two Cases Diagnosed in Singapore

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### Abstract

*PTEN* hamartoma tumour syndrome is associated with germline mutations in the tumour suppressor gene, *PTEN* (*phosphatase and tensin homolog gene*), leading to formation of hamartomas due to unregulated cellular proliferation. Two patients presented with complications of hamartomas, which subsequently revealed multiple polyposis of mixed histologies throughout their gastrointestinal tracts. There was no family history for *PTEN* hamartoma tumour syndrome and both were eventually detected to have *de novo* *PTEN* mutations. Despite fulfilling diagnostic criteria and having high probabilities of a *PTEN* mutation (computed using *PTEN* Cleveland Clinic score), there was delayed diagnosis of *PTEN* hamartoma tumour syndrome due to limited awareness amongst treating clinicians. Thus *PTEN* hamartoma tumour syndrome should still be considered as a differential in patients with similar gastrointestinal manifestations for early diagnosis and intervention.

**Keywords:** *PTEN*; *PTEN* hamartoma tumour syndrome; Gastrointestinal manifestations

### Introduction

*PTEN* hamartoma tumour syndrome (PHTS) is associated with germline mutations in the tumour suppressor gene, *PTEN* (*phosphatase and tensin homolog gene*). *PTEN* negatively regulates the phosphatidylinositol 3-kinase-AKT and mammalian target of rapamycin (mTOR) signaling pathways, which are critical for cell proliferation, cell cycle progression, and apoptosis. Loss of function of *PTEN* contributes to tumorigenesis—specifically, hamartoma formation [1]. Multiple systems are involved and patients often demonstrate a wide spectrum of manifestations and presentations, including complications of gastrointestinal hamartomas, mucocutaneous abnormalities and an increased cancer risk [2]. There remains limited literature on cases reported in Asia. In this report, we discuss two patients diagnosed in Singapore, with variable gastrointestinal presentations.

### Case Report

A 32-year-old female patient first presented to our institution with multiple episodes of haematemesis and no other associated symptoms. She was noted to have a history of childhood epilepsy and intellectual impairment, as well as an adenomatous goiter with a left hemi-thyroidectomy done in 1992. Physical examination revealed multiple mucocutaneous papules over her face and palms. She also had palmar pits and macrocephaly. Careful endoscopic examination revealed multiple gastric, small bowel and colonic hamartomatous and hyperplastic polyps. However, there was no family history for polyposis syndromes, gastrointestinal or other malignancies. A repeat gastroscopy and biopsy one year later reported polypoidal change in the stomach and first part of duodenum, which was unable to exclude the presence of a stromal tumour. Computed tomography (CT) of the abdomen then revealed a large lobulated duodenal mass and a Whipple's procedure was performed. Pathologic examination showed benign hamartomatous polyposis without evidence of dysplasia. She later received genetic testing on the suspicion of a polyposis syndrome and

tested positive for a *PTEN* nonsense mutation in exon 5 (C.130C>T). The patient also had recurrence of thyroid nodules at 36-years-old and underwent a completion thyroidectomy with histology reporting a follicular thyroid carcinoma. She was further diagnosed with breast fibroadenomas at 41-years-old.

Subsequent surveillance scans reported development of pulmonary nodules, which were suggestive of hamartomas. Further CT scans also discovered multiple liver nodules, including hamartomas, haemangiomas and two vascular shunts, on a background of fatty infiltration of the liver. This progressed to Child-Pugh B liver cirrhosis, with steatosis and fibrosis, and multiple other complications. In view of the continued progression of hepatic nodules, a liver biopsy was performed, which revealed metastatic adenocarcinoma from an unknown primary origin. Immunohistochemical (IHC) staining suggested that breast and colonic origins were less likely, but a mucinous ovarian or pancreatico-biliary primary tumour could not be excluded entirely. No further investigations were carried out to determine the primary tumour as the joint decision between the patient's family and clinicians was for palliative management.

The second patient is a 56-year-old male patient who first

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Received July 26, 2015; Accepted May 18, 2015; Published May 21, 2015

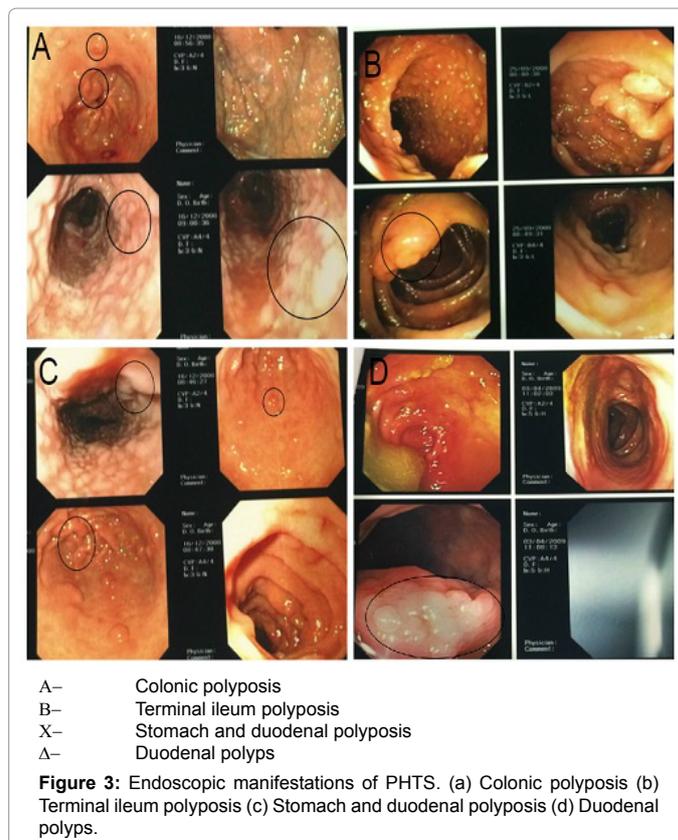
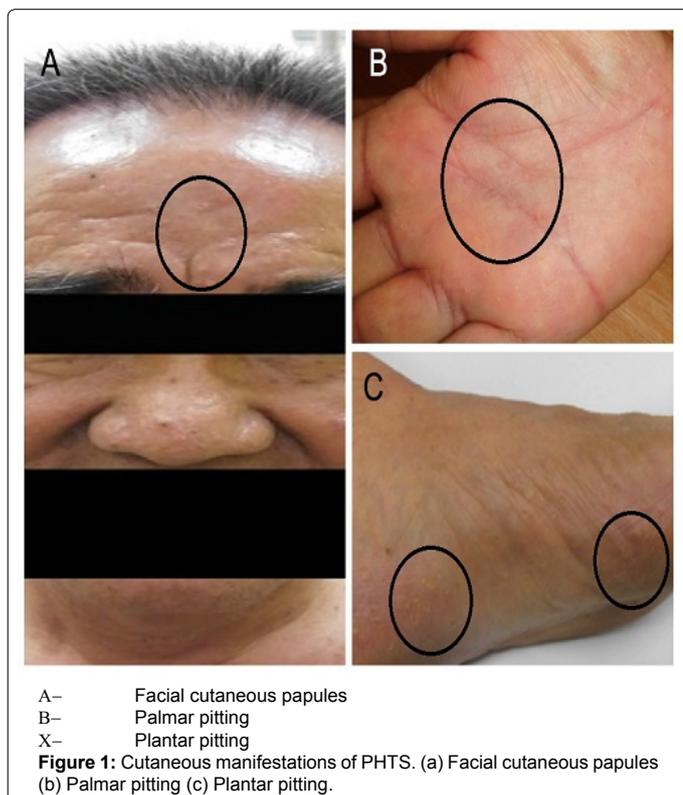
**Citation:** Chua CS, Loi CTT, Koh PK, Cheah PY, Lee HY, et al. (2015) *PTEN* Hamartoma Tumour Syndrome: Gastrointestinal Manifestations of Two Cases Diagnosed in Singapore. Hereditary Genet 4: 148. doi:10.4172/2161-1041.1000148

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presented with severe abdominal pain, mild jaundice and pyrexia. A cholecystectomy was done and on pathologic examination of the gallbladder, it reported an infarcted pedunculated adenomatous polyp with no evidence of malignancy. Physical examination revealed multiple papules over his face (Figure 1a), palms, soles, neck, limbs and trunk. He also had palmoplantar pits (Figure 1b and 1c), pigmented macules of the glans penis (Figure 2), macrocephaly of 61.5 cm, and oral mucosal papillomas. There was similarly no family history of malignancies or polyposis syndromes. CT of the abdomen and pelvis was performed in view of three echogenic liver nodules found incidentally during his ultrasound on admission. It revealed a hepatic haemangioma. Screening colonoscopy revealed benign multiple polyposis throughout the whole colon (Figure 3a) and terminal ileum (Figure 3b), and gastroscopy revealed multiple benign duodenal hyperplastic polyps (Figure 3c and 3d). He was tested positive for a *PTEN* insertion mutation in exon 8 (C.319\_320insT). Multiple thyroid nodules were detected on follow-ups and he underwent a prophylactic total thyroidectomy, which revealed a multi-nodular goiter. Biopsies from his palms, neck and ears were compatible with acral keratosis and a papillomatous lesion over the nape was that of a sclerosing fibroma. Subsequent surveillance endoscopies further discovered oesophageal glycogenic acanthosis with no other progression or malignant change of disease to date.

### Discussion

There are varied gastrointestinal manifestations of PHTS as detailed in Table 1 [3-17], of which upper and lower gastrointestinal tract (GIT) polyposis is most common. PHTS patients are reported to have a wide spectrum of polyp histologies throughout their upper and lower GIT [3,4], with many having more than a single histology [5]. In particular, a mixture of polyp histologies such as hyperplastic (43.6%), adenomatous (40.4%), and hamartomatous (38.3%) polyps etc. [5] are more commonly found in patients with *PTEN* mutations. Both patients demonstrated mixed polyp histologies, in keeping with current



Gastrointestinal feature	References
Gastrointestinal polyposis	[2-12]
Glycogenic acanthosis	[2,8,11,13]
Intestinal hyperplasia	14
Intestinal ganglioneuromatosis	[11,12,15-17]

**Table 1:** Gastrointestinal manifestations of PHTS.

literature. However, in spite of extensive endoscopic examination that reported this discovery for both patients, there was insufficient clinical suspicion of PHTS then. Both patients also met the diagnostic criteria for PHTS as defined in current operational criteria in Table 2 [18]. The first patient fulfilled 4 major and 3 minor criteria, and the second patient fulfilled 4 major and 3 minor criteria.

Given their clinical history prior to diagnosis, their *PTEN* Cleveland Clinic scores [19] were later computed to estimate the individual patient probability of a *PTEN* mutation. The first patient had a total risk score of 39 and estimated probability of 98% and the second patient had a

Major Criteria	
Breast cancer	
Endometrial cancer (epithelial)	
Thyroid cancer (follicular)	
Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps; ≥3)	
Lhermitte-Duclos disease (adult)	
Macrocephaly (≥97 percentile: 58 cm for females, 60 cm for males)	
Macular pigmentation of the glans penis	
Multiple mucocutaneous lesions (any of the following):	
Multiple trichilemmomas (≥3, at least one biopsy proven)	
Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)	
Mucocutaneous neuromas (≥3)	
Oral papillomas (particularly on tongue and gingiva), multiple (≥3) OR biopsy proven OR dermatologist diagnosed	
Minor Criteria	
Autism spectrum disorder	
Colon cancer	
Esophageal glycogenic acanthosis (≥3)	
Lipomas (≥ 3)	
Mental retardation (ie, IQ ≤ 75)	
Renal cell carcinoma	
Testicular lipomatosis	
Thyroid cancer (papillary or follicular variant of papillary)	
Thyroid structural lesions (eg, adenoma, multinodular goiter)	
Vascular anomalies (including multiple intracranial developmental venous anomalies)	
Operational diagnosis in an individual (either of the following):	Operational diagnosis in a family where one individual meets revised PTEN Hamartoma tumour syndrome clinical diagnostic criteria or has a PTEN mutation:
1. Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas; or	1. Any two major criteria with or without minor criteria; or
2. Two major and three minor criteria.	2. One major and two minor criteria; or
	3. Three minor criteria.

Table 2: Revised PTEN hamartoma tumor syndrome clinical diagnostic criteria [18].

total risk score of 52 and estimated probability of greater than 99%. Despite meeting the diagnostic criteria, demonstrating gastrointestinal polyp histologies similar to PHTS and in retrospect, having extremely high probabilities of PTEN mutations, there was delayed diagnosis of PHTS for both patients, especially for the female patient. This could possibly be attributed to limited awareness amongst treating clinicians. PTEN IHC was carried out on both patients polyps, of which one patient had normal PTEN expression and the other had a loss of PTEN expression with abnormal loss seen, despite both testing positive for PTEN mutations. Thus, PTEN IHC on the polyps may or may not be useful in screening for patients with germline PTEN mutations. Also, a study by Mester and Eng [20] revealed a 10% de novo PTEN mutation frequency and demonstrated the potential of a 47% de novo mutation frequency, which may still be an underestimate given that patients without positive family histories may not have been referred for genetic testing. Thus, patients who present in future with similar gastrointestinal manifestations as the two patients reported, with clinical correlation, should be referred early for genetic testing, even if there is no positive family history for PHTS, as evidenced by the rate of de novo PTEN mutation frequency.

PHTS is also known to have an increased risk of malignancy compared to the general population; in particular for breast, thyroid and endometrial cancers [21]. The first patient was diagnosed with metastatic adenocarcinoma of an unknown primary and was too ill for subsequent evaluation of the primary cancer. Despite close surveillance of the patient after her diagnosis of PHTS, there was delayed detection, once again suggesting a missed opportunity for early detection. Given the known increased risks of malignancy, management of PHTS patients should therefore be more intensive in screening for cancers associated with PHTS such that early detection and intervention is possible.

## Conclusions

In conclusion, clinical suspicion of PHTS needs to be heightened in our region such that early diagnosis and intervention can ensue, given

the increased cancer risk in PHTS patients.

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