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Practice Guideline

Clinical Guidelines for Diagnosis and Management of Cowden Syndrome/PTEN Hamartoma Tumor Syndrome in Children and Adults—Secondary Publication

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Abstract

Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) is a rare autosomal dominantly inherited condition caused by germline pathogenesis. It is associated with multiple hamartomatous lesions occurring in various organs and tissues, including the gastrointestinal tract, skin, mucous membranes, breast, thyroid, endometrium, and brain. Macrocephaly or multiple characteristic mucocutaneous lesions commonly develop in individuals in their 20s. This syndrome is occasionally diagnosed in childhood due to the occurrence of multiple gastrointestinal polyps, autism spectrum disorders, and intellectual disability. CS/PHTS can be diagnosed taking the opportunity of multigene panel testing in patients with cancer. Appropriate surveillance for early diagnosis of associated cancers is required because patients have a high risk of cancers including breast, thyroid, colorectal, endometrial, and renal cancers.

Under these circumstances, there is growing concern regarding the management of CS/PHTS in Japan, but there are no available practice guidelines. To address this situation, the guideline committee, which included specialists from multiple academic societies, was organized by the Research Group on Rare and Intractable Diseases granted by the Ministry of Health, Labour, and Welfare, Japan. The present clinical guidelines explain the principles in the diagnosis and management of CS/PHTS, together with four clinical questions and the corresponding recommendations, incorporating the concept of the Grading of Recommendations Assessment, Development, and Evaluation system. Herein, we present an English version of the guideline, some of which have been updated, to promote seamless implementation of accurate diagnosis and appropriate management of pediatric, adolescent, and adult patients with CS/PHTS.

Keywords

cancer, colorectal polyp, Cowden syndrome, *PTEN* hamartoma tumor syndrome

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Introduction

Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) is a rare autosomal dominantly inherited condition caused by germline pathogenesis. It is associated with multiple hamartomatous lesions occurring in various organs and tissues, including the gastrointestinal tract, skin, mucous membranes, breast, thyroid, endometrium, and brain. Macrocephaly or multiple characteristic mucocutaneous lesions commonly develop in the people in their 20s. This syndrome is occasionally diagnosed in childhood due to the occurrence of multiple gastrointestinal polyps, autism spectrum disorders, and intellectual disability. CS/PHTS may be diagnosed using multigene panel testing in patients with cancer. Appropriate surveillance is required as patients may develop malignant tumors such as breast, thyroid, endometrial, colorectal, and renal cancers.

However, owing to the diversity of clinical features and a low incidence of this disease, there are no established Japanese guidelines for the diagnosis, treatment, and surveillance of this syndrome. The medical management of patients and their relatives with this syndrome may be required based on the results of cancer genome testing or the characteristic features of this disease; however, overseas guidelines on the management of this syndrome are difficult to implement in Japanese patients because of the high cost of healthcare, clinical applicability, and the medical health insurance system. Therefore, seamless clinical practice guidelines for both children and adults in Japan should be developed.

In 2017, as a project of the Research Group to Improve the Medical Standard and Reduce the Disparity in the Treatment of Benign Multiple Tumors of the Gastrointestinal Tract (presenter: Ishikawa H.), which was a study on rare and intractable diseases granted by the Ministry of Health, Labour and Welfare, a working group was established to develop “Clinical Guidelines for Diagnosis and Managements of CS/PHTS in Children and Adults.” The committee members included specialists in internal medicine, gastroenterology, surgery, pediatric gastroenterology, pediatric surgery, dermatology, gynecology, pathology, genetics, genetic counselling, and nursing. From 2019, the Japanese Society for Hereditary Tumors, the Gastrointestinal Polyposis Study Group of the Japanese Gastroenterological Association, and Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition continued developing the guidelines with the cooperation of other organizations. In 2020, the Research Group for Establishing a Seamless Medical Care System from Children to Adults with Gastrointestinal Hamartoma Predisposition Diseases (presenter: Nakayama Y.) granted by the Ministry of Health, Labour and Welfare, Japan as a study on rare and intractable diseases published the clinical guidelines in Journal of Hereditary Tumors in Japanese[1].

Table 1. Quality of Evidence.

Quality of evidence at the start of the evaluation	Systematic review, meta-analysis, randomized controlled trial = "high" Cross-sectional study, cohort study, case-control study = "Low" Case series, case report = "very low"
When to lower the grade*	There are very serious limitations to the quality of the research. There are significant inconsistencies in the results. The directness of the evidence is somewhat or considerably uncertain. Data is inaccurate or inconsistent. Publication bias is highly likely.
When to raise the grade*	The degree of effect is large. There's a dose-response gradient. Possible confounding factors weaken the true effect.
Defining the quality of evidence about research on outcomes in general	
A: "High"	It is certain that the estimated of effect is virtually identical to the actual effect.
B: "Moderate"	Confidence in the estimate of effect is moderate.
C: "Low"	Confidence in the estimate of effect is limited.
D: "Very low"	The estimate of effect is quite uncertain.

*If the degree of effect is large, or if it is considered difficult to conduct a randomized controlled trial because Cowden syndrome/PTEN hamartoma tumor syndrome is a rare disease, the grade can be increased.

Herein, we present an English version of the Clinical Practice Guidelines for CS/PHTS, some of which have been updated.

1. Developing the Guidelines

In developing the guidelines, the concept of evidence-based medicine (EBM) was emphasized, and a project to promote the distribution of the EBM guideline development guide[2] and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[3] system was used. The guidelines included detailed explanations of the CS/PHTS, clinical questions, and recommendations.

1.1. Collecting the evidence

Based on the identified key clinical issues and each clinical question (CQ), evidence was extracted using P (Patients), I (Intervention), C (Control) or (Comparison), and O (Outcome) as search keywords. We searched PubMed from January 1998 to December 2018 and the Internet version of the Central Journal of Medicine was searched from inception until December 2018.

1.2. Evaluating the articles and defining the quality of evidence

Articles selected for use in the guidelines were classified based on the study design (clinical practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, cohort studies, case-control studies, cross-sectional studies, case series, case reports, and reviews). As CS/PHTS is a rare syndrome, case reports and case series were included in the systematic review. A structured abstract was developed for each article to evaluate the risk of bias. The overall evidence was determined using the systematic review method (Table 1); the overall level of evidence for each CQ is listed from A to D.

1.3. Defining the strength of recommendation

The strengths of these recommendations are listed in Table 2. Decisions were made upon agreement among committee members after careful consideration of the (i) quality of evidence and (ii) balance of benefits and harms (balance between disadvantages such as patient burden, cost, and benefits acquired by implementing the recommended practice). The consensus was formed by voting according to the GRADE grid method[4], and a decision was made when more than 70% of the votes were in favor.

1.4. Public comments

A draft of the guidelines was published on the website, and public comments were solicited from the members of the Japanese Society for Hereditary Tumors; the Japanese Gastroenterological Association; the Japanese Society of Gastroenterology; the Japan Gastroenterological Endoscopy Society; the Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition; and the Japanese Society of Pediatric Surgery. Further revisions were made based on public comments, and the Japanese version was published in 2020[1].

Table 2. Strength of Recommendations.

1. Strong recommendation	Implementation is recommended "do it"
	Implementation is recommended "do not do it"
2. Weak recommendation	Implementation is proposed "probably do it"
	Implementation is proposed "probably do not do it"

2. Detailed Explanations of CS/PHTS

2.1. Overview

CS is a syndrome characterized by presence of multiple hamartomatous lesions in various organs, including the skin, mucosa, breast, thyroid gland, endometrium, gastrointestinal tract, and brain. It is thought to be caused by a germline pathological variant in the *PTEN* and is inherited in an autosomal dominant manner. It is a variant of PHTS, which includes the Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome (PS), and Proteus-like syndrome. Patients with CS have a high risk of developing complications from the different types of malignancy, such as breast cancer, thyroid cancer, endometrial cancer, colorectal cancer, and renal cell carcinoma; hence, appropriate surveillance is necessary.

2.1.1. Clinical features

Most patients develop macrocephaly and multiple cutaneous mucosal lesions in their late 20s, both of which are not subjective. Several patients show polyps on gastrointestinal endoscopy, especially esophageal glycogen acanthosis. The risk of developing malignant tumors such as breast, thyroid, endometrial, colorectal, and renal cell carcinomas is relatively high. Moreover, the presence of macrocephaly, autism spectrum disorder, and intellectual disability triggers the diagnosis of this condition during childhood.

2.1.2. Disease frequency

The incidence of CS is 0.5 cases per 100,000 population. However, several patients with this syndrome have not been diagnosed, and the actual number may be higher than this estimate[5,6].

2.1.3. Pathogenesis of hamartoma and carcinoma

Dysfunction of the *PTEN* gene product leads to activation of the PI3K/AKT/mTOR pathway, resulting in hamartomatous lesions, and other genetic abnormalities are thought to contribute to tumorigenesis. The detailed mechanism of *PTEN* product dysfunction that contributes to oncogenesis remains unclear, and may include inactivation of both PTEN alleles by two hits, haploinsufficiency of *PTEN*, dominant-negative effects of mutants, DNA methylation of the promoter region, and expression of miRNAs and lncRNAs that regulate PTEN. The miRNAs and lncRNAs that regulate PTEN may be involved in this process[7,8].

2.2. Diagnosis

2.2.1. Clinical diagnostic criteria for Cowden syndrome/PHTS (see Table 3)

The National Comprehensive Cancer Network (NCCN) criteria are used worldwide in diagnosing CS/PHCS[9]. Therefore, we adopted the NCCN criteria for diagnosis of CS/PHTS, which included 8 major criteria and 10 minor criteria, as shown in Table 1. Moreover, a diagnostic flowchart of this syndrome, including clinical manifestations and *PTEN* testing criteria are shown in Supplementary Figure 1[9].

2.2.2. Clinical diagnostic criteria and germline pathological variants of PTEN (see CQ4)

The prevalence of the pathological variants of *PTEN* in patients who meet the clinical diagnostic criteria for this syndrome is reported to be 30% to 92%[10,11]. However, with the widespread use of genetic testing for diagnosing *PTEN,* the prevalence has increased. In a recent study, 80% of patients with CS were found to have a pathological variant of *PTEN*[6]. Germline mutations in the *PTEN* cause CS, BRRS, PS, and protein-like syndromes. Recently, owing to the widespread use of genetic testing, an increasing number of studies have been conducted to examine PHTS, including those that evaluated the risk of carcinogenesis in a large number of PHTS cases (403 cases)[9,11]. In addition, the phenotype of the disease varies with age in patients with PTEN pathological variants. Adults often present with CS, while children often present with macrocephaly, autism spectrum disorder (ASD), and BRRS. As most PHTS patients present with CS, the term CS/PHTS is often used nowadays.

2.2.3. Characteristics of the clinical symptoms

a) Multiple mucocutaneous lesions (see CQ1)

Characteristic mucocutaneous lesions occur by the age of 30 years in almost all patients[12,13]. Lesions in the oral mucosa, such as the gingiva, appear during adolescence, with irregular thickening of the gingiva and papillomatous lesions arranged in a paving-stone pattern (Figure 1). The face, dorsum of the fingers and toes, dorsum of the hands and feet, and palms and soles were frequently covered with small keratotic papules (Figure 2a-c). Multiple neuromas, lipomas, vascular malformations, sclerosing fibromas, and macular pigmentation of the glans of the penis (characteristic of BRRS) may also be observed. Histopathologically, multiple external pilosebaceous sheath tumors on the face (Figure 2d) are characteristic of BRRS. However, biopsies

Table 3. Clinical Diagnostic Criteria for Cowden Syndrome/PTEN Hamartoma Tumor Syndrome.

Major criteria
1. Breast cancer
2. Endometrial cancer
3. Follicular carcinoma of the thyroid gland
4. Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps; ≥3)
5. Adult-onset Lhermitte-Duclos disease
6. Macrocephaly (>97th percentile: 58 cm in women and 60 cm in men)
7. Macular pigmentation of the glans penis
8. 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 neuroma (≥3)
   · Oral papillomas (≥3, particularly on gingiva and tongue)

Minor criteria
1. Autism spectrum disorder
2. Colorectal cancer
3. Esophageal glycogenic acanthosis (≥3)
4. Lipoma (≥3)
5. Intellectual disability (IQ ≤75)
6. Renal cell carcinoma
7. Testicular lipomatosis
8. Thyroid cancer (papillary carcinoma or follicular variant of papillary)
9. Thyroid structural lesions (adenoma, adenomatous goiter, etc.)
10. Vascular anomalies (e.g., multiple developmental venous anomalies)

A diagnosis of CS is established if the patient fulfills one of the following criteria:
(1) Three or more major criteria, one of which is macrocephaly, adult-onset Lhermitte-Duclos disease, or gastrointestinal malrotation
(2) Two or more major criteria and three or more minor criteria
The patient's family members would be diagnosed with CS/PHTS if they meet one of the following criteria:
1) Two or more major criteria
2) One major criterion and at least two minor criteria
3) At least three sub-criteria

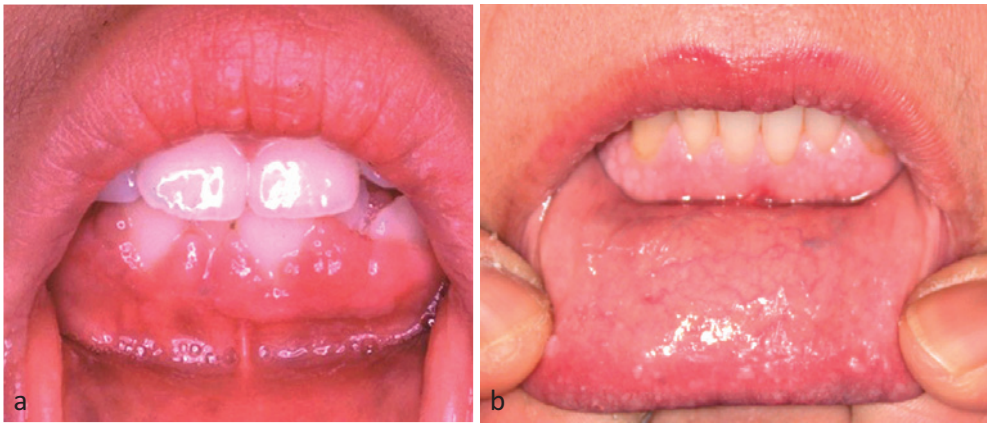

Figure 1. Oral mucosal lesions.
a. The lower gingiva is irregularly thickened and elevated, covering part of the tooth.
b. Slightly white papillomatous lesions arranged in a paving stone pattern on the lower gingiva and similar lesions with mild change on the mucosal side of the lower lip.

of many lesions are required, and a typical histological picture is difficult to obtain until old age.

b) Breast lesions (see CQ3)

Breast cancer is the most frequent type of malignancy in this syndrome (Figure 3). The lifetime risk of breast cancer in women with this syndrome is reported to be 25%-85%

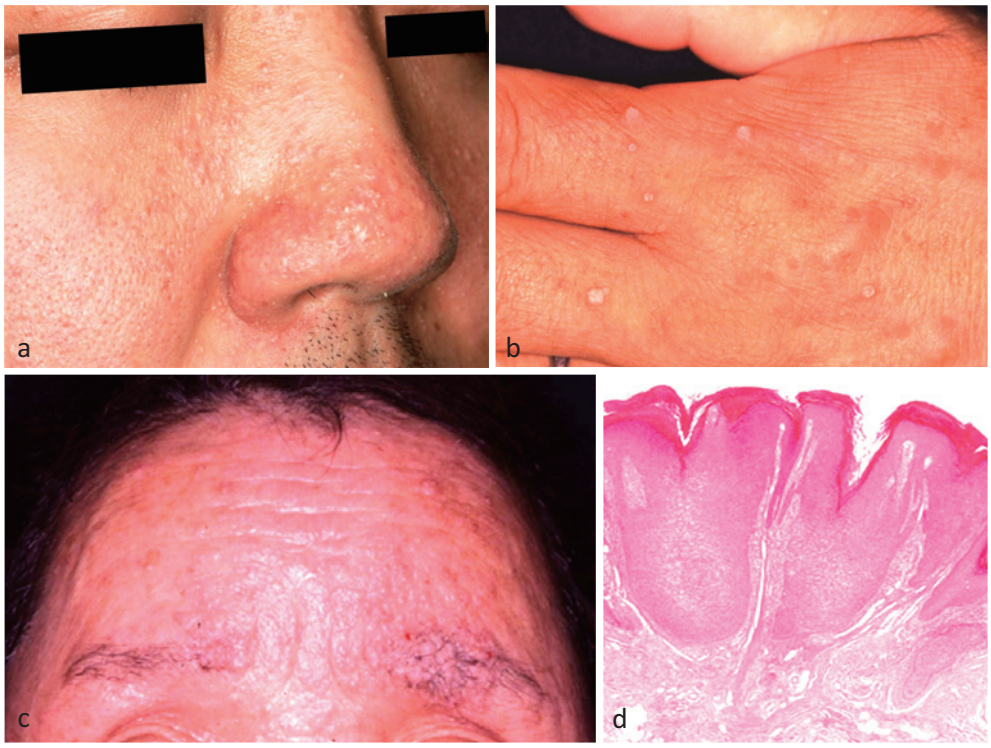

Figure 2. Small keratotic papules on the face and hands and multiple trichilemmomas on the face.

a. Numerous normal-colored papules on the dorsum and wings of the nose from the medial cheek area.

b. Scattered verrucous, keratotic papules on the dorsum of the hands and fingers.

c. Multiple trichilemmomas: scattered keratotic pits on the forehead and eyebrows of an older patient, some clustered.

d. Histopathology of trichilemmomas (histopathology of one of the trichilemmomas in c, hematoxylin and eosin staining): epidermal thickening composed of bright cells with hyperkeratosis is prominent.

(mean age of onset: 38-50 years); in a recent study of 205 women with germline pathological variants of *PTEN*, the lifetime risk of breast cancer was calculated to be 85%[11]. The incidence of simultaneous and metachronous bilateral breast cancer is 29%-32%. By contrast, only two cases of breast cancer occurring in men have been reported to date. In this syndrome, fibrotic hyalinized nodules with fibrosis and hyalinization of the stroma are frequently observed in 67% to 89% of patients[14]. Fibrous adenoma, ductal hyperplasia, and cysts were also observed. Therefore, benign diseases should be noted in the diagnosis and surveillance of breast cancer. However, there is insufficient evidence showing that women with this syndrome have a higher incidence of benign lesions compared with that in the general population.

c) Thyroid lesions

Thyroid carcinoma is the second most common type of malignancy associated with this syndrome, and the lifetime risk of disease in *PTEN* germline variant carriers has been reported to be 10%-35%. Histopathologically, thyroid cancers are either papillary or follicular in nature. In a study of 36 thyroid cancers in *PTEN* variant carriers, 72% (26/36) were papillary type and 25% (9/36) were follicular type[15]. On the contrary, since the histological types of thyroid cancer in the general population are papillary carcinoma (76%) and follicular carcinoma (8%), the frequency of follicular carcinoma is relatively high in patients with CS/PHTS[10]. Therefore, follicular carcinoma is one of the major diagnostic criteria, while papillary carcinoma (or follicular papillary carcinoma) is a minor criterion. The formation of multiple goiters may precede carcinogenesis of thyroid gland. Thyroid cancer is the most common type of cancer that can develop at a young age (pediatric), with a case reported at the age of 7 years. In addition, benign diseases such as benign multinodular goiter, adenomatous nodule, and follicular adenoma occur in 30%-68% of *PTEN* germline variant carriers (Figure 4).

d) Gastrointestinal lesions

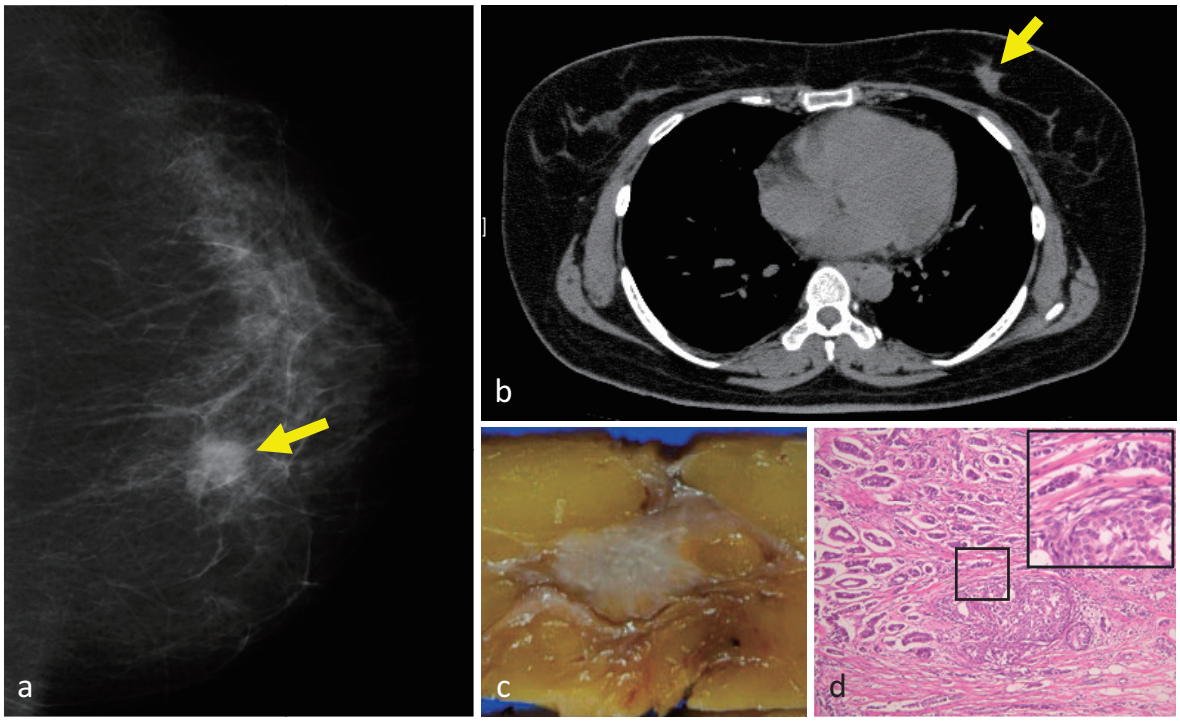

Figure 3. Breast cancer.
a. Mammography shows an irregularly shaped mass in the breast.
b. CT image shows an irregular mass in the left mammary gland.
c. Gross examination of the surgically removed specimen reveals a whitish mass.
d. Histopathological examination revealed ductal carcinoma of the breast. Enlarged image with black frame.

Gastrointestinal polyps are found in the majority (>90%) of patients who have undergone at least one upper gastrointestinal endoscopy or colonoscopy. Histopathologically, hamartomatous polyps (especially juvenile polyps) are the most common type of colorectal polyps. However, hyperplastic polyps, adenomatous polyps, and gangliocytomas are also frequently observed (Figure 5). Because hyperplastic polyps frequently occur in the general population, it remains unclear whether they are more common in this syndrome. In addition, distinguishing histological differences between these polyps using small biopsy specimens is challenging. The lifetime risk of colorectal cancer is 9%-16%, which is significantly higher than the lifetime risk of healthy individuals (5.5%)[11,16]. Patients with colorectal cancer tend to have more polyps and more than one histological type[16].

Although a few studies have reported the findings of upper gastrointestinal endoscopy of patients with this syndrome, polyps are frequently found in the stomach, and bleeding and other symptoms occur (Figure 6). In a nationwide survey conducted in Japan, most of the patients with this syndrome showed presence of glycogen acanthosis in the esophagus (Figure 7). However, such esophageal lesions have been observed in only 20% of cases reported in the literature, and this difference may be due to the fact that the results of upper gastrointestinal endoscopy have not been described adequately[17]. The overlapping cases of Cowden syndrome and Juvenile polyposis syndrome showing gastrointestinal hamartomatous polyposis due to de novo chromosome 10 deletion involving *BMPR1A* and *PTEN* have also been reported[18].

e) Uterine lesions

The lifetime risk of endometrial cancer in patients with germline variants of the *PTEN* is reported to be 19%-28%[11,15]. The standardized incidence ratio was 28-49 times higher. The mean age at diagnosis was 44 years, with most cases occurring before the age of 50 years. Benign diseases such as uterine fibroids occur frequently, but it remains unclear whether they are significantly more frequent in this syndrome, as they are often found in women in the general population.

f) Renal lesions

The lifetime risk of renal cell carcinoma is 34% in patients with germline variants of the *PTEN*, with onset in the 40s[11]. Histopathologically, papillary renal cell carcinoma is common, and anaerobic renal cell carcinoma has also been reported.

g) Macrocephaly

Most patients present with a macrocephaly. Macrocephaly was defined as a condition in which the head circumference

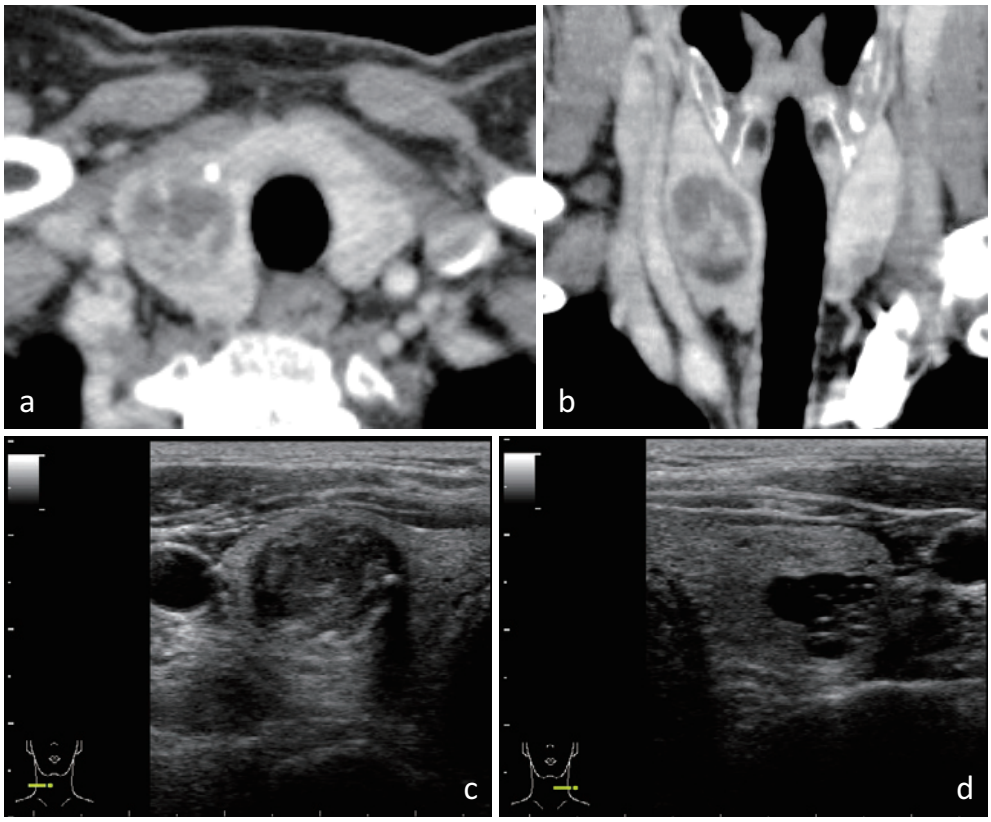

Figure 4. Multiple nodular goiter.
a. CT image. A mass-like lesion approximately 20 mm in size with relatively clear borders is observed in the right lobe of the thyroid gland.
b. CT images. CT MRP images show heterogeneity within the mass.
c. Ultrasound image. The mass in the right lobe of the thyroid gland is hypoechoic with well-defined borders, and a small cyst is observed inside.
d. Ultrasound image. The left lobe shows a cyst with a septum.
In the present case, puncture aspiration of the mass in the right lobe was performed; however, no cells suggestive of malignancy were observed.

measurements are 58 cm or more in adult women and 60 cm or more in adult men.

h) Adult-onset Lhermitte-Duclos disease (LDD)

LDD is a cerebellar dysplastic gangliocytoma, a benign tumor of the cerebellum that commonly occurs in patients in their 30s and 40s, and grows slowly. As the disease progresses, the patient develops cerebral hypertension (headache and vomiting), visual impairment, and cerebellar ataxia. Approximately 6% of patients with this syndrome have LDD[19], and the lifetime risk of morbidity is 32%[20]. On the contrary, 50% of LDD patients have CS.

i) Vascular abnormalities

Multiple vascular malformations often occur in the cranium, trunk, and extremities and are reported in approximately half of the patients who carry pathological variants in the *PTEN* germline gene[11]. Among vascular malformations, fast-flow vascular malformations and venous malformations are the most common type, and arteriovenous malformations are also observed.

j) Autism spectrum disorder (ASD)

ASD is a disorder of mental development with two signs: 1) impaired social communication and interpersonal interactions, and 2) restricted and repetitive patterns of behavior, interests, and activities. It occurs in 17% of individuals who carry a germline variant of *PTEN*[21]. The germline variant of *PTEN* is reportedly detected in 10-20% of patients with autism spectrum disorder and macrocephaly.

k) Intellectual disability

Intellectual disability (IQ < 70) occurs in 12%-20% of patients[12,22].

l) Autoimmune disease and lymphoid tissue hyperplasia

PHTS is associated with autoimmune diseases such as chronic thyroiditis (Hashimoto's disease), hemolytic anemia, and bronchial asthma[23]. Lymphoid follicular hyperplasia of the gastrointestinal tract (particularly in the rectum), tonsils, and thymus has also been reported. The possible cause

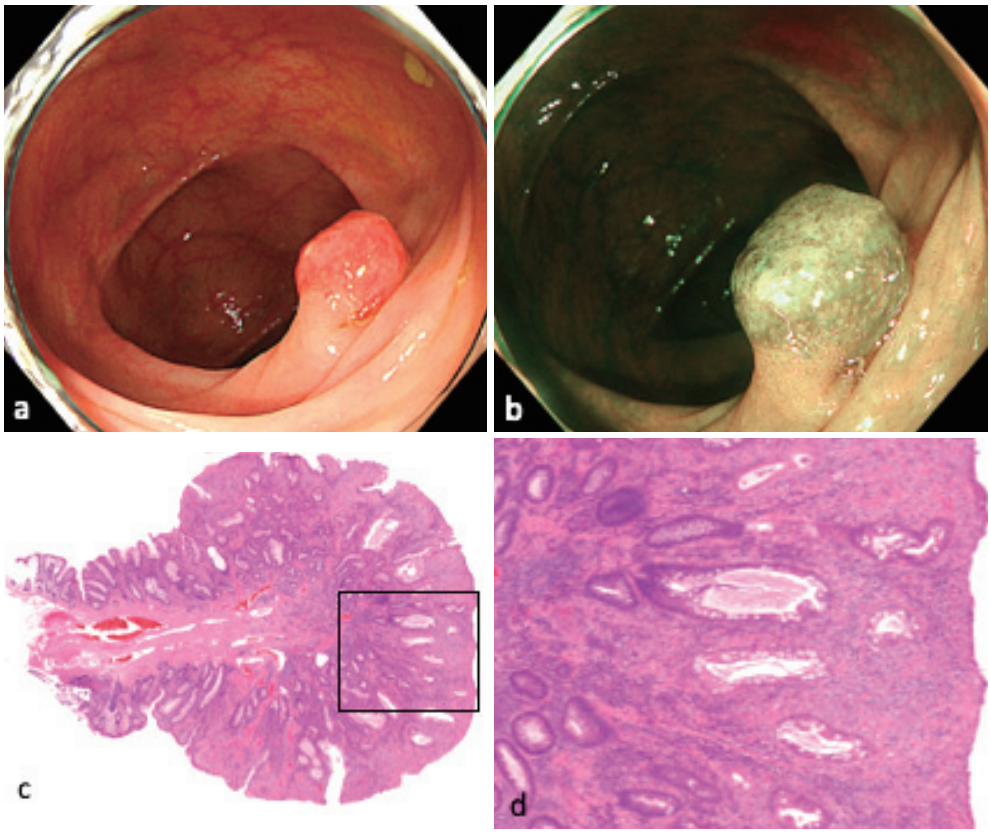

Figure 5. Colorectal polyps.
a. Colonoscopy showing a reddish pedunculated polyp 8 mm in size in the transverse colon.
b. NBI observation does not show appearance of neoplastic vessels on the surface.
c. Loupe image of excised polyp.
d. Higher magnification of the black square in c. The histological findings are consistent with those of a hamartomatous polyp.

is impaired maturation of B lymphocytes due to the inactivation of *PTEN*. However, the incidence of these disorders has not been investigated in sufficient number of cases.

m) Fatty liver and liver cell cancer

PTEN knockout mice develop non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC)[24]. Cases of CS/PHTS complicated by non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma have also been reported. However, the frequency of fatty liver and NASH in humans has not been sufficiently investigated, and only one case of hepatocellular carcinoma has been reported.

n) Other malignant tumors and tumors

Other malignant tumors include malignant melanoma[25], pituitary tumor[26], osteosarcoma[27], gastrointestinal stromal tumor[28], and dermatofibrosarcoma protuberans[29].

2.2.4. Differential diagnosis

1) Hereditary breast and/or ovarian cancer syndrome (HBOC)

Hereditary breast and/or ovarian cancer syndrome (HBOC) is an autosomal dominant inherited disease caused by a germline pathological variant of the *BRCA1* or *BRCA2 genes*, resulting in a high incidence of breast and ovarian cancer. However, polyps do not usually occur in the gastrointestinal tract. In patients with HBOC, no hamartoma, macrocephaly, or vascular malformations were observed.

2) Peutz-Jeghers syndrome (PJS)

PJS is an autosomal dominant genetic disorder characterized by hamartomatous polyposis of the gastrointestinal tract and hyperpigmentation of the lips, mouth, and digits. Mucocutaneous lesions in PJS are characterized by hyperpigmentation and differ from those in CS. Gastrointestinal polyposis in PJS is predominantly found in the small intestine and pedunculated polyps are common.

3) Cowden syndrome/PHTS-like diseases caused by germline variants of other genes

Some patients with a syndrome similar to this syndrome do not have a germline variant of *PTEN*. Germline variants of succinate dehydrogenase subunit X (*SDHx*), *KLLN*, *AKT*, *PIK3CA*, and *SEC23B* have been reported. Some of these genes are involved in the PI3K/AKT/mTOR pathway; however, others are unrelated to this pathway and remain unclarified.

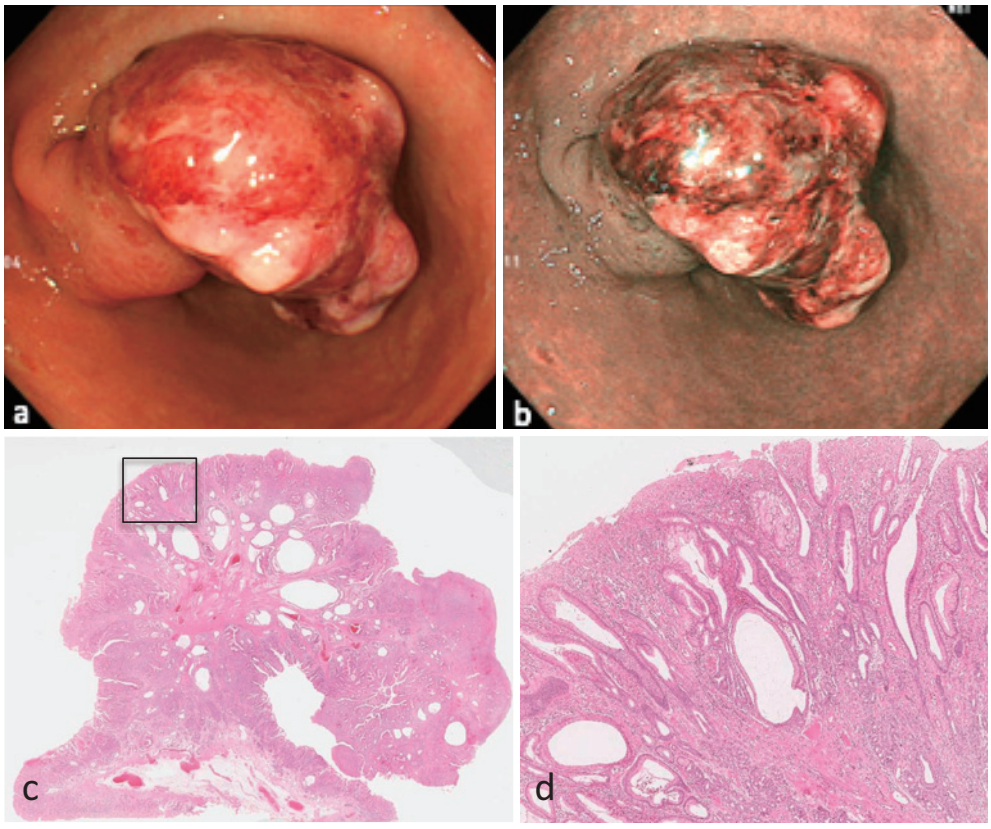

Figure 6. Gastric polyp.
a. Gastroscopy shows a reddish pedunculated polyp in the pylorus.
b. NBI observation shows slightly rich vascularity, but no tumor-like findings.
c. Loupe image of excised polyp.
d. Higher magnification of the black square in c. The histological findings are consistent with those of a hamartomatous polyp.

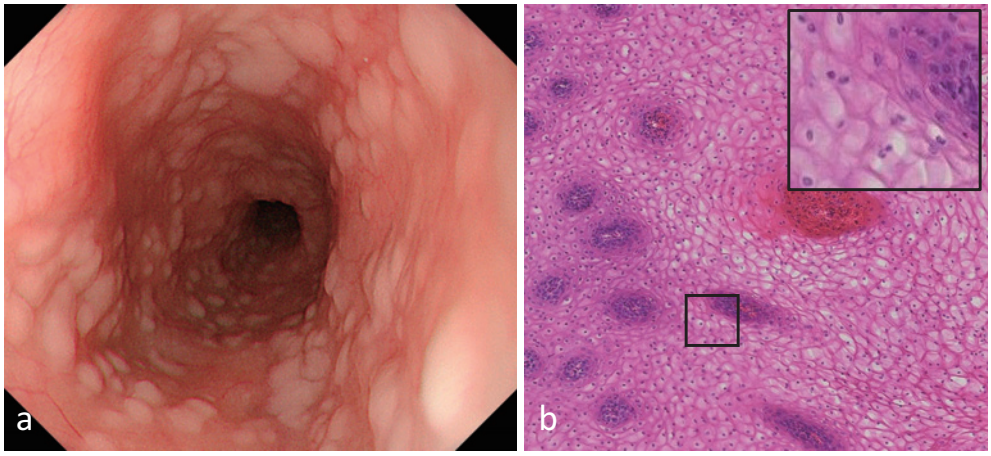

Figure 7. Glycogenic acanthosis of the esophagus.
a. Endoscopic examination of the esophagus reveals numerous white elevations.
b. Diagnosis of glycogenic acanthosis due to the presence of an increased number of spinous cells with bright and abundant cytoplasm. The inset is the magnified black square image.

2.3. Treatment

Although the characteristics of cancers occurring in patients with CS/PHTS have not yet been fully elucidated,

they all commonly have inactivation of *PTEN*. Therefore, proliferation rate, metastatic and invasive potential, and drug sensitivity are expected to be similar to those of cancers with somatic lineage variants of *PTEN*. Drugs that inhibit the PI3K/AKT/mTOR pathway, downstream of PTEN, may be effective, and clinical trials are currently underway.

1) Breast cancer

To our knowledge, no study has reported the characteristics of breast cancer in patients with this syndrome. However, hereditary breast cancer has a higher rate of intramammary recurrence than normal breast cancer when treated with breast-conserving therapy, and mastectomy is the preferred surgical option. No study has provided specific information on drug and radiation therapies for breast cancer in this syndrome, and the same treatment methods for breast cancer in the general population are currently selected. Risk reduction mastectomies should be considered based on the patient's individual clinical status as there is no evidence that prophylactic mastectomy improves the overall survival of this syndrome.

2) Thyroid cancer

As described above, thyroid cancers that occur in patients with this syndrome are follicular or papillary carcinomas. The characteristics of follicular and papillary carcinomas in this syndrome have not yet been documented. Therefore, surgical treatment, anticancer drug therapy, and intravenous radioiodine therapy are performed as the standard treatments for follicular or papillary carcinoma. Surgical treatment includes adenomectomy, subtotal thyroidectomy, or total thyroidectomy depending on the degree of progression and lymph node dissection.

3) Gastrointestinal polyps (see CQ2)

The polyps in this syndrome are pathologically diverse, including hamartomatous, adenomatous, hyperplastic, and inflammatory. Adenomatous polyps should be resected endoscopically if they are ≥6 mm in size, as in sporadic polyps. Other polyps, which generally have low carcinogenic potential, can be followed up if they are less than 10 mm in size.

4) Endometrial cancer

The characteristics of endometrial cancer in patients with CS/PHTS have not been investigated in detail. In general, the basic treatment for endometrial cancer is surgical resection of the uterus and bilateral adnexa. Pelvic and paraaortic lymph node dissection is additionally performed, where necessary, including the case with myometrial invasion. Resected organ tissues are evaluated for residual cancer and the risk of recurrence, and chemotherapy is administered if the risk of recurrence is high.

The prognosis of sporadic endometrial cancers with somatic *PTEN* mutation is relatively good, although currently no different treatment strategy for endometrial cancers is adopted between this syndrome and sporadic patients. Prophylactic resection of the uterus in this syndrome has not yet been fully discussed, and should be discussed individually.

5) Renal cell cancer

No study has reported the characteristics of renal cell cancer in patients with CS/PHTS. Therefore, surgical treatment and drug therapy are performed according to treatment strategies for sporadic renal cell cancer. Surgical treatment includes partial nephrectomy, radical nephrectomy, intravenous tumor resection, and lymph node dissection depending on the degree of progression.

2.4. Surveillance

As patients with CS/PHTS have a high risk of cancer, appropriate monitoring is necessary to detect cancer at a curable stage. The NCCN surveillance criteria are often used.

1) Breast cancer (see CQ3)

Women should start monthly regular breast self-examination at the age of 18 years and undergo interviews and palpation at the age of 25 years or 5-10 years prior to the youngest age of cancer onset in the family. Women should undergo annual mammography and gadolinium contrast-enhanced MRI at the age of 30 or 5-10 years prior to the youngest age of cancer onset in the family.

2) Thyroid cancer

A case of thyroid cancer has been reported a patient aged of 7 years, and the risk of carcinogenesis is 5% in patients aged < 20 years. Therefore, annual thyroid ultrasonography is recommended at the time of diagnosis, including in childhood.

3) Endometrial cancer

Transvaginal ultrasonography or biopsy of the endometrium is recommended once a year at the age of 30 years. However, biopsies have not been actively performed in Japan.

4) Colon cancer

Patients should undergo a total colonoscopy 5-10 years before the age of 35 years or the youngest age of cancer onset in the family. The frequency of subsequent examinations depended on the degree of polyposis.

5) Renal cell carcinoma

Annual renal ultrasonography is recommended from the age of 40 years.

2.5. Medical Expense Subsidy System

CS/PHTS is a chronic pediatric disease in Japan. Pediatric patients (under 20 years old) can receive financial support to cover the medical costs of a government-funded medical aid project for children with chronic diseases.

3. Clinical Questions and Recommendations

CQ1 Is referral to a dermatologist recommended when mucocutaneous lesions associated with CS/PTEN hamartoma tumor syndrome (PHTS) are observed?

We strongly recommend referral to a dermatologist to assess the presence of mucocutaneous lesions associated with this syndrome (genetic testing was not performed).

Evidence level D

Recommendation level: 1, strong

Explanation

CS/PHTS presents almost invariably with characteristic mucocutaneous lesions such as facial papules (trichilemmoma), acral keratoses on the dorsum of the hands and feet, palmoplantar keratoses, and oral mucosal lesions (99%-100%)[13,30]. As most of these lesions occur in the 10-20-year age group, they should be assessed to obtain an early diagnosis of this syndrome[13,30].

Small papules (trichilemmoma)(1-5 mm) with a flat elevated or papillomatous appearance occur in the central part of the face (eyes, mouth, nose, and forehead); 82.6%-98.3% of cases[13,31,32]. Histological examination revealed a typical finding of trichilemmoma only in 5.7% to 24.8% of cases, and it is particularly difficult to make a histological diagnosis in patients aged <18 years[20,31,32].

Acral keratoses on the dorsum of the hands and feet are flat papules (1-4 mm) with normal to slightly brownish color scattered on the dorsum of the hands and feet, occurring in 63-95% of cases[13,31,32]. Palmoplantar translucent keratoses were scattered on the palms and soles. It is sometimes accompanied by a central depression and is observed in 41.3% to 91.0% of cases[13,31,32].

Oral mucosal lesions consist of papillomatous papules (1-3 mm) arranged in a paving stone pattern on the gingiva, lips, buccal mucosa, and tongue, with a smooth surface and a slight whitish tinge to the surrounding mucosa; and are observed in 82.6%-95% of cases[13,31,32].

Recently, mucocutaneous neuromas have been added to the list of mucocutaneous lesions. Mucocutaneous neuromas are normal-colored to translucent dome-shaped elevated papules on the face, hands, palms, shins, and back, occurring in 5%-10% of cases[20,33]. It is particularly important for diagnosis when found in areas other than the face; five of the twelve cases reported so far occurred in children aged <10 years, which may provide a clue to the diagnosis during childhood[33]. Other symptoms include lipomas (38.0%-56.7%), vascular malformations (6.4%-21.7%), fibromas (0.6%-57.0%), and pigmented spots on the penis (29.4%-54.3%)[13,20,32].

Among these mucocutaneous lesions, facial papules are clinically difficult to distinguish from other skin tumors such as fibrofolliculoma, trichoepithelioma, and trichodiscoma. Therefore, it is necessary to perform a biopsy of at least one facial lesion in cases with only a few facial lesions[10]. Biopsy of multiple lesions is also suggested in young patients because the typical histological findings of an exophytic schwannoma is rarely observed[31,32]. However, the risk of skin cancer in Japanese patients remains unknown.

In the systematic review, no high-quality studies, such as randomized controlled trial cohort studies and case control studies, showing the significance of dermatologists for the diagnosis of this syndrome were found; therefore, the evidence is low. However, when summarizing previous case series, it is important to properly diagnose these cutaneous mucocutaneous lesions. If a physician other than a dermatologist suspects these lesions, they should collaborate with the dermatologist to establish an appropriate diagnosis, including a pathological diagnosis through biopsies.

CQ2 Is it recommended to resect the gastrointestinal polyps in patients with CS/PHTS?

As the risk of developing colorectal cancer is higher in patients with this syndrome than in the general population, resection of colorectal polyps, which are considered precancerous lesions, is weakly recommended.

Evidence level C

Recommendation level: 2, weak

Explanation

In this syndrome, polyps frequently occur throughout the entire gastrointestinal tract[34]. Polyps often develop in childhood, with the youngest case reported at the age of 2 years and 10 months[35]. Clinically important features of polyps include bleeding, intestinal obstruction, and carcinogenesis. The frequency at which gastrointestinal polyps in this syndrome cause bleeding and intestinal obstruction is unknown, and cases of polyp carcinogenesis have not yet been reported. However, cases of bleeding from gastric and colonic polyps and intestinal obstruction in the small and large intestines have been reported; therefore, polyps that cause bleeding or intestinal obstruction should be endoscopically resected.

Most cancers were colorectal among the gastrointestinal cancers reported in this syndrome, with the frequency of colorectal cancer being 2%-15%. The average age of the patients was 44-47 years[16,36]. The histological types of colorectal polyps in this syndrome are diverse, including hyperplastic, inflammatory, hamartomatous, and adenomatous. Some of these polyps supposedly develop into cancer, but the details of precancerous polyps and their mechanisms are unknown.

There is no existing evidence to confirm whether resection of colorectal polyps inhibits the development of colorectal cancer and improves its prognosis. However, based

on accumulated cases, the risk of developing colorectal cancer is higher in patients with this syndrome than in the general population, and thus resection of colorectal polyps considering precancerous lesions is weakly recommended. In particular, resection of endoscopically suspicious cancer, and adenoma and hamartoma, which are generally considered precancerous lesions, are expected to reduce the risk of advanced colorectal cancer. Although there is no existing evidence to confirm whether polypectomy is indicated for this disease, adenomatous polyps that are 6 mm or larger in size should be removed as in sporadic adenomatous polyps. Hamartomatous polyps 10 mm or larger in size should be removed according to the treatment strategy for hamartomatous polyps in other gastrointestinal polyposis syndromes[37]. However, it is not easy to differentiate hamartomatous polyps from the other polyps, such as hyperplastic polyps, by using biopsy alone.

For surveillance of colorectal cancer, the NCCN Clinical Practice Guideline recommends "total colonoscopy every 5 years starting at age 35 years (5 to 10 years earlier than the youngest age of onset of colorectal cancer if a close relative has colorectal cancer at age 40 years or younger)"[9]. More frequent surveillance, depending on the symptoms and presence of polyps, is proposed. Surveillance is performed every 3 years in patients with polyposis[38], every1-2 years in those with adenoma or multiple polyps[39], and every 3-5 years in those without adenoma or polyps[36]. By contrast, upper gastrointestinal endoscopy is recommended at the age of 15 years and every 2 to 3 years in patients with duodenal polyps[39]. However, no previous study on the surveillance of small-intestinal polyps has been reported.

CQ3 Is breast surveillance recommended in CS/PTEN?

Owing to the high risk of developing breast cancer in women with this syndrome, breast surveillance using mammography or contrast-enhanced MRI is strongly recommended.

Evidence level B

Recommendation level: 1, strong

Explanation

The lifetime incidence of breast cancer in female patients with this syndrome is high in all studies, although it varies from 25% to 85%[11,13,14,38,40]. In particular, a recent study of a large number of patients with germline pathological variants of *PTEN* gene reported that 77% to 85% of them developed breast cancer[11,38]. The average age of onset is 38-50 years, and the risk increases from the age of 30 years[11,38]. Histopathologically, most patients develop ductal carcinoma, but lobular carcinoma has also been reported[2]. However, selection bias was observed in the incidence of breast cancer. By contrast, breast cancer has been reported in only two male patients with this syndrome; the breast cancer in male patients with this syndrome is rare[41].

CS/PHTS is characterized by abnormalities in the mammary gland, such as ducts, lobules, and interstitium[14]. Fibrosis and hyalination of the interstitium are the characteristic features of this syndrome. Particularly, fibrous hyalinated nodules are frequently noted, similar to those observed in hamartomas[42]. Approximately 67%-89% of patients with this syndrome have these findings of mammary hamartomas, and 74% have malignant findings (mostly ductal carcinoma)[14,42,43]. Other benign lesions include fibroadenomas, ductal hyperplasia, and cysts. Benign lesions are often multiple, and carcinomas may be present in combination with benign lesions; therefore, care should be taken to differentiate carcinomas from benign lesions. However, these studies have not always examined a sufficient number of cases and there is insufficient evidence to show that women with this syndrome have a higher incidence of benign lesions than the general population.

To date, no study has examined the significance of breast surveillance in CS/PHTS. However, evidence from women at a high risk of breast cancer, such as hereditary breast and ovarian cancer syndrome (HBOC), suggests that mammography or gadolinium contrast-enhanced MRI may be effective surveillance modalities. Although the sensitivity of MRI is higher than that of mammography, MRI alone is not universally recommended because of its high cost and the risk of using contrast media. Benign lesions commonly develop in patients with this syndrome; hence, it is important to distinguish them from cancer.

As described above, the incidence of breast cancer in CS/PHTS is high, and the risk is almost certain to increase around the age of 30. Therefore, breast surveillance is strongly recommended, as in other high-risk groups, to screen for breast cancer.

Although a breast surveillance method for this syndrome has not been established in Japan, surveillance should be performed according to the NCCN guidelines 2023 Genetic/Familial High-Risk Assessment: Breast and ovarian[9]:

Breast self-examination should be started at age of 18 years.

Patients were interviewed and palpated every 6-12 months from the age of 25 years or 5-10 years prior to the youngest age of breast cancer onset in the family (whichever came first).

Screening with annual mammography or gadolinium contrast-enhanced MRI should be initiated at the age of 30-35 years or 5-10 years prior to the youngest age of breast cancer onset in the family (whichever came first).

CQ4 Is genetic testing for PTEN recommended in cases of suspected CS/PHTS?

Genetic testing for *PTEN* is weakly recommended in

cases where this syndrome is suspected.

Evidence level C

Recommendation level: 2, weak

Explanation

Genetic testing for *PTEN* is not included in the clinical diagnostic criteria for CS/PHTS. However, if a pathological variant of *PTEN* is found, the tested person can be diagnosed with this syndrome even if the clinical criteria are not met. Moreover, they have a high lifetime risk of developing breast, thyroid, endometrial, renal, and colorectal cancer[11]. Therefore, genetic testing for *PTEN* is important to diagnose this syndrome, understand the risk of carcinogenesis, and conduct appropriate surveillance. Genetic testing for *PTEN* is also recommended for the accurate diagnosis, risk evaluation of carcinogenesis, and appropriate surveillance of this syndrome in relatives. Genetic testing for *PTEN* should be performed after obtaining informed consent from the patient, following the provision of correct information on the sensitivity and limitations of the test and appropriate genetic counseling.

No previous studies have reported a high level of evidence regarding which patients should undergo genetic testing. Therefore, the NCCN Clinical Practice Guidelines recommend *PTEN* genetic testing for the following cases[1-4]:

1) Relatives of families with known pathological variants of the *PTEN* gene

2) Patients with a history of BRRS

3) Meets the clinical diagnostic criteria for CS

4) Patients who do not meet the clinical diagnostic criteria for CS, but meet

- Two or more major criteria (one must ne macrocephaly); or
- Three major criteria, without macrocephaly; or
- One major and 3 ≥ minor criteria; or
- ≥ 4 minor criteria

5) *PTEN* pathogenic variant detected by tumor genomic testing on any tumor type in the absence of germline analysis

Recent genetic testing for *PTEN* has shown that approximately 80% of patients with CS have pathological variants, but approximately 10% have deletions, duplications, or sequence abnormalities in the promoter region that cannot be detected using conventional testing[6,10]. Therefore, CS cannot be ruled out even in the absence of *PTEN* abnormalities. In other words, CS can be diagnosed if the clinical criteria for CS/PHTS are met, even if a pathological variant is not identified by *PTEN* genetic testing at this stage.

In conclusion, genetic testing for *PTEN* is recommended for patients with suspected CS/PHTS, considering the benefits for definitive diagnosis of this syndrome and for cancer surveillance. However, the level of evidence is C, as there is insufficient information on the type of genetic testing that should be performed, in which patients obtain benefits for definitive diagnosis and cancer surveillance.

Appendix

Members of the working committee who created and evaluated the "Clinical Guidelines for the Diagnosis and Management of Cowden Syndrome/PTEN Hamartoma Tumor Syndrome in Children and Adults" are listed bellow.

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Conflicts of Interest

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TT, MI, SO, SO, FK, YK, HK, MS, TS, KS, YT, HD, KB, SF, YF, TH, NM, HI, TI, YO, YS, NM, MM, NT, TA, TY, HI, and YN developed the clinical guidelines. All authors critically revised the report, commented on the drafts of the manuscript, and approved the final report.

Ethics Statement

The authors have no ethical conflicts to disclose.

Disclaimer

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Supplementary Files

Supplementary Figure 1. Diagnostic flowchart for Cowden syndrome/PHTS including PTEN testing criteria. CS: Cowden syndrome, PHTS: PTEN hamartoma tumor syndrome, LDD: Lhermitte-Duclos disease (adult form).

Please find supplementary file(s);
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