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Neurofibromatosis and its Unusual Variants with Clinical and Histopathological Correlation - A Study in a Tertiary Care Centre

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Abstract: ***Introduction: Neurofibromatosis is an autosomal dominant genetic disease that affects ectoderm and mesoderm. The most common member of this group is neurofibromatosis 1, which varies in severity and has an incidence of 1 in 4000-5000. Plexiform neurofibromas have a 10% lifetime risk of developing peripheral nerve tumors. Changes in the cytomorphological and stromal features of neurofibromatosis lead to distinct histopathological features. Sometimes histopathological abnormalities and rare location may delay recognition of tumors (e.g. neurofibromas). Therefore, this study aims to elucidate the area of neurofibroma, and histomorphological and immunohistochemical studies as well as clinical examination may help diagnose the disease. Material and methods: Retrospective study of 26 cases was done over a period of 2 years. The cases of Neurofibromas were diagnosed with the help of H&E and immunohistochemical studies. Results: There were 14 men and 12 women. Age group was from 14 -70 years of age. In this study out of 26 cases, 65.38% cases were Sporadic lesions, 15.38% cases with Diffuse neurofibromas presented with multiple nodular lesions over the body with recurrence of lesions and had history of multiple hyperpigmented patch, cherry haemangioma, optic nerve atrophy, uveitis. 15.38% cases of Plexiform neurofibroma had familial association and were diagnosed on histopathological examination as Mixed type, Pigmented type and also presented at rare sites such as Vulva, Nose, Breasts. They were also associated with café au lait macules over neck, arm, buttock, thigh with axillary freckles and 1 case (3.84%) as Pacinian neurofibroma. Conclusion: The identification of areas of neurofibromatosis along with histomorphological and immunohistochemical study are helpful in management and proper treatment of the patients. Local and systemic examination of the patient to look for stigmata of NF1 and relevant family history is of the utmost importance.***

Keywords: neurofibromatosis, NF1, histologic variants, pigmented type, plexiform neurofibroma

1. Introduction

Neurofibromatosis is a multifactorial neurocutaneous and hamartomatous disease. [1,2] Derived from neural crest cells, they are mainly histologically benign (WHO grade 1) peripheral nerve sheath tumors with cellular components of various origins, such as Schwann cells, fibroblasts, perineural cells, mast cells, and macrophages (Figures 2, 3, 4).[2,3,27] NF1, also known as von Recklinghausen disease, is the most common form of the disease. A mutation on the long arm of chromosome 17 (17q11.2) causes a defect in neurofibromin, the protein product of the NF1 gene. Neurofibromin is a tumor suppressor that accelerates the conversion of the oncogene Ras to its inactive form. Therefore, its absence increases Ras activity in Schwann cells, leading to uncontrolled growth and various benign and malignant tumors, primarily in the central nervous system, orbit, vascular system, and cutaneous system.[3] Neurofibromas are most often associated with the peripheral nervous system and are rarely seen in the vagina, cervix, labia, clitoris, and other organs. Vulvar neurofibromas are very rare. Only 31 cases of urogenital neurofibroma have been reported to date.[2,4] Incidence rate of neurofibroma is 1 in 2500-3300 and prevalence rate is 1 in 5,000.[5,6] Only NF1 causes about 85% - 97% cases of neurofibromatosis.[7] Categorisation of neurofibroma is as follow: Cutaneous neurofibroma (both localized and diffuse type), intraneural neurofibromas (plexiform and localized) and massive soft tissue neurofibromas and sporadic neurofibromas or neurofibromas associated with neurofibromatosis1 . Plexiform neurofibroma is pathognomonic criteria for NF1 (or Von Recklinghausen disease). [8,11] The clinical diagnostic features are (1) Café-au-lait spots, (2) 2 or more neurofibromas of any type or 1 plexiform neurofibroma, (3) Crowe sign (groin or axillary freckles), (4) Visual pathway tumors, (5) 2 or more Lisch nodules, (6) a specific skeletal lesion called sphenoid wing dysplasia, (7) first-degree relatives [Table 4]. [1,2,4,9]

2. Material and Methods

A retrospective study was conducted on 26 patients. The study period is from April 2022 to December 2023. Fix the samples in 10% formalin. 5 µm thick microscopic sections were taken and stained with hematoxylin and eosin. Tumors were classified according to the WHO classification.

3. Results

Twenty six patients had clinical and histological diagnosis of neurofibromatosis1 during the 2 year study period. There were 14 males (53.84) and 12 females (46.15) [Table 1]. Age group was from 14 -70 years of age. The peak age of presentation was in the third decade with a mean age of 28.88 years. Out of 26 cases ,17 cases (65.38%) were diagnosed as

Localized, 4 cases (15.38%) were Diffuse, 4 cases (15.38%) were Plexiform, and 1 case (3.84%) as Pacinian neurofibroma (Figure 7-19) [Table 2, 6]. Head & neck was the commonest site of neurofibroma with 13 (50%) followed by trunk and abdomen with 06 (23.07%) then the lower limbs 4 (15.38%) and upper limbs 3(11.53%) (Figure 1-3) [Table 3, 5]. In this study out of 26 cases, 65.38% cases were Sporadic lesions, 15.38% cases with Diffuse neurofibromas presented with multiple nodular lesions over the body with recurrence of lesions and had history of multiple hyperpigmented patch, cherry haemangioma, optic nerve atrophy, uveitis (Figure1,2,3). 15.38% cases of Plexiform neurofibroma had familial association and were diagnosed on histopathological examination and Immunohistochemical studies as Mixed type, Pigmented type, and also presented at rare sites such as Vulva, Nose, Breasts (Figure 11- 18) [Table 3,6]. They were also associated with café au lait macules over neck, arm, buttock, thigh with axillary freckles (Figure 5,6) [Table 4]. The main treatment was surgical excision of the lesions.

Table 1: Distribution according to patients' age

•Age ranges from 14 -70 years and maximum no. of cases were observed in third decade with mean age of 28.88 years & M=14, F=12

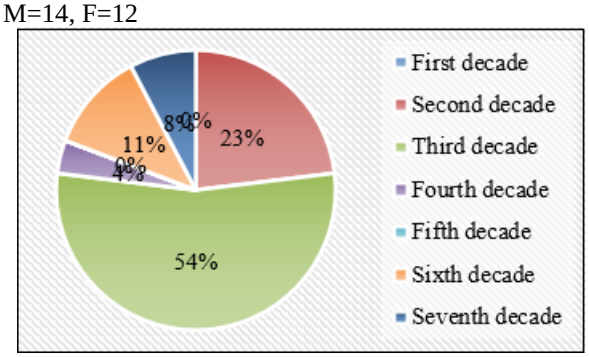

Table 2: Distribution of cases according to order of commonest frequency

Microscopic type	No. of cases	Percentage
Localized	17	65.38
Diffuse	4	15.38
Plexiform	4	15.38

Table 3: Distribution according to mode of clinical presentation

Presentation	No. of cases	Percentage
Multiple swelling over body part	23	88.46
Breast mass	1	3.84
Nasal mass	1	3.84
Vulval mass	1	3.84

Table 4: Diagnostics criteria for neurofibromatosis

Café au lait macules 6 or more	2
Axillary or inguinal freckling	2
Dermal fibroma 2 or more	11
Plexiform neurofibroma	4
First degree relative with NF1	2
Optic nerve	1
Two or more Lisch nodule	2
Osseous lesion	0

Table 5: Distribution according to site of lesions

Site	No. of cases	Percentage
Head & Neck	13	50
Neck	1	3.84
Trunk & Abdomen	6	23.07
Perineal region	1	3.84
Upper limb	3	11.53
Lower Limb	4	15.38
Multiple Site	5	19.23

Table 6: Distribution according to Histologic type of Conventional Cutaneous Neurofibroma

Variation in cell and stromal morphology	No. of cases	Percentage
Classic cutaneous type	22	84.61
Pacinian	2	7.69
Pigmented /Melanotic	1	3.84
Lipomatous	1	3.84

Clinical pictures of neurofibroma:

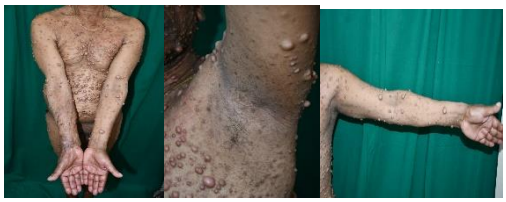

Figure 1, 2 & 3: Show diffuse nodular lesion involving face, trunk and hands

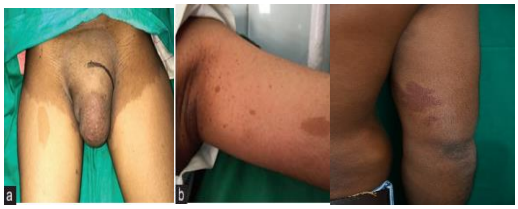

Figure 4, 5 & 6 Show hyperpigmented patch over bilateral inguinal region and vulval mass and café au lait macules arm.

Gross and Microscopic Pictures

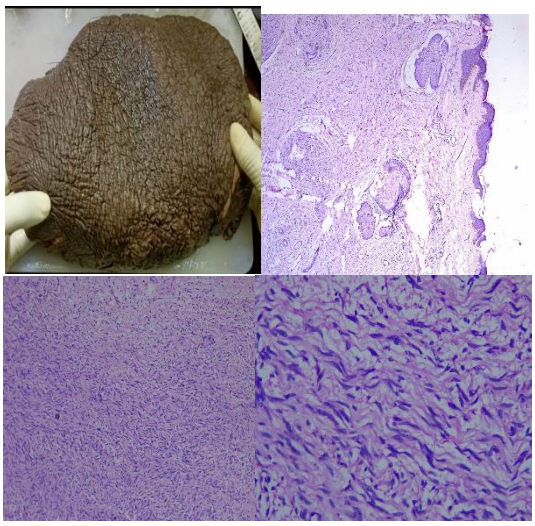

Figure 7, 8, 9 & 10: Gross and microscopic pictures of mixed type neurofibroma

Figure 8, 9 & 10 : Microscopic 10x, 20x and 40x (H&E) view of Plexiform and Diffuse (Mixed type) Neurofibroma : Show multiple tortuous, swollen nerves expanded by tumor cells having scant to moderate eosinophilic cytoplasm with spindled wavy nuclei and inconspicuous nucleoli along with intervening endoneurial mucocytes in collagenous and variable myxoid stroma. Tumor cells are also infiltrating the dermis and subcutaneous tissue in diffuse pattern.

Case of neurofibroma of vulva:

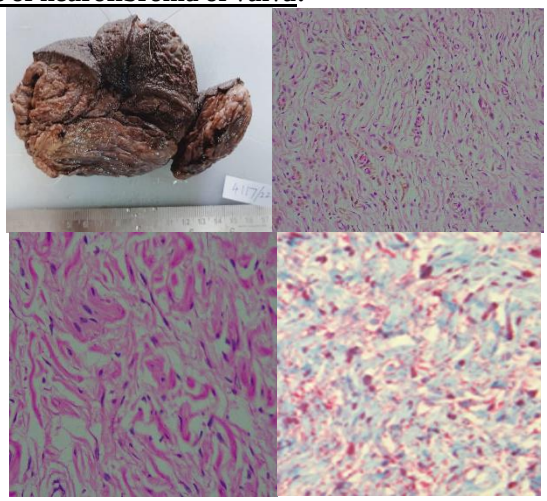

Figure 11, 12, 13, 14: Gross, microscopic and IHC picture of pigmented neurofibroma of vulva

Microscopic 10x and 40x (H&E) show mass composed of spindle cells with thin wavy nuclei and delicate pale eosinophilic cytoplasm in a collagenous stroma admixed with mast cells. Focal areas show variable presence of melanin pigment. Tumor is infiltrative involving the subcutaneous tissue entrapping the adipocytes and showed the presence of Meissner bodies and Pacinian corpuscles. IHC shows S-100 positivity.

Case of neurofibroma of breast

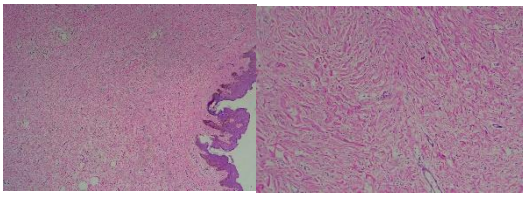

Figure 15, 16

Microscopic 10x and 40x (H&E) show unencapsulated dermal tumor composed of spindled cells with thin wavy nuclei and delicate pale eosinophilic cytoplasm in a collagenous stroma admixed with mast cells. Tumor is infiltrative involving the subcutaneous tissue entrapping the adipocytes and adnexal glands. In addition , Meissner bodies and Pacinian corpuscles are also noted.

Case of recurrent neurofibroma of face and nose with uveitis:

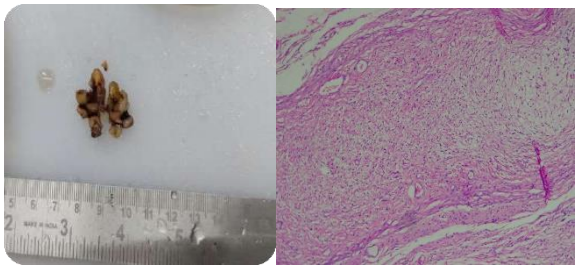

Figure 17, 18: Microscopic 20x and 40x (H&E)

Microscopic 20x and 40x (H&E) show an unencapsulated well circumscribed tumor composed of tumor cells arranged in fascicles in a loose myxoid stroma. Individual tumor cells are narrow elongated with moderate eosinophilic cytoplasm with wavy thin nuclei with tapered ends and are normochromatic. Also seen are perineural cells, fibroblasts and mast cells.

Case of Pacinian neurofibroma:

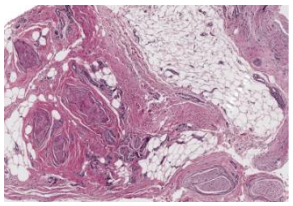

Figure 19: Microscopic 20x shows: Clusters of spherical bodies resembling rudimentary Pacinian corpuscles are embedded in mature adipose tissue.

Discussion

Neurofibroma is a mostly benign peripheral nerve sheath tumor with 10-15% risk of malignant transformation. The aim of the study is to assess the histopathological features of various types of neurofibroma through microscopic examination which helps in early diagnosis and timely management of patients to avoid the complications which follow the course of the diseases.

In the two year period twenty six histologically proven neurofibromatoses were seen, 14 and 12 were male and females respectively with no gender predilection. This conformed to the general presentation of neurofibromatosis that NF1 occurs equally in both sexes. Results were similar to the study done by Y.W. Nyandaiti et al and Friedman J. et al and Karen's P. S. et al [11-19,23]

In our study most common age groups affected belong to the third decade, which represent 53.9%. This study is concordant with Y.W. Nyandaiti et al and Karen's P. S. et al. [16,17,23] 84.61% of cases were Sporadic whereas 15.38% of patients had familial association along with temporal and occipital involvement is also concordant with the study conducted by Mulvihill JJ and Parry D.M et al.

Dermal neurofibroma was the commonest type with 22 cases presenting with cutaneous and subcutaneous neurofibroma while 4 cases had plexiform type. Results were similar to the study conducted by Nyandaiti and Karens P. S. et al.[21]

In our study head, face and trunk is the commonest area of affliction with 3 cases (11.53%) presented with rare site

manifestation including vulva , breast and nose. Results were similar to the study done by Dogra BB and Amer MI et al.[20] 7.69% of patients had recurrence of disease along with right eye buphthalmos, optic nerve atrophy and uveitis. Results were similar to the study done by H.A.Nggada et al. 15.38% of patients present with cutaneous manifestation such as skin folds, axillary freckles, café au lait macules with multiple hyperpigmented indurated plaque and cherry hemangioma as associated symptoms. This study differs from the study of Odebode et al and similar with the study done by Y.W. Nyanda Iti and A. A . Ndahi et al [23]

4. Conclusion

Variation in the cytomorphology and stromal characteristics in neurofibromatosis give rise to different histopathological subtypes.

The identification of areas of neurofibromatosis alongwith histomorphological and immunohistochemical study are helpful in management and proper treatment of the patients.

Local and systemic examination of the patient to look for stigmata of NF1 and relevant family history is of the utmost importance.

Plexiform neurofibromatosis has the potential for malignant transformation into highly malignant nerve sheath tumors and neurosarcoma. (3-15% risk).

Surgical resection can be challenging due to its infiltrative nature, high vascularity, and tendency to recur.

Long term follow up is needed where there is increased risk of recurrence and malignant transformation.

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