

Cowden Syndrome: A Case Report

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Cowden syndrome is a rare autosomal dominant hereditary cancer syndrome caused by pathogenic variants in the PTEN gene and characterized by multiple hamartomas and increased lifetime risk of malignancies, particularly of the breast, thyroid, and endometrium. Breast is one of the most clinically significant organs affected, with a reported lifetime breast cancer risk of approximately 25–50%, and up to 80–85% in some series. Patients frequently present with bilateral and multiple benign breast lesions, including fibroadenomas, tubular adenomas, epithelial hyperplasia, microcysts, and hamartoma-like lesions, which may coexist with invasive carcinoma at a relatively young age. Imaging findings often demonstrate multiple well-circumscribed masses on mammography and ultrasonography and T2 hyperintense masses on MRI. On breast MRI, enhancement kinetics may overlap with those of malignancy, making radiologic differentiation challenging without clinical and genetic correlation.

Index words: Cowden syndrome; PTEN hamartoma tumor syndrome; Breast neoplasm; Magnetic resonance imaging; Hamartoma

Introduction

Cowden syndrome is a representative disorder within the spectrum of PTEN hamartoma tumor syndrome (PHTS), which includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, and Proteus-like syndrome. These conditions share pathogenic variants in the PTEN tumor suppressor gene

located on chromosome 10q23.3 (1–4).

PTEN encodes a lipid phosphatase that negatively regulates the PI3K/AKT/mTOR signaling pathway, thereby inhibiting cellular proliferation and survival. Loss of PTEN function results in dysregulated cell growth, leading to the development of multiple hamartomas and increased susceptibility to various malignancies (1, 3).

Cowden syndrome is characterized by mucocutaneous lesions, including facial trichilemmomas, acral keratoses, and oral papillomas, as well as hamartomatous and neoplastic involvement of the thyroid, breast, endometrium, kidney, and gastrointestinal tract. Among these organs, breast represents one of the most clinically significant high-risk sites, with a markedly increased lifetime risk of breast

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cancer compared with the general population (1, 3, 5).

Case Report

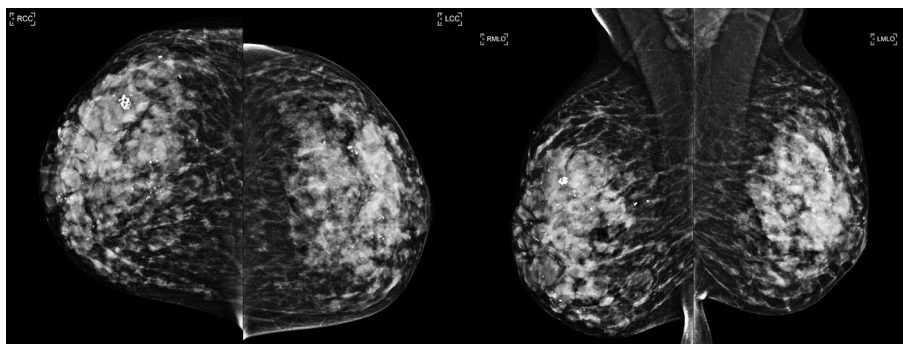
A 27-year-old woman presented with a 5-year history of bilateral serous nipple discharge and multiple palpable breast masses. She had no family history of breast cancer.

Mammography demonstrated numerous hyperdense and isodense masses diffusely scattered throughout both breasts. The masses were so extensive that evaluation of background parenchymal density was difficult. Round and coarse calcifications were observed (Fig. 1a).

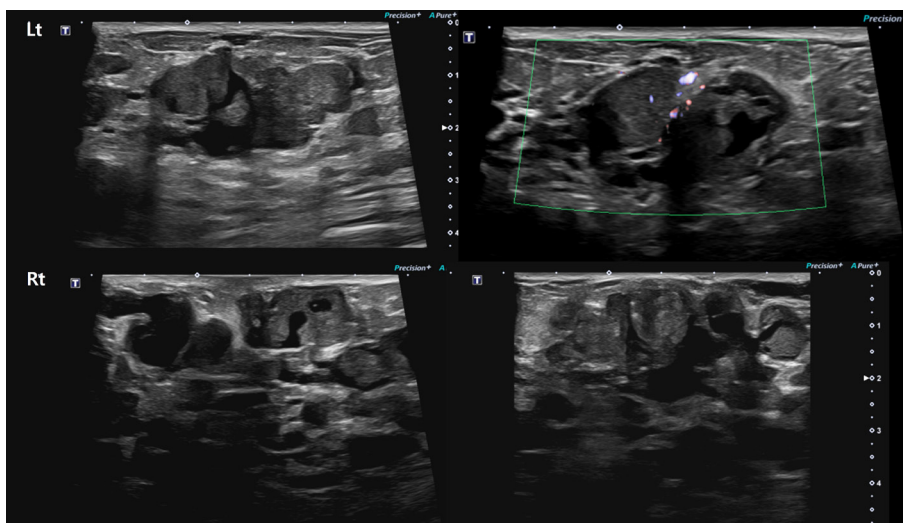
Ultrasonography revealed diffuse ductal dilatation in both breasts, accompanied by numerous isoechoic masses. Increased vascularity was observed within and around the masses. Diffuse papillomatosis was suspected. Core needle biopsy was performed for the largest lesions

in both breasts: a 3.8 cm mass at the 3 o'clock position in the left breast and a 4.7 cm mass at the 12 o'clock position in the right breast. Histopathologic examination revealed intraductal papilloma with florid ductal hyperplasia in the left breast and sclerosing papilloma with microcalcifications in the right breast (Fig. 1b).

Breast MRI demonstrated multiple enhancing solid masses in both breasts. T2-weighted images showed high-signal-intensity cystic lesions, and precontrast T1-weighted images demonstrated high-signal-intensity lesions consistent with hemorrhagic cysts. Ductal hemorrhage was observed in the left breast. Post-contrast images revealed multiple homogeneously enhancing solid masses. The biopsied right 12 o'clock lesion demonstrated delayed washout kinetics and diffusion restriction with an ADC value of $0.92 \times 10^{-3} \text{mm}^2/\text{s}$, which are typically considered suspicious imaging features.



a



b

Fig. 1. (a) Mammography shows numerous hyperdense and isodense masses diffusely involving both breasts, obscuring background parenchymal evaluation. (b) Ultrasonography demonstrates diffuse ductal dilatation with multiple isoechoic masses and increased vascularity. Core needle biopsy revealed intraductal papilloma with florid ductal hyperplasia (left) and sclerosing papilloma with microcalcifications (right).

However, because pathology was concordant with benign disease and similar imaging characteristics were present in multiple other lesions, short-term follow-up was recommended (Fig. 2a – f).

Additional systemic findings included multiple tiny facial papules present for 15 years. The patient had previously undergone right thyroidectomy, with histopathology revealing Hashimoto thyroiditis and follicular nodular disease. Colonoscopy demonstrated lymphoid hyperplasia and serrated polyps.

Direct sequencing of peripheral blood DNA identified a pathogenic PTEN mutation (Exon 5, c.388C>T, heterozygous). Based on the clinical, radiologic, and genetic findings, the patient was diagnosed with PTEN hamartomatous polyposis syndrome (Cowden syndrome).

Discussion

Breast involvement is observed in the majority

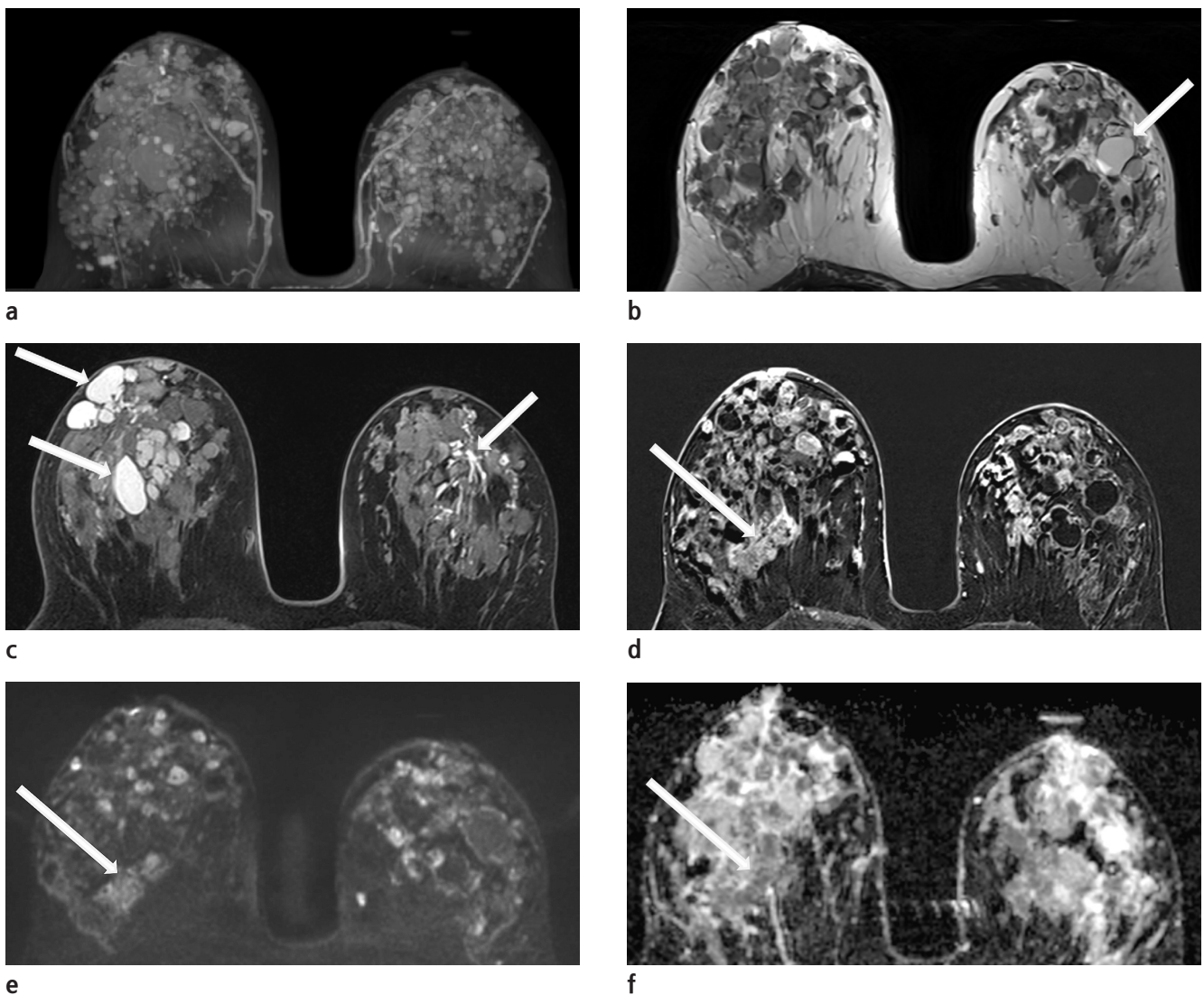


Fig. 2. (a) Breast MRI demonstrates numerous enhancing lesions diffusely involving both breasts. (b) T2-weighted image shows multiple high-signal-intensity cystic lesions (arrow). (c) Precontrast T1-weighted image reveals several high-signal-intensity lesions suggestive of hemorrhagic cysts, with ductal hemorrhage in the left breast (arrows). (d-f) The biopsied right 12 o'clock lesion demonstrates washout on delayed-phase imaging and diffusion restriction, with an ADC value of $0.92 \times 10^{-3} \text{ mm}^2/\text{s}$ (arrows).

of female patients with Cowden syndrome. A wide spectrum of benign lesions may be present, including fibroadenomas, tubular adenomas, epithelial hyperplasia, microcysts, apocrine metaplasia, and hamartoma-like lesions. These lesions are often bilateral and multiple, contributing to complex imaging findings (1, 3, 5, 6).

Malignant tumors most commonly manifest as invasive ductal carcinoma. Compared with the general population, patients with Cowden syndrome have a substantially elevated lifetime breast cancer risk, estimated at approximately 25–50%, with some studies reporting risks as high as 80–85%, far exceeding the ~12% lifetime risk in the general female population. In addition, breast cancer in this population tends to occur at a younger age, frequently in the third or fourth decade, and bilateral or multifocal disease is more common (1, 3, 5, 6).

Given this high-risk profile, patients with PTEN pathogenic variants are classified as high-risk individuals and require intensified surveillance. Current guidelines recommend annual mammography combined with annual breast MRI beginning at 30–35 years of age, or 5–10 years earlier than the age at which the youngest family member was diagnosed with breast cancer. (1, 3, 7, 8).

From a radiologic perspective, multiple bilateral well-circumscribed masses with associated ductal dilatation in a young patient should raise suspicion for an underlying genetic syndrome. MRI findings may demonstrate enhancement kinetics and diffusion characteristics that overlap with malignancy (5, 6). Therefore, radiologic interpretation must be integrated with clinical history, systemic findings, and genetic testing results to ensure appropriate management (1, 3, 6–8).

In the present case, a young woman with diffuse bilateral papillomatous breast lesions and associated systemic findings was ultimately diagnosed with Cowden

syndrome following identification of a pathogenic PTEN mutation. Despite suspicious MRI features in several lesions, histopathology confirmed benign disease. This case illustrates the importance of correlating imaging findings with clinical and genetic information in young patients presenting with multifocal bilateral breast lesions.

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카우덴 증후군: 증례 보고

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카우덴 증후군은 PTEN 유전자의 병적 변이에 의해 발생하는 드문 유전성 종양 증후군으로, 유방을 포함한 여러 장기에서 양성 및 악성 병변이 동반될 수 있다. 유방에서는 다발성 양성 종괴와 함께 악성 병변이 혼재할 수 있으며, 영상 소견만으로는 감별이 어려운 경우가 있다. 저자들은 다발성 유방 병변을 보인 카우덴 증후군 증례를 영상 소견과 함께 보고하고자 한다.

색인단어: 카우덴 증후군; PTEN 과오종 종양 증후군; 유방종양; 자기공명영상; 과오종

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