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A Case of Non-Hodgkin's Lymphoma in a patient with Neurofibromatosis Type 1

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Neurofibromatosis type 1 is characterized by cutaneous neurofibromas and pigmented lesions of the skin called *café au lait* spots. Although neurofibromatosis type 1 represents a major risk factor for the development of malignancy, especially of nervous system tumors, malignant lymphoma rarely occurs in a patients with neurofibromatosis type 1. Recently, a 77-year-old woman with neurofibromatosis type 1 was diagnosed as non-Hodgkin's Lymphoma (diffuse large B cell). She had multiple *café au lait* spots, neurofibromas and right axillary lymph node enlargement. An abdominal CT scan demonstrated a left pelvic mass and para-aortic lymphadenopathy. Because non-Hodgkin's Lymphoma in a neurofibromatosis patient has never been reported in Korea, herein, we describe this case and include a review of the literature.

Key Words : Neurofibromatosis 1, Lymphoma, Non-Hodgkin

INTRODUCTION

Neurofibromatosis type 1 (NF1), also referred to as von Recklinghausen's disease, is an autosomal dominant disorder and one of the most common genetic disorders, with an estimated prevalence of two to three cases per 10,000 of the population[1]. NF1 is characterized by cutaneous neurofibromas, axillary freckling and pigmented lesions of the skin called *café au lait* spots. Because NF1 is also a multisystem disorder, it has a wide variety of clinical manifestations, such as, learning disability, vascular stenosis and skeletal dysplasia. Although patients with NF1 are at risk of significant clinical manifestations, most patients are only mildly affected and live healthy lives[2].

NF1 is known as a risk factor for the development of malignancy. Thus, nervous system cancers including malignant peripheral nerve sheath tumors and gliomas and leukemia occur with increased frequency in the NF1 population[3]. However, the occurrence of malignant lymphoma in a patient with neurofibromatosis type 1 is a rare phenomenon.

CASE REPORT

A 77-year-old woman was admitted to our hospital with a chief complaint of a left lower quadrant pain. The pain had appeared 15 days previously, without any prior relevant history, and had increased in intensity three days before admission. The patient had also lost 5 kg in weight over the previous three months. She was a nonsmoker, did not drink alcohol.

A physical examination at presentation showed multiple pigmented lesions of the skin, called *café au lait* spots, and rubbery nodular skin lesions on the chest, abdominal wall and both arms (Figure 1). Her family members showed similar skin lesions over the whole body area. Several right axillary lymph nodes were palpated and mild tenderness was noted. An abdominal examination revealed left lower quadrant mass with

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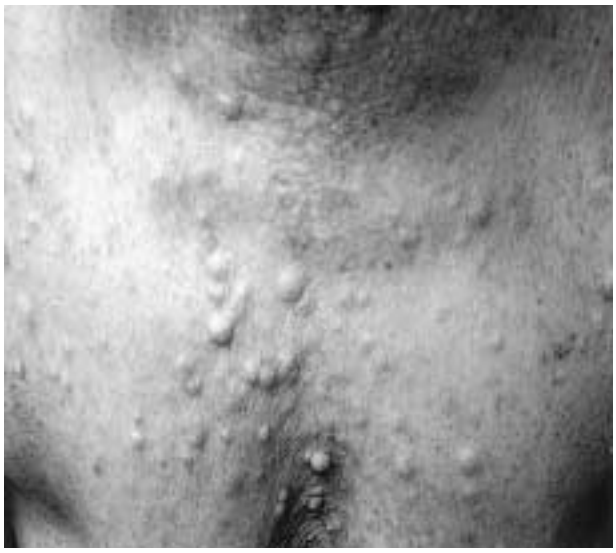

Figure 1. Numerous flesh-colored nodular skin lesions over the chest wall.

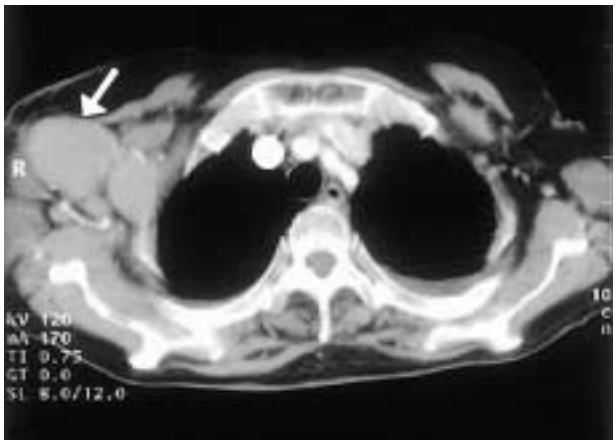

Figure 2. Chest CT scan showing well-defined hypodense masses (arrow) in the right axillary region.

tenderness and mild hepatosplenomegaly. On laboratory studies, platelets were 286,000/mm^3, leukocytes 4,990/mm^3 (65% neutrophils, 22% lymphocytes), and hemoglobin was 9.7 g/dL. ESR and CRP were 29 mm/hr and 1.2 mg/dL, respectively. Serum creatinine, liver function tests and urine analysis were within the normal ranges. Serum LDH and β2-microglobulin were 593 IU/L (normal range; 450~263 IU/L) and 2.35 mg/L (normal range; 2.4~0 mg/L), respectively.

A chest CT scan confirmed the presence of several lymph node enlargements in the right axillary region; the size of the largest enlargement was 3.5×3.0 cm (Figure 2). An abdominal CT scan showed isodense homogeneous conglomerated

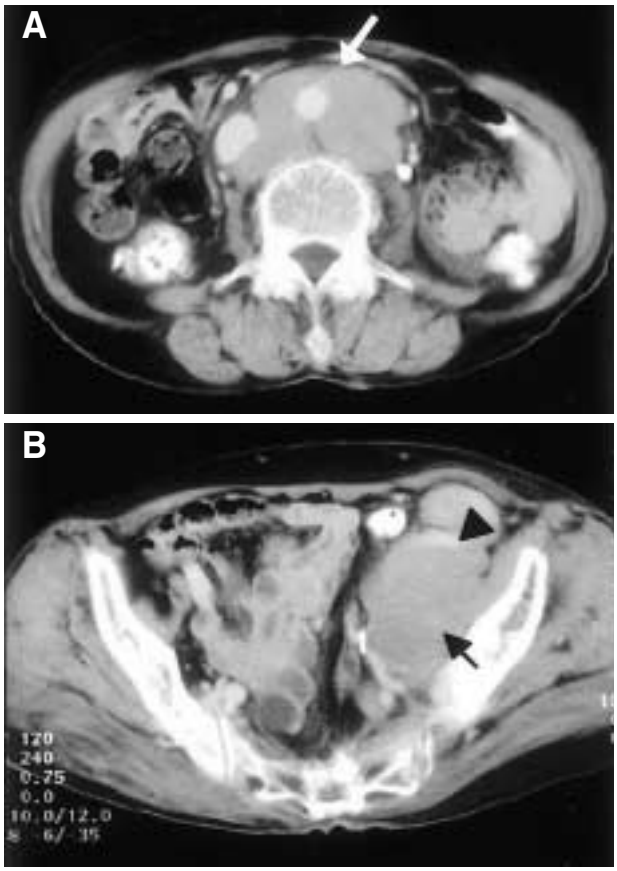

Figure 3. (A) Contrast enhanced CT scan showing well-defined, conglomerated, hypodense masses (arrow) around both para-aortic areas. (B) Hypodense, well-defined masses (arrow) were noted at the left side pelvic cavity, displacing the left distal ureter medially. Arrowhead: left external femoral vein.

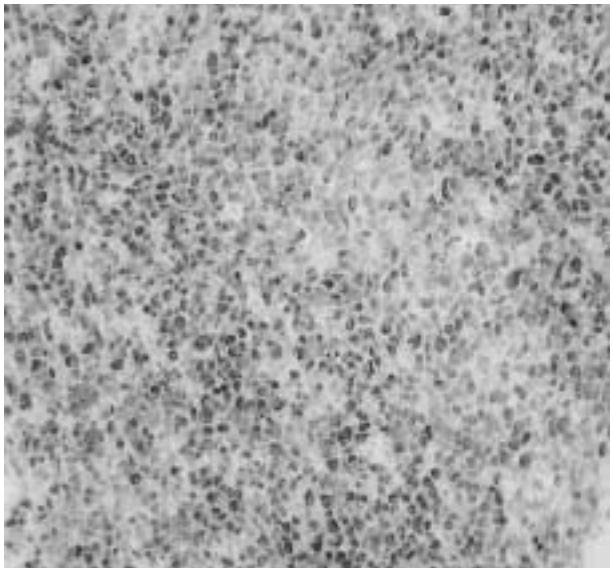

Figure 4. The mass was mainly composed of large cells with prominent nuclei and high mitotic activity (arrow). H&E, ×200.

para-aortic lymphadenopathy and a soft tissue density mass in the left pelvic cavity (Figure 3). For a pathologic confirmation, an ultrasound-guided needle biopsy was performed on the left pelvic mass and the right axillary lymph node. A microscopic examination showed irregular nests of malignant lymphoma cells with hyperchromatic and round nuclei (Figure 4). Immunohistochemical staining showed CD79a positive and CD3 negative. According to the microscopic examination, a diagnosis of diffuse large B cell lymphoma was made. A bone marrow examination showed no lymphoma cells, suggesting the absence of bone marrow involvement.

DISCUSSION

NF1 is one of the most common inherited disorders in humans and mutation of the NF1 gene is thought to be the main contributor to NF1 development. The NF1 gene has been cloned and mapped to the human chromosome 17q11.2 and encodes a protein referred to as neurofibromin, which consists of 2,818 amino acids[4, 5]. Although the functions of neurofibromin are not fully understood, it is known to contain a functional GTPase activating protein, (GAP)-related protein, and is homologous to GAP, which regulates the hydrolysis of the active form, Ras-GTP to the inactive form, Ras-GDP[6]. Thus, neurofibromin may act as a tumor suppressor by regulating the function of oncogenic Ras.

Although the clinical manifestations of NF1 are heterogeneous, even within patients a family, and only a small number of malignancies have been reported as a complications of this disorder, malignancy remains an important cause of morbidity and mortality in NF1.

The estimation of the frequency of malignancy in NF1 is difficult because reported malignancies, may be independent of NF1, per se. However, generally, NF1 is accepted to be related to the development of nervous system malignancies, including malignant peripheral nerve sheath tumors (MPNST), optic glioma, and other gliomas. In addition, leukemia is also known to more prevalent in NF1 and many other malignant tumors have been proposed to be associated with NF1 such as, rhabdomyosarcoma and pheochromocytoma[2].

Stiller et al. reported an increased relative risk of chronic myelomonocytic leukemia and acute lymphoblastic leukemia in children with NF1 in a population-based study. According to this study, five cases of non-Hodgkin's lymphoma were developed over a 17 year-study period among all children in Britain with leukemia or NHL (Non-Hodgkin Lymphoma) diagnosed[7]. Few reports concern the development of malignant lymphoma in NF1 patients, though diffuse mixed T cell[8] and B cell lymphoma[9] have been reported. However, the mechanism of development of malignant lymphoma in NF1 remains unclear, though the mutation of NF1 leading to Ras activation is believed to be responsible for the pathogenesis of cancer development.

In a study of risk factor for malignancy in children with neurofibromatosis, no identified risk factors could be related to NF patients with maligmant tumors[10]. Nevertheless, there is a possibility that the NF1 mutation may have a crucial role in the development of cancer. There is also evidence which indicates that mutations in other genes that predispose to malignancy in the general population may increase the risk of NF-1-associated malignancy. For example, Vogel et al. reported that mice with mutant *p53* and NF1 developed sarcoma[11] and Legius et al. found that *p53* mutation was frequently observed in the tissue of human MPNST in addition to the NF1 mutation[12].

In the presented case, immunohistochemical staining of lymphoma tissue showed that *p53* expression was up-regulated by more than 80%, suggesting the presence of a *p53* mutation (Figure 5). Thus, it is possible that the *p53* mutation contributes to the development of non-Hodgkin's lymphoma.

Because our patient was an 77 years old and her general health status was not good, we treated her with a chemotherapy regimen of COP (cyclophosphamide 400 mg/m^2 per oral on days 1-5, vincristine 1.4 mg/m^2 intravenous on day 1 and prednisolone 100 mg per oral on days 1-5) instead of CHOP. The maximal dosage of vincristine administered was 2 mg and the chemotherapy was repeated every 4 weeks. The lymph nodes and mass in the right axilla and left

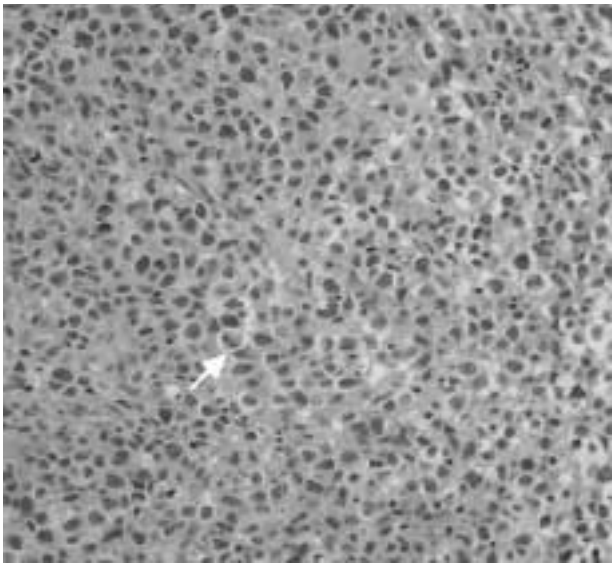

Figure 5. Tumor cells were strongly positive for p53, i.e., more than 80%, ×200.

pelvic cavity were found to have markedly reduced after the completion of the first cycle chemotherapy.

In summary, we experienced a rare case of a non-Hodgkin's lymphoma in a patient with NF-1, and we suggest a possible association between the two diseases. However, further study in necessary to evaluate the relationship between these disorders and the pathogenic mechanism of cancer development in NF1.

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