

CASE REPORT

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Hereditary breast cancer associated with Cowden syndrome-related PTEN mutation with Lhermitte-Duclos disease

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Abstract

Background: Cowden syndrome is characterized by multiple hamartomas in various tissues, including the skin, brain, breast, thyroid, mucous membrane, and gastrointestinal tract, and is reported to increase the risk of malignant disease.

Case presentation: We describe the case of a 52-year-old woman in whom a tumor was diagnosed in the left cerebellar hemisphere and treated by surgical resection. Phosphatase and tensin homolog (*PTEN*) mutation in exon 8 insertion was found in the brain tumor tissue and leukocytes. This finding supported the diagnosis of Cowden syndrome. She consequently developed endometrial cancer and underwent abdominal total hysterectomy with bilateral salpingo-oophorectomy. Four years later, hormone receptor-positive breast cancer was found in the right breast, and breast-conserving surgery with radiation therapy and sentinel lymph node biopsy was performed.

Conclusions: Herein, we describe a patient who was diagnosed as having familial breast cancer associated with *PTEN* mutation-related Cowden syndrome. We also reviewed reports of this syndrome in the literature for disease appraisal.

Keywords: Lhermitte-Duclos disease, Cowden syndrome, Breast cancer, Hereditary breast cancer, *PTEN* mutation

Background

Estimates show that up to 15% of breast cancer patients have one or more first-degree relatives with breast cancer [1]. Inherited breast cancer is caused by penetrant susceptibility genes and most often involves germ line mutations of the *BRCA1* and *BRCA2* genes in about 15% of familial breast cancer patients. Tumor protein 53 (*TP53*), cadherin 1 (*CDH1*), liver kinase B1 (*LKB1*), and phosphatase and tensin homolog (*PTEN*) are rarely associated with the development of breast cancer, which occurs in only about 3% of patients with familial breast cancer. Breast cancer in approximately half of women with a familial history may also result from unexplained genes [2].

Cowden syndrome (CS) is an autosomal dominant inherited cancer syndrome associated with germ line mutations in *PTEN*, a tumor suppressor gene. CS is characterized by

multiple hamartomas and developing breast, thyroid, and endometrial malignancies. Dysplastic cerebellar gangliocytoma called Lhermitte-Duclos disease (LDD) is also associated with CS [3, 4]. The cumulative lifetime risks of any cancer diagnosis is 89% for CS patients, and the morbidities are 85% in breast cancer, 32% in LDD, 21% in thyroid cancer, 19% in endometrial cancer, 15% in renal cancer, 16% in colon and rectum cancers, and 15% in kidney cancer [4, 5]. Herein, we report a case of *PTEN*-mutated hereditary breast cancer with LDD.

Case presentation

The patient was a 52-year-old woman with a prior history of chronic thyroiditis. Her sister was diagnosed as having congenital hydrocephalus and her mother as having heart valve disease. Her father died of myocardial infarction. The patient had a fall and sustained a head injury. Brain T2-weighted magnetic resonance imaging (MRI) revealed alternating isointense and hyperintense bands in the left cerebellar hemisphere (Fig. 1a). Surgical resection of the tumor in the cerebellar hemisphere was

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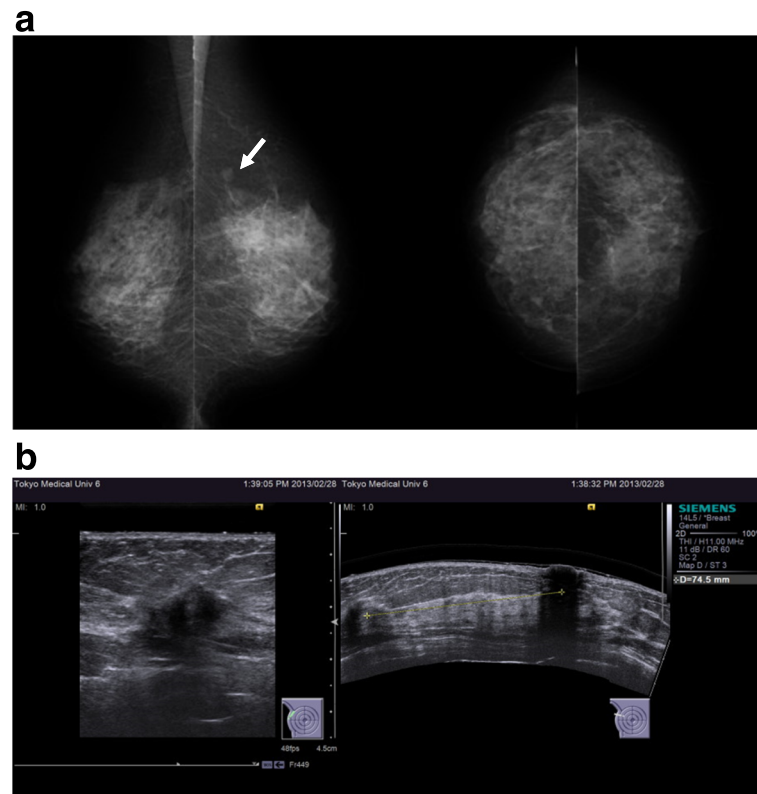


Fig. 3 MMG and US examinations at the age of 55 years. **a** A smooth mass was detected in the left breast by MMG. **b** An irregular indistinct mass (12 × 11 × 10 mm) was found in the right breast by US

in the codon of exon 8, resulting in the rearrangement of the amino acid sequence from valine to serine (Fig. 2). There were 27 reported cases of CS with deleterious mutation in Japan from 1984 to 2017 (May) according to *Igaku Chuo Zasshi* which is updated by the Japan Medical Abstracts Society.

PTEN participates in regulating the phosphoinositide 3 kinase (PI3K)-AKT and mTOR signaling pathways for negative regulation, controls cell proliferation and cell cycle progression, and promotes apoptosis. Thus, a loss of PTEN function correlates with the development of various human cancers [10]. It has been reported that *PTEN* is a gene in which mutation is most frequently found in primary breast cancers [11]. It remains controversial how the abnormality of this gene function may affect the prognosis of breast cancer patients. Previous reports of cases with CS revealed that most breast cancers were hormone receptor-positive including the present case (Table 1) [12–25]. Based on the history of the present case representing a slow-growing tumor, the clinical course of this case may be favorable. CS has a high risk of transforming into malignant tumors; thus, cancer surveillance is an important management for other organs [26]. The National Comprehensive Cancer Network (NCCN) recommendation is to undergo thyroid

ultrasound, colonoscopy, renal ultrasound, annual dermatologic examination, and annual endometrial biopsies. After genetic diagnosis, we performed screening for breast, thyroid, and endometrial malignancies. Endometrial adenocarcinoma was found. Usually, the recommended treatment for hereditary breast cancer associated with *BRCA1* mutation is mastectomy because it is a more aggressive cancer with a poor prognosis. However, as *PTEN*-related breast cancer tends to grow slowly, patients are not always required to undergo mastectomy. We therefore performed breast-conserving surgery in the present case.

The American Cancer Society and NCCN guidelines recommend MRI in addition to MMG for high-risk patients including those with *PTEN* hamartoma tumor syndrome [27, 28]. It may be necessary to apply screening of breast MRI to patients with a high risk for high-grade hereditary breast cancers such as *BRCA1* mutation carriers. However, screening breast MRI may not be practical to apply to all hereditary breast cancer cases because of its relatively low specificity and the high cost of enhanced breast MRI. It is also difficult to perform pathological examination if the lesion is detected only by MRI.

However, the usual screening management for breast cancer may be insufficient for patients with CS, because

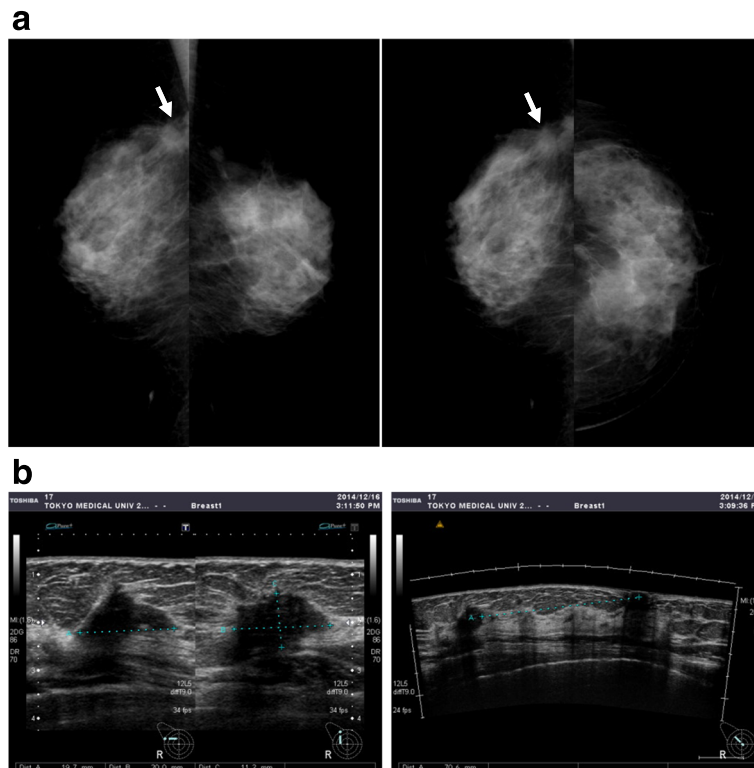


Fig. 4 MMG and US at the age of 57 years. **a** A spiculated mass was observed in the right breast. **b** The size of the irregular indistinct tumor in the right breast increased (20 × 20 × 11 mm) as shown by US

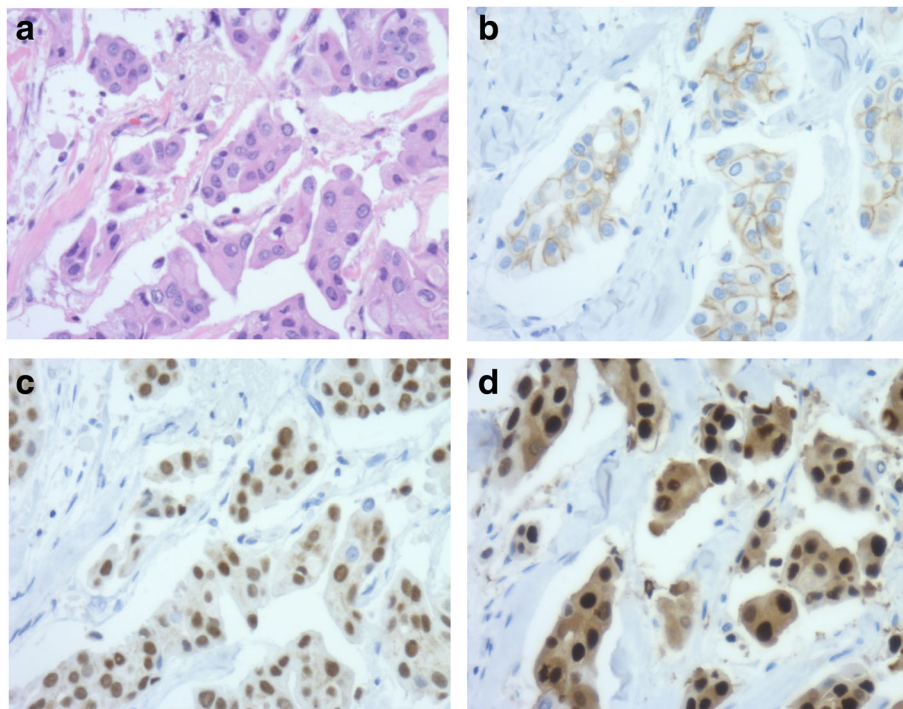


Fig. 5 Histopathological features of the tumor in this case. **a** Invasive micropapillary carcinoma (H&E staining, ×200). **b** Immunohistochemistry showed Her2 receptor 2+ (×200). **c** Estrogen receptor-positive staining of 100% (×200). **d** Progesterone receptor-positive staining of 100% (×200)

Table 1 Expression of hormone receptor in Cowden disease after 2000

Case	Age at surgery (Sex)	ER	PR	Her2	Pathology	Stage	Bilateral subtype	PTEN mutation
Kanayama Y, et al. (2011) [12]	61 (F)	+	Unknown	–	Invasive ductal carcinoma	T4cN2aM0	ER-PR-Her2-	Exon 5 exon 7 mutation
Morse CB, et al. (2015) [13]	40 (F)	n/a	n/a	n/a	ADH			Missense mutation
Kalin A (2013) [14]	37 (F)	+	+	–	Invasive ductal carcinoma	Stage IIb		Mutation
Peiró G, et al. (2010) [15]	44 (F)	+	+	–	Invasive ductal carcinoma	T2N0M0	ER+PR+Her2-	Exon 8 splice-acceptor site mutation
Erickson J, et al. (2010) [16]	39 (F)	+	+	Unknown	Invasive ductal carcinoma	Stage II		n/a
Winter H, et al. (2012) [17]	35 (F)	+	+	–	Invasive ductal carcinoma	T3N1M1		Frameshift mutation
Seo M, et al. (2014) [18]	22 (F)	n/a	n/a	n/a	DCIS			Frameshift mutation
Sabaté JM, et al. (2006) [19]	42 (F)	–	–	+	Invasive ductal carcinoma	T2N0M0		Mutation
Sabaté JM, et al. (2006) [19]	38 (F)	–	–	+	Invasive ductal carcinoma	T1N0M0		Mutation
Ball S, et al. (2001) [20]	38 (F)	+	Unknown	Unknown	Invasive ductal carcinoma	T2N0M0	DCIS	n/a
Walsh S, et al. (2011) [21]	34 (F)	+	Unknown	–	Invasive ductal carcinoma	T2N0M0		Exon 7 deletion and insertion
Fackenthal JD, et al. (2001) [22]	41 (F)	+	Unknown	Unknown	Invasive ductal carcinoma			Exon 7 splicing mutation
Baù MG, et al. (2004) [23]	50 (F)	+	Unknown	Unknown	Invasive ductal carcinoma	T1bN1aM0		Mutation
Nakamura T, et al. (2012) [24]	38 (F)	+	+	–	Invasive ductal carcinoma	T1N0M0		Exon 5 missense mutation
Kikuchi S, et al. (2014) [25]	40 (F)	+	+	–	Invasive ductal carcinoma	T1cN0M0		Exon 7 nonsense mutation
Kimura F, et al. (2017) [this case]	55 (F)	+	+	–	Invasive ductal carcinoma	T2N0M0		Exon 8 insertion

F female, M male, ADH atypical ductal hyperplasia, DCIS ductal carcinoma in situ

the mean age at diagnosis of breast cancer is reported to be about 40 years old in women with CS [29], which is younger than in the usual population. Thus, it is necessary to consider starting MMG screening at an earlier age and performing it more frequently such as once a year. Ultrasound could be another option, which may be useful for younger women and women with dense breasts [30].

Conclusions

In conclusion, we report the case of a rare familial breast cancer syndrome of CS. Unlike other familial breast cancers such as those with *BRCA1* mutation, breast cancers with CS are generally hormone receptor-positive and may have a favorable clinical course.

Abbreviations

CS: Cowden syndrome; CT: Computed tomography; LDD: Lhermitte-Duclos disease; MMG: Mammography; MRI: Magnetic resonance imaging; PTEN: Phosphatase and tensin homolog; US: Ultrasonography

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Authors' contributions

FK and TI wrote the manuscript. AU, JA, and TI performed the operation. ES diagnosed the disease pathologically. HK, KY, MH, YK, ST, MO, and TI contributed to the design and drafting of the manuscript. All authors read and approved the final version of the manuscript.

Consent for publication

Informed consent was obtained from the patient for the publication of this case report.

Competing interests

The authors declare that they have no competing interests.

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