Case Report

A Case of Cowden Syndrome

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Abstract: The association between breast cancer and Cowden syndrome due to the *PTEN* gene mutation is well known. We herein present the case of a 38-year-old woman who underwent a laparoscopic D2 right hemi-colectomy and sigmoidectomy for colon cancer, and at the same time, the patient was diagnosed with Cowden syndrome by gene analysis and the typical clinical manifestations of Cowden syndrome.

She returned to our clinic approximately one year later with a left infra axially palpable mass. Subsequently, a tylectomy was performed and the histopathological analysis revealed an accessory breast cancer. The patient immediately underwent an extended resection, and an axillary level I lymph node dissection. Pathological findings showed no remaining carcinoma or lymphoid metastasis. She then received hormone therapy with tamoxifen and LH-RH analog.

Approximately eight months thereafter she experienced a new onset right breast cancer for which we successively, performed a modified radical mastectomy.

In summary, given her genetic history and high potential for malignancy, radical mastectomy was the best procedure of choice. Obviously, she will continue to need close observation, with particular attention paid to the contralateral breast, thyroid, and to continue to monitor her for any recurrence of colon cancer.

Key Words: Accessory Breast Cancer, Breast Cancer, Colon Cancer, PTEN Hamartoma Tumor Syndrome, Cowden Syndrome.

Introduction

Cowden syndrome, also termed Cowden disease, is an autosomal dominant disorder characterized by multiple hamartomas, which develop especially in the gastrointestinal (GI) tract, breast, thyroid, skin, and brain. Cowden syndrome increases the risks of developing breast, GI tract[1], thyroid, and other cancers[2]. Due to the fact that Cowden syndrome is rare and often goes unnoticed, it is important to

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consider in cases of early onset or in synchronous bilateral breast carcinoma (SBBC) as these suggest a hereditary cause[3-4]. In some cases of diagnosed Cowden syndrome, observation alone with careful tumor surveillance is all that is required. The fact that approximately 80%-90% of hereditary breast cancer cases are caused by mutations in the *BRCA1* and *BRCA2* genes is well known, however clinicians should also recognize Cowden syndrome and other syndromes that predispose patients to the development of breast cancer. Genetic testing can then afford our patients and their family members the opportunity to make informed and appropriate medical management decisions leading to improved future quality of life.

Here we report a typical case of Cowden syndrome with onset of accessory breast cancer, breast cancer, and colon cancer in order to promote awareness of this potentially fatal disease.

Case presentation

A 38-year-old woman had previously undergone screening esophagogastroduodenoscopy (EGD) and was found to have pharyngeal polyposis, esophageal glycogen acanthosis (Fig. 1). And, she was diagnosed with ascending and sigmoid colon cancer (Fig. 2), found on screening colonoscopy

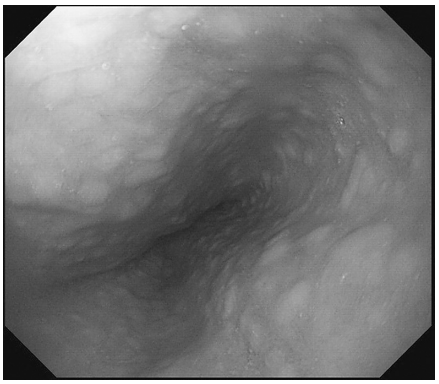

Fig. 1. Esophageal acanthosis and multiple hamartomatous polyps should suggest Cowden syndrome.

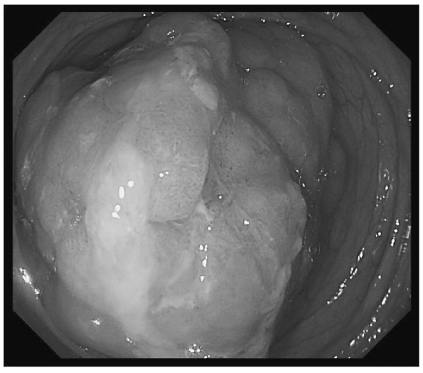

Fig. 2. Colonoscopy revealed ascending colon cancer.

simultaneously.

The patient subsequently underwent a laparoscopic D2 right hemi-colectomy and sigmoidectomy (both of them are adenocarcinoma, T1N0M0). We were very suspicious of a tumor suppressor gene mutation, given her young age, findings of multiple polyps in her GI tract, glycogen acanthosis, and GI tract cancer.

Genetic analysis revealed a mutation of the *PTEN* gene (chromosome 10q 22-23 at exon 5, codon 130). This mutation resulted in a missense mutation where the normal codon of CGA (Arg) was replaced with the codon CAA (Gln). This is one of the most common sites influenced by genetic mutation. This, finding along with this patient's clinical presentation, led to the diagnosis of Cowden syndrome. Subsequently extensive imaging studies were performed to determine whether or not she had other malignant tumors, precancerous lesions, or other lesions associated with Cowden syndrome.

Mammography and Ultrasound Sonography (US) results revealed right breast mastopathy without suspicion for carcinoma. MRI results showed no evidence of cerebellar tumor, a common complication of Cowden syndrome, also referred to as Lhermitte - Duclos disease.

After the operation, the patient was discharged in stable condition, without complication, and given close follow up at our outpatient clinic.

She returned to our clinic approximately one year later with a left infra axially palpable mass (Fig. 3). US and mammography results revealed a 15 mm diameter left infra axially mass with an irregular rim (Fig. 4). The patient subsequently underwent tylectomy.

Histopathological analysis revealed atypical cells with formed cribriform configurations (Fig. 5). Micro-invasive ductal carcinoma was seen in a left accessory breast tissue. Immunohistochemical examination revealed that characteristics of cell surface markers as followed: CD7(+), CD20(−), ER(+), PgR(+) and HER2(−), which supported the diagnosis of an accessory breast cancer, but not metastasis from a colon cancer. In light of these pathological findings, the patient needed to undergo an extended resection of accessory breast tissue and a level I lymphoid resection as soon as possible. Pathological findings did not show either remaining carcinoma or lymphoid metastasis. This patient did undergo endocrinological therapy with tamoxifen and LH-RH analogue.

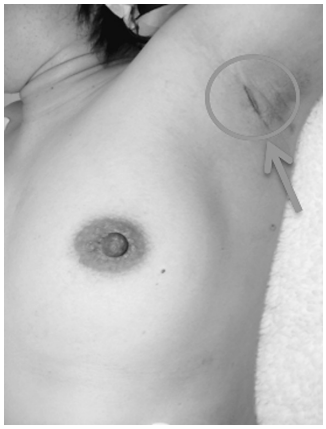

Fig. 3. There was a left infra axially palpable mass (red arrow).

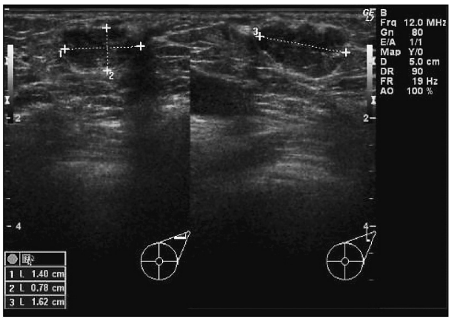

Fig. 4. US results revealed left infra axially mass with an irregular rim.

After eight months, a surveillance mammography and whole body CT scan, revealed a 15 mm diameter right breast mass with an irregular rim in the lateral region (Fig. 6) which had not been previously detected. A fine needle aspiration biopsy of the suspicious mass was preformed and histopathological examination revealed a ductal carcinoma, thus we performed a right modified radical

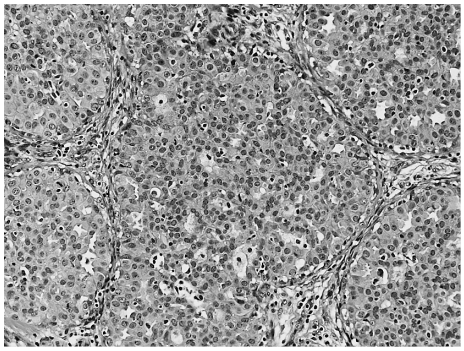

Fig. 5. Microscopy and histopathological analysis revealed heteromorphous cells with formed cribrational configurations (H&E).

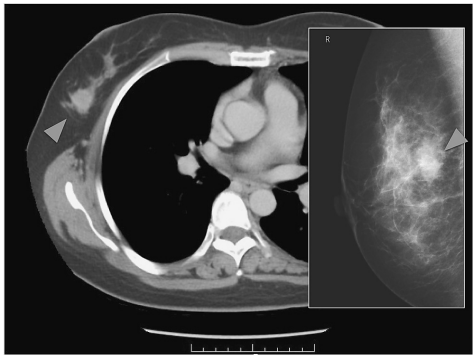

Fig. 6. Mammography and Computed Tomography scan revealed a 15 mm diameter right breast mass with an irregular rim in the CD region.

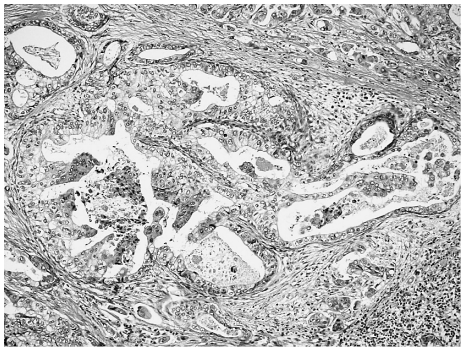

Fig. 7. Photomicrograph of right breast invasive ductal carcinoma H&E.

mastectomy in order to avoid recurrence of breast cancer in the remaining breast tissue. The results of the operation showed a papillotubular carcinoma, 2.0×1.5 cm, invasion f, and margin (−)(Fig. 7). Further pathological results showed the tumor was v(−), ly(+), n(1/21: Level I: 1/21), ER(−), PgR (−), and HER2(3+). Pathological staging revealed T1N1M0. Consequently, she underwent chemo-endcrine therapy with docetaxel, cyclophosphamide and trastuzumab. Currently, we followed up of her for one year without symptom and there is no evidence of any recurrent disease.

Discussion

Germline mutations in the *PTEN* gene have been found in about 80% of patients with Cowden syndrome. However, approximately 20% of patients with Cowden syndrome are negative for *PTEN* mutations and have no identifiable genetic explanation for their clinical features. Various other possible mechanisms of *PTEN* inactivation have been explored, but as yet no clear answer has been identified[5-6].

The *PTEN* gene encodes a dual specificity protein and lipid phosphatase that regulates the phosphoinositol-3-kinase/Akt signal pathway, which can result in cell cycle arrest in the G1-phase and lead to cell death[5-6].

The international Cowden Consortium operational criteria for the diagnosis of Cowden syndrome is being advocated, however diagnosing Cowden syndrome remains difficult due to the wide variation in its clinical features. A recent molecular-genetic study estimates that the incidence of Cowden syndrome approaches 1/200,000, although the actual incidence may be higher. The pathognomonic features of Cowden syndrome include mucocutaneous lesions such as trichilemmomas, acral keratoses, papillomatous lesions, and mucosal lesions, which are present in 99% of affected individuals by their late 20s. Major criteria include manifestations of breast cancer, thyroid cancer (non medullary), endometrial carcinoma, and macrocephaly accompanied by mental retardation[7]. The lifetime risk of breast cancer reaches up to 25-50% in women with Cowden syndrome. This is about three to four times higher than the general female population. The lifetime risk of epithelial thyroid cancer can be as high as 10% in both males and females with Cowden syndrome.

On the other hand, there is evidence that some individuals with known germline *PTEN* mutations never experience malignancy. It is believed that this is due to the fact that a second mutation interrupting the function of the gene, therefore the process of tumor formation never occurs. This is why malignancy in Cowden syndrome may appear to skip generations within a family. All individuals with the germline *PTEN* mutation, regardless of whether they contract cancer, have a fifty percent chance to pass the mutation on to the next generation[8].

In cases of Cowden syndrome in which breast cancer has been detected, it is best to perform radical mastectomy because of the high rates of malignancy. Due to this high risk it is recommended that mammography should be performed every six months, professional physical examination quarterly, and women should carry out a monthly self-examination. Furthermore, some authors have recommended prophylactic bilateral mastectomy for particularly high-risk women, even in those without a history of prior breast malignancy, for those with extensive fibrocystic breast disease, or those with unilateral breast carcinoma at any stage[9-11]. The rational here being to remove the breast before an underlying malignant lesion can develop or possibly reoccur. Of course this puts an emphasis on early recognition and diagnosis of Cowden syndrome by the presence of mucocutaneous lesions and careful history

taking. Again in all instances of this disease carful surveillance and close follow up is of utmost importance.

On the other hand some may argue that some patients prefer partial mastectomy instead of total resection. Furthermore, it may be argued that extended surgery is not indicated for patients whose breast cancer would be amenable to partial mastectomy. However, if partial mastectomy is performed for patients with Cowden syndrome the likelihood for subsequent breast cancer is high. Furthermore, after partial mastectomy patients generally undergo adjuvant radiation treatment on the remaining mammary tissue. This sort of treatment has been shown to subsequently induce the formation of multiple radiation-induced fibrous hamartomas in the surrounding irradiated regions within several months[12]. This is probably due to multiple loss of heterozygosity (LOH) events. Consequently, this latter approach can predispose patients to further malignancy and may be contraindicated for patients with Cowden syndrome.

Conclusion

In general, it is of vital importance to observe this patient for tumor progression, and to pay particular attention to the contralateral breast, thyroid, and other potential malignancies. Furthermore, recognition of Cowden syndrome and other genetic mutations give us the opportunity to anticipate the development of malignancies such as breast cancer and treat them as early as possible. Genetic counseling for our patients and their families in these situations is a must in order to provide appropriate and informed medical assessments and aid in decision-making.

These will lead to better results and improved survival rates in patients with Cowden syndrome.

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〈和文抄録〉

Cowden syndrome の一例

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PTEN 遺伝子変異による Cowden syndrome と乳癌との関連性は良く知られている．38 歳女性で腹腔鏡下に右半結腸切除及びS状結腸切除D2郭清術を施行し，同時に遺伝子検査で*PTEN*変異確認し，さらに典型的な臨床所見から Cowden syndrome と診断した症例を報告する．

術後約 1 年後に左腋窩腫瘤を自覚し，腫瘤摘出術を実施した．病理検査の結果，左副乳癌と診断され，続いて左腋窩の腫瘍摘出部周囲の拡大切除及び左腋窩 levelⅠリンパ郭清を実施した．病理検査の結果は癌の遺残は認めず，リンパ節転移は認めなかった．術後補助療法としてタモキシフェンと LH-RH analog 治療を実施した．さらに 8 ヶ月後に新規の右乳癌を発症し，右胸筋温存乳房切除術を実施した．

悪性腫瘍の発生率の高い Cowden syndrome と診断された患者が乳癌を発症した場合，部分切除の基準内であったとしも部分切除ではなく，胸筋温存乳房切除術の実施が推奨される．今後，特に対側乳癌，甲状腺癌，大腸癌の再発に特に注意を払いながら定期的な経過観察が必要と考えられる症例である．

キーワード：副乳癌，乳癌，大腸癌，PTEN Hamartoma Tumor Syndrome，Cowden 病．