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FACIAL PLEXIFORM NEUROFIBROMATOSIS IN A PATIENT WITH NEUROFIBROMATOSIS TYPE1: A CASE REPORT

NERWIAKOWŁÓKNIAK SPLOTOWATY W OBRĘBIE TWARZY U PACJENTA Z NEUROFIBROMATOZĄ TYPU I: OPIS PRZYPADKU

Iffat Hassan[1], Abid Keen[1], Parvaiz Ahmad Shah[2]

[1]*Deptament of Dermatology, STD & Leprosy Govt. Medical College & Associated SMHS Hospital, Srinagar-Kashmir, India*
[2]*Division of Neurology, Department of Medicine, Govt.Medical College & Associated SMHS Hospital,Srinagar-Kashmir, India*

***Corresponding author**:* Dr. Iffat Hassan *hassaniffat@gmail.com*

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Abstract
Plexiform neurofibroma is a poorly circumscribed, diffuse enlargement of neural sheets that typically involves major nerve trunks of the head and neck region because of the rich innervations of this area. It is a benign tumor and is a virtually pathognomonic and often disabling feature of neurofibromatosis type 1 (NF-1 or Von Recklinghausen's disease). We hereby report a case of facial neurofibroma in an adult female with neurofibromatosis type 1 (NF-1).

Streszczenie
Nerwiakowłókniak splotowaty to słabo odgraniczone, rozlane powiększenie osłonek nerwowych, które typowo dotyczy korzeni nerwowych okolic twarzy i szyi, co spowodowane jest ich bogatym unerwieniem. Jest to guz łagodny, w rzeczywistości patognomoniczny dla neurofibromatozy typu 1 (NF-1 lub choroba Von Recklinghausena), którego postać jest często traktowana jako cecha upośledzająca (zwł. wygląd pacjenta – przyp. redakcji). W tym artykule opisujemy przypadek nerwiakowłókniaka okolicy twarzy u dorosłej kobiety z NF-1.

Key words: plexiform neurofibroma; cafe-au-lait macules; neurofibromatosis
Słowa klucze: włókniak splotowaty; plamy cafe-au-lait; neurofibromatoza

Introduction

Plexiform neurofibroma is a relatively common but potentially devastating manifestation of neurofibromatosis type 1 (NF-1). It is a poorly defined benign tumor of the peripheral nerve sheath spreading out just under the skin or deeper in the body. The diffuse and soft nature of plexiform neurofibroma is often compared to 'a bag of worms' and is to be distinguished from a vascular malformation or a lymphangioma. Plexiform neurofibromas are locally invasive, non-metastasizing, and generally categorized by their location. Tumors of head, neck and face are the most common, followed by lesions of the spine, extremities, mediastinum and abdomen [1].

Facial plexiform neurofibroma may produce various degrees of cosmetic and functional deformities in the head and neck region. Surgical management is the mainstay of treatment, but within the head and neck region it is limited by the infiltrating nature of these tumors, inherent operative morbidity and a high rate of regrowth.

Case report

A 45-year old unmarried female, normotensive, nondiabetic, presented to the out-patient department of our institute with a history of a swelling on the right side of her face especially over the right infraorbital region, right side of nose, adjacent right cheek, chin and jaw.The patient reported that her facial disfiguring growth had started at birth and continuously increased in size since then. She had difficulty in speaking properly. She also complained of intermittent dull aching pain and itching on her face. There was no history of any regression in size or discharge from the swelling. The patient never noticed any similar swelling elsewhere in the body. There was no history of trauma over the area. Also, there

was no history suggestive of any constitutional symptoms, tingling and numbness elsewhere over the body. There was no history of seizures, deafness, tinnitus or any other neurological deficit. The past medical and surgical histories were unremarkable.There was no history of similar disease in any of the family members or first degree relatives. There was no known evidence of any hereditary disease in the family or first degree relatives.

General physical examination revealed an averagely built adult female with a steady gait, and satisfactory vital signs with no signs of pallor, icterus, cyanosis or lymphadenopathy. Systemic examination was also non-contributory.

Cutaneous examination revealed a large solitary swelling measuring approximately 6x5 cm in size with indistinct borders, overhanging on itself, present on the right side of face involving the right cheek, right side of upper lip, chin and right jaw. The overlying skin showed hyperpigmentation and hypertrichosis with follicular prominence (Fig. 1,2). On palpation, there was no local rise in temperature or any tenderness. The swelling had a peculiar consistency, soft in most of the areas with few firm nodular areas, similar to that described in literature as a 'bag of worms'. On auscultation, no bruit could be detected.

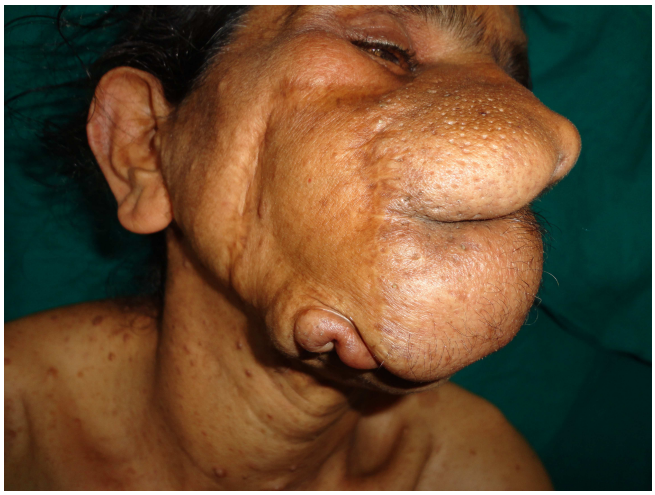

Figure 1. Facial plexiform neurofibroma

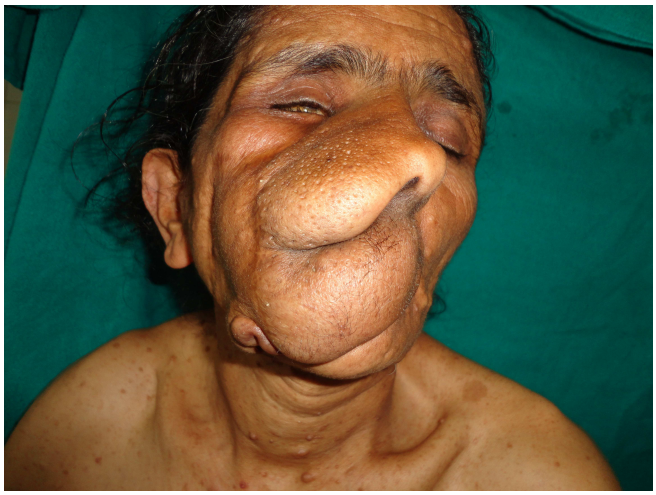

Figure 2. Facial plexiform neurofibroma (lateral view) with hypertrichosis and follicular prominence

Rest of the cutaneous examination revealed multiple hyperpigmented macules over her trunk and arms (Fig. 3). These macules were sharply defined, ranging in size from a few mm to more than 3 cm in diameter and were more fifteen in number. Axillary and inguinal freckling (Crowe's sign) was also present. There were also multiple skin coloured papules and nodules distributed over trunk and upper limbs, ranging in size from a few mm to more than 3 cms in size.

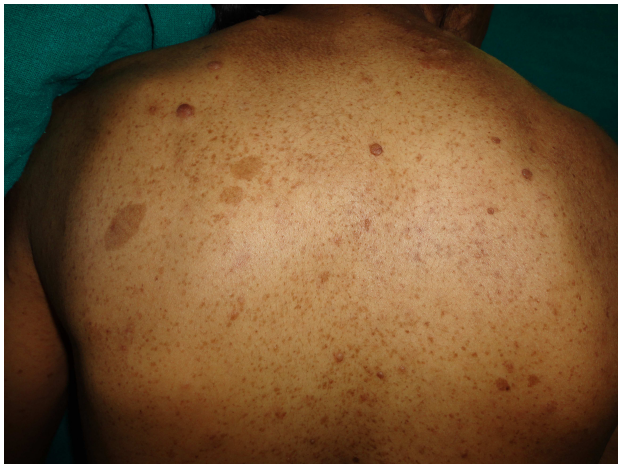

Figure 3. Cafe-au-lait macules and neurofibromas on trunk

Slit lamp examination did not reveal any Lisch nodules. Fundus examination was also normal. Routine haematological and biochemical investigations were normal. Chest X-ray, skull X-ray and X-ray of long bones did not reveal any abnormality. Ultrasonography of the abdomen was also normal. Craniospinal MRI did not reveal any abnormality. Excisional biopsy of ane of the cutaneous nodules was done and sent for histopathological analysis. It revealed features of neurofibroma. Based on the constellation of clinical and histological features, a diagnosis of facial plexiform neurofibroma with neurofibromatosis type 1 was entertained.

Discussion

Neurofibromatosis type-1 (NF-1) is a common neurocutaneous condition with an autosomal dominant inheritance. Descriptions of individuals reported to have neurofibromatosis have been discovered in manuscripts dating from 1000 A.D [2]. However, it was not until 1881 that Von Recklinghausen described neurofibromatosis in his patients Marie Kientz and Michael Bar [3]. His colleagues honoured his contribution by naming the condition as Von Recklinghausen's disease. However the different forms of neurofibromatosis were not separated and delineated until the latter part of the twentieth century. At last eight forms of neurofibromatosis have been recognized, the most common form being NF-1, or Von

Recklinghausen's disease. It accounts for about 90% of all the cases and is estimated to occur in one of every 3000 births. There is no sex predilection.

It is an autosomal dominant disease caused by a spectrum of mutations in the NF-1 gene. The NF-1 gene is located on the long arm of chromosome 17q 11.2 and encodes a 327 kDa protein called Neurofibromin [4]. The exact function of this protein is poorly understood, but the gene encoding neurofibromin has a sequence similar to a group of proteins called GTPase-activating proteins (GAP). This similarity suggests its involvement in negatively regulating the proteins coded by the Ras oncogene [5].

The Ras protein is like other G proteins and is dependent upon GTP binding for its full activity; GAP removes GTP by increasing the conversion of GTP to GDP. Enhanced Ras protein activity has been correlated with human cancer development, and dysfunction of neurofibromin could contribute to this [6]. Most NF-1 mutations result in reduced intracellular levels of the NF-1 gene product, neurofibromin. This appears to be sufficient to cause most of the clinical manifestations of this disorder.

A consensus development conference was held by the National Institute of Health (NIH) in 1987 to establish diagnostic criteria of patients with NF-1. There were seven diagnostic features recognized at this conference that have been applied without modification during the last 22 yrs. The diagnosis of NF-1 is established when two or more of these seven features listed below are present [7]:

- Six or more Café-au-lait macules larger than 5 mm in greatest diameter in prepubertal individuals: 15 mm in greatest diameter in postpubertal individuals.
- Two or more neurofibromas of any type or one plexiform neurofibroma.
- Freckling in the axillary or inguinal regions.
- Optic glioma.
- Two or more Lisch nodules (iris hamartomas).
- A distinctive osseus lesion such as sphenoid dysplasia or thinning of the long bone cortex, with or without pseudoarthrosis.
- A first degree relative with NF-1 according to the above criteria.

In our patient, three of the seven NIH diagnostic criteria were present.

Plexiform neurofibromas are benign peripheral nerve sheath tumours, often involving the trigeminal and upper cervical nerves [8]. They are diffuse, elongated fibromas, histologically similar to discrete neurofibromas and are usually seen in only 5-10 % of patients with NF-1. They often develop and become physically apparent within the first 2-5 years of life [9]. Their growth rate is highly variable. Often, overlying hyperpigmentation ('giant Café-au lait spot') or hypertrichosis can be seen.

There are two types of plexiform neurofibromas, nodular and diffuse. Diffuse plexiform neurofibroma is also known as elephantiasis neurofibromatosa and is characterized by an overgrowth of epidermal and subcutaneous tissue associated with a wrinkled and pendulous appearance. They can arise anywhere along a nerve and have poorly defined margins. They may appear on the face, legs, or spinal cord and frequently involve the cranial and upper cervical nerves. The cranial nerves most commonly involved in plexiform neurofibromas are the fifth, ninth and tenth nerves [10]. They can be quite disfiguring and hemifacial hypertrophy can occur secondary to a plexiform tumor involvement [11]. These tumors are known to cause symptoms ranging from minor discomfort to extreme pain. The consistency of the lesion has been compared to thtat of 'a bag of worms' because of the presence of soft areas interspersed with firm nodular areas and this very consistency was well appreciable in the lesions seen in our patient. They sometimes show vascular nature causing dangerous bleeding and may complicate surgical procedure. There appears to be an increase in the size of these tumors during puberty and pregnancy [12]. About 5% of the plexiform neurofibromas may turn malignant, usually into malignant peripheral nerve sheath tumors.

On microscopy, plexiform neurofibromas have a loose myxoid background with a low cellularity. They consist of poorly organized mixture of nerve fibrils with extensive interlacing of the nerve tissue. Small axons may be seen among the proliferating Schwann cells and perineural cells. These distorted masses are still contained within perineurium and surrounded by neurofibroma. The tumor is immunoreactive for S-100 protein.

The management of patients with plexiform neurofibromas is not well defined and is aimed mostly at controlling symptoms. Surgical excision is probably the only therapy available because there is no medication that can prevent or treat plexiform neurofibromas. However the results of surgical excisioin can be poor and the procedures can be complicated due to the size, location, vascular status, neural involvement, microscopic extension of the tumor, and the high rate of tumor regrowth. Tumors of the head / neck / face recur twice as compared to the plexiform neurofibromas of other locations. Also, subtotal resections recur more frequently than total resection of tumors. Retinoic acid therapy, angiogenesis inhibitors (such as interferons and thalidomide) are alternative therapies to surgery that have been tried. Oral Farnesyl protein transferase inhibitors and cytokine modulators are also under investigation.

The disfiguring nature of facial plexiform neurofibromatosis can be psychologically traumatic for most of the patients and often require good counseling. Psychological counselling with instilling of self confidence in such patients can possibly reduce their suffering and help them improve their quality of life.

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