



MALIGNANT TUMORS IN NEUROFIBROMATOSIS-1 PATIENTS IN A TERTIARY CARE CENTER : CASE SERIES

Radiation Oncology

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ABSTRACT

Neurofibromatosis (NF) is a neurocutaneous disorder caused by genetic mutations that are either inherited from a parent or that seem to develop randomly in an individual. It has an autosomal dominant inheritance pattern. The three types of NF are Neurofibromatosis type I (NF1), Neurofibromatosis type II (NF2), and Schwannomatosis. Neurofibromatosis type 1 makes up about 96% of all neurofibromatosis cases. It is caused by a loss of function mutation on the neurofibromin 1 (NF1) gene. It is located on band 17q11.2 and codes for neurofibromin. People with NF1 also develops some cancers at an earlier age and with poor prognosis. Cancers that are more common in people with NF1 are Glioma (low- and high-grade), Sarcoma (many types), Breast cancer, Endocrine cancers (including pheochromocytoma and neuroendocrine tumors) etc. This case series includes four female neurofibromatosis type 1 patients presented to a tertiary care center with different malignant tumors in a span of 8 months. All were aged between 35 to 50 years. Diagnosis of four patients were soft tissue sarcoma, glioblastoma, carcinoma hypopharynx and carcinoma breast. All were treated according to standard protocols. This case series is followed by a review of literature to have an insight of different malignant tumors in neurofibromatosis patients

KEYWORDS

Neurofibromatosis, Tumor, Glioblastoma, Breast Cancer

INTRODUCTION

Neurofibromatosis (NF) is a neurocutaneous disorder that describes three genetic diseases caused by mutations in genes that lead to increased risk of developing tumors.¹ It runs in families. It is caused by genetic mutations that are either inherited from a parent or that seem to develop randomly in an individual. It has an autosomal dominant inheritance pattern.¹ It causes tumors to form mainly in the nervous system. These tumors can also occur anywhere, including the brain, spinal cord, adrenal gland, eyes and muscle tissue.

The three types of NF are Neurofibromatosis type I (NF1), Neurofibromatosis type II (NF2), and Schwannomatosis.

Neurofibromatosis type 1 makes up about 96% of all neurofibromatosis cases.² While Neurofibromatosis type 2 makes up about 3% of all cases²

In NF1 which is also known as von Recklinghausen disease, symptoms include light brown spots on the skin (cafe-au-lait spots), freckles in the armpit and groin, small bumps within nerves, and scoliosis.³ In this type nerve tissue grows tumors (neurofibromas) that may be benign, but may cause serious damage by compressing nerves and other tissues.

In NF2, there may be hearing loss, cataracts at a young age, balance problems, flesh colored skin flaps, and muscle wasting.⁴ In this type bilateral acoustic neuromas (tumors of CN VIII) also known as schwannoma develop, often leading to hearing loss.

In schwannomatosis there may be pain either in one location or in wide areas of the body.⁵ And also painful schwannomas develop on spinal and peripheral nerves

The tumors in all types of NF are generally non-cancerous.

DISCUSSION

Neurofibromatosis type 1 is caused by a loss of function mutation on neurofibromin 1 (NF1) gene. It is located on band 17q11.2 and codes for neurofibromin.⁶ Neurofibromin is a tumor suppressor that functions in the RAS/MAPK and mTOR pathways.^{5,7} It also serves as a signal regulator of cell proliferation and differentiation.⁷ A dysfunction or lack of neurofibromin can affect regulation, and cause uncontrolled cell proliferation, leading to the tumors. Another function of neurofibromin⁶ is to bind to microtubules that play a role in the release of adenylyl cyclase and its activity. Adenylyl cyclase plays an essential role in cognition.

NF2 is caused by a loss of function mutation of the NF2 gene. It is located on band 22q12 and codes for merlin. Merlin is a cell membrane protein that is also a tumor suppressor that regulate the activity of multiple growth factors in the PI3kinase/Akt, Raf/MEK/ERK, and mTOR pathways.⁸

While in schwannomatosis, it is estimated that 85% of cases have no known cause (spontaneous) and 15% are inherited caused by a mutation on the SMARCB1 gene. The normal function of the SMARCB1 gene is to encode a protein called SMARCB1 which plays a role in tumor suppression.⁵

People with NF1 also develops some cancers at an earlier age and with poor prognosis compared with the general population.^{9,10}

Cancers that are more common in people with NF1⁹: Glioma (low- and high-grade), Sarcoma, Breast cancer, Endocrine cancers (including pheochromocytoma and neuroendocrine tumors), Melanoma, Acute lymphoblastic leukemia, Ovarian cancer, Prostate cancer, Meningioma etc.

CNS tumors occur in approximately 20% of patients with NF1 and are usually detected in early childhood.¹¹ Most are low-grade pilocytic astrocytomas of the optic pathway or brainstem, but high-grade tumors also occur.^{11,12}

MPNST which is an aggressive sarcoma often arises from plexiform neurofibroma and is one of the hallmark complications of NF1¹⁰

In addition to malignancies originating from the nervous system, it has been suggested that other cancers, such as breast cancer, gastrointestinal stromal tumor (GIST), and pheochromocytoma, are associated with NF1.^{13,14,15}

Mutations of the NF1 gene are also frequently found in cancers of the general population, especially in melanomas, glioblastomas, and lung tumors.¹⁶

The number of epidemiologic studies on cancer incidence in patients with NF1 is limited.

A Swedish study reported a relative risk of cancer of 4.0 in 70 patients with NF1.¹⁷ The most frequent sites of cancer were connective tissue and CNS, with standardized incidence ratios (SIRs) of 122 and 22.6, respectively.¹⁸

The most common cause of death in patients with NF1 is reported to be MPNST, which causes 26% of deaths of patients with NF1.¹⁸

The mutation of the NF1 gene may also alter the malignant cell population, leading to aggressive behavior of the malignancy.^{19,20}

CASES

This case series includes neurofibromatosis type 1 patients presented to a tertiary care center with different malignant tumors in a span of 8 months. Patients underwent biopsy from their skin lesions (Fig1) which are histopathologically proved as neurofibromatosis lesions (Fig2). All were females with age ranges from 35 to 50 years.



Fig 1-NF1 Skin Lesions

MICROSCOPIC EXAMINATION:

Sections shows skin covered tissue fragments. The epidermis lined by stratified squamous epithelium showing papillomatosis, parakeratosis. Subepithelium shows unencapsulated lesion composed of spindle cells with wavy nerve cells and collagenous stroma. Stroma shows few blood vessels. No mitosis seen. No verroccay bodies seen. No evidence of malignancy.

IMPRESSION: FEATURES ARE SUGGESTIVE OF NEUROFIBROMA

Fig 2-Histopathology of Skin Lesions

Case 1

A 43 year old menopausal women known neurofibromatosis type 1 patient presented with chief complaint of swelling over right shoulder and anterior chest wall since 6 months which is associated with pain. Biopsy from the swelling shows soft tissue sarcoma. CECT chest shows 5.5x9.9x6.1cm soft tissue density lesion present over right lateral chest wall overlaying one to third right ribs.

She underwent wide local excision with postop hpe showing features of malignant mesenchymal tumor (soft tissue sarcoma) with FNCLCC score 8 and grade 3 and mass of 10x6.5x5cm with no lymphnodes positive

She was finally diagnosed as soft tissue sarcoma of rt chest wall with stage T2N0M0

Patient received adjuvant radiotherapy of 60Gy in 30# and adjuvant chemotherapy of 4cycles of AIM regimen

Case 2

A 50year old postmenopausal known case of neurofibromatosis type 1 female presented with a complaint of difficulty in swallowing solids since one month. Her VLScopy shows a proliferative growth in post cricoid area. Biopsy of which shows moderately differentiated squamous cell carcinoma. MRI neck shows circumferential wall thickening of hypopharynx and post cricoid esophagus of 1.9cm thickness and 7.6cm length with enlarged necrotic bilateral level II and right level III lymphnodes largest of 2.7cms in SAD present.

She was finally diagnosed as carcinoma hypopharynx with stage T3N2cM0

She received treatment with radiotherapy of dose 70Gy in 35# along with concurrent chemotherapy of 6 cycles of carboplatin

Case 3

A 47year old postmenopausal neurofibromatosis type 1 female presented with complaint of headache since 3months. CE MRI brain shows well defined lobulated moderately enhancing lesion in frontal horn of left lateral ventricle along with associated dilated lateral ventricles with possible infiltration of brain parenchyma.

She underwent left anterior parasagittal craniotomy and subtotal excision of tumor. Of which post op hpe shows many multinucleate and bizarre tumor giant cells with increase in mitotic activity and large areas of necrosis and foci of vascular proliferation. Histology proves glioblastoma grade IV.

Followed postop MRI brain shows focal lesion of 4.1x3.3cm seen in frontal horn of left ventricle which is infiltrating cerebral parenchyma with perilesional edema.

She received adjuvant radiotherapy of dose restricted to 57.6Gy in 32# as tumor is in close vicinity to brainstem and optic chiasma with concurrent temozolamide followed by adjuvant temozolamide of 12cycles

Case 4

A 35year old unmarried neurofibromatosis type 1 female presented with lump in retroareolar region of right breast since 3months. Trucut biopsy shows Invasive ductal carcinoma with hormonal status of triple positive breast carcinoma

She underwent right modified radical mastectomy with axillary lymphnode dissection. Its hpe has features of IDC of grade 2 with tumor size of 5.2x3.5x1.8cm with LVSI+ and 2/12 lymphnodes positive with final stage of pT3N1aM0.

She received adjuvant chemotherapy of 4cycles adriamycin and cyclophosphamide and 4cycles of taxol and transtuzumab and followed adjuvant transtuzumab for one year. She also received adjuvant radiotherapy of dose 50Gy in 25# followed by 10Gy in 5# boost. She was planned to receive tab Tamoxifen for 10years.

Review of Literature

Chung et al reported a case of 77-year-old woman known case of NF1 presented with a mass on her left flank which was diagnosed as a cutaneous epithelioid MPNST²¹. MPNSTs are generally associated with the nerve plexuses, which are located deep in the subcutaneous tissue. MPNSTs of the skin are rarely reported. Approximately 50% of MPNSTs develop in patients with NF-1²²

Ferrari et al stated that patients affected by neurofibromatosis type 1 (NF1) are at higher risk of developing soft-tissue sarcomas (STS) than the general population.²³ They reported clinical findings and outcomes in 43 children and adolescents with NF1 treated for STS in the Italian protocols between 1988 and 2004. According to their study in a total of 43 patients, 37 patients are with neurogenic sarcomas and 6 cases of rhabdomyosarcoma (RMS). They found that five-year event-free and overall survival rates were 19% and 28%, respectively.

Finally they concluded that NF1 patients have a high risk of developing STS, and particularly MPNST, often with an aggressive clinical presentation and poor outcome

Li D et al stated that Postcricoid neurofibroma is an extremely rare hypopharynx tumor²⁴. They reported a case of 43-year-old man presented with a four months history of a persistent foreign body sensation and mild dysphagia with a biopsy confirmed solitary neurofibroma of the postcricoid region. They intervened the tumor surgically by resecting en bloc transorally through supporting laryngoscope. Patient was followed upto 6 months with no recurrences

Jeong et al²⁴ reported a 32year old male neurofibromatosis patient who was diagnosed as glioblastoma and underwent standard concomitant chemo-radiotherapy followed by adjuvant chemotherapy with temozolamide. And also they reviewed literature and said that it is more common in children and survival of glioblastoma patient with NF1 was better than those without NF1²⁶

Some stated that NF1 is a human GBM suppressor gene.²⁷

Picart et al²⁸ reported that NF1 was more frequently occurred in infratentorial GBMs compared with supratentorial GBMs

Cai et al²⁹ stated that Glioblastoma (GBM) is the most lethal and common malignant brain tumor but rare in patients with NF1. They reported a 51-year-old female patient complained of headache and left limb weakness lasting for 20 days with a pathological diagnosis of the intracranial lesion showed glioblastoma with Immunohistochemical results of the intracranial specimen showed that glial fibrillary acidic protein, oligodendrocyte lineage transcription factor 2, L1 cell adhesion molecule, S100, and vascular CD34 positive.

Huttner et al²⁷ reported that pediatric patients with NF1 are at higher risk of developing glioblastoma and have a better prognosis than children without NF1. The median survival rate of such cases with surgical resection, radiotherapy, and chemotherapy is 36 months, with maximum survival of 106 months.

Sarah et al³⁰ reported a case of A 27-year-old man with NF1 presented with symptoms of high intracranial pressure. Imaging and pathology showed left frontotemporal glioblastoma and underwent gross total resection and concurrent chemoradiotherapy. Recurrence of tumor was detected 48 months later, and the patient underwent tumor debulking and concurrent chemoradiotherapy. And he survived >10 years since then with good functional status. They also reviewed literature and stated that the survival rate in adult patients with NF1 diagnosed with glioblastoma is approximately 34 months, with maximal survival of 104.4 months from the time of diagnosis, with conventional treatment for primary and recurrent tumor.

According to uusitalo et al³¹, A total of 32 breast cancers were diagnosed in 1404 NF1 patients. They said that women with NF1 had an estimated lifetime risk of 18.0% for breast cancer and survival was worse in the NF1 group. They said that women with NF1 had a 4.7% risk of being diagnosed with breast cancer during 30–39 years of age.

In our case series the carcinoma breast patient age was also 35years

They also found that NF1 breast cancers were more often ER negative and PR negative and *HER2* positive but in our patient it was triple negative

According to Wallace et al³², they stated that *NF1* gene aberrations are frequent in breast cancers in patients who do not have the NF1 syndrome and the *NF1* gene might be a general driver in breast cancer

Evans et al³³ included 142 women with NF1 and breast cancer from five cohorts with a median age of 46.9 years. And they observed that cumulative risk for contralateral breast cancer was 26.5% in 20 years. Breast cancer-specific 10-year survival was low compared with non-NF1 age-matched population. **They finally suggested that early start of breast cancer screening may be a way to improve the survival in NF1 patients**

As described in several studies³⁴ there is a predominance of invasive ductal carcinoma in carcinoma breast patients associated with NF1 and our patient also had this most common subtype as well.

Elina et al³⁵ reported a case of a case of 48-year-old female with clinical diagnosis of neurofibromatosis type 1, who was diagnosed with stage IV HER2 positive breast cancer with hepatic and bilateral axillary lymph node metastasis, treated with chemotherapy and anti-HER2 antibodies.

CONCLUSIONS

Neurofibromatosis patients are at increased risk of developing both benign and malignant tumors with variant sites of presentation prognosis.

REFERENCES

1. Le C, Bedocs PM. Neurofibromatosis. [Updated 2023 Jan 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.-Available from <https://www.ncbi.nlm.nih.gov/books/NBK459329>
2. Uusitalo E, Leppävirta J, Koffert A, et al: Incidence and mortality of neurofibromatosis: A total population study in Finland. *J Invest Dermatol* 135:904-906, 2015
3. Jouhilahti EM, Peltonen S, Heape AM, Peltonen J. The pathoetiology of neurofibromatosis 1. *Am J Pathol.* 2011 May;178(5):1932-9. [PMC free article] [PubMed]
4. Asthagiri AR, Parry DM, Butman JA, Kim HJ, Tsilou ET, Zhuang Z, Lonsler RR. Neurofibromatosis type 2. *Lancet.* 2009 Jun 06;373(9679):1974-86. [PMC free article] [PubMed]
5. Kresak JL, Walsh M. Neurofibromatosis: A Review of NF1, NF2, and Schwannomatosis. *J Pediatr Genet.* 2016 Jun;5(2):98-104. [PMC free article] [PubMed]
6. Bergoug M, Doudeau M, Godin F, Mosrin C, Vallée B, Bénédicti H. Neurofibromin structure, functions and regulation. *Cells.* 2020;9:2365. [PMC free article] [PubMed]

7. Dunnett-Kane V, Burkitt-Wright E, Blackhall FH, Malliri A, Evans DG, Lindsay CR. Germine and sporadic cancers driven by the RAS pathway: parallels and contrasts. *Ann Oncol.* 2020;31:873–83. [PMC free article] [PubMed]
8. Galvin R, Watson AL, Largaespada DA, Ratner N, Osum S, Moertel CL. Neurofibromatosis in the era of precision medicine: development of MEK inhibitors and recent successes with selumetinib. *Curr Oncol Rep.* 2021;23:45. [PMC free article] [PubMed]
9. Elina Uusitalo, Matti Rantanen, Roope A. Kallionpa, Minna Poyhonen, Jussi Leppävirta, Heli Ylä-Outinen, Vincent M. Riccardi, Eero Pukkala, Janne Pitkaniemi, Sirkku Peltonen, and Juha Peltonen. Distinctive Cancer Associations in Patients With Neurofibromatosis Type 1: *Clin Oncol* 34. © 2016 by American Society of Clinical Oncology. 2016
10. Upadhyaya M, Cooper DN (eds): *Clinical diagnosis and atypical forms of NF1*, in *Neurofibromatosis Type 1 Molecular and Cellular Biology*. New York, NY, Springer, 2012, pp 17-30
11. Rosenfeld A, Listernick R, Charrow J, et al: Neurofibromatosis type 1 and high-grade tumors of the central nervous system. *Childs Nerv Syst* 26:663-667, 2010
12. Rodriguez FJ, Perry A, Gutmann DH, et al: Gliomas in neurofibromatosis type 1: A clinicopathologic study of 100 patients. *J NeuroPathol Exp Neurol* 67:240-249, 2008
13. Sharif S, Moran A, Huson SM, et al: Women with neurofibromatosis 1 are at a moderately increased risk of developing breast cancer and should be considered for early screening. *J Med Genet* 44:481-484, 2007
14. Maertens O, Prenen H, Debiec-Rychter M, et al: Molecular pathogenesis of multiple gastrointestinal stromal tumors in NF1 patients. *Hum Mol Genet* 15:1015-1023, 2006
15. Walthers MM, Herring J, Enquist E, et al: von Recklinghausen's disease and pheochromocytomas. *J Urol* 162:1582-1586, 1999
16. Gao J, Aksoy BA, Dogrusoz U, et al: Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci Signal* 6:pl1, 2013
17. Zoeller ME, Rembeck B, Ode n A, et al: Malignant and benign tumors in patients with neurofibromatosis type 1 in a defined Swedish population. *Cancer* 79:2125-2131, 1997
18. Walker L, Thompson D, Easton D, et al: A prospective study of neurofibromatosis type 1 cancer incidence in the UK. *Br J Cancer* 95:233-238, 2006
19. Evans DG, O'Hara C, Wilding A, et al: Mortality in neurofibromatosis 1 in North West England: An assessment of actuarial survival in a region of the UK since 1989. *Eur J Hum Genet* 19:1187-1191, 2011
20. Seminog OO, Goldacre MJ. Risk of benign tumours of nervous system, and of malignant neoplasms, in people with neurofibromatosis: population-based record-linkage study. *Br J Cancer* 2013; 108:193–198.
21. Chung YH, Jang JW, Cho JY. Soft tissue sarcoma in neurofibromatosis type 1: A rare case of malignant peripheral nerve sheath tumor of the skin. *Arch Plast Surg.* 2020 Jan 8;47(1):92-96. doi: 10.5999/aps.2019.01529. Epub 2020 Jan 15. PMID: 31964130; PMCID: PMC6976743.
22. Luzar B, Falconieri G. Cutaneous malignant peripheral nerve sheath tumor. *Surg Pathol Clin.* 2017;10:337–43.
23. Ferrari A, Bisogno G, Macaluso A, et al.: Soft-tissue sarcomas in children and adolescents with neurofibromatosis type 1. *Cancer.* 2007, 109:1406-12. 10.1002/cncr.22533
24. Li D, Niu K, Yuan T, Zhu W, Wang X, Yin W. A rare case report of an solitary neurofibroma in postcricoid region of hypopharynx. *Medicine (Baltimore).* 2021 Jan 8;100(1):e24017. doi: 10.1097/MD.00000000000024017. PMID: 33429765; PMCID: PMC7793459.
25. Jeong TS, Yee GT. Glioblastoma in a Patient with Neurofibromatosis Type 1: A Case Report and Review of the Literature. *Brain Tumor Res Treat.* 2014 Apr;2(1):36-38. <https://doi.org/10.14791/btrt.2014.2.1.36>
26. Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature* 2008;455:1061–8.
27. Huttner AJ, Kieran MW, Yao X, et al. Clinicopathologic study of glioblastoma in children with neurofibromatosis type 1. *Pediatr Blood Cancer* 2010;54:890–6.
28. Picart J, Barrिताult M, Berthillier J, et al. Characteristics of cerebellar glioblastomas in adults. *J Neurooncol* 2018;136:555–63.
29. Cai JW, Chen XY, Chen JY, Wu ZY, Wu XY, Yu LH, You HH. Glioblastoma in a female neurofibromatosis 1 patient without IDH1, BRAF V600E, and TERT promoter mutations: a case report. *Medicine.* 2021;100:13(e25346).
30. Sarah Basindwah, Hisham Alkhalidi, Ahmed Abdelwarith, Sherif Elwatidy : Ten-year survival in glioblastoma patient with neurofibromatosis type 1: illustrative case; 2022, <https://doi.org/10.3171/CASE21630>
31. Uusitalo E, Kallionpää RA, Kurki S, Rantanen M, Pitkaniemi J, Kronqvist P, Härkönen P, Huovinen R, Carpen O, Pöyhönen M, Peltonen S, Peltonen J. Breast cancer in neurofibromatosis type 1: overrepresentation of unfavourable prognostic factors. *Br J Cancer.* 2017 Jan 17;116(2):211-217. doi: 10.1038/bjc.2016.403. Epub 2016 Dec 8. PMID: 27931045; PMCID: PMC5243991.
32. Wallace MD, Pfeifferle AD, Shen L, McNair AJ, Cerami EG, Fallon BL, Rinaldi VD, Southard TL, Perou CM, Schimenti JC (2012) Comparative oncogenomics implicates the neurofibromin 1 gene (NF1) as a breast cancer driver. *Genetics* 192: 385–396. [PMC free article] [PubMed] [Google Scholar]
33. Evans DGR, Kallionpää RA, Clementi M, Trevisson E, Mautner VF, Howell SJ, Lewis L, Zehou O, Peltonen S, Brunello A, Harkness EF, Wolkenstein P, Peltonen J. Breast cancer in neurofibromatosis 1: survival and risk of contralateral breast cancer in a five country cohort study. *Genet Med.* 2020 Feb;22(2):398-406. doi: 10.1038/s41436-019-0651-6. Epub 2019 Sep 9. Erratum in: *Genet Med.* 2019 Oct 8; PMID: 31495828; PMCID: PMC7000349.
34. D.R. Stewart, B.R. Korf, K.L. Nathanson, D.A. Stevenson, K. Yohay Care of adults with neurofibromatosis type 1: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG) *Genet. Med.* (2018), pp. 671682, 10.1038/gim.2018.28