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DETAILED HISTOPATHOLOGICAL STUDY WITH IHC AND CLINICAL CORRELATION IN CASES OF NEUROFIBROMATOSIS - A RETROSPECTIVE STUDY IN A TERTIARY CARE CENTRE

Histopathology

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ABSTRACT

Introduction: Neurofibromatosis is an autosomal dominant genetic disease. Commonly seen is neurofibromatosis 1, and has an incidence of 1 in 4000-5000. Plexiform neurofibromas have a higher chance of developing malignancy. Distinct histopathological features in different cases are due to varying cytomorphology and stromal features. Manytimes unusual and rare location may delay recognition of tumors (e.g. neurofibromas). Therefore, this study aims to study in detail cases of neurofibroma, along with its histomorphological and immunohistochemical features. **Material And Methods:** Retrospective study of 17 cases was done over a period of 1 year. The cases of Neurofibromas were diagnosed with the help of H&E and immunohistochemical studies. **Results:** There were 9 men and 8 women. Age group was from 14 -70 years of age. In this study out of 17 cases, 47.05% cases were Localized lesions, 23.52% 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. 17.64% cases of Plexiform neurofibroma had familial association. 5.88% cases of Pigmented type of neurofibroma and 5.88% cases as Pacinian type of neurofibroma. Some cases presented at rare sites such as Vulva, Nose and Breasts. They were also associated with café au lait macules over neck, arm, buttock, thigh with axillary freckles. **Conclusion:** Making a complete diagnosis of neurofibromatosis along with supportive evidence of its histomorphological and immunohistochemical study are helpful in management and proper treatment of the patient. Detailed and thorough general examination of the patient to look for diagnostic criteria of NF1 and relevant family history is must.

KEYWORDS

neurofibromatosis, NF1, histomorphology, pigmented, Plexiform and Pacinian.

INTRODUCTION

Neurofibromatosis is a neurocutaneous and hamartomatous syndrome.[1,2] Originating from neural crest cells, they are predominantly benign peripheral nerve sheath tumors with cells of various origins, such as Schwann cells, fibroblasts, perineural cells, mast cells, and macrophages.[2,3,4] NF1, known as von Recklinghausen disease, is the most common form. Mutation on the long arm of chromosome 17 (17q11.2) leads to a defect in neurofibromin protein. Neurofibromin is a tumor suppressor that enhances the conversion of the oncogene Ras to its inactive form. Therefore, its absence stimulates Ras activity in Schwann cells, leading to development of tumors, primarily in the central nervous system, orbit, vascular system, and cutaneous system.[3] Neurofibromas are usually associated with the peripheral nervous system and are uncommonly seen in the vagina, cervix, labia, clitoris, and other organs. Vulvar neurofibromas are quite rare. Till date only 31 cases of urogenital neurofibroma have been reported.[2,4] Incidence rate is 1 in 2500-3300 and prevalence rate is 1 in 5,000.[5,6] Out of this NF1 contributes to 85% - 97% cases of neurofibromatosis.[7] Plexiform neurofibroma is pathognomonic criteria for NF1 (or Von Recklinghausen disease) diagnosis.[8,11] Other diagnostic features are enlisted in Table no.4.

MATERIAL AND METHODS

A retrospective study was conducted on 17 patients. The study period is from March 2022 to February 2023. Samples were fixed in 10% formalin. 5 µm thick microscopic sections taken and stained with hematoxylin and eosin.

RESULTS

Seventeen patients had clinical and histological diagnosis of neurofibromatosis during the one year study period. There were 9 males and 8 females [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 29.76 years. Out of 17 cases ,08 cases (47.05%) were diagnosed as Localized, 4 cases (23.52%) were Diffuse, 3 cases (17.64%) were Plexiform, and 1 case (5.88%) as Pacinian type neurofibroma (Figure 5-13) and 1 case (5.88%) as pigmented plexiform neurofibroma.(Figure 3,7,8&9) [Table 2] Head & neck was the commonest site of neurofibroma with 10 (58.82%) followed by trunk and abdomen with 04 (23.52%) then the lower limbs 2 (11.76%) and upper limbs 2(11.76%) (Figure 1-3) [Table 3]. In this study out of 17 cases, 47.05% cases were Localised neurofibroma, 23.52% 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). 17.64% cases of Plexiform neurofibroma had familial association and were diagnosed on histopathological examination and Immunohistochemical studied. 5.88% cases of Pigmented neurofibroma and 5.88% cases as Pacinian type of neurofibroma.

Some cases presented at rare sites such as Vulva, Nose and Breasts. They were associated with café au lait macules over neck, arm, buttock, thigh with axillary freckles. (Figure 7-12) [Table 3,6]. 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 29.76 years & M=9, F=8

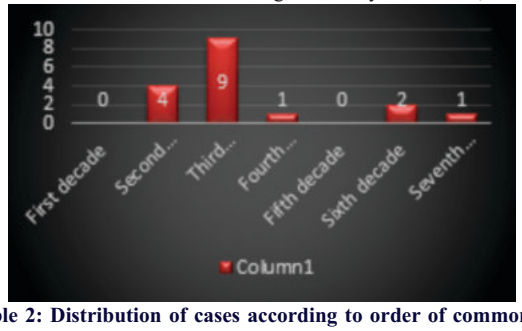

Table 2: Distribution of cases according to order of commonest frequency

Microscopic type	No. of cases	Percentage
Localized	08	47.05
Diffuse	04	23.52
Plexiform	03	17.64
Pigmented plexiform	01	5.88
Pacinian	01	5.88

Table 3: Distribution according to mode of clinical presentation

Presentation	No. of cases	Percentage
Multiple swelling over body part	14	82.35
Breast mass	01	5.88
Nasal mass	01	5.88

Vulval mass	01	5.88

Table 4: Diagnostics criteria for neurofibromatosis

Café au lait macules 6 or more	02
Axillary or inguinal freckling	02
Dermal fibroma 2 or more	05
Plexiform neurofibroma	03
First degree relative with NF1	02
Optic nerve	01
Two or more Lisch nodule	02
Osseous lesion	00

Table 5: Distribution according to Histologic type of Conventional Cutaneous Neurofibroma

Variation in cell and stromal morphology	No. of cases	Percentage
Classic cutaneous type	14	82.35
Pacinian	01	5.88
Pigmented /Melanotic	01	5.88
Lipomatous	01	5.88

Clinical pictures of neurofibroma:

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

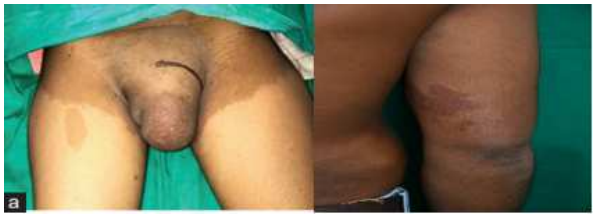

Fig 3 &4 Show hyperpigmented patch over bilateral inguinal region and vulval mass and café au lait macules arm.

Gross And Microscopic Pictures:

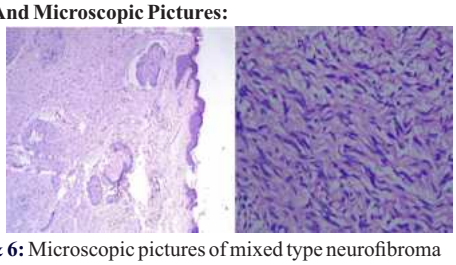

Fig:5 & 6: Microscopic pictures of mixed type neurofibroma

FIG 5 & 6: Microscopic 10x 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 :

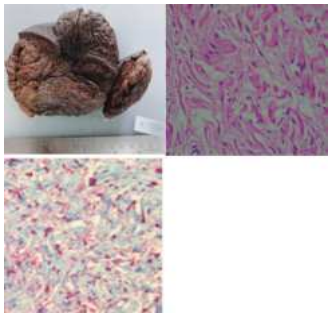

Fig 7, 8 & 9 : Gross, microscopic and IHC picture of pigmented neurofibroma of vulva

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

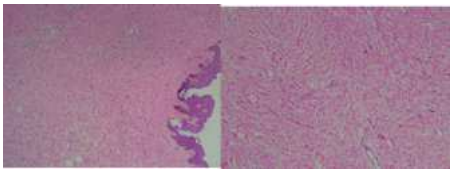

Fig 10 & 11 : Microscopic 10x and 40x (H&E) show unencapsulated dermal tumor composed of spindled cells with thin wavy nuclei and delicate pale eosinophilic cytoplasm in a collagenous stroma admixed with mast cells. Tumor is infiltrative involving the subcutaneous tissue entrapping the adipocytes and adnexal glands. In addition , Meissner bodies and Pacinian corpuscles are also noted.

Case of recurrent neurofibroma of face and nose with uveitis:

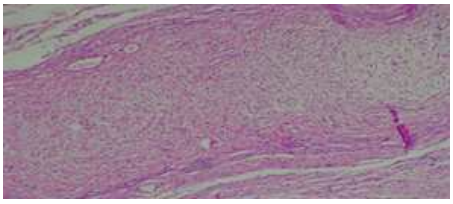

Fig 12: Microscopic 20x (H&E) show an unencapsulated well circumscribed tumor composed of tumor cells arranged in fascicles in a loose myxoid stroma. Individual tumor cells are narrow elongated with moderate eosinophilic cytoplasm with wavy thin nuclei with tapered ends and are normochromatic. Also seen are perineural cells, fibroblasts and mast cells.

Case of Pacinian neurofibroma:

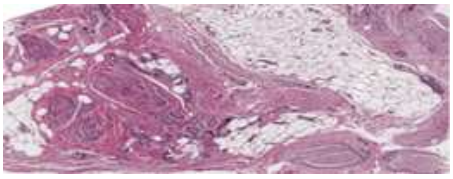

Fig 13: Microscopic 20x shows : Clusters of spherical bodies resembling rudimentary Pacinian corpuscles are embedded in mature adipose tissue.

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 Friedman J. et al and Karen's P. S. et al[11-19]

In our study most common age groups affected belong to the third decade, which represent 52.94%. This study is concordant with Karen's P. S. and Y.W. Nyandaiti et al.[16,17,]

47.05& of cases were Localized whereas 11.76% 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 05 cases presenting with cutaneous and subcutaneous neurofibroma while 3 cases had plexiform type. Results were similar to the study conducted by Karens P. S. and Nyandaiti et al.[21]

In our study head, face and trunk is the commonest area of affliction with 3 cases (17.64%) 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]

11.76% 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.

17.64% 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]

CONCLUSION:

Difference in the cytomorphological and stromal appearance in cases of neurofibromatosis give rise to varying histopathological subtypes. Diagnosing neurofibromatosis on histomorphology and confirming it with immunohistochemical study are very important in management and correct treatment of the patients.

Minute and detailed local and systemic examination of the patients to look for stigmata of NF1 and relevant family history is essential.

Plexiform neurofibromatosis may show malignant transformation into malignant nerve sheath tumor (MPNST) and neurosarcoma. (3-15% risk).

Complete resection with free margins can be challenging due to its infiltrative nature, vascularity, and tendency to recur.

Follow up is needed to rule out recurrence and malignant transformation.

REFERENCES:

1. The WHO Classification of Tumors Editorial Board. WHO Classification of Tumors Soft Tissue and Bone Tumors, 5th ed.; IARC Press: Lyon, France, 2020
2. Dogra BB, Ahmed S, Kandari A, Virmani R. Plexiform Figure neurofibromatosis of vulva. Int J Res Med Sci 2014;2:1771-3.
3. Gaillard F, Yap J, Yap J, et al. Neurofibromatosis Type 1. Available from: https://radiopaedia.org [Last accessed on 2022 Dec 07].
4. Amer MI, Alloob A. Vulvar plexiform neurofibromatosis, case report and review of literature. Madridge J Womens Health Emancipation 2017;1:7-10
5. Korf, BR.; Rubenstein, AE. Neurofibromatosis: A Handbook for Patients, Families, and Health Care Professionals. Vol. 2nd. New York: Thieme; 2005
6. Scheffzek, K.; Ahmadian, M.R.; Wiesmüller, L.; Kabsch, W.; Stege, P.; Schmitz, F.; Wittinghofer, A. Structural analysis of the GAP-related domain from neurofibromin and its implications. EMBO J. 1998, 17, 4313–4327. [CrossRef] [PubMed.
7. Crowe, FW.; Schull, WJ.; Neel, JV. A Clinical, Pathological and Genetic Study of Multiple Neurofibromatosis. Springfield, IL: Charles C Thomas; 1956.
8. Neville B, Damm D, Allen C, Bouquot J. Soft tissue tumors. In: Neville B, Damm D, Allen C, Bouquot J, eds. Oral and Maxillofacial Pathology. 2nd ed. Philadelphia, Pa: WB Saunders; 2002:458-461
9. Burger PC, Scheithauer BW, Vogel FS: Surgical Pathology of the Nervous System and Its Coverings, ed 4. New York: Churchill Livingstone, 2002
10. National Institutes of Health: Consensus Development Conference. Neurofibromatosis. Conference Statement. Arch Neurol. 1988;45:575-578.
11. Peltonen, S.; Kallionpää, R.A.; Peltonen, J. Neurofibromatosis type 1 (NF1) gene: Beyond café au lait spots and dermal neurofibromas. Exp. Dermatol. 2017, 26, 645–648. [CrossRef]
12. Halefoglu AM. Neurofibromatosis Type 1 presenting with plexiform neurofibromas in two patients: MRI features. Case Rep Med 2012;2012:498518.
13. Huson SM, Harper PS, Compston DA. Von Recklinghausen neurofibromatosis: a clinical and population study in south-east Wales. Brain 1988;111:1355–81. [PubMed: 3145091]
14. Friedman J. M. Epidemiology of neurofibromatosis type 1. Am J Med Genet 1999; 89: 1–6.
15. Neurofibromatosis Conference statement National institute of health consensus development conference Arch Neurol 1988; 45: 575–578
16. Karnes P. S., neurofibromatosis a common neurocutaneous disorder. Mayo Clinic Proc 1998; 73: 1071–1076
17. Morse RP., Neurofibromatosis type 1., Arch Neurol 1999 56: 364–365.
18. De Bella K., Szudek J., Friedman J. M. Use of the National Institutes of health criteria for the diagnosis of neurofibromatosis in children. Pediatrics 2000; 105: 608–614.
19. Grant R. Neurocutaneous syndromes. In Donaghty M., ed. Downloaded from http://journals.lww.com/nimj by Brain's Diseases of the Nervous System 11th Edn. Oxford University Press. 2001; 587–591
20. Tonsgard J. H. Clinical Manifestation and management of neurofibromatosis type 1. Semin Pediatr Neurol 2006; 13: 2– 7.
21. Kaufman D., Tinschert S., Algermissen B. Is the distribution of dermal neurofibromatosis type 1 NF1 related to the pattern of the skin surface temperature? Eur J Dermatol 2001; 11: 521– 525
22. Ruggieri M., Huson S. M., The Neurofibromatosis An overview. Ital J Neur Sci. 1999; 20: 89–108
23. Odebode T. O., Afolayan E. A. O., Adigun I. A., and Daramola O. O. M., Clinicopathological study of neurofibromatosis type 1: an experience in Nigeria. International Journal of Derm 2005; 44: 116–120