



A Case Report of Malignant Peripheral Nerve Sheath Tumour of the Left Thigh and Popliteal Fossa With Lungs, Spleen, and Brain Dissemination Related to Neurofibromatosis Type 1

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Abstract

A malignant peripheral nerve sheath tumour (MPNST) is a highly aggressive sarcoma. This disease develops in a number of people with neurofibromatosis type 1 (NF1), which is a common genetic disease. The paper presents a patient with typical manifestations of a malignant tumour of the peripheral nerve sheath, in the form of a large tumour of primary localisation in the distal part of the left thigh and left popliteal fossa and with significant dissemination into the lung parenchyma, which was accompanied by respiratory risk. The first operation of the tumour was done four years earlier, after which the patient did not come for regular check-ups. Nine cycles of chemotherapy were performed by Doxorubicin / Ifosfamide / Mesna protocol with clinical improvement and stabilisation, but without a significant impact on the dynamics of the disease and the overall survival was 14 months. It is of utmost importance to early recognise clinical presentation of the malignant form of this tumour and active supervision of a patient with a benign form by experts. In this way, it is possible to apply the optimal treatment modality in a timely manner.

Key words: Malignant peripheral nerve sheath tumour; Lung metastases; Neurofibromatosis type 1; Sarcoma.

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Introduction

A malignant peripheral nerve sheath tumour (MPNST) is a highly aggressive sarcoma. These tumours arise *de novo* or by the transformation of plexiform neurofibromas which are one of the manifestations in patients with an uncommon

variant of neurofibromatosis type 1 (NF1). NF1 is an autosomal dominant inherited disease that is caused by a mutation in the NF1 gene. The clinical presentation of NF1 is diverse: white coffee-coloured skin spots (*Café au lait*), pigmented nod-

ules in the iris, pseudoarthrosis, scoliosis, various cosmetic problems. NF1 affects an estimated 1 per 3,500 people, making it a common genetic disorder.^{1,2}

People with this mutation have an increased risk of developing benign but also malignant tumours, such as optic gliomas (15-20 %), pheochromocytoma (0.1-5.7 %), gastrointestinal stromal tumours (GIST) (4-25 %), rhabdomyosarcoma (1.4-6 %), MPNST (8-13 %), a seven times higher risk of developing leukaemia and a five-times higher risk of developing breast tumours.³ Almost one quarter (20-25 %) of patients with NF1 develop plexiform neurofibroma (PNF), most often at an early age, which has a high tendency of malignant alteration into MPNST.⁴

Poor prognostic factors are deeper tumour localisation, locally advanced disease and R2 resection, which are more common in patients with NF1-associated MPNST as opposed to the sporadic onset of the disease.¹² Treatment of the local disease is primarily surgical. Recurrence of the disease, after surgical treatment, can be expected in one-third to one-half of patients. The most common sites of dissemination are the lungs, followed by the bones and visceral organs of the abdomen, primarily the liver and peritoneum, central nervous system and the least common lymph nodes. Chemotherapy and radiotherapy are used in advanced and systemic diseases.^{5,6}

Case presentation

In May 2019, a 35-years old male was examined at the Oncology Clinic of the University Clinical Centre of Republic of Srpska, due to prior radiologically discovered multiple soft tissue lesions of the lung parenchyma bilaterally. At the time, the patient was respiratory insufficient, ECOG PS (Eastern Cooperative Oncology Group, ECOG, Performance Status, PS) was 3. The main difficulties were persistent productive cough, shortness of breath and weight loss with preserved appetite. Anamnestic data showed that he underwent surgery in 2015, during which the tumour was removed from the distal part of the left thigh and left popliteal fossa. A pathohistological finding of resected tissue confirmed that it was neurofibromatosis (non-malignant). Additional anamnestic data were acquired from the patient, which described a more significant number of relatives in the close family with the same skin nodules.



Figure 1: White coffee stains (*Café au lait*)

Clinical examination revealed several white coffee-coloured spots on the anterior abdominal wall (Figure 1) and a large number (> 10) of soft tissue subcutaneous nodular lesions of various sizes (neurofibromas). In the area of the previous operation, there was now a large tumour whose diameter exceeded the scope of the ultrasound field of the probe. It was decided to perform computed tomography (CT) guided percutaneous needle biopsy of available lung lesion.

Furthermore, the revision of the pathohistological findings of the material obtained by the operative procedure from 2015 was requested. The pathologist's report confirmed that the tumour tissue obtained by needle biopsy from the lungs and the revision report of the previous pathohistological finding were the same type of tumour which correspond to MPNST (Figures 2 and 3).

Histological characteristics in the primary tumour and metastasis in the haematoxylin and eosin (HE)-stained preparations were identical, while immunohistochemistry was different. In primary tumour, focal positivity of S100 and α -smooth muscle actin (SMA) was noted, while metastasis tissue was S100 negative and SMA positive. The difference in immunophenotype may be since staining in the primary tumour was done on a large section of the tumour, while metastasis sample was much smaller obtained by needle biopsy in which part of the tumour expressing S100 was not involved because expression in the primary tumour was focal (Figure 2).

The patient underwent additional diagnostics. Chest computerised tomography (CT) scan (Figure 4) showed numerous metastases (over 100) in the lungs, where the largest was measured 7.3 cm on the long axis. Magnetic resonance imaging (MRI) of the left thigh showed a large tumour mass (craniocaudal diameter 13.5 cm) in the dis-

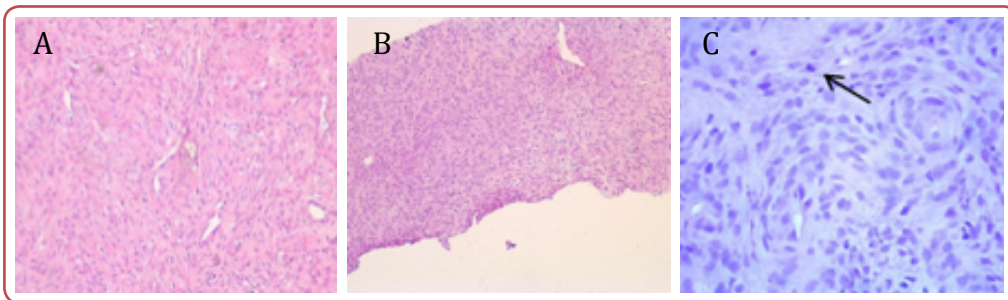


Figure 2: A) Primary tumour (HE 10x); B) lung metastasis (HE 10x); C) primary tumour (HE 40x) (arrow indicates mitosis)

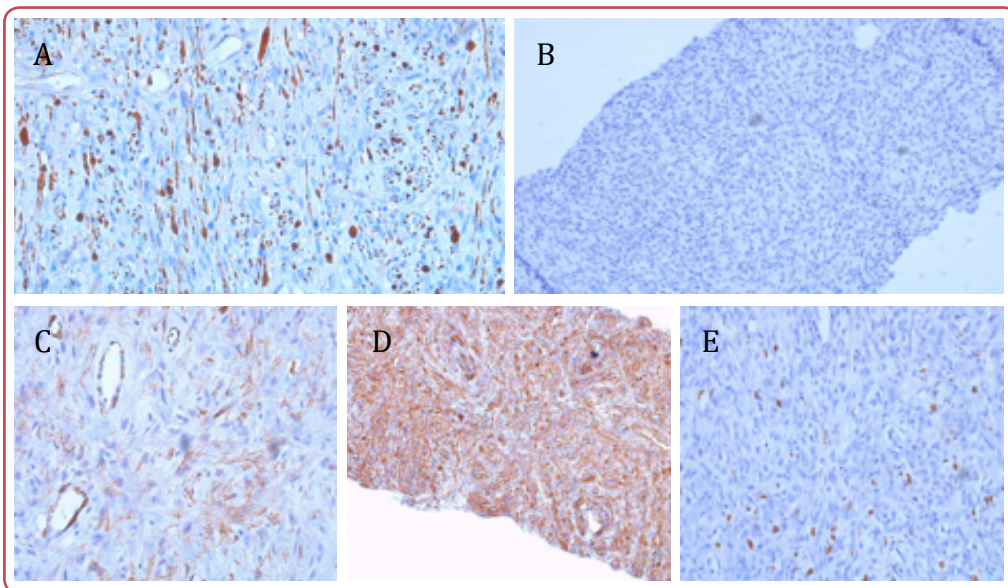


Figure 3: A) Primary tumour (S100 20x); B) lung metastasis (S100 10x); C) primary tumour (SMA 10x); D) lung metastasis (SMA 20x); E) primary tumour (Ki67 20x)

tal posterior thigh region and part of the popliteal fossa. Positron emission tomography-computed tomography (PET-CT) with 18F-FDG confirmed the existence of an expansive metabolically active tumour mass in that region, multiple metabolically active lesions in the lungs and spots of moderately increased metabolic activity in the posterior aspects of the right and left thigh and lower legs. It was decided to start treatment with chemotherapy according to the Doxorubicin / Ifosfamide / Mesna protocol. After three cycles of chemotherapy, the patient had minimal respiratory dis-

tress, ECOG PS 1. Control chest CT scan (Figure 5) showed a moderate decrease in the size of the lung metastases compared to the previous examination.

Treatment was continued according to the same chemotherapy protocol. A total of six cycles were applied by October 2019, with good tolerance, no cycle delay and with the support of Granulocyte Colony-Stimulating Factor (G-CSF). The achieved results were a partial response (PR) of the lungs metastases, followed by clinical improvement of

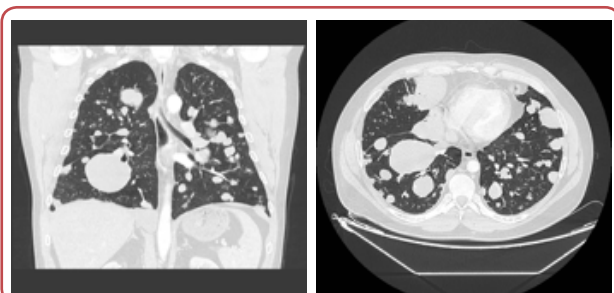


Figure 4: Chest computerised tomography (CT) scan prior to systemic therapy

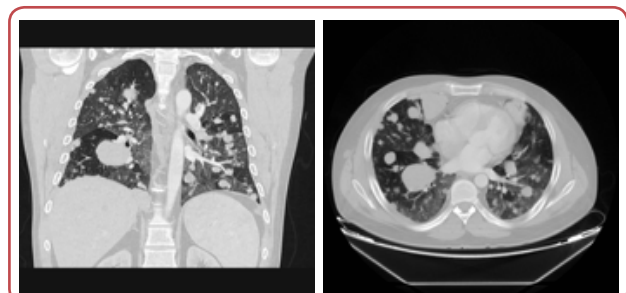


Figure 5: Chest computerised tomography (CT) scan after six cycles of chemotherapy

the general condition, while there was a local progression of the tumour mass in the distal part of the left thigh and popliteal fossa. The patient was referred for palliative surgery. As a result of the operation, paresis of the left foot was left behind. The patient was admitted to the oncologist again in February 2020 for a regular check-up. Chest and abdominal CT scans showed the progression of the lung metastases and multiple nodules in the spleen, which were highly suspicious for metastases. At that time, the progression-free survival (PFS) period for the patient was about eight months.

A tumour board decided to continue treatment with previously administered chemotherapy (Doxorubicin / Ifosfamide / Mesna), up to a cumulative anthracycline dose. Three more cycles (nine in total) were applied with good tolerability. After that, the patient was monitored regularly. In June 2020, the patient's general condition rapidly declined, accompanied by the onset of neurological symptoms. A head CT scan showed the presence of multiple metastases in the endocranium. Palliative radiotherapy was performed and supportive care was continued. The patient passed away in August 2020. Overall Survival (OS) was approximately 14 months.

Discussion

About 10 % of all soft tissue sarcomas belong to MPNST, whereby 50 % occur in people diagnosed with neurofibromatosis type 1. The disease is more often in male population. The most common localisations are the extremities and the trunk.⁷

This type of sarcoma most often metastasises to the lung, which was the case with the presented patient. Other possible localisations are bones, adrenal glands, liver, diaphragm, brain, mediastinum, ovary, retroperitoneum, and kidneys, which are other authors' conclusions.⁸

The two-year survival of patients with NF1, who develop MPNST, is 21 %, while the five-year survival is 18 %. Tumour size, localisation, sex, as well as choice of treatment have the most significant impact on OS. A poor treatment outcome is associated with the tumour size (> 10 cm) and the presence of NF1.⁹

In metastatic and inoperable diseases, research data has shown shorter OS survival in patients

associated with NF1. However, precise reasons were not yet concluded, even though leads are pointing out that chemotherapy sensitivity is lower in this population of patients. The OS for this patient was almost 14 months as previous statistic shows.¹²

Surgical treatment is the cornerstone in the treatment of localised disease with the tendency to achieve negative resection margins.¹² Chemotherapy and radiotherapy have not shown a significant effect on survival.⁸ A Dutch national study, published in the *European Journal of Cancer* last year, showed that primary surgical treatment was performed in 88 % of patients with localised MPNST and in whom R0 resection was achieved in 66.3 % of all patients. Additional radiotherapy was performed in 44.2 % of patients. Postoperative radiotherapy was mainly performed (in 42.5 %), but preoperative radiotherapy was preferred at the end of the study. Chemotherapy was mostly given to patients with retroperitoneal localisation of the primary tumour. In inoperable tumours, treatment options were radiotherapy and chemotherapy, but radiotherapy was generally preferred.¹⁰

Treatment options for advanced MPNS as well as metastatic disease are very limited and results are modest. The recommendations are mostly the same as for other forms of soft tissue sarcoma. An essential treatment recommendation is chemotherapy Doxorubicin as monotherapy or the Doxorubicin/Ifosfamide combination, with better results being achieved with combination therapy, primarily in PFS (EORTIC study 62012).¹¹ The other often used cytostatics are vincristine, cyclophosphamide, dactinomycin and etoposide. Preference should always be given to inclusion in clinical studies where experimental drugs are given if this is possible. In the search for new drugs, many studies were performed, mainly phase I and II, where the effects of new targeted therapy were examined, such as Erlotinib, Sorafenib, Imatinib, combinations Everolimus/Bevacizumab (SARC016), Sirolimus/Gantespib (SARC023). Even though studies were negative, they are becoming solid ground for future studies and new generation of drug modalities that will have possible promising results in the time ahead.¹³⁻¹⁵

It is worth mentioning the new drug Selumetinib (MEK1/2 inhibitor). The drug was approved in April 2020 by the FDA for paediatric patients two years of age and older with inoperable plexiform neurofibromas related to NF1. The drug was approved after a phase II clinical trial. The results of

the study showed a high percentage of partial response of about 70 % (reduction in tumour size) and maintenance minimally one year long or even longer, with acceptable tolerance and safety.¹⁶ Selumetinib holds out hope to this group of patients in reducing the risk of developing MPNST, although studies have yet to be conducted to confirm this, because prevention is always the best therapy. Furthermore, there are also promising expectations from study NCT02691026, which examines the use of pembrolizumab in patients with inoperable MPNST. The study should be finalised in 2025.

The therapy applied to the patient presented in the paper is in accordance with the world's leading recommendations. The decision to continue the same protocol after disease progression was made because he initially responded well to it, but also because of the limited treatment options available for these types of tumours in country.

Conclusion

Early recognition of the clinical signs of this genetic disease is essential. Moreover, active expert supervision is very important, primarily to identify all suspicious lesions promptly and apply optimal treatment modalities, in the first place surgical. It is significant not only for the patients but also for their relatives, who should be included in the supervision due to the hereditary nature of this disease. A multidisciplinary approach is needed to ensure an optimal treatment in patients with rare malignancies.

One of the steps in improving the treatment and care of patients with malignant tumours of the peripheral nerve sheath is undoubtedly the establishment of the Centre for Rare Tumours in the Republic of Srpska, where in one place, patients with this but also other rare malignancies would be supervised by experts, applied appropriate diagnostic procedures and implemented optimal treatment modalities.

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None.

Conflict of interest

None.

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