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Neurofibromatosis: A Clinical Case Report and Critical Review of Current Literature

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Abstract

Background: Neurofibromatosis type 1 (NF1) is a common autosomal dominant neurocutaneous disorder characterized by the development of multiple café-au-lait macules, neurofibromas, and a variety of systemic manifestations. Early diagnosis is crucial for surveillance and management due to its progressive nature and potential for complications such as malignant transformation.

Case presentation: We report the case of an 18-year-old female presenting with neurofibroma. The lesion extended from the infraorbital region to the inferior border of the mandible, involving the preauricular area and the corner of the mouth. It was distributed in a pattern resembling multiple scattered islands. The lesion was pigmented, exhibiting characteristics consistent with café-au-lait macules, and the patient had multiple similar lesions elsewhere on the body.This case highlights the classical features of NF1 in a young adult and underscores the variability in presentation. A comprehensive literature review is included, discussing the genetic basis, diagnostic criteria, imaging findings, complications and recent advances in targeted therapies including MEK inhibitors. The review also emphasizes the importance of long-term surveillance and psychosocial support.NF1 is a lifelong condition with diverse manifestations and significant clinical variability. Early diagnosis and multidisciplinary management are essential to monitor complications and improve patient outcomes. This case underscores the need for awareness among clinicians, especially in adolescents and young adults who may present with subtle or overlooked features.

Introduction

Neurofibromatosis (NF) is a group of genetically inherited disorders characterized by the development of multiple benign and malignant tumors, primarily of neural origin. It encompasses three major subtypes: Neurofibromatosis Type 1 (NF1), Neurofibromatosis Type 2 (NF2), and schwannomatosis. Each subtype has a distinct genetic cause and clinical presentation, though they share overlapping features such as the growth of nerve sheath tumors and systemic manifestations. NF1 is by far the most common form, with a global prevalence of approximately 1 in 2,500 to 3,000 individuals, whereas NF2 is rarer, affecting approximately 1 in 25,000 to 40,000 people worldwide (1). Schwannomatosis is the least understood and has only recently been recognized as a distinct clinical entity. Due to their complex, multisystem involvement, neurofibromatoses present considerable challenges in diagnosis, management, and long-term care. This review aims to explore the current understanding of the genetic basis, clinical manifestations, diagnostic approaches, treatment options, and recent advances in the management of neurofibromatosis, with an emphasis on NF1 and NF2.

Genetic and Molecular Basis

The pathogenesis of neurofibromatosis lies in the disruption of tumor suppressor genes, which are essential for regulating cellular proliferation and differentiation. NF1 is caused by mutations in the NF1 gene located on chromosome 17q11.2. This gene encodes neurofibromin, a GTPase-activating protein that functions as a negative regulator of the Ras-MAPK pathway (2). Loss-of-function mutations in NF1 lead to sustained Ras activation, resulting in uncontrolled cell division and tumor formation. The gene exhibits high mutational variability, with over 3,000 different mutations identified, contributing to the phenotypic heterogeneity observed among patients (2).

NF2, in contrast, results from mutations in the NF2 gene on chromosome 22q12.2, which encodes a cytoskeletal protein known as merlin or schwannomin. Merlin plays a role in regulating contact-dependent inhibition of cell growth and in maintaining cell junctions. Its loss leads to increased cellular proliferation, particularly in Schwann cells and other glial cell types (3). Unlike NF1, NF2 often presents later in life and has a distinct tumor profile.

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Clinical Manifestations

Neurofibromatosis Type 1 (NF1)

NF1 typically manifests during early childhood and is often diagnosed clinically due to its characteristic cutaneous signs. The NIH has established diagnostic criteria that include six or more café-au-lait macules, axillary or inguinal freckling, two or more neurofibromas or one plexiform neurofibroma, two or more Lisch nodules, optic glioma, a distinctive osseous lesion, and a first-degree relative with NF1 (5). Café-au-lait spots are often the first visible sign and may be present at birth or appear during infancy. Axillary and inguinal freckling generally develops in early childhood. Cutaneous neurofibromas emerge during adolescence and increase in number and size with age.

Plexiform neurofibromas are a hallmark feature of NF1, occurring in up to 50% of patients. These tumors are typically congenital, deeply located, and may grow aggressively, leading to pain, functional impairment, and cosmetic disfigurement (6). NF1 also has several non-tumorous manifestations. Learning disabilities affect up to 60% of children with NF1, with common issues including attention deficit hyperactivity disorder (ADHD), executive dysfunction, and visuospatial difficulties. Skeletal abnormalities such as scoliosis, tibial dysplasia, and sphenoid wing dysplasia are also seen. A serious complication of NF1 is the development of malignant peripheral nerve sheath tumors (MPNSTs), which arise in approximately 8–13% of individuals and are associated with poor prognosis (6).

Neurofibromatosis Type 2 (NF2)

NF2 typically presents in late adolescence or early adulthood and is most notably characterized by bilateral vestibular schwannomas (VS), which result in progressive hearing loss, tinnitus, and balance disturbances (3). Unlike NF1, skin findings are minimal in NF2. Other associated tumors include spinal schwannomas, intracranial meningiomas, and intramedullary ependymomas. These tumors can compress neural structures, causing pain, motor weakness, and sensory deficits. Ophthalmologic signs such as posterior subcapsular cataracts, retinal hamartomas, and optic nerve meningiomas are also observed in NF2 (7).

Although bilateral vestibular schwannomas are pathognomonic for NF2, patients may also present with unilateral tumors or family history, leading to diagnostic uncertainty. Mosaicism is particularly common in NF2 and may lead to milder phenotypes or delayed diagnosis (4). The disease course is generally progressive, withcumulative tumor burden contributing significantly to morbidity. Due to its potential to affect cranial nerves, spinal cord, and brainstem, NF2 often leads to more severe neurological deficits compared to NF1.

Diagnosis

The diagnosis of neurofibromatosis relies primarily on clinical evaluation supported by imaging and genetic testing. NF1 is usually diagnosed in childhood based on the NIH criteria, with most children meeting diagnostic thresholds by the age of 8 years (5). Genetic testing for NF1 mutations is available and may be particularly useful in patients with atypical presentations or for prenatal diagnosis. Whole-body MRI is increasingly used to evaluate the extent of internal tumors, particularly plexiform neurofibromas and spinal lesions (8). Optical coherence tomography (OCT) and visual evoked potentials may aid in the diagnosis and monitoring of optic pathway gliomas.

In NF2, MRI is essential for detecting vestibular schwannomas and other intracranial and spinal tumors. Gadolinium-enhanced MRI of the brain and spine is the imaging modality of choice. Genetic testing for NF2 mutations can confirm the diagnosis and is especially important in patients with no family history or unilateral disease (7). Additionally, recent advancements in imaging technologies and artificial intelligence have enabled automated tumor volumetric analysis, improving tumor monitoring and therapy response assessment (9). These tools are particularly valuable in clinical trials and longitudinal studies.

Neuroimaging

A key feature of NF2 is the presence of bilateral acoustic schwannomas, also known as vestibular schwannomas. Neuroimaging plays a crucial role in the diagnosis, characterization, and management of neurofibromas, particularly in patients with Neurofibromatosis Type 1 (NF1). Magnetic Resonance Imaging (MRI) is the modality of choice due to its superior soft tissue contrast and ability to delineate tumor margins and involvement of adjacent structures. On MRI, neurofibromas typically appear as well-defined, T1 hypointense and T2 hyperintense masses, often with a characteristic “target sign” a central area of low signal intensity surrounded by a hyperintense rim on T2-weighted images. Contrast enhancement can help differentiate benign lesions from those with potential malignant transformation, such as malignant peripheral nerve sheath tumors (MPNSTs), which often show irregular borders and heterogeneous enhancement. Computed Tomography (CT) may be used to assess bony changes or when MRI is contraindicated. Advanced imaging techniques, such as diffusion-weighted imaging (DWI) and positron emission tomography (PET), may provide additional insights into tumor biology and aid in distinguishing benign from malignant lesions. Overall, neuroimaging is essential not only for initial diagnosis but also for monitoring disease progression and guiding surgical planning.

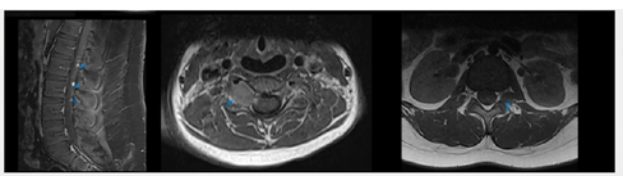

Image 1- CT

Management and Treatment

There is currently no cure for neurofibromatosis, and treatment is primarily symptomatic and multidisciplinary. Surgical intervention remains a cornerstone in the management of symptomatic tumors, especially those causing compression, disfigurement, or functional impairment. In NF1, surgical resection of plexiform neurofibromas can be difficult due to their infiltrative nature and proximity to vital structures. For this reason, not all tumors are amenable to surgery. In NF2, surgery may be required for vestibular schwannomas and spinal tumors; however, the risk of cranial nerve damage must be carefully weighed against potential benefits (3).

Pharmacological treatment has advanced significantly in recent years. The MEK inhibitor selumetinib has demonstrated promising results in shrinking inoperable plexiform neurofibromas in children with NF1 and received FDA approval in 2020 (10). Clinical trials have shown that selumetinib induces partial tumor regression in a majority of patients and improves quality of life and functional outcomes. For NF2, agents targeting angiogenesis and mTOR signaling have been investigated, although their clinical efficacy remains modest (11). Bevacizumab, an anti-VEGF monoclonal antibody, has shown some benefit in reducing tumor size and preserving hearing in NF2 patients with vestibular schwannomas.

Supportive care is an integral part of NF management and includes interventions such as physical therapy, occupational therapy, speech and language support, audiological rehabilitation, and special education services. Psychological support is also critical, particularly for children with cognitive impairments or adults facing disfigurement and chronic pain. Surveillance protocols vary depending on the disease subtype and age, but generally involve annual physical exams, ophthalmologic assessments, and periodic MRI imaging to monitor for tumor progression or malignant transformation (3,6).

Case Report

A 18-year-old medically fit female patient with no known drug allergies (NKDA) presented to king fahad general hospital with a pigmented, enlarged lesion on the right buccal mucosa. She had a history of surgical excision of the right submandibular and parotid glands a few years ago, which included the removal of a similar lesion.

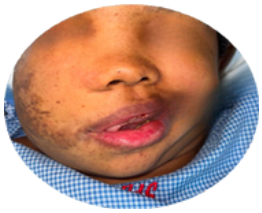

Image 2- Pre-operative

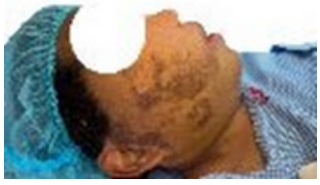

Image 3- Pre operative

Clinical examination

8 year old female patient presented to king fahad general hospital with a recurrent mass in the right buccal mucosa, which was since birth. The lesion extended from the infraorbital region to the inferior border of the mandible, involving the preauricular area and the corner of the mouth. It was distributed in a Patt-ern resembling multiple scattered islands. The lesion was pigmented, exhibiting characteristics consistent with café-au-lait macules, and the patient had multiple similar lesions elsewhere on the body.

Diagnosis

After a thorough clinical examination and based on the pathognomonic features observed in the patient, a final diagnosis of plexiform neurofibroma associated with Neurofibromatosis Type 1 (NF1) was established.

Surgical procedure

A decision was made to proceed with surgical excision using a preauricular facelift-style incision, with the possibility of extending the dissection into the neck if necessary. The planned incision was carefully marked along the natural preauricular crease, curving around the tragus in a rhytidectomy-style manner, and continuing into the postauricular sulcus and hairline.

Tumescent anesthesia was administered to aid with hemostasis and hydrodissection. A skin incision was then made along the marked lines using a #15 blade. Sharp and blunt dissection were performed in the subcutaneous plane anteriorly to elevate a skin flap over the parotid-masseteric fascia.

Meticulous dissection was carried out with continuous identification and protection of the facial nerve branches. Once the skin flap was adequately elevated, the buccal fat pad was identified. A firm, nodular tumor was found deep to the buccal fat pad, adjacent to the buccinator muscle.

Image 4- Peri operative

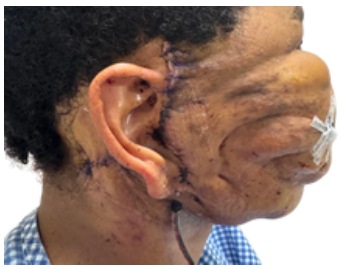

Image 5- Post operative

Dissection and excision

The mass was meticulously dissected from the surrounding buccal tissues, with particular care taken to preserve the buccal branches of the facial nerve, which were gently retracted throughout the procedure. Circumferential dissection was performed around the tumor until it was fully mobilized.

Intraoperative bleeding was observed but successfully controlled; further details regarding the bleeding will be discussed in the next slide. All feeding vessels were identified, cauterized, and ligated. The tumor was excised and delivered en bloc.

A surgical drain was placed in the wound to monitor postoperative bleeding. The incision was closed following the application of sterile dressing gauze.

Immediate Postoperative Examination:

In the Post-Anesthesia Care Unit (PACU), a formal facial nerve examination was performed. The patient demonstrated symmetrical movement across all branches of the facial nerve, with no weakness observed during eyebrow elevation, eye closure, or smiling.

Postoperative Instructions and Care:

The patient was educated on drain care and advised to monitor for signs of facial swelling or hematoma formation. The surgical drain was removed on postoperative day 4. Upon discharge, the patient was instructed to keep the surgical area dry and to avoid any strenuous activities.

Recent Advances and Future Directions

Research in neurofibromatosis is evolving rapidly, with significant advances in both basic science and clinical care. The use of high-throughput sequencing and improved genotype–phenotype correlation studies is enhancing our understanding of disease variability and paving the way for personalized medicine. Artificial intelligence and deep learning algorithms are now being employed to analyze whole-body MRI scans, facilitating automated tumor segmentation and volume calculation (9). These tools may enable better tracking of disease progression and response to therapy in both clinical and research settings.

Targeted therapies remain a key focus of current investigations. Beyond selumetinib, other MEK inhibitors and agents targeting downstream elements of the Ras-MAPK pathway are being explored for NF1. In NF2, research continues into therapeutics that can delay or prevent the development of hearing loss, with a growing interest in gene therapy and molecular repair techniques. Moreover, efforts are underway to better understand and address cognitive and behavioral manifestations of NF1, which are often overlooked but have a profound impact on quality of life (12).

Conclusion

Neurofibromatosis is a complex group of inherited disorders with diverse clinical manifestations, ranging from benign cutaneous findings to life-threatening tumors and neurological complications. While recent advances in genetic understanding, imaging, and targeted therapies have significantly improved patient outcomes, many challenges remain. These include the management of cognitive deficits, prevention of malignant transformation, and ensuring equitable access to care across regions. Continued research into molecular pathogenesis and therapeutic development holds the promise of transforming NF from a life-limiting disorder to a manageable chronic condition. A multidisciplinary approach involving neurologists, geneticists, oncologists, surgeons, psychologists, and allied health professionals remains essential for optimal care of individuals with neurofibromatosis.

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