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Case Report

A Neurofibromatosis Type I Patient Presenting with Four Different Cancer Types Including Malignant Peripheral Nerve Sheath Tumor, Gastrointestinal Stromal Tumor, Pancreatic Neuroendocrine Tumor, and Renal Cell Carcinoma within 1 Year

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Abstract

Neurofibromatosis type 1 (NF1) is a germline autosomal dominant disorder caused by the loss-of-function tumor suppressor gene NF1, which encodes neurofibromin protein. When multiple tumors arise within a short time in patients with the germline NF1 mutation, it is important to determine whether the tumors are metastatic or different primary tumors. We, herein, report a 35-year-old female with multiple tumors that were confirmed to be a malignant peripheral nerve sheath tumor, gastrointestinal stromal tumor, renal cell carcinoma, and pancreatic neuroendocrine tumor, and all were treated accordingly. This case further supports that tissue confirmation is important in patients with the NF1 germline mutation.

Keywords: Gastrointestinal stromal tumor, malignant peripheral nerve sheath tumor, neurofibromatosis type 1, pancreatic neuroendocrine tumor, renal cell carcinoma

Introduction

Neurofibromatosis type 1 (NF1), which is also known as von Recklinghausen's disease, is an autosomal dominant disorder caused by a heterozygous loss-of-function variant in the tumor suppressor gene NF1.[1] It is one of the most frequent hereditary neurocutaneous disorders with a prevalence in the general population of about one in 1900 to one in 3500 worldwide.[1] The disease is characterized

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by hyperpigmented macules of the skin called *café-au-lait* spots and benign tumors of peripheral nerve sheaths termed neurofibromas.[2] NF1 is associated with various benign and malignant tumors.

A Finnish population-based NF1 patient study (n = 1404) showed a five-fold increased risk of cancer, with an estimated lifetime cancer risk 59.6%. The estimated cumulative cancer risk by the age of 30 was 25.1% and 38.8% by the age of 50, compared to 0.8% and 3.9%, respectively, in the general population.[3] The 5-year survival of patients with cancer and NF1 was worse than comparable patients with cancers without NF1 (54.0% vs. 67.5%; P = 0.01).[3] Malignant peripheral nerve sheath tumors (MPNSTs) (standardized incidence ratio [SIR] = 2056) are considered to be a NF1-specific cancer, whereas other NF1-related cancers include pheochromocytoma (SIR = 74.3), malignant fibrous histiocytoma (SIR = 51.2), and gastrointestinal stromal tumors (GISTs) (SIR = 34.2) are also more common in NF1 patients.[3] However, when NF1 patients present with multiple lesions in a short period, then the choice of treatment depends on whether the lesions are from the same primary cancer or from multiple primary cancers. The coexistence of multiple malignancies in NF1 patients is rare and has mostly been reported in case reports. The current study presents an NF1 patient with a MPNST, pancreatic neuroendocrine tumor (NET), GIST, and renal cell carcinoma within 1 year.

Case Report

A 36-year-old female who had undergone resection of a left chest wall MPNST at another hospital 3 months before coming to our hospital (National Taiwan University Hospital [NTUH]) presented with intermittent abdominal distention and a painful hypogastric region for 2 months.

Tracing back her history, she had had *café-au-lait* spots of variable sizes and several skin nodules over her body since the age of 15. She also had schizophrenia and mild intellectual disability. She first noted a left posterior lateral chest wall painful mass in 2016. The chest wall tumor progressively enlarged in the following years to 15 cm × 12 cm, with hard and nonmovable characteristics. A computed tomography (CT) scan of the chest revealed a massive posterior lateral chest wall tumor with 9th rib invasion and left-sided pleural effusion [Figure 1]. She received video-assisted thoracoscopic surgery for chest wall tumor resection 3 months before visiting NTUH. The pathology report confirmed the diagnosis of a MPNST [Figure 2a]. Immunohistochemical (IHC) staining was diffusely positive for vimentin and S100, focally positive for MDM2, and negative for CK, myoD1, Smooth muscle actin (SMA), desmin, calretinin, CDK4, STAT6, P16, H-caldesmon, and myogenin. H3K27me3 expression was preserved. Overall, MPNST Stage III was impressed.

She developed intermittent abdominal distention and hypogastric pain 1 month before visiting NTUH. She denied weight loss, poor appetite, nausea, vomiting, diarrhea, constipation, or dysuria. Fluorodeoxyglucose positron-emission tomography/CT (FDG PET/CT) revealed hypermetabolic lesions with intense FDG uptake in the mesentery region, left upper back cutaneous region, axillary nodal region, and pancreaticoduodenal nodal region [Figure 3]. Therefore, she was referred to NTUH for treatment discussion.

At NTUH, a physical examination revealed alert and oriented consciousness, and vital signs were within the normal range. Her neck was supple with no palpable mass. An enlarged lymph node in the left axillary region (approximately 1.5 cm in diameter) was palpable. Heart sounds were regular and breathing sounds were symmetric and clear. Her abdomen was soft with mild local tenderness over the hypogastric region, with normoactive bowel sounds. No muscle guarding or rebound tenderness was noted. *Café-au-lait* spots of variable sizes were noted over her trunk, and several skin nodules were noted over bilateral upper extremities and neck region [Figure 4]. The hematocrit and red-cell indexes were normal, as were blood levels of calcium, magnesium, glucose, albumin, amylase, lipase, and lactic dehydrogenase and the results of renal and liver function tests. The tumor markers of carcinoembryonic antigen and CA 19-9 were also within the normal range.

NF1 was diagnosed based on the National Institutes of Health (NIH) criteria:[4] six or more *café-au-lait* macules larger than 15 mm after puberty, skinfold freckling over axillae, two or more neurofibromas, and affected first-degree relatives. Her father and paternal grandmother had multiple cutaneous nodules and *café-au-lait* spots involving the whole body. She received subcutaneous nodule excision over her right medial upper arm 2 months later, and the pathology confirmed neurofibroma [Figure 2b]. Her grandmother died of pancreatic cancer at the age of 63 years.

Magnetic resonance imaging (MRI) of her abdomen and pelvis 1 month later revealed a 6.8-cm tumor with heterogenous enhancement in the mesentery [Figure 5] and two nodules (1.6 cm and 1.2 cm) of low signal on a T1-weighted image, high signal on a T2-weighted image [Figure 6a], early

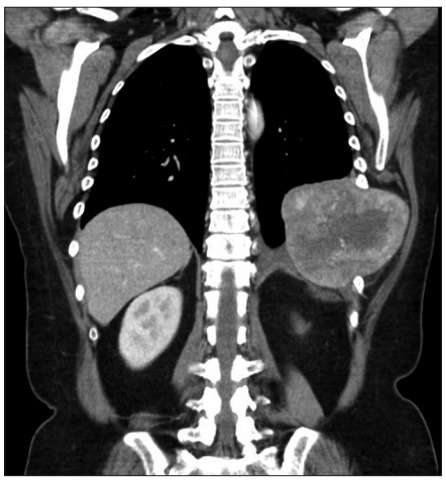

Figure 1: Computed tomography images of the chest with a malignant peripheral nerve sheath tumor

and persistent enhancement on contrast-enhanced T1WI at the pancreatic head, and a 1.3-cm lymph node near the pancreatic head [Figure 6b]. CT of her abdomen and pelvis showed compatible findings to the MRI findings, except for a 1.6-cm enhancing nodule in the left kidney [Figure 7]. After the image survey, surgery was arranged for a possible tumor-related bowel obstruction. After discussion with the surgeon, pancreatic fine-needle aspiration was suggested to decide whether or not the Whipple procedure was indicated. Endoscopic ultrasonography fine-needle aspiration over the pancreas was performed 1.5 months later, and the pathologic report showed atypical neuroendocrine cells [Figure 2c]. IHC staining was positive for cytokeratin, synaptophysin, and chromogranin, and the Ki-67 proliferation index was <2%. Therefore, a pancreatic NET was impressed, and the Whipple procedure was not favored.

She further received mesenteric tumor excision and left partial nephrectomy 3 months later. The operative findings revealed multiple intraperitoneal seeding tumors, with the biggest around 6 cm. The pathologic report further revealed a metastatic GIST over the peritoneum, pT3N0M1: WHO prognostic Group 6a [Figure 2d]. IHC staining was c-kit positive [Figure 2e], H3K27Me3 retained, and S100 negative. However, left kidney clear cell renal cell carcinoma [Figure 2f], pT1aNx, was diagnosed. Even though the patient's GIST was very likely to be associated with NF1 and thus be c-kit mutation negative, we still prescribed imatinib for treatment 4 months later after discussion.[5]

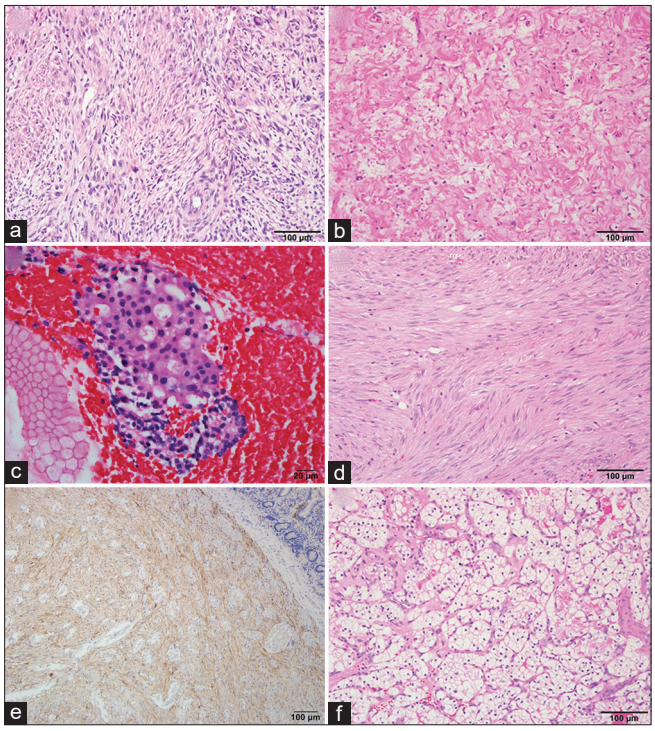

Figure 2: Hematoxylin and eosin stains. (a) Malignant peripheral nerve sheath tumor. Interlacing fascicles of tumor cells with prominent nuclear atypism. (b) Neurofibroma. Hypocellular spindle cells with wavy or curved nuclei. (c) Pancreatic atypical neuroendocrine cells. (d) Gastrointestinal stromal tumor, fascicles of spindle cells with pale to eosinophilic fibrillar cytoplasm. (e) Gastrointestinal stromal tumor with positive c-kit immunohistochemical stain. (f) Clear cell renal cell carcinoma, clear cytoplasm plasm with round nuclei

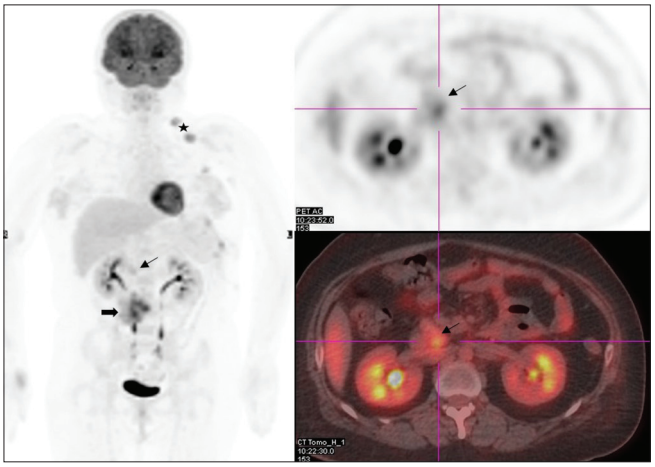

Figure 3: Fluorodeoxyglucose positron-emission tomography scan revealed fluorodeoxyglucose -avid areas in the neck and subcutaneous back lesions (★), pancreatic lesions (thin arrow), and mesenteric lesion (thick arrow)

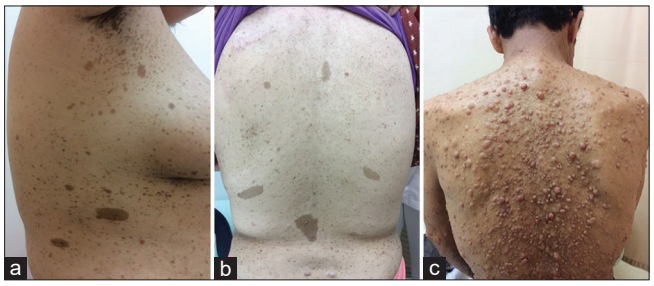

Figure 4: *Café-au-lait* spots of variable sizes and several skin nodules over the trunk of the patient (a) and (b). Multiple skin nodules over the back of the patient's father (c)

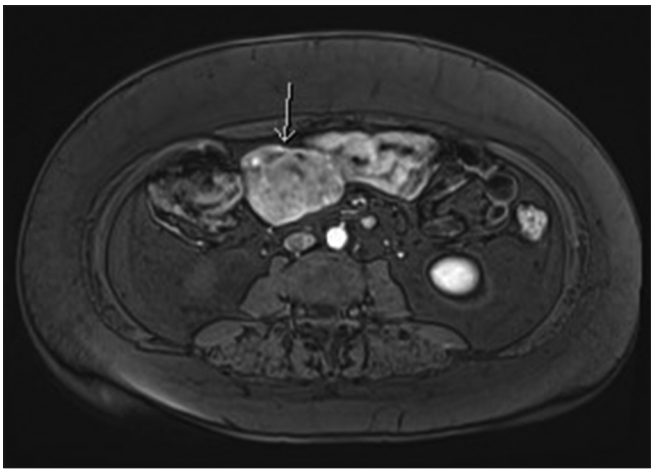

Figure 5: Magnetic resonance imaging of the abdomen and pelvis, a 6.8-cm tumor with heterogenous enhancement in the mesentery, proved to be a metastatic gastrointestinal stromal tumor

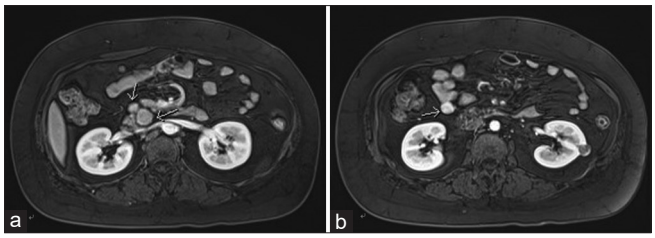

Figure 6: Magnetic resonance imaging of the abdomen and pelvis, (a) two nodules (1.6 cm and 1.2 cm) of low signal on T1WI at the pancreatic head; (b) a 1.3-cm lymph node near the pancreatic head with high signal on T1WI

Under imatinib treatment, a following FDG PET/CT taken 6 months later showed the progression of neck, bilateral axillary, and precaval and inguinal lymphadenopathy. New right middle lung lesions and soft-tissue lesions over the right thigh and left trunk were also noted. The spread was most likely due to MPNST. Due to the patient's mental health issues and inadequate supportive system, oral cyclophosphamide 50 mg once/day, instead of systemic intravenous chemotherapy, was further administered in addition to imatinib 7 months later.

At the most recent follow-up 1 year later, CT of the neck to pelvis revealed stable disease of pancreatic, mesenteric, and soft-tissue lesions, but progression of lung lesions without obvious clinical symptoms and signs.

Discussion

NF1 patients are prone to develop symptoms affecting multiple cells of origin and tissues.[4,6] Manifestations include cognitive, psychiatric, vascular problems, and benign and malignant tumors. Most adults with NF1 are clinically diagnosed according to National Institutes of Health (NIH) consensus criteria.[6] Commonly associated tumors include glioma of the optic pathway, pilocytic astrocytoma, glioblastoma, MPNSTs, GISTs, breast cancer, juvenile myelomonocytic leukemia, pheochromocytoma, duodenal carcinoid tumors, and rhabdomyosarcoma.[2,7] Numerous other tumors have been reported in NF1 patients; however, the true association is unclear.[2] The NF1 gene encodes neurofibromin and functions as a RAS-GTPase-activating protein, a negative regular of RAS activity.[8,9] It mainly results in the activation of the RAF-MEK-ERK pathway, but also interacts with the PI3K-AKT-mTOR and other pathways, consequently deregulating cell growth.[2] However, biallelic NF1 inactivation alone cannot fully explain tumor development according to experimental studies, and other factors such as a NF1 haploinsufficiency cellular environment or concurrent mutations in other genes also play a role.

About half of MPNST patients also have NF1 and are likely transformed from preexisting plexiform neurofibroma.[2] The estimated lifetime risk of NF1-associated MPNSTs is 8%–13%. Individuals with NF1 who report progressive or difficult-to-control pain, a rapid increase in the size of preexisting plexiform neurofibroma, or a change in tumor

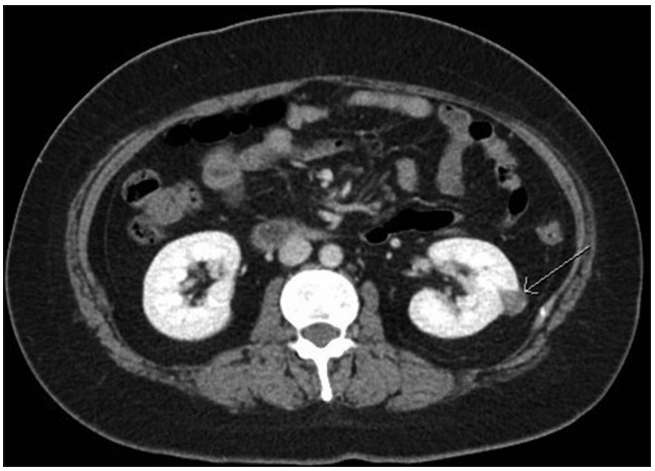

Figure 7: Computed tomography images of the abdomen revealed a 1.6-cm enhancing nodule in the left kidney, which proved to be clear type renal cell carcinoma

consistency (soft to hard) or new-onset neurological signs should receive early assessments for MPNSTs.[4] MRI may be helpful but cannot reliably distinguish between benign and malignant tumors, with a sensitivity of 61% and a specificity of 90%.[10] On the other hand, FDG PET/CT has been reported to have high sensitivity (0.89) and specificity (0.95) to diagnose NF1-associated MPNSTs.[11] Surgery is the only curative treatment for MPNSTs. In the metastatic setting, doxorubicin and ifosfamide have been shown to be modestly effective; however, there is currently no standard treatment for these poor prognosis tumors.[12]

Patients with GISTs and NF1 tend to be slightly younger at presentation than the general populations (median age 50 years vs. 60 years).[13] In terms of molecular features, NF1-associated GISTs typically do not have mutations or overexpression of v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) or the platelet-derived growth factor receptor alpha (PDGFRA), and CD117 may still be detected through immunohistochemistry.[5] Since NF1 inactivation affects the receptor's downstream pathway, the tyrosine kinase inhibitor imatinib is less effective in these patients.[2,7] However, some patients may still potentially benefit clinically with imatinib.[5]

In patients presenting with multiple tumors under the genetic background of cancer-predisposing syndromes such as NF1, the coexistence of multiple types of malignancies should always be kept in mind under the differential diagnosis of metastases. The causal relationship between the cancer-predisposing syndrome and certain types of malignancy can sometimes be uncertain. The present case had a coexisting MPNST, GIST, renal cell carcinoma, and pancreatic NET.

Although renal cell carcinoma is not a typical NF1-associated malignancy, NF1 loss has been reported in sporadic renal cell carcinoma patients, implicating the role of NF1 in renal cancer carcinogenesis. To distinguish the origin of each tumor in NF1 patients is a common clinical problem. Although FDG PET/CT may differentiate atypical lesions from malignant

lesions, a pathology examination may still be necessary for patients with multiple tumors and underlying NF1 or other hereditary germline genetic alterations.[14] In conclusion, this rare case highlights that clinicians should always be suspicious of the origin of different tumors under the genetic background of NF1, and that adequate tissue proof is essential to make the correct diagnosis and for appropriate management of the patient.

Ethical approval and declaration of patient consent

This study was approved by Research Ethics Committee of National Taiwan University Hospital (Reference no. 202002081RIND).

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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