Simultaneous presentation of malignant peripheral nerve sheath tumor and moyamoya disease associated with neurofibromatosis type 1 in a child

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Neurofibromatosis type 1 (NF-1) is a rare hereditary disorder, which is inherited as an autosomal dominant trait. It is characterized by multiple café-au-lait spots of the skin, benign cutaneous neurofibromas, skeletal dysplasia and learning disability. The association of NF-1 with benign and malignant tumors is well established. The lifetime risk of patients with NF-1 developing malignant peripheral nerve sheath tumors (MPNSTs) has been estimated to be 8–13%. Such tumors can develop in any part of the body, but their occurrence in the gastrointestinal tract is rare. Patients with NF-1 have a wide spectrum of vascular abnormalities. Cerebrovascular lesions have been found in approximately 2.5% of children with NF1. We encountered a case of NF-1 with MPNSTs in the gastrointestinal tract and moyamoya disease.

Key words: neurofibromatosis type 1, malignant peripheral nerve sheath tumors, moyamoya disease.

Neurofibromatosis type 1 (NF-1), or von Recklinghausen's disease, is a rare hereditary disorder inherited as an autosomal dominant trait, with an overall incidence of 1 in 3,000 individuals. It is characterized by multiple café-au-lait spots of the skin, benign cutaneous neurofibromas, skeletal dysplasia and learning disability. The association of NF-1 with benign and malignant tumors is well established, with the association between NF-1 and pediatric cancers being highly evident[1]. The lifetime risk of patients with NF-1 developing malignant peripheral nerve sheath tumors (MPNSTs) has been estimated to be 8–13%[2]. MPNSTs can develop in any part of the body, but their occurrence in the gastrointestinal tract is rare in childhood[3]. Few data are available for children[4].

Patients with NF-1 also have a wide spectrum of vascular abnormalities, most notably aneurysms or stenosis of the aortic, renal and mesenteric circulation. However, cerebrovascular lesions have been found in approximately 2.5% of children with NF-1[5]. Moyamoya disease associated with spontaneous occlusion of the circle of Willis[6] is rare in NF-1. Therefore, the risk of having both MPNST and moyamoya disease at the same time is approximately 0.20-0.33% in children with NF-1. Here we report a boy with NF-1 who had moyamoya disease and malignant peripheral nerve sheath tumors of the gastrointestinal tract.

Case Report

A 15-year-old boy visited our outpatient clinic in the Department of Pediatric Surgery at Chonbuk National University Medical School with multiple brownish macules on the trunk and a soft tissue mass on the left lower abdomen, first detected 3 years previously, which had gradually increased in size. It had originally showed at 3.0 x 2.0 cm. The patient's past medical history and family history were not significant. The physical examination revealed numerous café-au-lait spots (Fig. 1G), whereas the neurological examination and abdominal skin reflexes showed normal results. The

patient reported feeling a slightly dull sensation above the abdominal mass in the sensory examination, but it was not prominent. He underwent surgical excision of the abdominal wall mass. During the surgery, gross findings of the cut surface showed a 3.9 x 3.4 cm, relatively well-circumscribed, glistening, yellowish-white mass with necrosis and hemorrhage. Histologically, the tumor was hypercellular and composed of irregularly arranged tumor cells. The areas of hypercellularity consisted mainly of spindle-shaped cells, which had wavy or comma-shaped nuclei with hyperchromasia. Significant cytological atypia and mitoses of 42/10 high-power fields were identified (Fig. 1A). Immunohistochemically, the tumor cells were positive for S-100 protein and negative for cytokeratin, smooth muscle actin, desmin, CD34 and HMB-45 (Fig. 1B). Therefore, pathologists concluded that the tumor was MPNST, and the resection margins were negative for malignancy.

Two weeks later, the patient was admitted to the Department of Pediatrics for further evaluation of the MPNST. Chest X-ray showed multiple nodules in the right pleural area (Fig. 1C), and the patient was subjected to additional radiological imaging studies. Magnetic resonance imaging (MRI) of the chest showed multiple localized fibrous tumors in the right pleura (Fig. 1D), whereas MRI of the abdomen identified multifocal tumors below the body of the pancreas as being suspect for neurogenic tumors. (Fig. 1E). Positron emission tomography with CT (PET-CT) showed multiple masses with minimal to mild fluorodeoxyglucose uptake at the right pleural and abdominal cavities (Fig. 1F). MRI of the brain showed a multifocal infarction on the left frontal lobe (Fig. 2A). Magnetic resonance angiogram showed obstruction of the distal portions of both posterior communication arteries, characteristic of moyamoya disease (Fig. 2B, 2C).

Pleural needle biopsy confirmed a neurofibroma. The patient had multiple masses of about 1 cm diameter on the right side of the neck and in the right arm. Fine needle aspiration biopsy revealed these masses to be neurogenic tumors. Based on these histopathological features of the abdominal wall mass and the MRI and MRA findings of the brain, the diagnosis was

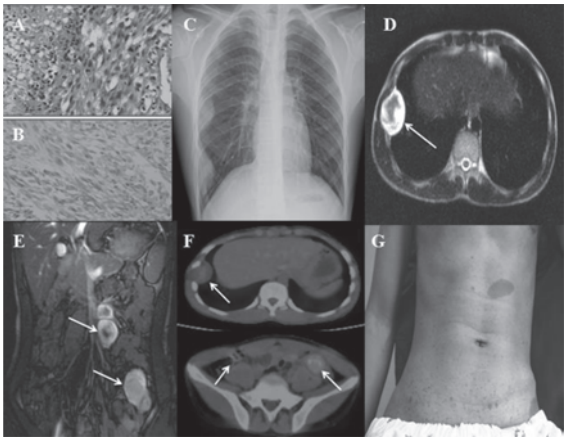

Fig. 1.
(A) The tumor is hypercellular and composed of irregularly arranged spindle-shaped cells with frequent mitoses and necrosis. (B) The tumor cells are immunoreactive for S-100 protein. (x400) (C) Chest X-ray shows multiple nodules in the right pleural area. (D) T2 chest MRI showing the localized fibrous tumors of the right pleura. (E) T2 abdominopelvic cavity MRI revealing multiple tumors with high signal intensity below the body of the pancreas and the left side of the pelvic cavity. (F) Positron emission tomography with computed tomography showing multiple masses with minimal to mild fluorodeoxyglucose uptake at the right pleural and abdominal cavities. (G) Photograph showing multiple café-au-lait spots of varied sizes scattered over the chest wall and trunk.

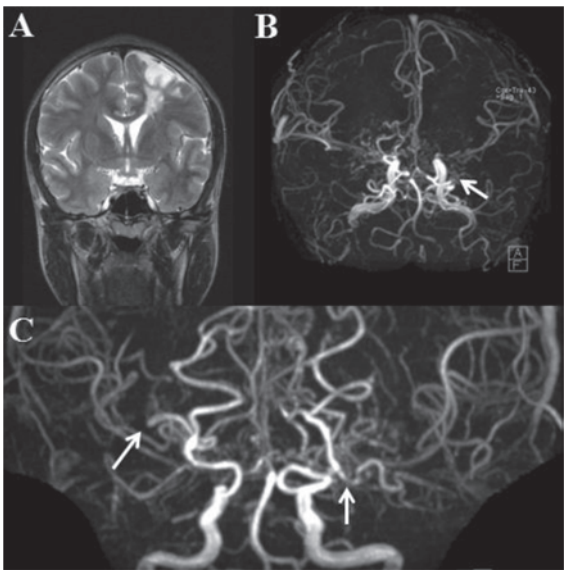

Fig. 2.
(A) T2 brain MRI showing high signal intensity in the left medulla, indicating chronic infarction. (B, C) Magnetic resonance angiogram showing small collateral vessels with obstruction of the distal portions of both posterior communicating arteries.

confirmed as MPNST with moyamoya disease.

The patient did not undergo surgical revascularization for the treatment of moyamoya disease due to the risk of sudden death and the potential for a poor outcome. Chemotherapy with eight cycles of ifosfamide, carboplantin and etoposide was given for MPNST.

Subsequently, PET-CT showed a lesion in the lower left lobe of the lung after four more cycles of chemotherapy. A new mass developed in the right lung 4 months later, and the patient was operated on and treated in conjunction with chemotherapy. However, metastatic malignant brain tumors developed at left frontal base and left temporoparietal area 10 months later. Three rounds of Gamma Knife were administered for the brain tumor. Symptomatic treatments such as antiepileptic drugs, mannitol and dexamethasone were given to alleviate seizures and headaches. The patient expired without improvement 19 months after development of the brain tumors.

Discussion

NF-1 is an autosomal dominant disorder resulting from a mutation of the NF-1 gene, located on the long arm of chromosome 17 (17q11.2). NF-1 is associated with a variety of benign and malignant neoplasms such as neurofibromas, pheochromocytomas, myelogenous leukemia and MPNST. MPNST is one of the most clinically aggressive cancers associated with NF-1. The lifetime risk in NF-1 patients has been estimated to be 8-13%, compared to 0.001% in the general population[2]. The characteristic genetic finding of a MPNST is the loss or mutation of the NF-1 gene.

The main clinical manifestation of a MPNST is an enlarging soft tissue mass with or without pain and dysesthesia. These tumors occur most frequently at axial sites, and most lesions are deep seated. The common sites are the lower and upper extremities, trunk, head and neck. Intra-abdominal or intrathoracic manifestations, as observed in the present case, are rare. Few data are available for children[4]. Most MPNSTs in patients with NF-1 develop from pre-existing plexiform neurofibromas (PNF)[7]. Individuals with subcutaneous neurofibromas are approximately three times more likely to have internal PNFs or MPNSTs than individuals without subcutaneous neurofibromas[8]. Individuals with internal PNFs are 20 times more likely to have MPNSTs than individuals without internal PNFs[8]. Even though our patient had MPNST associated with NF-1, we did not identify an internal PNF.

Magnetic resonance imaging is the most useful imaging technique to clearly identify the extent of the MPNST and to determine its neurogenic origin. Certain radiographic findings, such as invasive or displacement growth patterns of PNFs in patients with NF-1, should be considered as signs of a malignancy, particularly MPNST[9].

Because of the rarity of this tumor, little information is available on its clinical management, particularly in the pediatric age group. A multidisciplinary approach for the treatment of MPNST has been adopted in many centers despite debate over treatment[10]. Surgical resection represents the mainstay of treatment, whereas the role of adjuvant treatment is unclear. Adjuvant radiotherapy is usually given in the case of high-grade tumors or microscopic residual disease. However, MPNST of the gastrointestinal tract does not appear to respond to radiation therapy. The role of chemotherapy is not currently established, but its use appears to be limited to disseminated rather than localized disease.

The prognosis of MPNST depends on many factors. The most commonly proposed prognostic factors are extent of surgery, tumor size, local invasiveness, site of primary lesion, presence of NF-1 and age at diagnosis. Recent reports of Italian and German studies of children and adolescents with MPNST demonstrated poor survival rates of NF-1 patients in comparison with patients without NF-1 (the 5-year progression free survival and overall survival rates were 19% and 32%, respectively, in NF-1 cases vs. 42% and 55% in non-NF-1 cases).[1]

Cerebrovascular lesions such as moyamoya disease are rare in NF-1[11]. Because NF-1 is a disorder that results from dysplasia of the mesodermal and neuroectodermal tissues, concomitant vascular abnormalities are a complication of NF-1, especially in the intracranial arteries[5]. The most frequent cerebrovascular complications of NF-1 are cerebral artery occlusive disease of the moyamoya type and aneurysms. Weakness,

involuntary movement and seizures as a result of cerebral ischemia are clinical features of children with NF-1 and moyamoya[12], but, as in our case, most patients are clinically asymptomatic[13].

The diagnosis of moyamoya disease with NF-1 is based on MRI and MR angiography of the brain. Using MRI and MRA scanning in conjunction increases sensitivity to 92%[14]. There is no cure for patients with simultaneous presentation of NF-1 and moyamoya disease. Therefore, multicenter studies are needed for patients with NF-1 and cerebral vasculopathy. The suggested treatments range from medical management with an antiplatelet agent to surgical revascularization[12].

MPNSTs are very rare sarcomas derived from various cells in the peripheral nerve sheath. MPNSTs have a known association with NF-1. In addition to neoplastic processes, patients with NF-1 are also at risk for several cerebrovascular conditions such as moyamoya disease. Herein, we have reported a very rare case of concurrent MPNSTs and moyamoya disease in a 15-year-old boy with NF-1. In conclusion, a careful follow-up plan should be in place for patients with NF-1 to allow for the early diagnosis of MPNST and cerebral vasculopathy.

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