CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 77 (2020) 618–623

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

Malignant peripheral nerve sheath tumour – A long story: Case report

Y.M. Fazil Marickar[a,*], Betty Abraham[b]

[a] Mount Zion Medical College, Adoor, India
[b] DDRC SRL, Trivandrum, India

ARTICLE INFO

Article history:
Received 18 September 2020
Received in revised form
11 November 2020
Accepted 11 November 2020
Available online 19 November 2020

Keywords:
Case report
Malignant peripheral nerve sheath tumour
Neurofibromatosis-1
Immunohistochemistry
Fluorescence in-situ hybridisation

ABSTRACT

INTRODUCTION: We present a rare case of Malignant Peripheral Nerve Sheath Tumour (MPNST) of the upper limb, which was excised thirteen times in thirteen years and ultimately ended in above elbow amputation.

PRESENTING COMPLAINT AND INVESTIGATIONS: A 48 year old female presented initially with a localised swelling of 2 cms diameter in the front of the left elbow in 2007, which was excised. It recurred repeatedly and was excised. In the earlier presentations, the swellings were firm, mobile and not fixed to bone. In the last stage alone, bone fixity was identified. All the fourteen surgeries were performed by the primary author from 2007 to 2020, as the patient was particular.

THE MAIN CLINICAL DIAGNOSES: had been neurofibroma and fibrosarcoma. There was no evidence of distant metastasis all these years. She did not respond to radiation or chemotherapy. Initially it was single, but later multiple. She had no clinical features of Neurofibromatosis 1 (NF1) or any family history. As the history progressed, the swellings became muscle deep and later encircled the radial nerve. The radial nerve was salvaged on three occasions. On the last three occasions, the tumour had to be shaved off from the humerus. The final amputation specimen showed a single tumour infiltrating the humerus and x-ray revealed bone destruction and tumour calcification. Final diagnosis was aided by immunohistochemistry (IHC) and cytogenetic study (FISH).

CONCLUSION: The case is presented for the rarity of the presentation and the trust and dependence of the patient on her personal surgeon.

1. Introduction

Malignant Peripheral Nerve Sheath Tumours (MPNST) are rare aggressive sarcomas of peripheral nerve sheaths which account for 5–10% of soft tissue sarcomas [1]. They may occur anywhere along the course of myelinated nerves, but they commonly appear in or near a nerve of the trunk or the limbs. In 50% of cases, they occur in the context of neurofibromatosis type 1(NF1). 40–47% develop sporadically and rest following radiation treatment [2]. They are associated with a high risk of local recurrence ranging from 32% to 65% and hematogenous metastasis [3]. The most frequent sites of MPNST metastasis are lung, liver, brain, soft tissue, bone, regional lymph nodes, and retro-peritoneum.

The aim of this paper is to report a rare case of segmental neurofibromatosis with multiple recurrent MPNST in an otherwise clinically non-established NF1. The pattern of recurrence and histomorphological diversity possess both diagnostic and management dilemmas. The long duration of disease course and absence of distant metastasis are unique in this case. The report has been arranged in line with SCARE 2018 guidelines [4].

2. Presentation of case

2.1. Patient information

The patient was a 48 year old married female with low financial background, unemployed but carrying out petty works for livelihood with a body mass index of 23.7. She was a right hand dominated individual.

She walked in to the consultation room in 2007 with complaints of a swelling in front of the left elbow. The swelling was gradually increasing over a period of six months. It was not associated with pain, weakness or mobility restriction.

She had no significant medical or surgical history. She had two normal deliveries and had no surgery performed earlier.

She was not on any regular medications. There was no history of substance abuse or smoking. She had no family history of similar condition or features of NF1.

* Corresponding author at: Mount Zion Medical College, Shamier Manzil, Mosque Lane 12, Kumarapuram, Trivandrum 695011, India.
E-mail addresses: fazilmarickar@hotmail.com, fazilmarickar@gmail.com (Y.M.F. Marickar).

https://doi.org/10.1016/j.ijscr.2020.11.061

2.2. Clinical findings

On physical examination, the swelling was firm, 2 × 2 cm, non tender and superficial to muscles in location. She had no established clinical features of NF1. Excision biopsy was done and reported as neurofibroma.

2.3. Therapeutic intervention

The patient underwent thirteen excisions in thirteen years and ultimately ended up in above elbow amputation. Chemoradiation was administered twice during the early course of disease.

2.3.1. Disease course

After five months of the first surgery, the patient returned with a recurrent swelling in the same site. Excision was reported as MPNST intermediate grade. Tumour cells were seen in fascicles with cellular condensation around the vessels. Immunohistochemistry (IHC) of the tumour cells showed strong S100 positivity. There was no evidence of distant metastasis. The patient received a full course of external irradiation and a course of Adriamycin. The patient returned in 2011 with a recurrence of two swellings of size around 3 cm and 2 cm diameter. Both were excised and were reported as cellular neurofibroma with peripheral plexiform pattern. In 2012, the patient had fourth recurrence in five years. Excised specimen was reported as favouring synovial sarcoma monophasic type. Review at the cancer centre with IHC confirmed it as recurrent MPNST (CK-, S100+). She was administered adriamycin and external radiation of 40 Gy. In 2014, the patient came back with recurrence and wide excision was reported as MPNST or fibrosarcoma. IHC showed positive vimentin and negative bcl-2, SMA and EMA.

The patient returned in 2015 with multiple local swellings. During surgery, one was adherent to the joint capsule of the left elbow. The tumour was shaved off from the adjacent radial nerve. Histology was reported as possibly MPNST. Tumour was infiltrating the muscle and fat. The swelling recurred in July 2016 and the multiple swellings were excised from the arm and elbow. The histopathology was reported as benign spindle cell neoplasm possibly plexiform neurofibroma and spindle cell neoplasm with cellular areas and increased mitotic activity with invasion of the skeletal muscle fibers. Margins were not free. The patient came back in March 2017 and there were two swellings over the original sites. Wide excision was done and histopathology report was cellular spindle cell neoplasm of neural origin, probably malignant. The patient was not willing for any further radiation or chemotherapy. The patient returned in November 2017 with bigger swellings in both the primary surgical sites (Fig. 1a). Metastatic work up was done, but there was no evidence of distant metastasis. Question of amputation was considered by the tumour board, but the patient was not willing for amputation then. During excision, the radial nerve was seen not involved by the lesion (Fig. 1b). The multiple nodular tumour was excised free of the nerve (Fig. 1c). The histopathology report was suggestive of MPNST.

The next visit in September 2018 needed excision of multiple swellings being shaved off from the radial nerve. The surgery did not produce any radial nerve palsy. The report was neurofibroma. The patient again reported in May 2019 with multiple swellings and all were excised incompletely, as they were deeply adherent to the bone, from where the tumour had to be shaved off. The report came as intermediate grade spindle cell neoplasm, consistent with myxofibrosarcoma. Deeper margin showed facial coverings. There was adherence to the bone and the resection was incomplete. Now the recurrence became faster and in October 2019, multiple swellings were resected including the skin and muscles and shaved off from the radial nerve and the humerus. The report was grade 1 sarcoma infiltrating the overlying skin, adjacent bone and soft tissues.

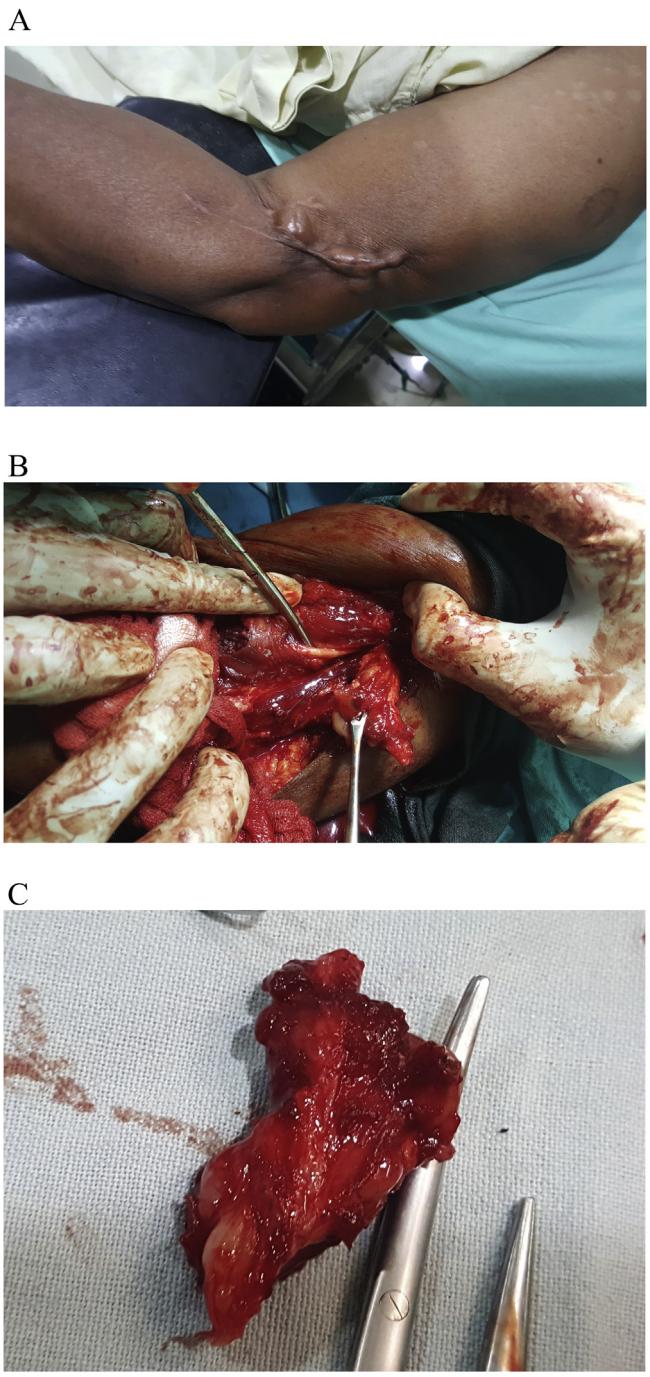

Fig. 1. (a) Clinical picture of multiple recurrent nodular swellings at scar site in the left upper limb during eighth recurrence in 2017. (b) Operative photograph showing the radial nerve pointed with artery forceps separate from the tumour being excised. Tumour is held with Alice forceps. (c) Excised swelling during eighth recurrence.

Now tumour board advised against radiation and chemotherapy. The post-operative wound did not heal and the swelling started expanding proximally and laterally. In February 2020, wide excision with resection of skin was done and reported as MPNST. The wound would not heal and in two months, the tumour recurred at the site of the unhealed area and extended proximally towards the shoulder (Fig. 2). At this time, the spread of the tumour appeared very fast. So the patient was detailed about the possibility of further spread and non-healing wound. She was convinced now and gave consent for above elbow amputation which was done in April 2020. During surgery, the proximal end of the swelling was noticed as

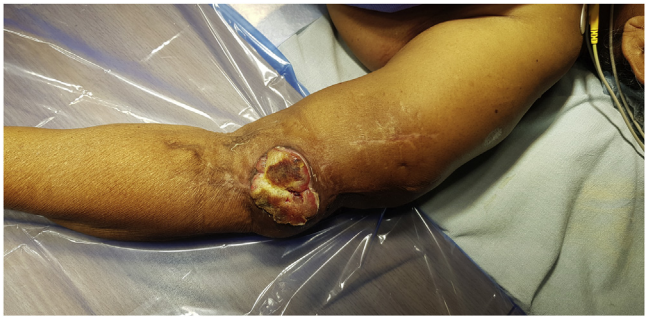

Fig. 2. Clinical picture of non healing wound with proliferating swellings at scar site after 13th excision. This appearance forced the patient to accept amputation.

rounded and firm to hard in consistency. The proximal amputated margin was free of tumour.

All the surgeries were performed by a single surgeon who currently has completed 50 years of surgical practice in teaching hospitals and continuing in academic position.

2.3.2. Follow up

The patient used to come for follow up regularly after all the surgical procedures and she was very particular not to go to any other doctor for any treatment. The patient adhered to all the advice given during the different visits. She was from low income group and had difficulty in doing costly investigations. After the last surgery of above elbow amputation, she has been followed up for six months. She has no recurrence of local swellings in the amputated limb or any evidence of distant metastasis. She is not on any current medication.

2.4. Diagnostic assessment

A thorough gross examination of the amputated limb (Fig. 3a) showed a fleshy whitish growth of size 17 × 7 × 6.5 cm, seen in the subcutaneous plane with deep extension and eroding bone cortex (Fig. 3b). X-ray showed irregularity of the humerus indicating tumour infiltration and loss of cortical density with extraneous calcifications near the elbow portions of the soft tissue tumour (Fig. 4). On dissecting the specimen, the radial nerve was not identifiable separately. Microscopically, the neoplasm showed cellular and hypocellular areas in a myxoid stroma. The neoplastic cells were monomorphic, arranged in fascicles. Periphery showed muscle bundles, cortical bone and marrow spaces being infiltrated by the neoplasm (Figs. 5, 6). Extensive areas of metaplastic bone formation were noted (Fig. 7). No lymphovascular emboli were identified. Overlying skin was ulcerated. The report was low grade sarcoma, suggestive of MPNST.

IHC sarcoma panel showed patchy positivity for S100, diffuse strong positivity for CK (Fig. 8) and BCL2.IHCERG, SOX10, EMA, CD34, CD99, DESMIN, SMA, TLE1 and STAT-6 were negative. However molecular methods were recommended to exclude synovial sarcoma further. The patient was free at six months follow up. We proceeded with cytogenetic study - FISH test for SYT break apart analysis in tissue block. This was negative, hence we excluded the possibility of synovial sarcoma.

The histopathology reports on the different occasions of surgery are detailed in Table 1.

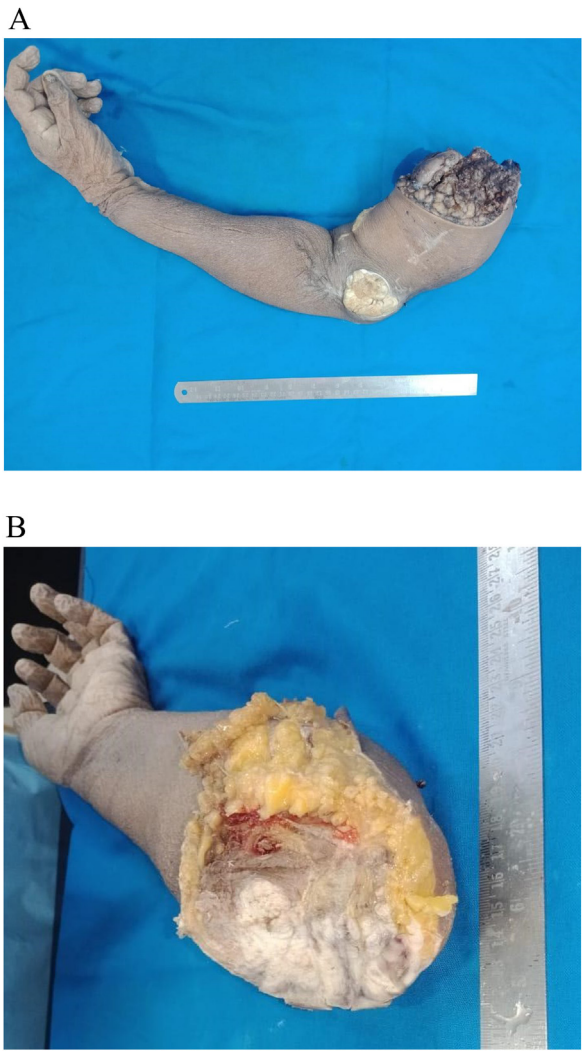

Fig. 3. a & b-Amputated limb with ulcerated growth and Cross-section showing tumour eroding bone cortex with marrow infiltration grossly.

Table 1
List Of Operations Date wise And Histopathology Reports.

1)	06/02/2007	Neurofibroma
2)	24/07/2007	MPNST
3)	17/10/2011	Cellular neurofibroma with peripheral plexiform pattern
4)	06/12/2012	Spindle cell neoplasm favouring monophasic synovial sarcoma → Reviewed as MPNST following IHC study.
5)	12/02/2014	Malignant spindle cell neoplasm-MPNST/Fibrosarcoma
6)	17/10/2015	Possibly MPNST
7)	25/06/2016	Plexiform neurofibroma
8)	18/03/2017	Cellular spindle cell neoplasm neural origin
9)	04/11/2017	MPNST
10)	15/09/2018	Neurofibroma
11)	14/05/2019	Intermediate grade spindle cell neoplasm possibly Myxofibrosarcoma
12)	30/10/2019	Grade 1 sarcoma
13)	29/02/2020	MPNST
14)	11/05/2020	MPNST

3. Discussion

A sarcoma is assumed to be an MPNST when at least one of the following criteria are met; it arises from a peripheral nerve; it arises from a pre-existing benign nerve sheath tumour (neurofibroma) or it demonstrates Schwann cell differentiation on histologic examination [5].

All the excised swellings in the present case were located in the same segment of upper limb, along the course of radial nerve or superficial nerve branches. During the earlier occasions, the

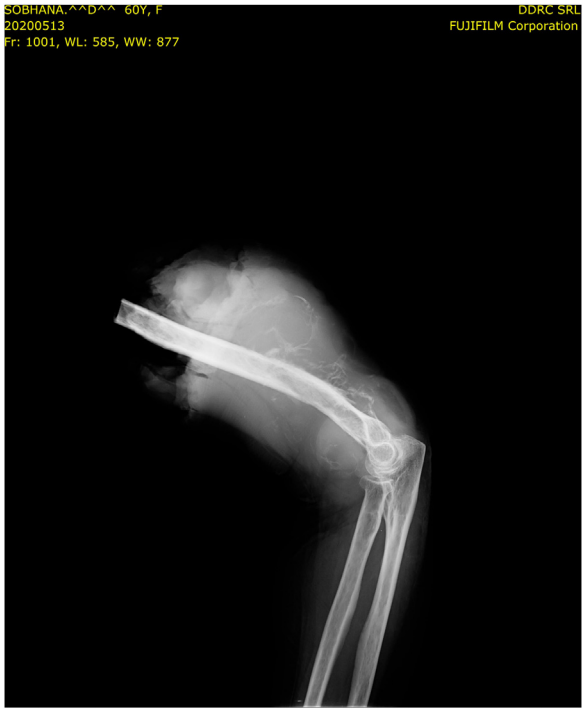

Fig. 4. X-ray of amputated specimen showing tumour calcification and involvement of humerus.

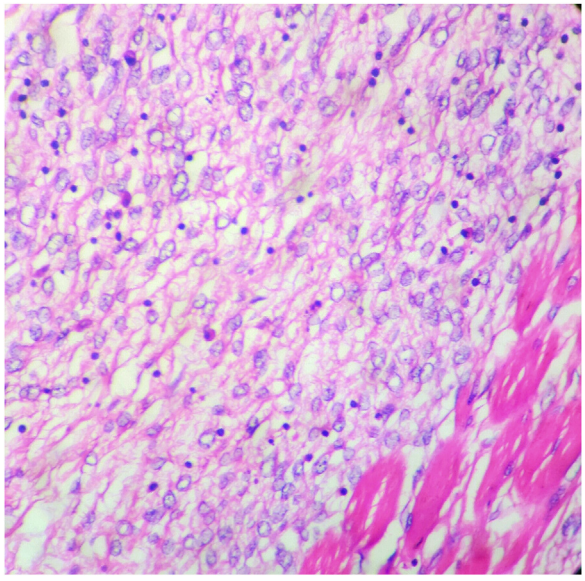

Fig. 5. Microscopy showing monomorphic spindle cells in fascicles infiltrating muscle bundles at periphery (H&E ×400).

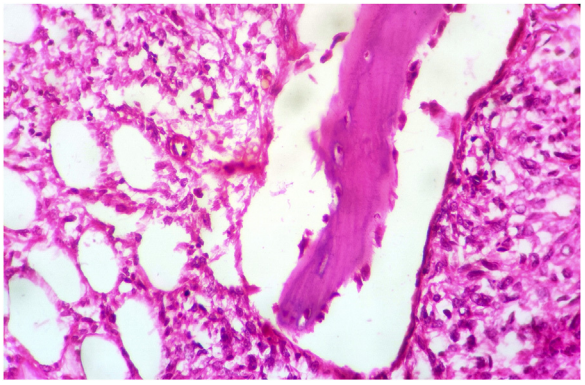

Fig. 6. Tumour infiltrating bone cortex and involving marrow spaces (H&E ×400).

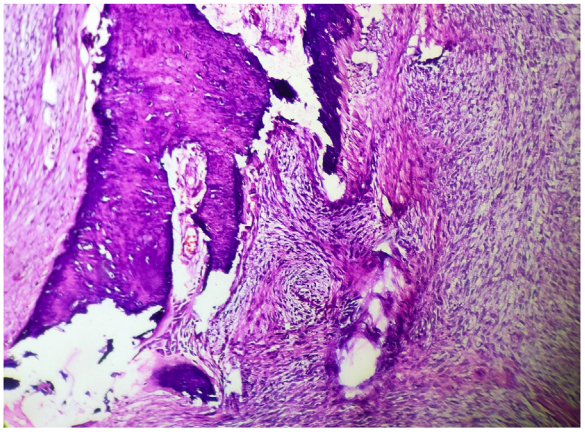

Fig. 7. Metaplastic bone formation within the tumour (H&E ×400).

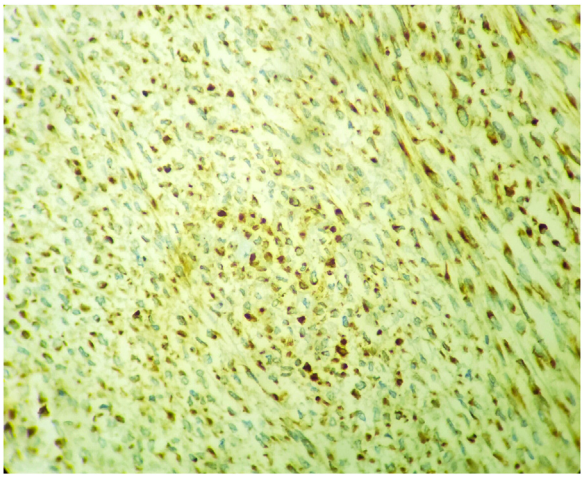

Fig. 8. Cytokeratin (CK) immunostaining: diffuse strong positivity with intense perinuclear zone reactivity (CK IHC ×400).

swellings appeared to be superficial to the muscles and multiple swellings appeared to be separate entities. During the last three excisions, the lesion had to be shaved off from the humerus and from all around the radial nerve. In spite of repeated shaving of the tumour from the radial nerve, nerve weakness was not observed till the 13th excision.

The segmental distribution of the lesions in the same limb in a background of multiple neurofibroma satisfies Riccardi's criteria of type V or segmental NF1 [6]. It is defined as localised manifestations of neurofibromatosis limited to dermatomal distribution of a particular nerve root and not crossing the midline, no family history and no systemic involvement. In 1982, Riccardi proposed the classification of NF into eight subtypes. NF5 is segmental NF, which is defined by the limitation of café-au-lait spots, freckles, and/ or cutaneous neurofibromas in a single unilateral segment of the body [7,8]. Roth et al. subdivided segmental NF into 4 subtypes -true segmental, localised with deep involvement, hereditary and bilateral [9]. In 2000, Tinschert et al. showed that this mosaic localized NF1 was caused by the somatic mutation of the NF1 gene rather than germline mutation [10]. Presence of cellular/ plexiform neurofibromas associated with recurrent localised low to intermediate

grade MPNST has led us to suspect MPNST associated with mosaic localised NF1 in this case.

The prevalence rate of mosaic localized NF1 is approximately 0.0018%, whereas that of NF1 ranges from 0.02 to 0.03% which indicates rarity of the condition [7,10]. Progression of NF1 into MPNST is well established but NF5 has rarely been associated with MPNST. Only 4 such cases have been reported in literature to date [11–13] of which only 2 cases showed recurrence during follow up. Studies were not conducted about the survival rates of such patients due to its extreme low incidence.

The slow process of progression of the disease in the present case taking 14 years with increased rate of growth and deep infiltrating nature in the last one year is also perplexing. The absence of secondary deposits in the lungs or skull bones is also a notable feature. It was only after the above elbow amputation, that the tumour was recognized to be a single lesion. The upper end of the lesion was palpable in the distal cut end of the left arm during the above elbow amputation, indicating that the lesion was growing proximally in a deep level without being palpable, particularly on the medial aspect of the arm. It was only the macroscopic pathological examination of the specimen which showed that the tumour was a single mass, involving the humerus and also producing calcification in the soft tissue. During the gross examination, the radial nerve could not be separately dissected out from the tumour.

MPNST is usually a diagnosis of exclusion. Histopathology aided by immunohistochemistry remains the mainstay for diagnosis. Other spindle cell sarcomas like mono and biphasic synovial sarcoma show overlapping morphologic features. Such sarcomas are also described within and in association with major nerves [14]. The initial IHC study showed S100+, CK- and BCL2-. But amputation specimen showed a different pattern (CK+, BCL2+, S100 patchy positivity) with similar histology. This variation in expression pattern can be explained by the trans differentiation which may occur with multiple recurrences. However the diagnosis of MPNST is strongly supported by clinical history of recurrent neurofibroma, plexiform pattern, involvement of radial nerve and exclusion of synovial sarcoma by cytogenetic study.

Review of previous biopsy slides was done. It was found that all the lesions shared similar morphologic features with varying cellularity and stromal predominance, some with peripheral plexiform pattern. Presence of infiltration to surrounding structures favoured diagnosis of sarcoma in most cases. Otherwise all tumours showed low grade nuclear features and mitotic activity. Cellular neurofibroma diagnosed twice in the disease course would rather represent periphery of low grade MPNST/precursor lesion, as there is no significant mitotic activity/invasive features in the slides reviewed. The sections with features of Myxofibrosarcoma showed a predominant myxoid background with thin vasculature that favoured a different morphologic diagnosis. But on review workup, IHC showed patchy S100 positivity favouring MPNST. The morphologic diagnosis of synovial sarcoma was excluded by molecular study (absence of SYT–SSX gene fusion by FISH). Thus the overlapping histomorphologic features in spindle cell sarcomas warrant advanced techniques like IHC/genetic studies for definite diagnosis.

Negative margin resection remains the main stay of curative treatment, but is often compromised by large tumour size and extensive nerve involvement [15,16]. Better understanding of the genetics and the molecular biology of this case needs Next Generation Sequencing (NGS) study. Future development of defining characteristics at molecular level will pave the way for targeted therapy [17].

The purpose of presenting this case report is to impress upon the importance of establishing emotional rapport between the treating doctor and the patient. It also implies the importance of retaining records of patients from the beginning of any illness to the current date, so that prospective analysis of the disease process can be done and reported for the benefit of the patient.

4. Conclusion

The paper presents the various histological appearances of the lesion during different excisions of the tumor. No similar case of a single patient having 13 recurrences of low grade MPNST in a period of 14 years ending up in above-elbow amputation is reported in literature. The emotional commitment of the patient towards the surgeon and the maintenance of old records are to be stressed for the new generation clinicians with emphasis on doctor-patient relationship.

5. Takeaway lessons

- The histomorphologic diversity of soft tissue sarcomas warrants, correlation with advanced techniques like IHC, FISH and other genetic studies for definite conclusion.
- The prognosis and chance of survival of patient with MPNST is extremely variable.
- AETCOM (Attitudes, Ethics and Communication) forms the hall mark of doctor patient relationship.

6. Learning points

- Proper communication with patients will retain patient relations for life.
- Maintenance of records is very essential for proper management of any patient.
- Not all malignancies behave uniformly.
- Individual treatment decisions should be taken on patient considerations

7. Patient perspective

A very important message, which comes out of the experience is the confidence imposed on the surgeon by the patient. She refused to go to any other surgeon. It was with great difficulty that she was sent to the cancer centre for radiation or chemotherapy. The whole family pleaded with the author not to discard her or send her away. As the patient was poor, the authors had to pay for some of the costly final tests for confirming the diagnosis.

Declaration of Competing Interest

The authors report no declarations of interest.

Sources of funding

There was no source of any funding. There were no study sponsors.

Ethical approval

This is not a research study and hence ethical approval is not necessary.

Consent

Written and signed consent for publication is obtained and available with the corresponding author.

Author contribution

Primary author performed all the surgeries and was the primary treating physician. Second author is pathologist who made the final diagnosis and wrote the pathological part of the paper. She also actively participated in the finalisation of the paper.

Registration of research studies

This paper does not require registration in research registry.

Guarantor

The primary author Dr. YM Fazil Marickar is the Guarantor, accepting full responsibility for the work and conduct of the study. He has access to data and has controlled the decision to publish the paper.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Role of authors

Author 1 performed the surgeries and followed up the patient, maintained records and wrote the paper. Author 2 performed the pathological studies and discussed the implications of the diagnosis and treatment.

References

[1] R.E. Ferner, D.H. Gutmann, International consensus statement on malignant peripheral nerve sheath tumors in neurofibromatosis, Cancer Res. 62 (2002) 1573–1577.
[2] M. Farid, E.G. Demicco, R. Garcia, L. Ahn, P.R. Merola, A. Cioffi, et al., Malignant peripheral nerve sheath tumors, Oncologist 19 (2014) 193–201.
[3] R.H. Hruban, M.H. Shiu, R.T. Senie, J.M. Woodruff, Malignant peripheral nerve sheath tumors of the buttock and lower extremity. A study of 43 cases, Cancer 66 (6) (1990) 1253–1265.
[4] R.A. Agha, M.R. Borrelli, R. Farwana, K. Koshy, A. Fowler, D.P. Orgill, For the SCARE Group, The SCARE 2018 statement: updating consensus surgical CAse REport (SCARE) guidelines, Int. J. Surg. (60) (2018) 132–136.
[5] Sharon W. Weiss, John R. Goldblum, Enzinger & Weiss's Soft tissue Tumours, fifth edition, Mosby Elsevier, Philadelphia, 2008.
[6] V.M. Riccardi, Neurofibromatosis: clinical heterogeneity, Curr. Probl. Cancer 7 (1982) 1–34.
[7] V. Ingordo, G. D'Andria, S. Mendicini, M. Grecucci, A. Baglivo, Segmental neurofibromatosis: is it uncommon or underdiagnosed? Arch. Dermatol. 131 (1995) 959–960.
[8] R.R. Roth, R. Martines, W.D. James, Segmental neurofibromatosis, Arch. Dermatol. 123 (1987) 917–920.
[9] S. Tinschert, I. Naumann, E. Stegmann, A. Buske, D. Kaufmann, G. Thiel, D.E. Jenne, Segmental neurofibromatosis is caused by somatic mutation of the neurofibromatosis type 1 (NF1) gene, Eur. J. Hum. Genet. 8 (2000) 455–459.
[10] M. Lammert, J.M. Friedman, L. Kluwe, V.F. Mautner, Prevalence of neurofibromatosis 1 in German children at elementary school enrolment, Arch. Dermatol. 141 (2005) 71–74.
[11] J. Schwarz, A.J. Belzberg, Malignant peripheral nerve sheath tumors in the setting of segmental neurofibromatosis. Case report, J. Neurosurg. 92 (2000) 342–346.
[12] K. Li, H.W. Chong, E.M. Sang, A superficial form of malignant peripheral nerve sheath tumour associated with segmental neurofibromatosis, Acta Derm. Venereol. 85 (2005) 540–541.
[13] H. Hagizawa, S. Nagata, T. Wakamatsu, et al., Malignant peripheral nerve-sheath tumors in an adolescent patient with mosaic localized NF1: a case report, Mol. Clin. Oncol. 12 (February (2)) (2020) 155–159.
[14] R. Vang, D.A. Biddle, W.R. Harrison, K. Heck, L.D. Cooley, Malignant peripheral nerve sheath tumor with a t(X;18), Arch. Pathol. Lab. Med. 124 (June (6)) (2000) 864–867.
[15] D. Bradford, A. Kim, Current treatment options for malignant peripheral nerve sheath tumors, Curr. Treat. Options Oncol. 16 (2015) 328.
[16] S.R. Grobmyer, J.D. Reith, A. Shahlaee, C.H. Bush, S.N. Hochwald, Malignant peripheral nerve sheath tumor: molecular pathogenesis and current management considerations, J. Surg. Oncol. 97 (2008) 340–349.
[17] M.A. Watson, A. Perry, T. Tihan, R.A. Prayson, A. Guha, J. Bridge, R. Ferner, D.H. Gutmann, Gene expression profiling reveals unique molecular subtype of Neurofibromatosis Type I-associated and sporadic malignant peripheral nerve sheath tumors, Brain Pathol. 14 (3) (2004) 297–303.