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 polyps 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 tumourigenesis—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 pancreato-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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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 glycanogenic 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 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
with PHTS such that early detection and intervention is possible. Once again suggesting a missed opportunity for early detection. Given the patient after her diagnosis of PHTS, there was delayed detection, subsequent evaluation of the primary cancer. Despite close surveillance metastatic adenocarcinoma of an unknown primary and was too ill for metastatic adenocarcinoma of an unknown primary and was too ill for genetic testing.

Patients without positive family histories may not have been referred for genetic testing.

Also, a study by Mester and Eng [20] revealed a 10% PTEN mutation frequency and demonstrated the potential of a 47% de novo mutation frequency.

PTEN 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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| Major Criteria | Minor Criteria |
|---------------|---------------|
| Breast cancer | Autism spectrum disorder |
| Endometrial cancer (epithelial) | Colon cancer |
| Thyroid cancer (follicular) | Esophageal glycogenic acanthosis ≥3 |
| Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps; ≥3) | Lipomas ≥3 |
| Lhermitte-Duclos disease (adult) | Mental retardation (ie, IQ ≤ 75) |
| Macrocephaly (≥7 percentile: 58 cm for females, 60 cm for males) | Renal cell carcinoma |
| Macular pigmentation of the glans penis | Testicular lipomatosis |
| Multiple mucocutaneous lesions (any of the following): | Thyroid cancer (papillary or follicular variant of papillary) |
| Multiple trichilemmomas ≥3, at least one biopsy proven | Thyroid structural lesions (eg, adenoma, multinodular goiter) |
| Acral keratoses (≥3 palmarplantar keratotic pits and/or acral hyperkeratotic papules) | Vascular anomalies (including multiple intracranial developmental venous anomalies) |
| Mucoceleles neumomas ≥3 | |
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