

[CASE REPORT]

Neurofibromatosis Type 1 with the Development of Pheochromocytoma and Breast Cancer

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Abstract:

A 40-year-old woman presented with a left adrenal incidentaloma. Based on the presence of café-au-lait spots, cutaneous neurofibroma, and family history, she was diagnosed with neurofibromatosis type 1 (NF1). Adrenal incidentaloma screening showed an elevated normetanephrine level; the left adrenal mass showed the uptake of I-123 meta-iodobenzylguanidine. She underwent left adrenalectomy, and pheochromocytoma was diagnosed. One year later, the results of a biopsy of a palpable mass in the left breast suggested invasive ductal carcinoma. The patient underwent neoadjuvant chemotherapy followed by left breast-conserving surgery. We herein report a rare case of an NF1 patient who developed both pheochromocytoma and breast cancer.

Key words: neurofibromatosis type 1, pheochromocytoma, breast cancer

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Introduction

Although the frequency varies by country, neurofibromatosis type 1 (NF1), also called von Recklinghausen's disease, is an autosomal dominant genetic disorder with an incidence of approximately 1 in 2,600 to 3,000 individuals (1, 2). The elevated incidence of cancer is a major cause of decreased life expectancy (8-21 years) among this patient population (3-7). The diagnostic criteria for NF1, as presented by the National Institutes of Health (NIH), state that NF1 can be diagnosed if two or more of the following conditions are met: six or more café-au-lait spots; freckling in the axillary or inguinal regions; two or more neurofibromas of any type or one plexiform neurofibroma (PNF); unilateral or bilateral optic glioma; two or more iris Lisch nodules; a historically distinctive osseous lesion such as dysplasia of the sphenoid bone or thinning of long bone cortices, with or without pseudoarthrosis; or a first-degree relative with NF1 (8). Additional genetic testing for the *NF1* gene can be performed in cases in which a patient does not meet the NIH diagnostic criteria but in which NF1 is strongly sus-

pected (9).

The higher incidence rate of benign and malignant tumors among patients with NF1 in comparison to the general population is well known. Reports suggest that the incidence of malignant peripheral nerve sheath tumors, intracranial gliomas, gastrointestinal stromal tumors, pheochromocytoma and rhabdomyosarcomas is particularly high (10).

Despite the higher incidence of benign and malignant tumors in patients with neurofibromatosis, cases in which several types of tumor concurrently affect a patient are rare. We herein describe the case of a woman who developed both pheochromocytoma and breast cancer.

Case Report

A 40-year-old woman presented to our hospital with a left adrenal incidentaloma that was identified on an abdominal CT scan taken at another hospital on the previous day due to abdominal pain (Fig. 1). At the time of admission, a physical examination revealed the following: blood pressure, 100/60 mmHg; 66 beats/min, respiratory rate, 17 breaths/min; and body temperature, 36.4°C. The patient displayed

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six or more café-au-lait spots across her body and had several cutaneous neurofibromas that had started to develop 8 years previously (Fig. 2). During the documentation of her history, we discovered that her mother and younger brother had neurofibromatosis. We were able to clinically diagnose the patient with NF1 using the NIH diagnostic criteria for the disease. The patient had an elevated plasma level of normetanephrine (18.7; reference <0.90 nmol/L) and normal plasma metanephrine (0.30; reference <0.50 nmol/L). We therefore performed an I-123 MIBG scan (Fig. 3). After 2 weeks of alpha blockade, left adrenalectomy was performed due to the suspicion of pheochromocytoma. A postoperative pathological examination confirmed the diagnosis of pheochromocytoma (Fig. 4). After left adrenal resection, the patient's plasma normetanephrine level normalized and her plasma metanephrine level was normal. Four months later, the patient visited our neurosurgery department due to a headache. Brain MRI taken at the time showed no notable findings other than focal areas of signal intensity, a neurofibromatosis-specific finding (Fig. 5). At one year after left adrenalectomy, the patient developed a palpable mass in



Figure 1. Computed tomography of the abdominal pelvis. An adrenal incidentaloma (4.4 cm × 3.5 cm × 6.1 cm) was detected in the left adrenal gland (arrow), and a hemangioma was detected in the liver (arrowhead, biopsy proven).

the left breast. She was diagnosed with invasive ductal carcinoma by needle biopsy (Fig. 6). The patient underwent neoadjuvant chemotherapy followed by left breast-conserving surgery. She is currently receiving adjuvant radiotherapy, hormonal therapy with tamoxifen (20 mg, daily), and trastuzumab therapy.

Discussion

The development of pheochromocytoma in NF1 patients is well known; however, our case is unique in that both breast cancer and pheochromocytoma coexisted in the same patient. The incidence of breast cancer in NF1 is lower in comparison to malignant peripheral nerve sheath tumors, intracranial gliomas, gastrointestinal stromal tumors, pheochromocytoma and rhabdomyosarcomas (10). Until recently, the simultaneous occurrence of these two tumors in NF1 patients has only been reported in 1 case (11).

The incidence of pheochromocytoma in NF1 patients is high (0.1-5.7%) in comparison to the general population (2-8 per 100,000) (12, 13). Although the patient in this case did not have hypertension, the incidence of pheochromocytoma is reported to increase to 20-56% in NF1 patients with hypertension (12). The mean age at presentation for NF1-associated pheochromocytoma is 42 years, while the mean age at presentation for sporadic cases is 47 years (12, 14). Symptoms related to pheochromocytoma are seen in 61% of patients with NF1-associated pheochromocytoma and hypertension is noted in 61% (12). However, the patient in the present case was incidentally diagnosed with pheochromocytoma as a result of adrenal incidentaloma screening, even though there were no symptoms or signs suggesting pheochromocytoma. Pheochromocytoma may be fatal if not diagnosed, suggesting that routine screening for pheochromocytoma may be considered in NF1 patients, even if there are no symptoms or signs of pheochromocytoma.

Cancer has been known to be more common among patients with NF1 and studies on the increased incidence of



Figure 2. The patient's upper body. Front (A) and back (B). Six or more café-au-lait spots and multiple cutaneous neurofibromas were observed across the body.

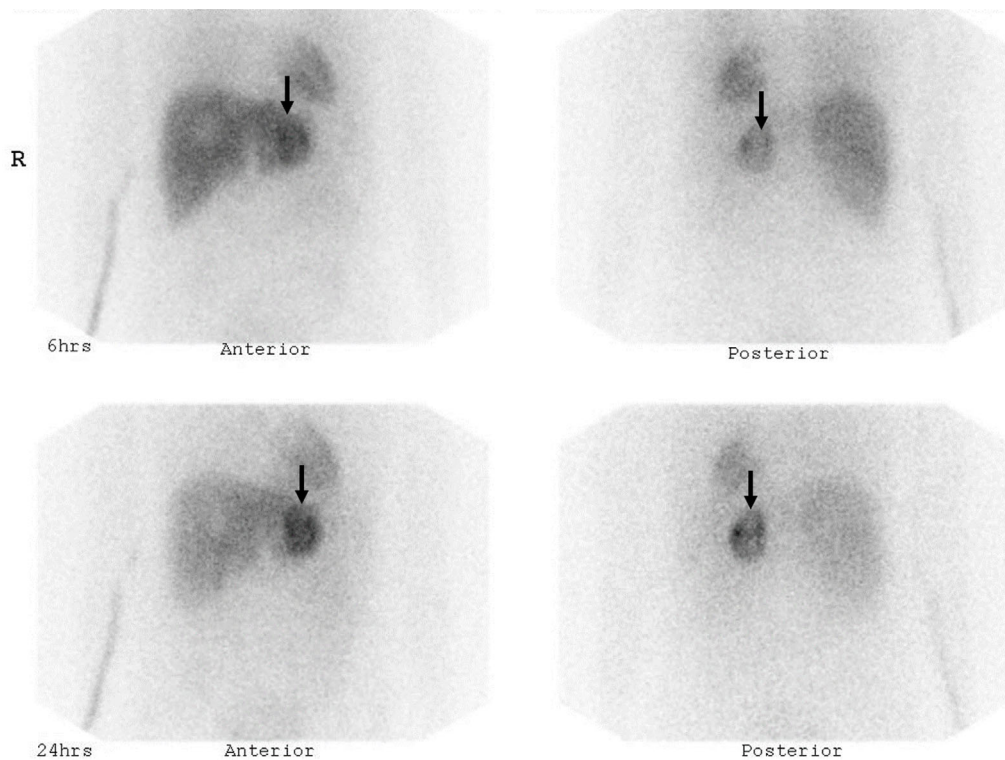


Figure 3. I-123 MIBG scan. A mass with the uptake of I-123 meta-iodobenzylguanidine was observed in the left adrenal gland (arrows).

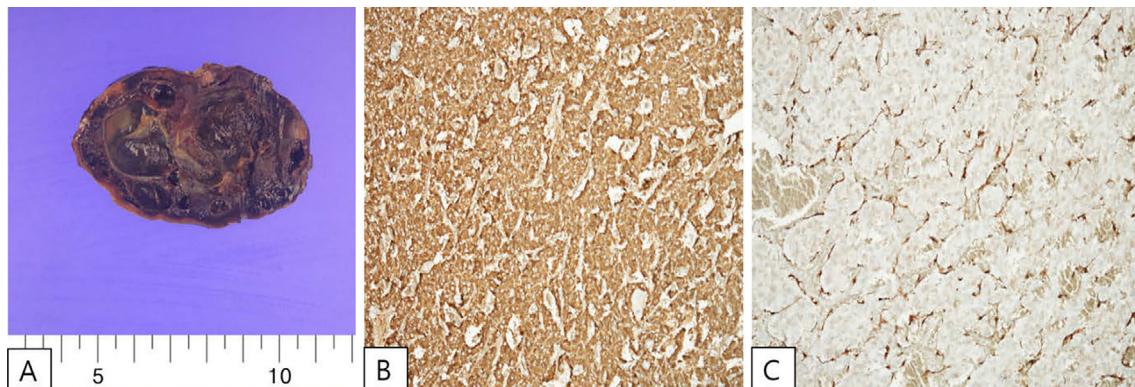


Figure 4. The pathological examination of the resected adrenal gland. A: The cut section of the adrenal gland mass measuring 6.5 cm×4.3 cm×3.0 cm was dark brown and showed cystic change. B: The tumor was composed of chromaffin cells (positive chromogranin staining; 100× magnification). C: The Zellballen pattern was well-recognized (S100 immunohistochemical staining; 100× magnification).

breast cancer in this patient population have been clearly documented over the past several decades. According to a recent study, the incidence of breast cancer in patients with NF1 is significantly higher in comparison to the general population (15-17). A large Finnish study conducted from 1987 to 2011 reported an unequivocally increased risk of breast cancer, with standardized incidence ratios (SIRs) of 3.04 (95% CI, 2.06 to 4.31) among women with NF1. In particular, the SIR was 11.1 (95% CI, 5.56 to 19.5) for breast cancer among women with NF1 under 40 years of age. NF1 patients with breast cancer are not rare; however,

it is important to know the risk of malignancy (10). In addition, NF1 patients with breast cancer are more likely to develop cancer in the contralateral breast in comparison to the general population. According to one study, 26.5% of NF1 patients who survived for 20 years from the first diagnosis of breast cancer developed cancer in the other breast (18). Such risk serves as evidence to consider prophylactic mastectomy of the unaffected breast in patients with neurofibromatosis and breast cancer. Since the patient in this case did not undergo prophylactic resection of the unaffected breast, periodic follow-up would be needed to detect the develop-

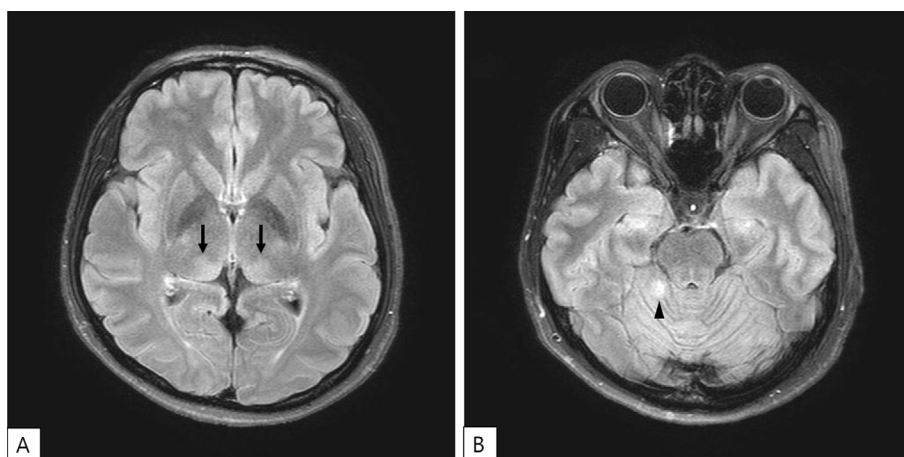


Figure 5. Brain MRI (axial FLAIR images) at the levels of the basal ganglia (A) and cerebellum (B). Multifocal hyperintense lesions were observed in both thalami (arrows) and the right cerebellum (arrowhead), suggesting focal areas of signal intensity (FA SI), a neurofibromatosis-specific finding.

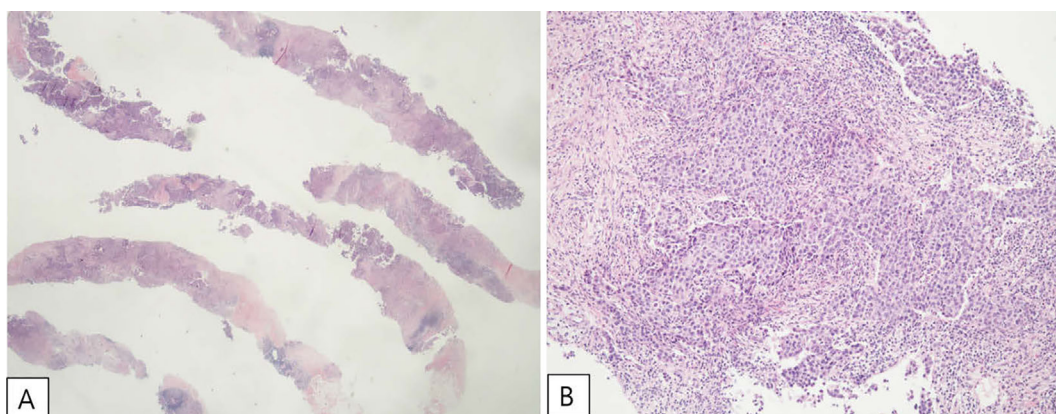


Figure 6. Left breast needle biopsy. Left breast biopsy revealed high grade, invasive ductal carcinoma [A: Hematoxylin and Eosin (H&E) staining; 10× magnification. B: H&E staining; 100× magnification].

ment of breast cancer of the contralateral breast.

Although the precise mechanism of the elevated incidence of breast cancer in these patients is unknown, there are several possibilities. The *NF1* gene acts as a tumor-suppressor; thus, *NF1* gene deficiency results in the overexpression of the RAS pathway followed by varying cancer developments including breast cancer. According to a recent study, *NF1* gene deletion is associated with *NF1*-ER-FOXA1-AR networks and causes endocrine-resistant breast cancer (19). Another study suggested that it may be attributable to the fact that the *BRCA1* gene, the gene with the most susceptibility to mutation in breast cancer patients, is located near the *NF1* gene in the long arm of chromosome 17 (20). This increases the possibility that mutation, deletion, or duplication of the *NF1* gene may affect the *BRCA1* gene. There is another possibility that types of *NF1* mutations, including nonsense mutations and missense mutations determine the different breast cancer risk between individuals (21). Epidemiological studies have shown that the peak incidence of breast cancer in Asia and the West varies, ranging from between 40 and 50 years in Asia and 60 and 70 years in the

West (22-24). Among patients with neurofibromatosis who develop breast cancer, breast cancer is often discovered at a later stage in patients under 50 years of age and it is therefore important to encourage this population of patients with neurofibromatosis to undergo periodic checkups with earlier screenings than the general population (25). In addition, since it is difficult for patients with several cutaneous neurofibromas to palpate breast masses in a self-exam, these patients should be classified as a high-risk group and should be encouraged to undergo breast ultrasonography or breast MRI early in life (18, 26).

We described the case of a patient with *NF1* who developed breast cancer and pheochromocytoma in a short period of time. Since pheochromocytoma occurs more frequently in patients with *NF1* than in the general population, routine screening may be necessary for patients with *NF1* who require surgery under general anesthesia, even if there are no symptoms or signs of pheochromocytoma.

The authors state that they have no Conflict of Interest (COI).

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