Neurofibromatosis Type 1: A Case Report and Review of the Literature

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Neurofibromatosis is the most common single-gene disorder of the nervous system. The chromosomal defects for at least two forms of neurofibromatosis have been delineated and mapped to chromosomes 17 (type 1) and 22 (type 2). The clinical course for either type of neurofibromatosis is unpredictable, and serious neurologic and systemic manifestations frequently arise in patients with this disorder. A 66-year-old woman presented with rapidly progressive myelopathy requiring operative decompression of the spinal canal to preserve function of the lower extremities. It is important to recognize the characteristics of neurofibromatosis and understand the natural history of this condition. Conservative treatment is the rule, treating new manifestations as they arise.

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Neurofibromatosis is the most common single-gene disorder of the nervous system.[1] The chromosomal defects for at least two forms of neurofibromatosis have been delineated and mapped to chromosomes 17 (type 1) and 22 (type 2).[2] Both types of neurofibromatosis affect cells derived embryonically from the neural crest.[3] Both cause abnormal cell growth in the central and peripheral nervous system, which often develops into benign and malignant tumors. Patients with neurofibromatosis have more frequent neoplasms of nonneural origin as well. These neoplasms include leukemia, Wilms's tumor, neuroblastoma, pheochromocytoma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, and thyroid carcinoma.[4] Although the clinical course of neurofibromatosis is unpredictable, serious neurologic and systemic manifestations frequently arise.[4] Involvement of the nervous system leads to the most serious effects of neurofibromatosis, including paraplegia and quadriplegia. Adults with neurofibromatosis frequently have multiple nerve root tumors that may cause progressive compressive myelopathy.[4] This paper focuses on findings characteristic of neurofibromatosis type 1.

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Case Report

A 66-year-old white woman presented to the family practice center with worsening right-sided abdominal discomfort of 1 year's duration. Physical examination revealed an abdominal mass on her right side. Ultrasound and computed tomography (CT) imaging revealed a 6 cm × 6 cm × 5 cm complex retroperitoneal mass inferior to the right kidney. Two additional retroperitoneal masses of uncertain etiology were also noted. On the day following the imaging procedures, the patient developed left lower extremity discomfort and fever, and was unable to rise from a sitting position. She returned to the family practice center for reevaluation. Her gait was unsteady and she complained of increasing pain in the right abdomen and chest. She denied having previous chest pain, shortness of breath, nausea, vomiting, diaphoresis, headache, visual disturbance, dysphagia, or stridor. Past medical records were not available. The patient had no known allergies. Her family history included breast cancer in her mother. The patient also reported that her mother and brother had unusual "skin lesions," the nature of which had never been determined. The patient did not smoke tobacco or drink alcohol. A review of systems proved unremarkable.

An examination revealed a frail, tremulous woman who appeared older than her stated age. Her vital signs included temperature of 38.3°C (101.0°F), pulse of 86 beats per minute, and blood pressure of 120/74 mm Hg. Integumentary examination revealed a 15 cm × 6 cm area of erythema and increased warmth over the left

lower extremity posteriorly. Additionally, she had a 4 cm × 6 cm solid, nontender, mobile mass, which she claimed had been present for 2 years, over the dorsal aspect of her right foot. A right mid-anterior neck mass of similar characteristics had reportedly been present for several years. Virtually identical subcutaneous lesions were noted on the right arm and left forearm. She stated that these had been present for several months. No café-au-lait spots or freckling were noted.

Other than the palpable right lower quadrant mass, an examination of the abdomen revealed no significant findings. Neurological examination revealed weakness of the right lower extremity. Cranial nerves were intact and sensation was normal. Vibratory sensation and proprioception were normal. The remainder of the physical examination was unremarkable.

Laboratory evaluation included hematologic measurements showing a white blood count of 22.8×10^9/L ($22,800/mm^3$), hemoglobin level of 146 g/L (14.6 g/dL), and a hematocrit of 42.7%. White blood cell count differential included 3% bands, 88% polymorphonuclear leukocytes, 6% lymphocytes, and 3% monocytes. Standard chemistries showed the following levels: creatine phosphokinase, 2781 U/L; aspartate aminotransferase, 119 U/L; total protein, 66 g/L (6.6 g/dL), and calcium, 2.04 mmol/L (8.2 mg/dL). A Papanicolaou smear was normal. An electrocardiogram showed only sinus tachycardia with nonspecific ST and T wave changes. A chest radiograph revealed a superior mediastinal mass.

The initial clinical impression was that the patient had left lower extremity cellulitis, and possibly metastatic cancer from an unknown primary site. The patient's right lower quadrant mass was consistent with an abscess, an ovarian tumor, colonic adenocarcinoma, or mesenteric adenitis; the patient had a markedly elevated creatine phosphokinase level (non-MB) that was attributed to muscle involvement of the tumor.

Initial management included intravenous cefazolin for cellulitis. Further evaluation of what was presumed to be a malignancy included a Papanicolaou smear, a mammogram, and a bone scan, the results of which were all unremarkable. An oncology consultant recommended fine-needle biopsy of peripheral lesions and a CT scan of the chest. The CT scan of the chest revealed large peritracheal and axillary soft tissue masses on the right side that were suggestive of metastatic disease. The peritracheal mass was complex, with necrotic components, and extended from the supraclavicular region inferiorly to the junction of the brachiocephalic and the subclavian artery. No vascular invasion was seen. The mass displaced the brachiocephalic artery, the trachea, and pulmonary soft tissues. These findings made it unlikely that the alleged carcinoma originated in the breast, bone, or lungs. A fine-needle biopsy of the left forearm mass revealed undifferentiated spindle cells (a very nonspecific finding).

An excisional biopsy of the right axillary mass showed tumor involving axillary nerve. Several serum markers were evaluated to determine the cause of the tumor. Serum levels of carcinoembryonic antigen, cancer antigens 125 and 19-9, α-fetoprotein, and vitamin B_{12} were within normal ranges, and the fluorescent treponemal antibody absorption test was nonreactive. The level of β-subunit of human chorionic gonadotropin, however, was slightly elevated at 2.2 IU/L (normal range <1.56 IU/L). Immunoperoxidase stains were positive for S100 and vimentin, and negative for cytokeratin, factor VIII (antihemophilic factor), and actin. These stains are useful tumor markers for the interpretation of biopsy specimens. This information made it possible to narrow the histological differential diagnosis of her lesions to neurofibrosarcoma, neurofibromatosis, or schwannoma.

Nine days following admission, the patient's cellulitis had completely resolved; however, she began to experience accelerated neurological decline. At that point, we realized that the cellulitis had clearly been a coincidental and confounding variable in the patient's clinical course. The patient was barely able to move from the chair to the bed with assistance, although she remained alert and oriented. She exhibited marked right-sided lower extremity weakness and bilaterally positive Babinski's signs. Upper extremity findings included weakness bilaterally despite normal muscle tone, no fasciculation, and no gross atrophy. The patient's cerebellar function was poor, as evidenced by worsening action (intention) tremor and difficulty in performing a heel-to-shin test.

Acute deterioration of the patient's motor control and progressive muscle weakness, combined with cerebellar findings, prompted further evaluation to rule out central nervous system (CNS) disease. A CT scan of the patient's head was unremarkable, showing only cerebral atrophy consistent with the patient's age. Plain films of the spine showed diffuse osteopenia, with no lytic lesions or spondylolisthesis. A CT myelogram was remarkable for multiple intradural filling defects including complete blockage at the T-7 to T-9 levels with cord deviation, anterior extradural defects from L-2 to L-5, secondary to spondylosis, extensive degenerative joint disease, and spinal stenosis at L-3 to L-5 (Figures 1 and 2). This compressive myelopathy is consistent with any of the previously mentioned histological differential diagnoses, including metastatic carcinoma. The patient refused examination by magnetic resonance imaging (MRI).

Fifteen days after admission to the hospital, the patient was unable to walk. Muscles supplied by L-5 to S-1 became extremely weak and the intrinsic muscles of the hand supplied by C-7 to T-1 lost function. Admin-

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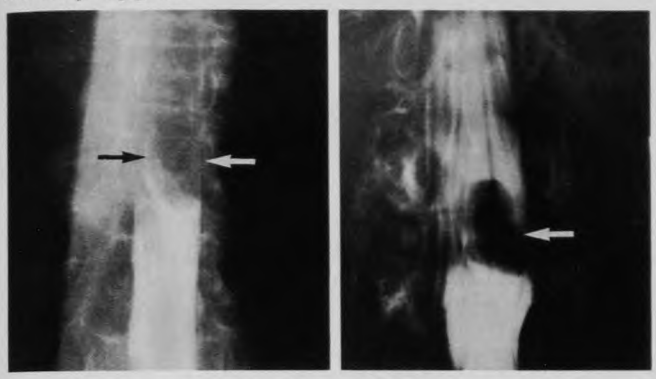

Figure 1. Myelogram showing complete blockage of spinal canal (above T-9) by intradural neurofibroma (left) and large intradural neurofibroma at L-2 to L-3 (right).

istration of dexamethasone was started. The patient underwent subsequent thoracolumbar laminectomy at T-7 to T-10 with extradural excision of tumor, as well as laminectomy of L-2 through L-4. Examination of the pathological specimens was consistent with neurilemmoma (neurofibromatosis) at all levels.

The patient did well postoperatively and required no chemotherapy or radiation. One month following her admission, the patient transferred to a rehabilitation center. The patient regained her ability to walk without significant difficulties.

Discussion

Natural History and Epidemiology

Neurofibromatosis was a recognized clinical syndrome before von Recklinghausen wrote his classic paper in 1882. By 1918, neurofibromatosis was established as an autosomal-dominant condition with variable penetrance.[5] Approximately 50% of cases represent new mutations.[6] Two forms are currently recognized, but additional variants may exist. Both primary forms are characterized by café-au-lait spots, subcutaneous neurofibromatous tumors, CNS tumors of different histological types, and benign intracranial calcifications. The disease may be clinically static or progress toward stepwise deterioration.[4]

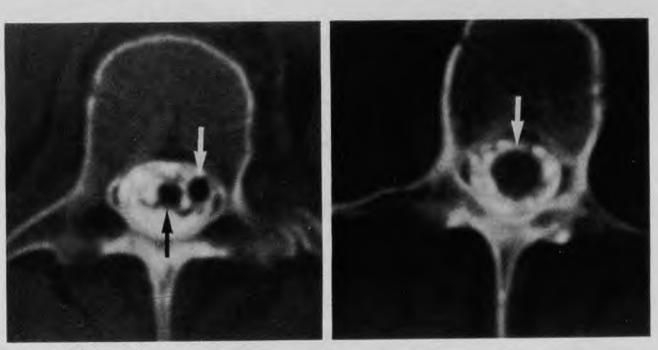

Figure 2. Computed tomography myelogram showing large intradural defect from tumor at L2-3 (right) and smaller neurofibromas in the L1-2 region (left).

Table 1. Diagnostic Criteria for Neurofibromatosis Type 1

- Six or more café-au-lait maculas of over 5 mm in diameter in prepubertal persons or of over 15 mm in diameter in postpubertal persons
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Freckling in the axillary or inguinal regions
- Optic glioma
- Two or more iris hamartomas (Lisch nodules)
- Distinctive osseous lesions, such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudarthrosis
- A first-degree relative with neurofibromatosis type 1

Neurofibromatosis type 1 affects 1 in 2500 to 4000 individuals and is related to an abnormality of chromosome 17.[7,8] It is further characterized by systemic, neurologic, cosmetic, and orthopedic manifestations.[4,6,9,10] Type 2 affects 1 in 50,000 individuals and results from a chromosome 22 abnormality.[11,12] The most prominent feature of neurofibromatosis type 2 is bilateral acoustic nerve tumors.

Diagnostic criteria for type 1, set by the National Institutes of Health (NIH) in 1987, are presented in Table 1. Café-au-lait spots are generally the first feature to appear and may be accompanied (in from one to two thirds of affected people) by axillary freckling that develops in middle childhood.[13,14] Peripheral neurofibromas begin to appear at the onset of puberty. Subcutaneous neurofibromas are readily palpable and have multiple cells of origin. They are made up of neurons, Schwann cells, fibroblasts, blood vessels, mast cells, and pigment cells. Large neurofibromas may grow rapidly, causing distal weakness, atrophy, and paresthesia. They also may invade adjacent vital structures. Neurofibrosarcoma is a rare neoplasm that may arise independently or in association with neurofibromatosis; it is one of the most lethal diseases.[15] Sarcomatous degeneration of neurofibromas is accompanied by a characteristic inflammatory response including erythema, warmth, and pain.[4] Lisch nodules (dome-shaped, pigmented nodules of the iris) are present in over 90% of type 1 patients by the age of 5 years.[16] Other optic manifestations of neurofibromatosis type 1 include optic glioma and sphenoid wing dysplasia. Optic glioma usually presents with proptosis and decreased visual acuity. Gliomas may involve the optic chiasm and lead to diminished visual field, headaches, and increased intracranial pressure. However, most of these lesions are asymptomatic. Sphenoid wing dysplasia most commonly

presents in children with a pulsating exophthalmos. Optic glioma is best evaluated with CT or MRI, and sphenoid wing dysplasia is best seen with CT of the orbits.[9]

Complications of neurofibromatosis type 1 affect all body systems, and thus their occurrence cannot be adequately predicted.[6] Common complications of neurofibromatosis include hypertension secondary to pheochromocytoma or renal artery stenosis, visceral tumors leading to obstruction, interstitial pulmonary fibrosis, scoliosis, developmental delay, learning disability, epilepsy, and optic gliomas, the most common CNS tumor in patients with type 1. Neurofibromatosis may cause multiple brain or spinal tumors. Many of the major complications of type 1 in adulthood are secondary to spinal cord or spinal root impingement by neurofibromas, meningiomas, or schwannomas.[9] Brasfield et al noted that spinal cord tumors tended to occur most commonly between 20 and 30 years of age.[17] Nonetheless, the age range of spinal neurofibromas is lifelong, with a frequency of occurrence of 2.1%, making it one of the most common complications of neurofibromatosis following scoliosis (5% to 6%).[6,13] Large retroperitoneal or retropleural neurofibromas may follow the nerve roots through the intravertebral foramina, becoming dumbbell lesions and compressing the spinal cord as well. The manifestations of a compressive myelopathy include back pain and progressive paraparesis or quadriparesis. Sensory or level findings, or both, as well as sphincteric incontinence, may also be present.[4]

Management

Conservative management is the rule for neurofibromatosis patients. Management may be complicated by mental retardation, learning and behavioral disorders, and seizures.[4] Fortunately, approximately two thirds of individuals with type 1 have a mild disorder and never develop major disabilities.[9] The 1987 Consensus Development Conference on Neurofibromatosis of the National Institutes of Health determined that evaluation of patients without major complications can be performed in a standardized clinical setting. During physical examination, the emphasis should be on the common, specific signs of the disorder such as café-au-lait maculas, neurofibromas, and Lisch nodules (iris hamartomas) as well as on less common features, such as impaired vision, optic atrophy, developmental disabilities, possible auditory system abnormalities, short stature, and signs of precocious puberty or hypogonadism. Tests should be dictated by findings on clinical evaluation. Computerized and magnetic resonance imaging, electroencephalography, and evoked potentials are unlikely to be of value in asymptomatic patients. Counseling that addresses prognosis, genetics, psychological and social adjustment, and evaluation of relatives (particularly parents); annual review by an informed clinician; and referral to specialized clinics and patient support groups must be provided for all patients and their families. Personal counseling should be reinforced with a written report and include mention of the availability of prenatal and presymptomatic diagnosis with DNA markers. Genetic counseling and periodic follow-up examinations provide opportunities to educate these individuals and recognize new findings as they occur.[4]

The treatment of new manifestations of neurofibromatosis as they arise is important in order to maintain the patient's functional viability, as exemplified by this case presentation. Of greatest concern are intramedullary astrocytomas and extramedullary lesions causing spinal cord compression. Unilateral or bilateral plexiform spinal or paraspinal neurofibromas may extend over many segments, as in our patient. Sudden and rapid deterioration is not unusual, and represents a major challenge in the ongoing care of persons with neurofibromatosis. Magnetic resonance imaging is considered to be superior to CT for evaluating most brain and spinal lesions.[18] Neoplasms affecting the spine are most clearly seen on gadolinium-enhanced magnetic resonance images. Syringomyelia, included in most lists of lesions of neurofibromatosis type 1, is most likely secondary to intramedullary tumor or tumorous compression of the spinal cord rather than to a primary defect.[19]

Current Research

The observation of infiltration of tumors with mast cells as well as the occasional occurrence of pruritus has led Riccardi[20] to suggest the possible control of growth of aggressive neurofibromas and associated pruritus by use of the drug Ketotifen, which blocks mast cell secretions. Ratner et al[21] have identified a proteoglycan present on dorsal root ganglion neurons that stimulates Schwann cell growth. A similar substance might be the stimulus for rapid neurofibroma formation in patients with neurofibromatosis. Nerve growth factor and the biological regulation of this substance may provide new avenues for investigation in this area.[22]

This neurofibromatosis patient exhibited an initially confusing, but quite characteristic rapid deterioration as a result of CNS involvement. Concomitant medical conditions complicated timely management. Her condition was characterized only by spinal tumors. She had no café-au-lait spots, Lisch nodules, or axillary freckling, and no family history of the disease. Therefore, she may represent a new mutation of the gene for neurofibroma-

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tosis type 1 (chromosome 17) with manifestations of both types of the disease. This suggests the possibility of an atypical form of neurofibromatosis or a mutant gene.[23] The symptoms associated with compressive myelopathy were quite evident, and aggressive surgical intervention preserved this patient's neuromuscular function. This case underscores the importance of recognizing the characteristics of neurofibromatosis, understanding the natural history of this disorder, and intervening appropriately when symptoms develop.

For further information on neurofibromatosis and support organizations for afflicted individuals, contact the National Neurofibromatosis Foundation at 141 Fifth Ave, Suite 75, New York, NY 10010.

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