Case Report

Late Relapse of Malignant Peripheral Nerve Sheath Tumor After 18 Years. Case Report with Differential Diagnosis.

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ABSTRACT

Malignant mesenchymal tumors represent a heterogeneous group of neoplasms. Diagnostics is based on a comprehensive clinical and pathological assessment that takes into account the results of imaging methods and molecular genetics. The exact diagnosis of these neoplasms is important for their subsequent therapeutic management. Authors describe a case of a 47-year-old female patient with poorly differentiated sarcoma in the left neck region which they, based on histomorphological features, a wide immunohistochemistry panel, and detailed history, diagnosed as a late recurrence of MPNST 18 years after the primary diagnosis. Tumors of the Ewing sarcoma/PNET, synovial sarcoma, which have similar histomorphological features, were excluded in the process of differential diagnostics. MPNST is characterized as a malignant tumor with unpredictable biological behavior, and as the case described above indicates, it may even return many years after the primary diagnosis.

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Introduction

The diagnosis of soft-tissue sarcomas, although much rarer than carcinomas, is much more difficult as it requires a careful and comprehensive evaluation of clinical, microscopic, histomorphological, and immunohistochemistry features supplemented by an analysis of molecular genetic alterations. Moreover, many cell and growth characteristics overlap between individual subjects, which makes their exact diagnosis more difficult. Advancements in cancer treatment result in the relative healing of some malignancies, which often manifest as a late recurrence many years later. The authors describe an interesting case of a late recurrence of a malignant peripheral nerve sheath tumor (MPNST), whose histomorphological and immunohistochemistry features were the same as in **Ewing sarcoma/primitive neuroectodermal tumor (PNET), synovial sarcoma (SS), in differential diagnostics**.

Case Report(S)

We have examined a tumor in the left supraclavicular region of the neck in a 47-year-old female patient. As far as the medical history is concerned, in 1997 the patient underwent surgery of the left axilla due to a plexus brachialis tumor with a diagnosis of "neurofibrosarcoma" (malignant peripheral nerve sheath tumor, MPNST). Following surgery, the patient had 6 chemotherapy cycles and was given local radiotherapy. The patient was observed until 2004, when she stopped coming for follow-up evaluations. She returned in 2015 with severe lymphadenopathy and infiltration in the left supraclavicular region. Clinically speaking, there was a tumor resistance of 30x25x30 cm in size, from which several small fragments were taken for biopsy. In terms of histomorphology, it was a heterologous, poorly differentiated or even anaplastic tumor proliferation mainly of a histoid type and to a lesser degree, organoid in origin. The growth of cell population was solid and focally storiform, with the presence of cells of a round, oval, and sporadically even fusiform shape, while cells in other regions were literally small and round and densely pressed together. Focally, they were epithelioid elements with eosinophilic cytoplasm, as well as cells with lighter cytoplasm or even intracytoplasmic vacuoles that resembled lipoblasts. The tumor cell nuclei prevailed over the cytoplasm with visible nucleoli, irregular fragmented chromatin masses, numerous mitoses and abnormal mitoses (up to 40 mf/10 HPF), anisokaryosis, and with the presence of anaplastic cells. In the interstitial space, there were obvious plexiform vascular formations. In terms of immunohistochemistry, the cells were diffuse positive for vimentin, proto-oncogene B cell lymphoma 2 (Bcl-2).[4] The expression of acidic protein (S100 protein), cell to cell adhesion glycoprotein (CD56), synaptophysin, and epithelial membrane antigen (EMA) was a bit weaker and focal. The receptor for kit protein (CD117) was focally positive. The expression of cell proliferation marker Ki67 was 35%.

Table 1: Antibody information

Antibody	Source	Pretreatment	Dilution	Incubation (min.)
CK5/6	Dako	Tris-EDTA,pH9	1:70	30
CK7	Novocastra	Tris-EDTA,pH9	1:100	30
CK20	Novocastra	Tris-EDTA,pH9	1:50	30
EMA	Dako	Tris-EDTA,pH9	1:75	30
p63	Dako	Tris-EDTA,pH9	1:70	30
Vimentin	Dako	Citrat, pH6	1:150	30
α-Aktin (SMA)	Dako	Tris-EDTA,pH9	1:420	30
Desmin	Novocastra	Tris-EDTA,pH9	1:80	30
CD117	Dako	Tris-EDTA,pH9	1:370	30
S100 protein	Dako	Citrat, pH6	1:420	30
LCA (CD45)	Dako	Tris-EDTA,pH9	1:80	30
CD34 Class II	Dako	Tris-EDTA,pH9	1:100	30
CD56	Dako	Tris-EDTA,pH9	RTU	30
Chromogranin	Dako	Tris-EDTA,pH9	1:170	30
Synaptophysin	Novocastra	Tris-EDTA,pH9	1:140	30
CD99	Dako	Tris-EDTA,pH9	RTU	30
Bcl-2	Dako	Tris-EDTA,pH9	1:100	30
Ki67	Dako	Citrat, pH6	1:120	30

Table 2: The results and differential diagnosis within immunohistochemistry.

	MPNST	ES/PNET	SS
CK5/6	-		
CK7	-	-	+
CK20	-		
EMA	+/-	+/-	+
p63	-		
Vimentin	+	+	+
Aktin	-		
Desmin	-		
CD117	+/-		
S100	focal +	+	+
LCA	-		
CD34	-	-	-
CD56	+/-	-	+
Chromogranin	-	-	-
Synaptophyzin	+/-	+/-	-
CD99	+ cytopl.	+ membr.	+ cytopl. and membr.
BCL-2	+	+	+
Ki 67	35%		

MPNST: Malignant peripheral nerve sheath tumor, ES/PNET: Ewing sarcoma/Primitive neuroectodermal tumor, SS - Synovial sarcoma, + positivity, - negativity, +/- focal positive to negative, + cytopl.: cytoplasmatic positivity, + membr.: membranous positivity;

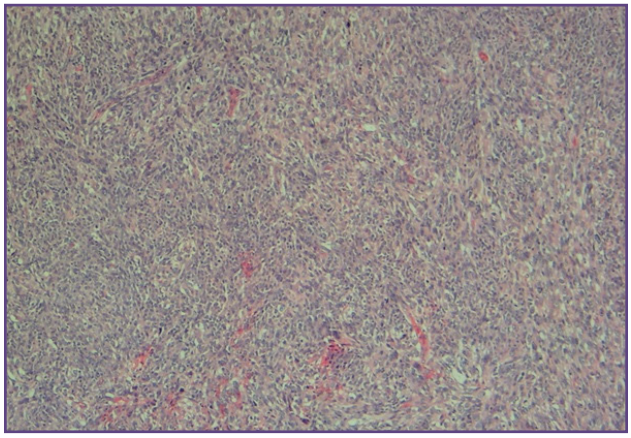

Fig. 1: The proliferation of poorly differentiated round, oval, spindle-shaped , epithelioid cells, H&E, 10x.

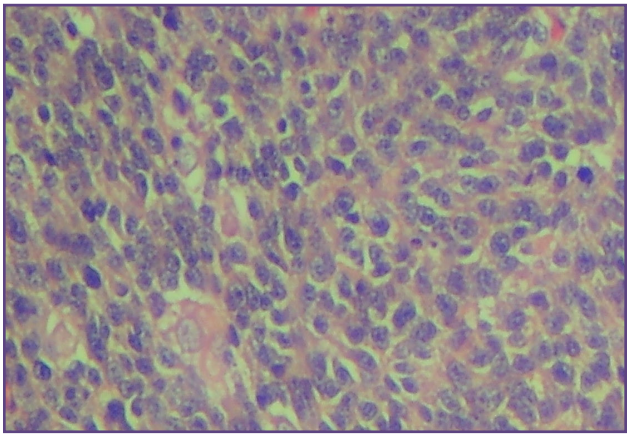

Fig. 2: The area of the proliferated round, oval cells with mitosis, H&E, 20x.

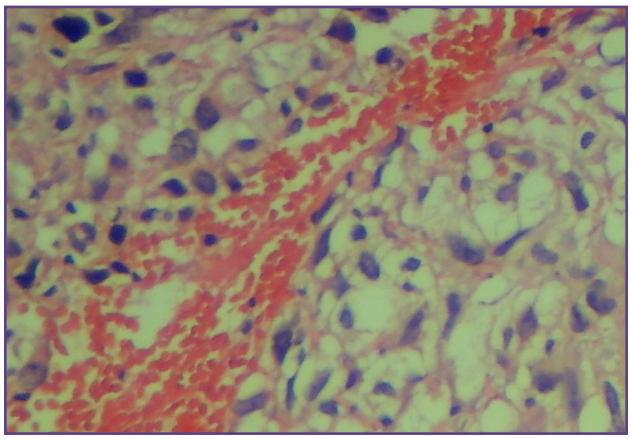

Fig. 3: The area of the proliferated cells resembling lipoblasts, H&E, 20x.

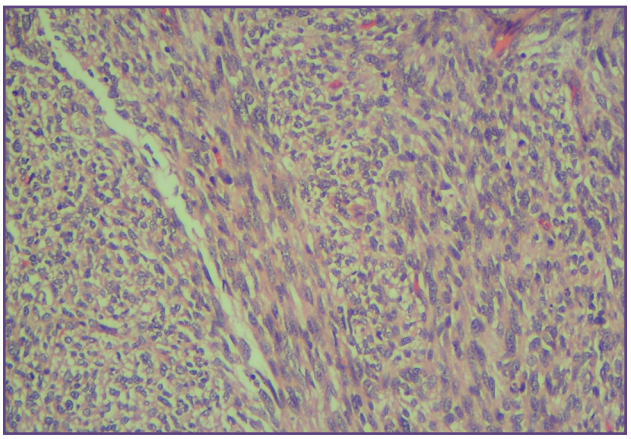

Fig. 4: Proliferated cells - storiform architecture development, H&E, 10x.

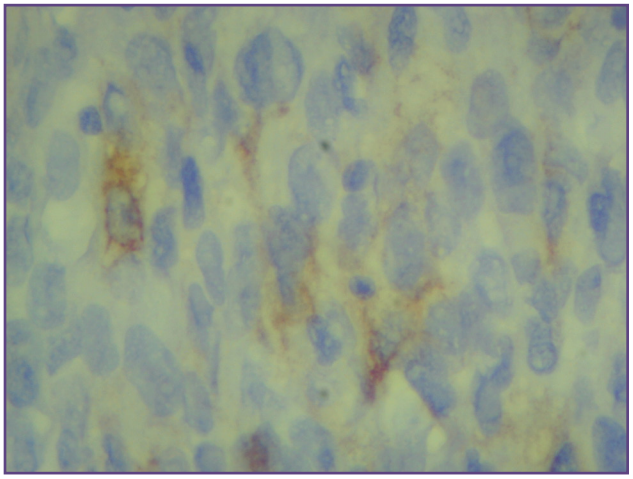

Fig. 5: EMA, focal positivity, 20x.

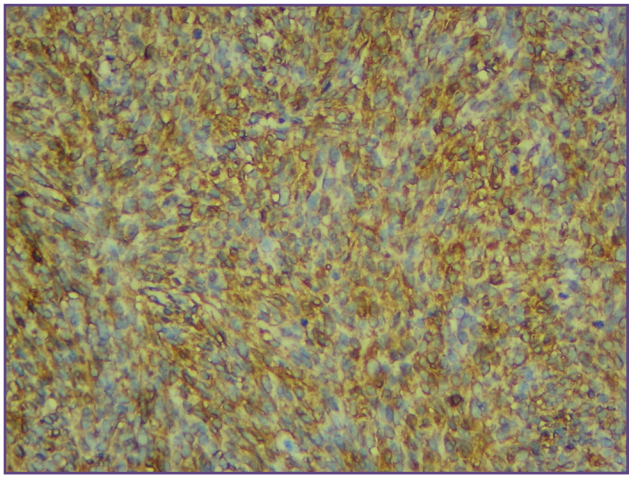

Fig. 6: Vimentin, diffuse positivity, 10x.

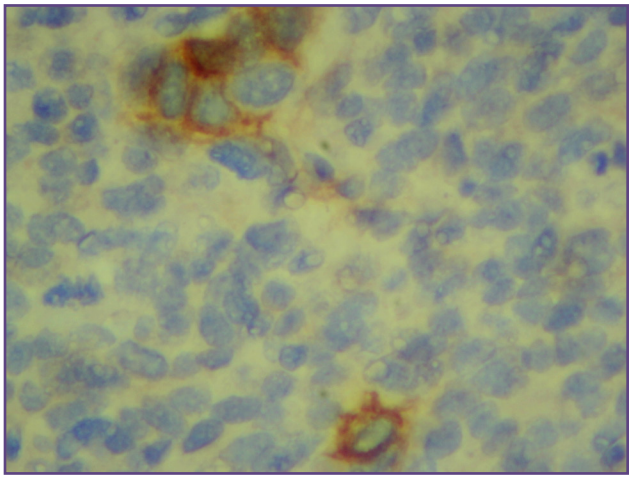

Fig. 7: CD117, focal positivity, 20x.

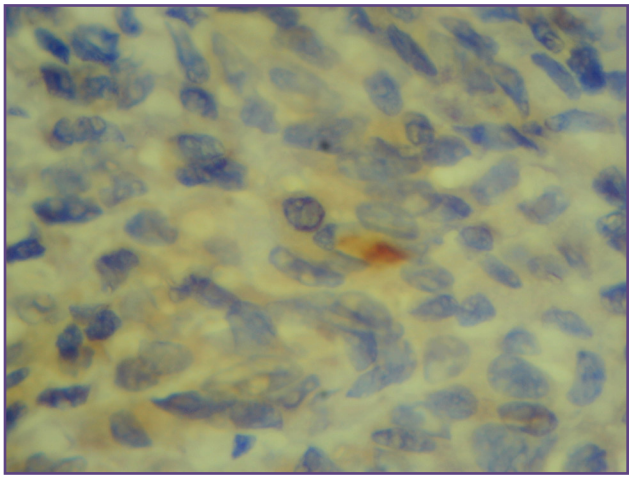

Fig. 8: S100 protein, weak focal positivity, 20x.

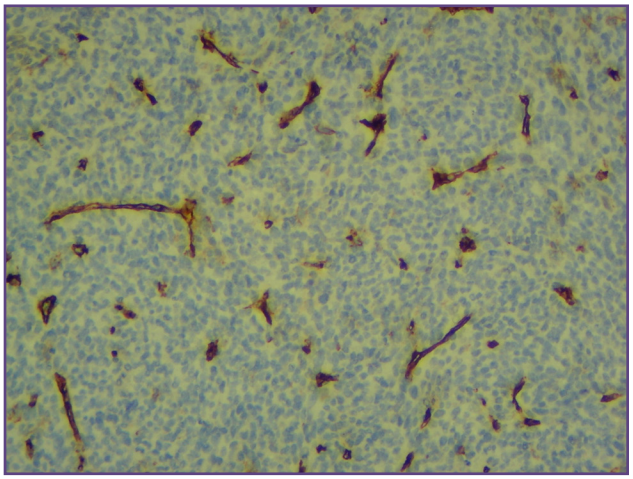

Fig. 9: CD34, negative reaction in the cells of the tumor, positive reaction in the blood vessels , 10x.

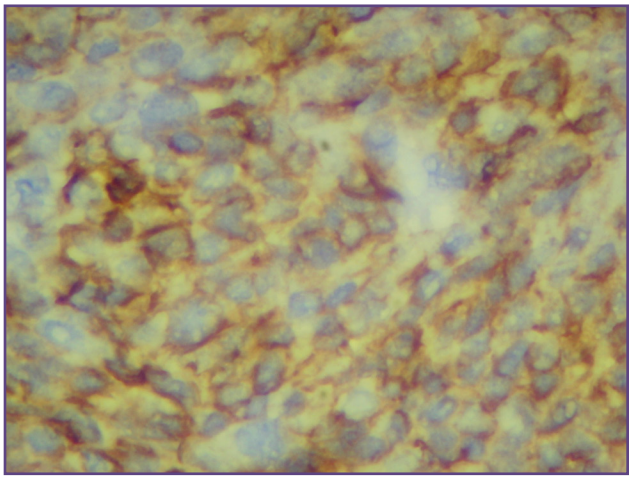

Fig. 10: CD56, positive reaction, 10x.

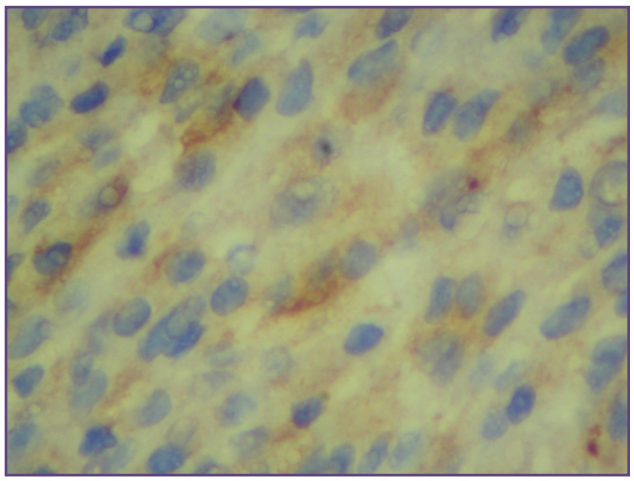

Fig. 11. Synaptophysin, positive reaction, 10x.

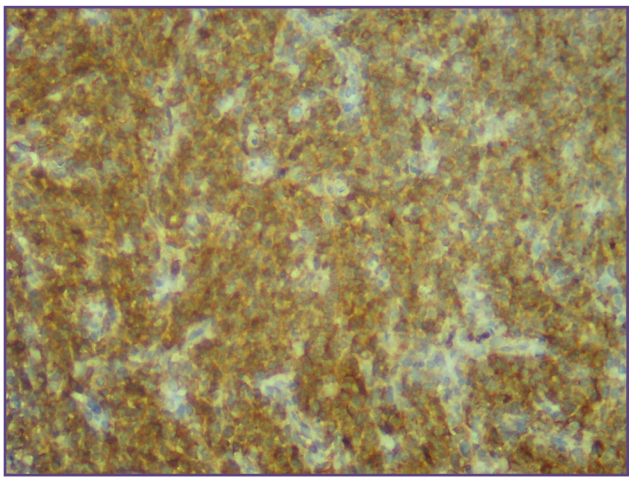

Fig. 12: Bcl-2, diffuse positivity, 10x.

Tumour samples were fixed in 10 % buffered formalin and embedded in paraffin. Histological sections were studied after staining with hematoxylin and eosin (H&E) and 18 antibodies by methods of standard immunohistochemical techniques. Information about antibody with pre-treatment and incubation are shown in Table 1, were used for visualization systems DAKO EnVision : K5007 and Bond Polymer Refine DS9800 Leica Biosystems.

Discussion

Malignant peripheral nerve sheath tumors (MPNST, neurofibrosarcoma) most frequently occur between 35 and 45 years of age and between 60 and 80 years of age. MPNST affects women more than men and is most common in the proximal parts of the extremities, in the paraspinal region of the trunk and the neck.[3] The five-year survival rate ranges from 15 to 40%; patients with neurofibromatosis type 1 (NF1) have a worse prognosis. Local relapses are frequent, occurring in more than half of cases. MPNST metastasizes to the lungs, bones, pleura, liver, and brain meninges. MPNST is difficult to diagnose; its various histomorphological forms may mimic synovial sarcoma (SS) or Ewing sarcoma (ES/PNET) and in 15% of cases may contain epithelioid or other heterologous components such as a rabdomyoblast, smooth muscle, cartilage, bone, glandular structures, liposarcoma, and neuroendocrine components.[1]

Tumors of the Ewing sarcoma/primitive **neuroectodermal** tumor (ES/PNET) group occur most frequently in children and adolescents (so called pediatric tumors).[2] They develop mostly in bone diaphysis and are most frequently located in the paravertebral area, in the thoracic basket. In 15% of cases, they develop extra-ostially (e.g., in the retroperitoneal region) and epidurally, where they can mimic MPNST, since MPNST may also contain PNET-like foci. Bone lesions are destructive, with a 5-year survival rate of 70% in patients with metastases and relapses; in treatment-resistant forms, the survival rate drops to 20-30%.

Synovial sarcoma (SS) affects mostly men around the age of 30 and is relatively frequent in children as well, but rarely occurs under 5 years of age and at an older age. It grows in deep structures, e.g., in intramuscular areas, most often in the proximal parts of extremities, in the groin area, abdominal wall, neck region, hypopharynx, in the temporal, orofacial region of the head, in the retroperitoneum, mediastinum, femoral veins, heart, oesophagus, duodenum, and in the kidneys. If not completely removed surgically, it recurs with typical distant metastases, most frequently to the lungs, liver, and brain. Metastases to the lymph nodes are rare. The five-year survival rate of patients with well-differentiated SS is 60-70%; five-year survival for patients with poorly differentiated SS is 20-30%.

The best marker in the immunohistochemistry diagnosis of MPNST is the S100 protein, although it is known that it is positive in only 50% of cases.[4] The S100 protein is also positive in 40% of SS and ES/PNET cases. Another usable marker is the marker of hematopoietic progenitor cells and endothelial cells (CD34), which is only focally positive in MPNST, and anti-Nestin (NES)[5], with a sensitivity of 78% and specificity of 96%. In the diagnosis of MPNST, it is best to combine NES and S100 protein, since this combination is specific and nearly 100% positive and can safely differentiate MPNST from SS and ES/PNET. It has been established that there are various rare and poorly differentiated histomorphological forms in the MPNST group. These forms are associated with neurofibromatosis and are S100 protein and NES negative, but focally positive for CD117.[6] The primary marker for the diagnosis of ES/PNET is the E2 surface glycoprotein of T cells (CD99),

although nowadays we know that it can be positive in other tumors as well, such as in synovial sarcoma. ES/PNET is characterized by significant membrane positivity for CD99. Today, the Friend leukemia integration-1 protein (Fli-1), with significant strong nuclear positivity and 70% sensitivity, is successfully used. The combination of CD99/Fli-1 is recommended for the diagnosis of ES/PNET versus MPNST and SS. Important markers in the diagnosis of synovial sarcoma (SS) include EMA, keratin cocktail (AE1/AE3), type II keratin of simple nonkeratinizing epithelia (CK7), Bcl-2, CD56, and CD99. In terms of specificity and sensitivity, the combination of CK7 and EMA with a sensitivity of 50% and an almost 100% specificity is most suitable. In the synovial sarcoma, Bcl-2 is 85% positive, CD56 70% positive, and CD99 up to 70% positive, with 30% of that strongly in the membranes. This may be useful in differential diagnostics with regard to MPNST, in which this form of CD99 positivity is not demonstrated.[5] In biphasic SS, there were cases with a strongly positive reaction to EMA and AE1/AE3 and also cases of monophasic SS with EMA positivity, AE1/AE3 negativity, and positivity for S100 protein and CD99, thus mimicking MPNST and ES/PNET. SS, which is negative for AE1/AE3, is significantly positive for CD56 (in 30%). The summary of the results of all MPNST immunohistochemistry exams with differential diagnostics for ES/PNET and SS is provided in Table 2.

Conclusion

During the assessment of clinical results, medical history, and morphological and immunohistochemistry results, the tumor was diagnosed as a poorly differentiated malignant peripheral nerve sheath tumor with a focal epithelioid and neuroendocrine component, recurring after 18 years from the time when it was primarily diagnosed.

Funding

None

Competing Interests

The authors declare that they have no conflict of interests.

Reference

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