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Huge Malignant Peripheral Nerve Sheath Tumors Originating In Neurofibromatosis Type 1

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Abstract

Malignant peripheral nerve sheath tumours (MPNST) are malignant soft tissue neoplasms which account for 2% of all soft tissue sarcomas. These tumours are associated with poor prognosis, have a propensity to metastasize and have high recurrence rates. About half of the MPNST arise from pre-existing neurofibromas and are associated with Neurofibromatosis type I (NF1), 10% are radiotherapy induced others are sporadic. Pathogenesis of MPNST is not fully understood yet. MPNSTs are common in extremities followed by the trunk but are less common in the head and neck area. MPNST show limited sensitivity to radiotherapy and chemotherapy and wide surgical resection is a mainstay of treatment. We present a series of 3 cases of MPNST of head and neck region originating in patients having NF1.

Keywords: Mesenchymal malignancies; Neurofibromatosis; Malignant peripheral nerve sheath tumour; soft tissue tumours

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1. Introduction

Malignant peripheral nerve sheath tumours (MPNST) are connective tissue tumours, and the tumour cells may show a variable differentiation to Schwann cells, fibroblasts or peri-neural cells[(1)]. MPNST accounts for 2% of soft tissue sarcomas[(2)]. They may originate *de novo* or from pre-existing neurofibromas. MPNSTs are often aggressive with a high tendency for recurrence and show poor prognosis. Targeted molecular therapies are not available till now[(1)].

NF1 is a well-recognized neurocutaneous disorder that is caused by a gene mutation. The patients have their life expectancy reduced by an average of 15 years. Neurofibromatosis is associated with several malignant neoplasms which include; malignant peripheral nerve sheath tumours (MPNST), rhabdomyosarcoma, pheochromocytoma, leukaemias, melanoma, lymphomas and carcinoid tumors. These tumours are the major cause of mortality and morbidity in patients with NF1[(3)]. Patients with NF1 have a 6-13% chance of developing MPNST in their lifetime. The diagnosis of MPNST originating in pre-existing NF1-associated neurofibromas is relatively easy as compared to the sporadic cases where the non-availability of specific diagnostic tools makes it difficult to distinguish from other soft tissue malignancies[(2)]. Here we present a case series in which MPNST originated in undiagnosed cases of NF1.

2. Case Presentation

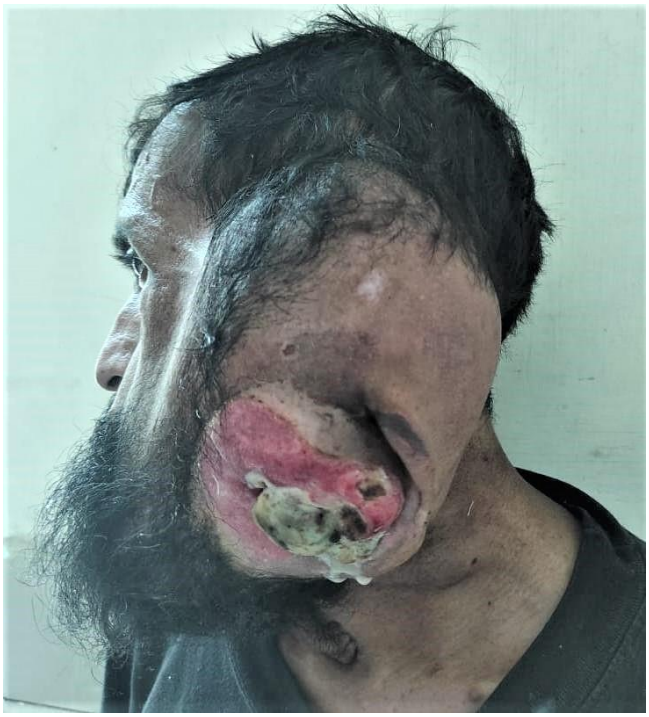
Case 1: A 14-year-old female patient presented with a large swelling on the left side of the face and neck. The swelling was present since birth and gradually increased in size; the mass was irradiated, considering it to be a cystic hygroma which led to ulceration of the overlying skin. Furthermore, it didn't respond to the radiotherapy. When the patient presented to us the swelling was almost 23x15cm in size and it was extending supero-inferiorly from the base of the left auricle to the second neck crease, and the lesion was crossing midline and involving almost half of the neck and posteriorly extending 3cm behind the auricle (Fig-1).

Another soft tissue swelling was present in the occipital region since birth. There was a large brown spot with smooth margins on the left side of the face, and excessive hair growth was also present on the face on the same side. According to the CT scan the lesion was encasing a carotid artery and an incisional biopsy showed it to be a spindle cell neoplasm. Excision was planned under general anaesthesia; soft tissue defect was reconstructed using a pedicled supra-clavicular flap (Fig 2). On excisional biopsy the lesion was MPNST. Three weeks post-surgery MRI showed multiple metastatic nodules in both the lungs, while no signs of metastasis were present on imaging performed one month before surgery. One week after surgery patient felt difficulty breathing and was admitted to the hospital but expired 4 weeks after the surgery.

Figure-1 Cystic hygroma which led to ulceration of overlying skin

Figure-2 Soft tissue defect reconstruction using a pedicled supra-clavicular flap

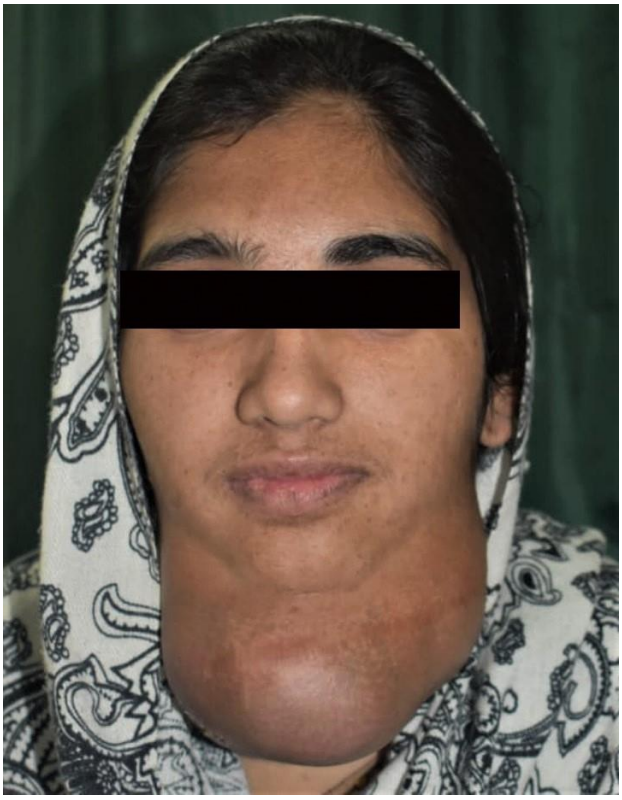
Case 2: A 32-year-old male patient presented with a swelling on the left peri-auricular area since birth, which became painful, and rapidly increased in size for the last 4 months. The swelling was about 18x11cm in size, extending supero-inferiorly from the temporoparietal region to the base of the mandible and anteroposteriorly from mid-cheek level to about 4cm behind the auricle. On examination, the mass was ulcerated and infected (Figure 3).



Few maggots were seen coming out of the central necrotic area. The patient had short stature by birth, multiple small nodules (Neuro-fibromas) distributed throughout the patient's body, and multiple smooth-bordered, flat brown spots on extremities, back and abdomen**.** There was no cervical lymphadenopathy. The incisional biopsy had been performed in a local hospital and showed the lesion to be a spindle cell neoplasm. C.T. scan showed multiple variable-sized metastatic intra-parenchymal nodules in both the lungs and kyphoscoliosis changes in the thoracic spine. The left lower limb was thinned about half the diameter of the right one, and there was a soft tissue swelling involving the left heel. Maggots were mechanically removed using Maggot oil and the wound was irrigated using normal saline for one week along with intravenous antibiotic (Ceftriaxone). The patient was transfused blood as his haemoglobin was 7g/dl due to previous bleeding episodes. Based on clinical and

radiographic examination, our definitive diagnosis was MPNST. The patient was referred to oncology for further management, where chemotherapy was started and the patient died after one month.

Case 3: A 21-year-old female patient presented with a swelling on the left submandibular region for 1 year. The patient was operated on for a lesion at the same location 2 years ago from the time of presentation, however, no record was available.



The patient complained of mild pain and a rapid increase in the size of the lesion for the last 3 months which led to difficulty in swallowing. At the time of presentation, the lesion was 19x10cm in size, extending from the left angle of the mandible to the right angle region. Supero-inferiorly it extended from the base of the mandible to the neck's first crease. There was a small area of ulceration (Fig4). There were multiple brownish spots scattered throughout the body of the patient; especially prominent on the neck and arms and multiple small neuro-fibromas on the back of the patient. The incisional biopsy report was suggestive of malignant spindle cell neoplasm. On computed tomography the lesion was centred in the region of the left submandibular gland reaching up to the contralateral submandibular gland, it was extending medially to the ramus of the mandible thus displacing the tongue, posteriorly it was displacing the carotid sheath and superiorly it was extending up-to the base of the skull.

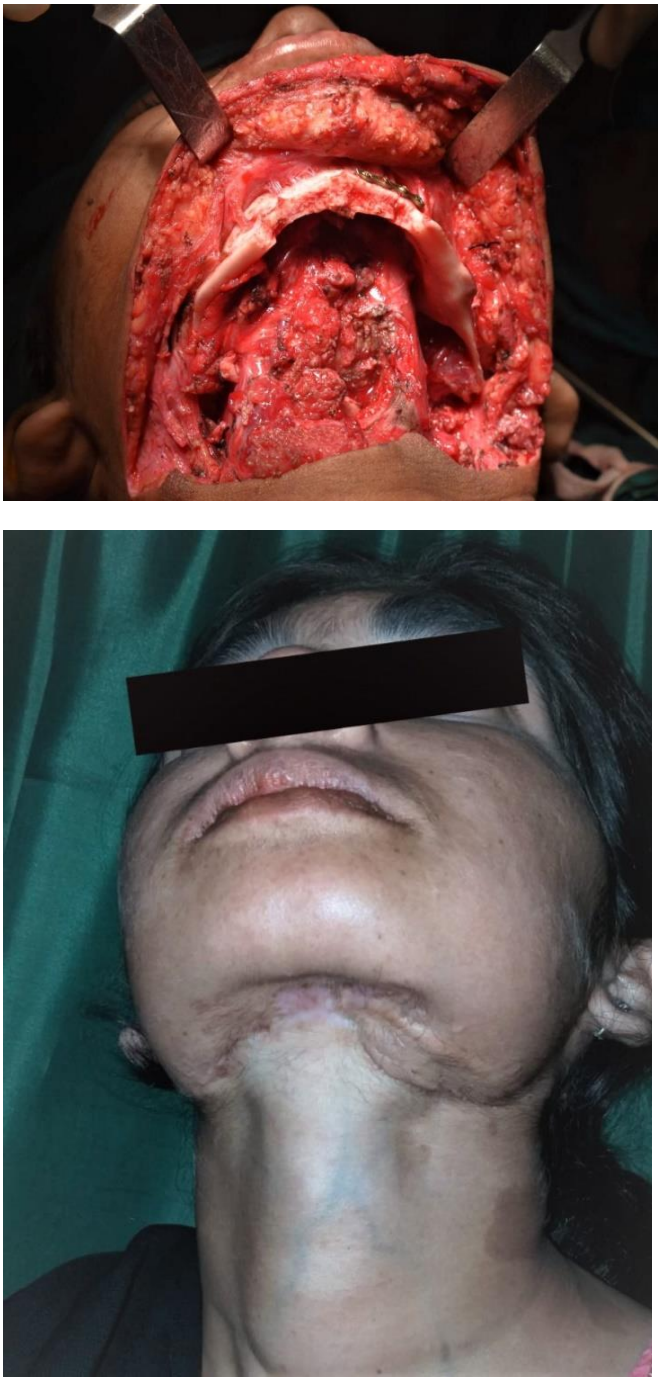


Figure-6 Patient after Surgery

However, there was no bony resorption. Resection of the lesion taking wide safe margins was planned under general anaesthesia. The lesion was exposed using bilateral submandibular incisions a small portion of

bone in the symphysis region was resected with the lesion (Fig). The excisional biopsy report showed the lesion to be MPNST. The patient is on regular follow and she has been recurrence-free for 24 months (Fig).

Table 1: Comparison of all the cases

Sr.	Age (Years)	Gender	Site	Size (cm)	Presentation
1	14	Female	The left side of the neck	23x15	A large swelling with ulceration.
2	32	Male	Left peri-auricular area	18x11	A large swelling with bleeding episodes and maggot infestation.
3	21	Female	Left submandibular region	29x10	A large swelling with mild pain and swallowing difficulty.

3. Discussion

MPNSTs are soft tissue sarcomas and show nerve cell differentiation potential. About 40-50 % of the cases originate from pre-existing neuro-fibromas, some are induced by radiotherapy and others are sporadic cases. The median age of the patients diagnosed with MPNST is 41 years, and it tends to occur earlier in patients with NF1 with a median age of 28 years. [4] In the present case series all the cases originated in preexisting NF1 and the median age of the patients was 23.5 years. The incidence of sporadic cases is equal among males and females but in cases originating from preexisting neuro-fibromas a male predilection has been reported. [5] In the present case series there were two female patients and one male. The pathogenesis of MPNST is not fully understood but experimental studies have shown that loss of tumour suppression (PTEN, P63, P16), and up-regulation of the signalling system for growth factors (PDGFR, EGFR), along with interactions with the extra-cellular matrix is the possible mechanism[6].

The most common sites of occurrence are the extremities followed by the trunk head and neck are the least commonly affected. Patients commonly present with a mass rapidly increasing in size and pain. The unfavourable factors leading to poorer prognosis include a size larger than 7cm, high-grade tumours, truncal location, association with NF1, increased mitotic index, and inadequate surgery [1][7][8]. Two-thirds of the MPNSTs metastasize to lungs or bones and it has a high rate of recurrence [1].

In the present case series (table 1), all of the cases were associated with NF1, tumour location was in the head and neck region, tumour size was larger than 7cm and there was an increased mitotic index. Surgical resection taking tumour-free margins is the mainstay of treatment for MPNST. Due to the propensity for micro spread of the tumor, small head and neck area and proximity to vital structures achieving negative margins is not possible in all the cases located in the head and neck region. These factors lead to high recurrence rates (22-52%) and distant metastasis (18-33%), so multimodality treatment is recommended [9]. Despite multimodality treatment, the 5-year survival rate remains low between 23 and 69% [2]. Chemotherapy and radiotherapy are of limited use [1]. In the present case series, surgery was planned for two out of three cases, one (case 2) was referred to oncology for management. Out of these three one patient (case 1) expired due to distant lung metastasis and one patient (case 3) has been tumor-free for 24 months. No nodal involvement was seen in any of the cases. The five-year survival rate of pediatric patients with MPNST has been increasing since 2005, which may be due to the availability of centralized medical care for the patients [10].

5. Conclusion

MPNSTs associated with neurofibromatosis are very aggressive soft tissue tumours, having poor prognoses and respond poorly to different treatment modalities. Different screening programs should be devised to make the early diagnosis possible. Patients having NF1 and

their families should be made aware of the possibility of originating aggressive neoplasms.

CONFLICTS OF INTEREST- None

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Contributions:

N.R - Conception of study
N.R - Experimentation/Study Conduction
S.Y - Analysis/Interpretation/Discussion
S.Y - Manuscript Writing
N.R - Critical Review
S.Y - Facilitation and Material analysis

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