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Case Report

ASSOCIATION OF STROMAL CELLS IN DEVELOPMENT OF ORAL NEUROFIBROMATOSIS AND PLEXIFORM NEUROFIBROMA: A REVIEW OF LITERATURE

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A B S T R A C T

Neurofibroma and plexiform neurofibroma are relatively uncommon nerve tissue tumors, affecting one person out of 3000 population. The pathogenesis of neurofibroma follows hereditary dominant trait, resulting through its protein neurofibrimin-1(NF-1), this is activated by dGAP and related domain (GRD), which stimulates to p21-RAS, and there is further damage of Schwann cells, which enhance growth and proliferation of tumor cells. At the same time other common factors get activated during growth of plexiform neurofibroma and NF-1, such as stromal components have exuberant response of EGFR, Stat3, stem cell population (SCP) and mast cells. All these biological substances govern growth and proliferation of these neural tumors. In spite of common pathogenesis, prognosis is different in both variants. The plexiform type shows comparatively unfavourable prognosis due to rapid and unpredicted proliferation. Pathogenesis of this nerve tissue tumor can reflect interventions, so its basic understanding can help in better prognosis.

INTRODUCTION

Historical Background

Neurofibroma is a benign tumor of nerve tissues and was first time introduced by Mark Akenside in 1768, but was scientifically reported in 1849 by R. Smith. After that many documents were published and von Recklinghausen was first person to publish elaborative information on neurofibroma in 1882. [1] There is contribution of many cells in growth of this neural tumor and importance of mast cells in growth and proliferation of neurofibroma was explained by H. Greggio in 1911, further knowledge was added by Vincent Riccardi in late nineties, who explained that, along with mast cells, melanocytes also contribute equally during activation of TGF-ß, VEGF, macrophages, and pericytes to promote proliferation and pigmentation of neurofibroma. [2]

Introduction

There is direct association between neurofibroma and neurofibromin-1(NF1), a protein that transmits through genetic expression, and this tumor is also termed as somatic mosaic and segmental neuromas. This protein shows complex structure such as 220 kD mass, 350 kb spans and around 60 axons; located at chromosomal arm 17q11.2. This is commonly located at spinal region, brain, neural organs, keratinocytes, blood capillaries, nerve sheaths, medullary cavities and dendrietic tissues. So far activation of NF1 is through Ras GTP; via GAP and related domain (GRD), which is responsible for stimulation of p21-RAS; leading to damage of Schwann cells. Further interaction between guanine exchange factor (GEF) and phosphoinositol 3 kinase (PI3K) activates Ras; to delay cell death and Raf- mitogenic factor that helps in cell proliferation. According to Knudson et al, genetic defects and loss of heterozygocity is done by two ways, first at germ line changes caused by NF1 and second changes at somatic level. Similarly association of P^{53} with multiple cells such as perineural tissues, neural tissues, Schwann cells, mast cells, fibroblasts and glandular tissues contribute to enhance growth and proliferation of neural tumors. Usually in high risk tumors, Schwann cells are seen in extracellular matrix with variable architecture and functions, that later on becomes challenge during intervention. [3]

Plexiform neurofibroma (PNF) is an activated Schwann cell (SC) derived benign nerve sheath neoplasm, originated in peripheral neural elements. There is close association between plexiform neurofibroma and neurofibromatosis-1(NFM-1), particularly in case of genetic instability in multiple tissues. Usually neurofibromatosis-1 affects multiple tissues including nerves, skin, mucous membrane, and eyes etc. Neurofibromin-1 protein is common source of origin for plexiform neurofibroma and cutaneous neurofibromatosis. [4, 5]

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Pathogenesis

Defective allele in chromosome leads to loss of heterozygocity (LOH); this aberrancy in future contributes in development of many disorders such as, plexiform neurofibroma, benign neurofibroma, dermal neurofibroma, leukemia and MPNST. The Neurofibromin-1 (Nf-1) gene is primary cause of this tumor, mainly transmits through autosomal dominant trait. In fact this is tumor suppressor gene, but due to genetic alterations there is discrepancy of proteins $p21^{ras}$ (Ras) or Guanosine Triphosphatase (GTP)–activating protein (GAP), which is responsible for loss of heterozygocity (LOH) *at different cell lineages in tumor formation. [2] This* gene was genetically formulated by combine efforts of Wallace, Viskochil and Cawthon, and they suggested that, different mediators such as mitogen-activated protein kinase (MAPK) and the mammalian target of rapamycin (mTOR) support during growth and proliferation of neurofibroma. So far, complex but coordinated pattern of all molecular components is responsible in growth of neurofibroma and plexiform neurofibroma. [6]

Clinical Aspect

The incidence rate of Neurofibroma is comparatively rare, showing involvement of one person out of 3000 people, and worldwide prevalence rate is around 1:7800 to 1:21904 while plexiform variant is quite uncommon. There are different clinical variations of neurofibroma, among these are small pigmented freckles of around 5-6 mm, located at axillary or inguinal sites and termed as Crowe sign, after Frank Crowe who first introduced it with neurofibroma in 1964. [1, 6]

The plexiform variant shows single ulcero-proliferative growths, and may be associated with pain and paresthesia. [7] Further Neurofibroma is divided into two types on basis of clinical presentations such as Neurofibroma-I & Neurofibroma-II. So far Neurofibroma-I comprises of many criterias, such as freckling of axilla, brownish spots in iris, ocular defect, and macular spots of variable sizes, bony defects, evidence of one or more such clinical issues in family and association of plexiform neurofibroma. Whereas Neurofibroma-II shows clinical presentations like, lenticular opacities in early age group, soft tissue growth along with two nerve tissue tumors and bilateral involvement of trigeminal nerve[8] Some of the common comparative points between MPNST and Plexiform neurofibroma are as follows;

1. Ras-GTP and Ras are more in MPNST than Neurofibroma.
2. Gene P^{53} attached on 17p13.1, is suggestive of aggressiveness and poor prognosis, mostly seen with MPNST than Neurofibroma.
3. Defective P^{53} and related cell cycle issues are less in benign neurofibroma.

There are different concepts regarding clinical presentations but unanimous reason behind this is involvement of multiple cells during its development, which reflects on clinical presentations. This becomes major challenge during data collection and analysis, but according to available sources, this tumor is commonly found without any racial or gender discrepancies. Intra orally plexiform Neurofibromas are commonly seen on soft tissues; such as cheek mucosa, lips, vestibule, and tongue. But in rare circumstances bone is affected, in this case involvement of mandible is more common than maxilla. The tumors of central locations should be kept under periodic follow ups due to rapid spread and aggressiveness. [9]

DISCUSSION

Neurofibroma is derived from genetically altered Schwann cell populations, where many factors involve in its growth and proliferation. Out of these EGFR and Stat3 play crucial role in regulation of stem cell population (SCP), to provide favorable environment to growing cells of tumor. [10] Similarly there is crucial role of Nerufibromin-1 in activation of RAS and AKT signaling channels and this mutual activation between cells is responsible for proliferation and growth of neural tumors. So understanding these signaling pathways can unfold the mystery behind many faces of this tumor that challenges during interventions. [11] Similarly crucial association between mast cells, fibroblasts, blood cells and NF1in pathogenesis of neurofibroma particularly plexiform variant can determine treatment protocol. According to studies, this is also noticed that, apart from neurofibroma, these proteins also play important role in blood cancers, bony deformities, ocular lesions etc. So far this tumor is aggressive and causes massive damage to cranial nerve and surrounding structures, resulting in many clinical manifestations such as, sleep disorders, gastric issues, numbness, paralysis, ocular defects and progress of lesion. However matrix metalloproteinase (MMPs) generated mast cells help in production of cytokines (TNF- α and IL-6) and growth factors such as VEGF, PDGF and NGF to enhance proliferation and growth of nerve tissue tumors. Some workers also explained that, during multifactorial tumorigenesis cascade, stem cell factor (SCF) and macrophages such as M1 & M2 are also equally important, specifically M1 affects prognosis by enhancing proliferations, of plexiform neurofibroma and malignant peripheral nerve sheath tumors (MPNST). [12] On the basis of cellular structures involved, there are two variants of neurofibroma, such as plexiform and dermal. Plexiform neurofibroma arises due to synthesis of multiple bundles of neural cells, while dermal variant can develop even from minimal neural components, and apart from neural cells, extra neural tissues such as epitheloid, myxoid and glandular cells also contribute in plexiform type. Further this classification was elaborated on basis of cells involved in development; they were named as diffuse, pacinian, plexiform, glandular, xanthomatous, cellular, epitheloid and myxoid neurofibroma. This is also clear that, growth of tumors not only depend on contribution of early growth factors but, there are some late companions also, such as SCs (Schwann cells), SCPs (stem cell population), fibroblasts and mast cells, which properly maintain aggressive behaviour during malignant transformation, particularly in case of plexiform neurofibroma. [13] Similarly some other genetic alterations in NF1due to imbalance with signaling cascade RAS and ErbB4 cell lineages are responsible for malignant peripheral nerve sheath tumors (MPNSTs), which is aggressive nerve tissue tumor. This neural tumor shows rapid progression and restricted survival of affected patients. [14] Stromal components of inflammatory cells such as T cells, CXCL10 and Stat3 regulate neural cell kinetics, particularly of plexiform neurofibroma. This activation helps in development, proliferation and remodeling of these tumors. Stat3 pathway is additive factor in tumor changes in SC and Schwann cells progenitors (SCPs); particularly after inactive state of Nf-1, which lead to malignant conversion and phenotypic changes in converted cells.[15,4] Association of

growth factors with nerve tissue tumors play important role during interventions. Such as vascular endothelial growth factor (VEGF) is commonly found with plexiform neurofibroma and (MPNST), that clinically shows aggressive behaviour, while fibroblast growth factor (FGF) is associated with mild form of nerve tissue tumors. So authors concluded that, the tumors with aggressive growth have thick vessel walls as compared to benign counterpart, which may show recurrence and bad prognosis. [16] Origin of Schwann cells is through activation of proteins heregulin and neuregulin, which are transformed by fibroblasts growth factors, PDGF, and group of other growth factors such as; hepatocyte growth factor, insulin growth factor1, pigment epithelium-derived growth factor , nerve growth factor- released from mast cells, and vascular endothelial growth factor. Similarly hedgehog proteins also help in tumor development; from their hedgehog receptor patched (PTCH-2). There is important role of Indian hedgehog and Sonic hedgehog in neurofibroma of plexiform variants. Though standard therapy for plexiform neurofibroma is surgery, but this has many limitations such as many post treatment disabilities. So to rule out this in 1993 Riccardi introduced new concept for inhibition of mast cells, through ketotifen and imatinib to inactivate PI3K. So understanding the basic genetic remodeling can help for developing therapies against this tumor. According to authors kit ligand is secreted by Schwann cells influenced with tumors; deficient with NF-1 gene. This association between kit ligand and mast cells give rise to neoplastic changes in plexiform neurofibroma.[17,3] Genetic instability result in loss of heterozygocity through Guanosine Tri-Phosphatase (GTP), leading to defect in activation of p21ras (Ras). Later damages NF1 protein and initiate neural tissue tumor. [2]

CONCLUSION

Oral neurofibroma is uncommon nerve tissue tumor particularly plexiform type, with prevalence of 1:7800 to 1:21904 people. Pathogenesis of this tumor lies in complexity of different components such as, primary genetic protein Neurofibromin-1 (Nf-1) is altered due to action of stromal elements such as mast cells, vascular cells, cytokines and growth factors. After that some other molecules cause secondary changes, due to action of $p21^{ras}$ (Ras) or Guanosine Triphosphatase (GTP)–activating protein (GAP) that leads to loss of heterozygocity (LOH). This becomes turning point for proliferation and growth of tumor, as well as different clinical behaviour. So understanding this basic pathogenesis of nerve tissue tumor can be helpful during interventions.

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