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A CASE REPORT OF MALIGNANT PERIPHERAL NERVE SHEATH TUMOR IN NEUROFIBROMATOSIS I

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Abstract

NEUROFIBROMATOSIS TYPE 1 (NF1) is one of the most common autosomal dominant conditions affecting the nervous system, occurring with an estimated incidence of 1 in 2500 to 3000 individuals independent of ethnicity, race, and gender. Patients with NF1 harbor a 10% lifetime risk of developing a highly aggressive spindle cell sarcoma termed Malignant Peripheral Nerve Sheath Tumor. We therefore present a 46-year-old Liberian female with Neurofibroma Type I complicated by a Malignant Peripheral Nerve Sheath Tumor.

Abbreviations: GIST- Gastrointestinal Stromal Tumor, MPNST- Malignant Peripheral Nerve Sheath Tumor, NF-Neurofibromatosis, FDG-PET- Fluorodeoxyglucose Positron Emission Tomography

Introduction

NEUROFIBROMATOSIS TYPE 1 (NF1) is one of the most common autosomal dominant conditions affecting the nervous system, occurring with an estimated incidence of 1 in 2500 to 3000 individuals independent of ethnicity, race, and gender (2). Approximately one-half of the cases are familial (inherited). The remainder are the result of de novo (sporadic) mutations [4]. The de novo mutations occur primarily in paternally derived chromosomes, and the likelihood of de novo NF1 increases with advanced paternal age [5]. The incidence of segmental NF1 is estimated at 1 in 36,000 to 40,000 [6].

There are three major clinically and genetically distinct forms of neurofibromatosis: neurofibromatosis types 1 and 2 (NF1 and NF2) and schwannomatosis (1). NF1, also known as von Recklinghausen disease, is the most common type (1). The hallmarks of NF1 are the multiple café-au-lait macules and neurofibromas (1). The condition is called segmental NF1 when clinical features are limited to one area of the body (1).

Von Recklinghausen described NFI in detail in a case report published in 1882, but because of the varied presentation and pleiotropic nature of the disease, formal diagnostic criteria were not established until 1987 by the National Institutes of Health Consensus Development Conference (3). Currently, the diagnosis of NF1 is made in an individual with any 2 of the following clinical features: cafe-au-lait spots, intertriginous freckling, Lisch nodules, neurofibromas, optic pathway gliomas (OPGs), distinctive bony lesions; and a first-degree family relative with NF1 (3).

Case Report

A 46-year-old Liberian female with Neurofibroma Type I since childhood presented with a history of a rapidly growing right upper thigh swelling for 6 months. It started as one of the many previous body lumps that rapidly grew and ulcerated causing anterolateral thigh pain but she remained ambulant. No associated visual or auditory symptoms. No history of headache or seizures. No previous history of hypertension, diabetes or immunosuppression. No previous history of surgery, or transfusion. Her mother as well as her daughter has similar condition. She is a high school dropout, a single parent para 2, regular menses, with no contraceptive use. She neither smoke nor drink alcohol. General exam showed diffuse cutaneous dark, nodular, soft, mobile masses involving the entire body with café-au-lait spots. Local exam revealed a huge 15cm/20cm fungating mass on the upper third of the anterolateral thigh, firm with irregular border, mobile only in the transverse direction, non-pulsatile, and no lymphadenopathy. She was diagnosed of a Locally Advanced Neurofibrosarcoma in Neurofibromatosis I. Based to limitations in preoperative histological assessment, a wide local excision was done initially removing the vastus lateralis muscle without radiotherapy. Histological diagnosis was consistent with a Peripheral Nerve Sheath Tumor. The tumor recurred rapidly within a week. With the absence of radiotherapy in our setting, patient underwent a wide local re-excision removing the tumor along with the Tensor Fascia Lata and Rectus Femoris. The tumor bed was cauterized using a bipolar at frequency of 100 and wound irrigated with warm normal saline. The wound was grafted after 10 days with split thickness skin graft and the patient discharged home with follow-up through the out-patient department.

A **B** **C**

Figure 1. Panel A shows a soft tissue opacity without bony involvement. Panel B displays Peripheral Nerve Sheath Tumor. Panel C shows excised tumor bed.

PATHOGENESIS

NF1 is due to mutations in the NF1 gene, located at chromosome 17q11.2 [1]. Neurofibromin, the protein product encoded by the gene, is expressed in many tissues, including brain, kidney, spleen, and thymus [7]. Mutations in the NF1 gene result in loss of production or reduced function of protein, causing the wide spectrum of clinical findings, including NF1-associated tumors [7]

Oncogenic mutations in Ras genes or inactivation of NF1 favor the active state (p21ras -GTP) and, consequently, result in the permanent stimulation of a cascade of signals and excessive cell division. Loss of neurofibromin, in a variety of tumors and cells of NF1- deficient mice, is associated with elevated levels of p21ras -GTP and subsequent activation of its secondary effectors (8). These findings and the frequent presence of neoplasms in patients with neurofibromatosis type 1 occur because the *NF1* gene is a tumor and neurofibromin suppressor and participates in the process of tumorigenesis by inactivating both alleles of the gene (8).

CLINICAL MANIFESTATIONS

The typical order of appearance of clinical manifestations is café-au-lait macules, axillary and/or inguinal freckling, Lisch nodules (iris hamartomas), and neurofibromas [9]. Osseous dysplasias, if present, usually appear during the patient's first year after birth, and symptomatic optic pathway glioma (OPG) usually occurs by the time the patient is three years of age (1). Other tumors and neurologic complications typically begin to appear after the first year of life. Hypertension is a frequent finding in adults with NF1

and may develop during childhood (12). A much less common cause of hypertension in NF1 is pheochromocytoma, which has been clinically identified in 0.1 to 5.7 percent of patients (1).

Cutaneous Manifestation

Café-au-lait macules are flat, uniformly hyperpigmented macules that appear during the first year after birth and usually increase in number during early childhood (1). However, the presence of six or more café-au-lait macules is highly suggestive of NF1 (10). Freckling occurs mostly in regions of skin apposition, especially the axillary and inguinal areas (1). Freckling usually is not apparent at birth but often appears by age three to five years, typically first in the inguinal region (10). Patients with NF1 develop both benign and malignant tumors at increased frequency throughout life [11]. Neurofibromas are the most common type of benign tumor that develops in patients with NF1 (1).

Neurofibromas are benign Schwann-cell tumours composed not only of neoplastic Schwann cells but also of non-neoplastic fibroblasts, mast cells, macrophages, endothelial cells, pericytes, and perineural cells (22). There are four subtypes: cutaneous, subcutaneous, nodular or diffuse plexiform, and spinal (22).

Discrete cutaneous neurofibromas are the most common type and consist of soft, fleshy, sessile or pedunculated tumors (1). They move with the skin on examination and are not tender while some are located within the dermis and can be palpated as a soft spot in the skin, often with an overlying violaceous discoloration (1).

Plexiform neurofibromas represent a major cause of morbidity and disfigurement in individuals with NF1, and symptomatic plexiform neurofibromas are associated with increased mortality (23). Plexiform neurofibromas may compress the airway or spinal cord and can transform into malignant peripheral nerve sheath tumors (MPNSTs). The most common feature of malignant transformation of an existing plexiform neurofibroma is a painful, expanding lesion (24).

Nodular neurofibromas are discrete lesions that may grow under the skin, where they appear as firm, rubbery masses that may be tender, or occur deeper inside the body but they do not tend to invade surrounding tissues like plexiform neurofibromas (1). Nodular neurofibromas can also transform into MPNST (1). Spinal neurofibromas can occur at single or multiple nerve roots and are associated with both sensory and motor deficits (22).

Orthopedic

Osseous lesions in patients with NF1 include short stature, dystrophic scoliosis, tibial pseudoarthrosis, and sphenoid wing dysplasia (3). Scoliosis (lateral curvature of the spine) is the most common orthopedic finding in NF1, occurring in up to 10% of patients (25). Dysplasia of a long bone is another common manifestation of NF1, most commonly affecting the tibia, which will bow in an anterolateral direction (25).

Ophthalmologic

Lisch nodules are raised, tan-colored hamartomas of the iris and represent a specific finding for NF1 which do not affect vision in any manner (1). Visualization requires slit-lamp examination by experienced practitioners (25). For patients or family members in whom the diagnosis of NF1 is uncertain, referral for a complete eye examination is necessary (25).

Neurologic/Psychiatric

In the broadest sense, learning disabilities occur in nearly half of all NF1 patients and are a chief concern of parents. No consistent profile of the specific deficiencies in NF1 exists but an extensive review in 2006 found that patients have academic deficiencies, particularly in math and reading, slightly lower intelligence quotients (IQs), and a high preponderance of Attention-Deficit Hyperactivity Disorder (ADHD) (26).

Cardiovascular

Cardiovascular manifestations of NF1 include congenital heart disease, vasculopathy, and hypertension (3). NF1 vasculopathy includes stenoses, aneurysms, and arteriovenous malformations and is the second leading cause of death in this population (29). Pheochromocytomas occur at a frequency of 0.1% to 5.7% (3). Most (90%) are benign and typically occur in the adult population (3). However, because of the risk of malignancy, any patient with hypertension, especially paroxysmal hypertension or with symptoms of catecholamine excess such as headache, sweating, palpitations, or anxiety, should undergo measurement of 24-hour urinary excretion of total plus fractionated catecholamines and their metabolites (30). Only after the presence of a pheochromocytoma has been biochemically confirmed should MRI be used to localize the tumor (30).

Associated Tumors

Optic pathway gliomas are typically low-grade pilocytic astrocytomas and can arise anywhere along the anterior visual pathway to the optic radiations and involve the optic nerves, chiasm, and postchiasmal optic tracts (16, 17). In addition to Optic pathway gliomas, individuals with NF1 are at an increased risk for developing other CNS neoplasms, particularly brainstem gliomas (18). Patients with NF1 are at an increased risk of developing soft tissue sarcomas, such as MPNSTs, rhabdomyosarcoma and gastrointestinal stromal tumors (GISTs) (1). NF1 patients have an increased risk of certain other malignancies, such as juvenile myelomonocytic leukemia of childhood and pheochromocytoma, although genetic etiologies other than NF1 are more common causes of these malignancies (19). Women with NF1, particularly those under 50 years of age, are at increased risk of breast cancer (1).

Malignant Peripheral Nerve Sheath Tumors

Patients with NF1 harbor a 10% lifetime risk of developing a highly aggressive spindle cell sarcoma termed MPNST (14). MPNSTs, previously called neurofibrosarcomas, usually arise within pre-existing plexiform or nodular neurofibromas that have undergone malignant transformation (1). The primary care provider should be alert to the possibility of this highly malignant tumor, particularly in teenagers and young adults (1). The first presentation of malignant transformation often is development of significant and constant pain, change in consistency, or rapid growth of a nodule within an existing plexiform neurofibroma (1). Recent experience with fluorodeoxyglucose positron emission tomography (FDG-PET) imaging has proven it to be a sensitive and specific test to differentiate benign plexiform neurofibromas from MPNSTs (15). In addition, although tumor grade and histopathology correlate poorly with prognosis, FDG-PET measurements of MPNSTs are significantly related to survival (3). MPNSTs are frequently resistant to therapy and frequently metastasize and have a poor overall prognosis (3). Standard of care for MPNSTs typically consists of wide surgical excision with postoperative radiotherapy (3). Although this regimen does not improve long-term survival rates, it does delay the

time to local recurrence (20). The use of chemotherapy as a second adjuvant option in the treatment of MPNSTs remains controversial (21).

DIAGNOSIS

The diagnosis of NF1 is basically clinical, and the criteria for diagnosing the disease were established in more detail in 1987, on the *'National Institute of Health Conference* "in Bethesda, USA (8). It was established that, for NF diagnosis in its classic form, the presence of at least two or more of the following is necessary: six or more cafe au lait spots, two or more neurofibromas, at least one plexiform neurofibroma, axillary and inguinal freckling, optic glioma, two or more hamartomas in the iris (Lisch nodules), a typical bone lesion, and family recurrence in at least one first-degree relative (8).

Management of Patients with NF1

The first step in management is genetic counseling (28). Specific counseling may be warranted for patients, particularly adolescents, with NF1 who face issues with self-esteem and the psychosocial impact of this condition (1). Counseling should be provided for patients and families and should include information on the inheritance of the disorder (including potential recurrence risk in other offspring), prognosis, and psychosocial adjustment (1).

Regular medical appointments to a multidisciplinary clinic are also essential and in the first 10 years of life, annual examinations are recommended (28). Annual eye examinations by a pediatric ophthalmologist are essential until 8 years of age (28). Because of the high incidence of learning problems, cognitive development and school performance must be carefully monitored (28).

Cutaneous and subcutaneous neurofibromas are not removed unless there is a specific need for removal (e.g., pain, bleeding, interference with function, disfigurement) (1). Some patients experience pruritus that does not usually respond to antihistamine treatment but may improve with gabapentin (1). Plexiform neurofibromas usually involve multiple nerve fascicles, with serpiginous growth and significant vascularity (27). These lesions can be a significant challenge in surgical treatment and pain management, especially with progressive growth along the spinal column that may result in compression of the spinal cord (27). Surgical resection often is limited to debulking of a specific area of a large lesion, for example, when a component is impinging on the spinal cord or airway or a large soft tissue component is removed to improve cosmesis (1). No chemotherapy has yet been identified to treat plexiform neurofibromas (28). Radiation therapy should be avoided except with malignant tumors because it can stimulate the growth of plexiform lesions (28).

Conclusion

The diagnosis of NF1 is basically clinical and the first step in management is genetic counseling. Regular medical appointments to a multidisciplinary clinic are also essential and annual eye examinations are recommended. Cutaneous and subcutaneous neurofibromas are not removed unless there is a specific need for removal (e.g., pain, bleeding, interference with function, disfigurement). No chemotherapy has yet been identified to treat plexiform neurofibromas and radiation therapy should be avoided except with malignant tumors because it can stimulate the growth of plexiform lesions.

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