Synchronous Double Tumor of Breast Cancer and Gastrointestinal Stromal Tumor in a Patient with Neurofibromatosis Type 1: Report of a Case

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Abstract. *We report a rare case of synchronous double tumor formation of breast cancer and gastrointestinal stromal tumor (GIST) in a patient with neurofibromatosis type 1(NF-1). A 76-year-old woman with a history of NF-1 who had undergone left modified mastectomy for breast cancer seven years previously was admitted to our hospital because of a right breast tumor and abdominal discomfort. Computed tomography revealed an enhanced irregular tumor in the right breast and peripheral enhanced tumors in the abdomen. The patient underwent right modified mastectomy and laparoscopic tumor resection combined with small intestine surgery. Histopathological examination revealed the presence of invasive lobular carcinoma in the right breast and GIST in the abdomen. The synchronous development of breast cancer and GIST in a patient with NF-1 is extremely rare, with this being the second case ever reported.*

Neurofibromatosis type 1 (NF-1), also called von Recklinghausen's disease, is the most common autosomal dominant disorder, with a prevalence of approximately 1 in 3000 individuals. NF-1 is associated with the formation of various benign and malignant neoplasms (1). Although malignant tumors are reported four times as often in NF-1 patients than in the general population, the synchronous double formation of breast cancer and gastrointestinal stromal tumor (GIST) in NF-1 patients is extremely rare, with only one case being reported previously (2). Herein, a case of synchronous formation of breast cancer and GIST in an NF-1 patient is reported. Clinicopathological characteristics are discussed along with a review of the relevant literature.

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Case Report

A 76-year-old woman with a history of NF-1 from the age of 18 years was admitted with complaint of a solid tumor in the right breast and abdominal discomfort. On examination, there were multiple cafe au lait spots and discrete cutaneous neurofibromas over the patient's body. Seven years previously, she had undergone left modified mastectomy with axillary dissection for the treatment of invasive ductal carcinoma (T2N1M0) in another institute. Immunohistochemical analysis of the invasive ductal carcinoma showed negative staining for estrogen receptor protein (ER), progesterone receptor protein (PgR), and human epidermal growth factor receptor 2 (HER2). The patient was administered 4 courses of 80 mg/m^2 Paclitaxel.

On physical examination, an irregular hard lump with skin retraction measuring approximately 3.0×2.0 cm was palpable in the upper outer quadrant of her right breast. Chest computed tomography (CT) confirmed a 3.1×2.0 cm enhanced irregular lesion (Figure 1). Neither lymphadenopathy nor distant metastasis was detected. Core needle biopsy of the right breast tumor yielded a diagnosis of invasive lobular carcinoma. Abdominal CT showed solid and peripherally enhanced tumors with calcification in the upper left and lower right quadrants (Figure 2). The patient was successfully treated with right mastectomy with sentinel lymph node biopsy for invasive lobular carcinoma; subsequently, laparoscopic tumor resection combined with that of the small intestine was performed for abdominal tumor. Upon laparotomy, a few parenchymal lesions of the small intestinal wall (3-5 cm) and many peritoneal nodules (1 cm) were found. Parenchymal lesions of the small intestine in the right lower abdominal quadrant were removed because the small intestine was involved and the intestinal lumen was

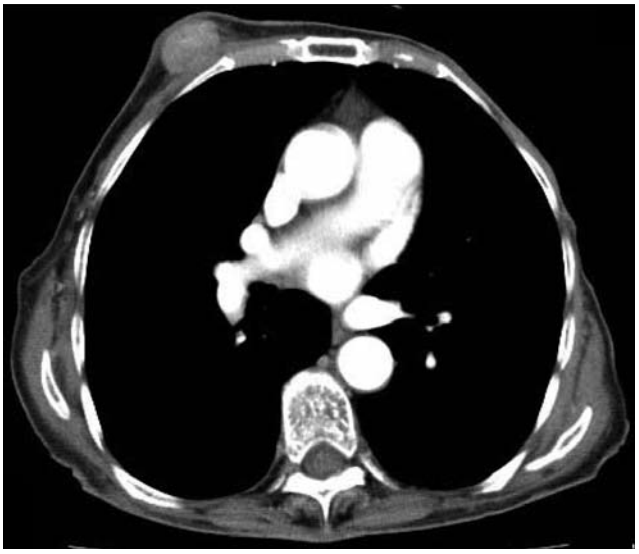

Figure 1. *Computed tomographic image of the breast, showing 3.1×2.0 cm enlarged tumor in the left breast without lymphadenopathy.*

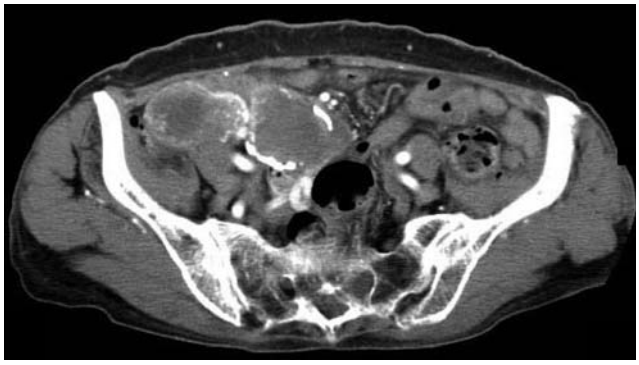

Figure 2. *Computed tomographic image of the abdomen, showing solid and peripheral enhanced tumors with calcification in the right lower abdomen.*

narrowed by the tumor which could have led to future obstruction. The parenchymal lesions in the upper left quadrant were not removed, as there was persistence of macroscopic peritoneal disease. Histological examination of the right breast showed invasive lobular carcinoma (T2N0M0; ER–, PgR–, HER2–; Figure 3). Histological examination of the abdominal tumors revealed proliferation of spindle tumor cells arranged in a bundular pattern (Figure 4A). A mitotic count showed 3 mitoses per 50 high-power fields. Immunohistochemical staining was positive for c-KIT (Figure 4B) and CD34 and negative for S-100 and αsmooth muscle actin. The tumor was diagnosed as a GIST. The patient was administered epirubicin/cyclophosphamide (EC) therapy with 90 mg/m^2 epirubicin, and 600 mg/m^2 cyclophosphamide, followed by 400 mg/day imatinib mesylate (IM). She is now in a satisfactory condition without complaint at 6 months after surgery. Upon follow-up, CT imaging demonstrated that the size of the GIST in the left upper quadrant had not changed.

Discussion

NF-1, which was first reported by von Recklinghausen in 1882, is characterized by abnormal skin pigmentation, and cutaneous and plexiform neurofibromas. It is mainly caused by mutation of the NF-1 gene, which is located in chromosome band 17q 11.2. The NF-1 gene encodes a 327-kDa protein known as neurofibromin. In most cases, the mutations responsible for NF-1 result in truncations of neurofibromin (1). Patients with NF-1 have an estimated 3- 15% additional risk of developing malignancy during their lifetime (3).

GIST is the most common type of gastrointestinal mesenchymal tumor and is thought to form via the activation of c-KIT receptor tyrosine kinase through mutation of the c-KIT gene (4). The incidence of GIST in patients with NF-1 rangs between 3.9% and 25% (5). Both the characteristics and the tumor genesis of GISTs in patients with NF-1 are different from those of sporadic GISTs. GIST in NF-1 patients develops in the small intestine and forms multiple lesions in most cases. On the other hand, sporadic GISTs occur as solitary lesions, most commonly in the stomach (6). GIST associated with NF-1have a better prognosis than sporadic GISTs of the same size and stage (7). As c-KIT mutation is rare in GIST associated with NF-1 (8), the mechanism of development of these GISTs may be explained by loss of heterozygosity of NF-1, rather than a mutation of the c-KIT gene (9).

The association of NF-1 with breast cancer has been rarely reported. Maruyama *et al*. (10) reported that breast cancer associated with NF-1was commonly staged higher than T2. This may be because multiple neurofibromas obscure breast mass at palpation, leading to delayed detection of the cancer. In a previous Japanese review, Nakamura *et al*. (11) found that in 18.5% of NF-1 cases, patients with breast cancer were younger than 35 years, in contrast to the rate of 6.7% reported in earlier case series. Recently, Sharif *et al*. reported that women with NF-1 have a 5-fold increased risk of developing breast cancer at less than 50 years of age, compared with women in the general population. This is likely because of linked mutations in NF-1 and the breast cancer susceptibility gene BRCA1, both of which are located in the same long arm of chromosome 17 (9). BRCA1-positive patients with breast cancer are more often premenopausal (12). Women with NF-1 are advised to have yearly screening for breast cancer from the age of 40 years (9).

Cancer associated with NF-1 can be treated and managed with anticancer drugs, following the same clinical principles

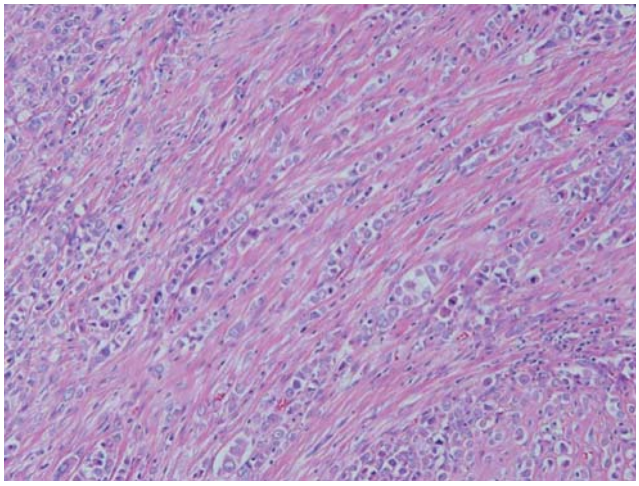

Figure 3. *Microscopic findings in the left breast, indicating the presence of invasive lobular carcinoma. Small and round cancer cells infiltrate the breast tissue, showing Indian file arrangement. (hematoxylin and eosin, ×100).*

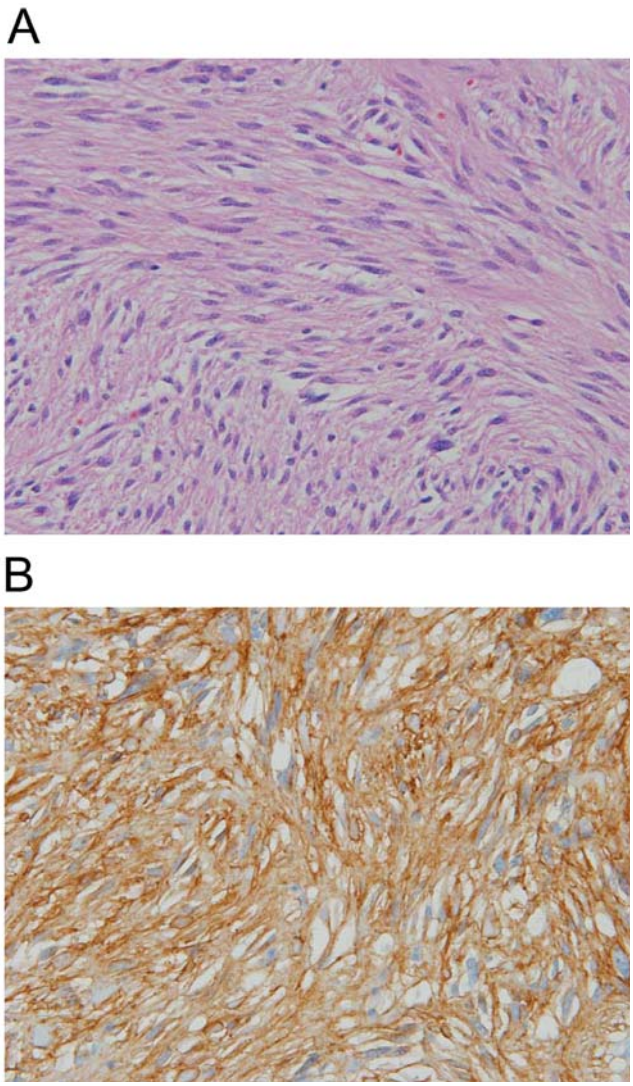

Figure 4. *Microscopic findings in the abdominal tumor, showing that tumors were composed of spindle tumor cells arranged in fascicles (A, hematoxylin and eosin, ×400). The tumor cells were immunohistochemically positive for c-KIT (B, ×400).*

as those used for patients without NF-1. In the current case, the patient was administered EC followed by 400 mg/day IM, which acts by inhibiting active mutant c-KIT. However, the response rate to IM treatment is lower in NF-1 patients than in non-NF-1 patients due to differences in exon mutations (13). If tumor progression occurs after daily administration of 400 mg IM, the daily IM dose is increased to 800 mg (14). IM can influence intestinal fluid pressure (IFP). Increased IFP, present in malignancies, has been postulated to interfere with drug uptake. Preclinical data has shown that IM combined with paclitaxel reduces tumor IFP and is more effective in the treatment of KAT-4 tumors in vivo than either agent alone (15). Complete response has also been reported in patients with stage IV seminoma after the administration of IM in combination with cytotoxic drugs (16). However, a phase I trial recently showed that the continuous use of IM at a dose of 400 mg per day in combination with cytotoxic drugs for the treatment of patients with solid tumors was associated with unacceptable toxicity (17). As increasing the entry of anticancer drugs into cells by reducing IFP with IM administration may be both concentration- and time-dependent (18), it was not possible to establish a regimen with IM and anticancer drugs in the current case. Therefore, we administered IM therapy after EC therapy and did not administer synchronous treatment.

It is unclear whether the NF-1 gene plays a role in the development of both breast cancer and GIST. Synchronous development of breast cancer and GIST in NF-1 patients is extremely rare, with only one case being reported previously (2); a 60-year-old woman affected by NF-1 who was coincidentally diagnosed with GIST, breast cancer and peripheral nervous system tumor. The average lifespan of patients with NF-1 is reduced by 10-15 years, and malignant tumors are the most common cause of death in individuals with this syndrome (3). Screening tests for the detection of cancer are strongly recommended for NF-1 patients. In addition, systemic and careful exploration is essential for detection of malignancies in patients with NF-1.

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