Malignant peripheral nerve sheath tumour (MPNST) belongs to the group of rare soft tissue sarcomas. High histological grade is a common feature, explaining its poor prognosis irrespective of the aggressiveness of local treatment. Standard therapy of inoperable local relapses or distant metastases has not been established, as phase II or III clinical trials are lacking and treatment strategies are based on anecdotal reports on the effectiveness of standard chemotherapy or different novel agents. Here we present a long-term survivor of the sporadic type of MPNST – a giant thoracic tumour with an uncommon presentation of haemothorax. Despite radical excision of the tumour, followed by high-dose radiotherapy to the tumour bed, the patient was diagnosed with multiple metastases located in the postpneumonectomy thoracic cavity and the right lung. First-line doxorubicin followed by somatostatin analogue resulted in a six-month PFS, while second-line ifosfamide-based chemotherapy resulted in good and long lasting symptom palliation.

Key words: malignant peripheral nerve sheath tumour, haemothorax, treatment.

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Case report

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Introduction

Malignant peripheral nerve sheath tumour (MPNST) constitutes about 5% of all soft tissue sarcomas [1]. Approximately 25–50% of cases accompany neurofibromatosis type 1 (NF1) – a dominant autosomal defect in which a NF1 gene product – neurofibromin – lacking RAS-GAP function, does not act as a tumour suppressor gene [2, 3]. Depending on the type of NF1 mutation, 2–29% of carriers develop MPNST in their lifetime. Sporadic MPNST cases are not linked to any specific mutations; however, numerous chromosomal aberrations including –22 (in 40% of tumours), +3, +14, –13, –17 and –18 have been described [3]. Typical molecular changes include retinoblastoma tumour suppression pathway, aberrant expression of CHFR and aberrant expression of immune system-related genes [4–6]. The tumour originates from proliferating Schwann or perineural cells, most frequently surrounding sciatic, brachial and maxillofacial nerves [2]. The most common clinical presentation is a painful, invasively growing mass with accompanying neurological deficit [7, 8]. Spontaneous bleeding has been reported in NF1 mutation carriers as a consequence of vascular abnormalities – aneurysm rupture or arteriovenous fistula [9, 10].

The aim of this paper was to present a long-term survivor of the sporadic type of MPNST – a giant thoracic tumour with an uncommon presentation of haemothorax – and to discuss different therapeutic options.

Case report

In August 2004 a 28-year-old man was admitted to the hospital with symptoms of rapidly progressing dyspnoea, cough, weakness and chest pain. His medical history was unremarkable, except for a dull back pain lasting for several months. Physical exam revealed tachycardia, tachypnoea and left pleural effusion up to the level of the third intercostal space, confirmed by a chest X-ray. A CT-scan of the chest showed pleural effusion and a large (18 cm) tumour located in the posterior mediastinum. Transthoracic fine needle biopsy suggested sarcoma. A radical excision of the tumour, left lung, thymus, mediastinal lymph nodes and distal parts of the 4th and 5th left ribs was performed and a histopathological examination established a diagnosis of high-grade (G3) MPNST, with positive staining of S-100 and vimentin at immunohistochemistry. The patient received postoperative radiotherapy at a dose of 66 Gy in 33 fractions. Four months later he developed dyspnoea, hectic fever and fatigue and a PET CT scan revealed a recurrent tumour infiltrating the chest wall in the left pericardial region, and multiple metastases in the right lung. Six cycles of palliative chemotherapy consisting of dacarbazine and doxorubicin resulted in stabilization of the disease. Six months later, in September 2005, a CT scan showed further progression. Of
note, the patient had moderate cardiac insufficiency with
tachycardia and intermittent oedema of the scrotum mak-
ing him incapable of further doxorubicin-based treatment.
Additional immunohistochemical analysis performed at
that time showed negative EGFR [11], negative VEGFR and
equivocal CD117 expression. A tumour specimen was sent
for sequencing of c-Kit (exons 9, 11, 13, and 17), PDGFR-α
and PDGFR-β (exons 12, 14, and 18) coding genes [12, 13].
After obtaining the patients’ consent and a positive opinion
from a local Ethics Committee, a 3-month empirical treat-
ment with imatinib given orally at a daily dose of 400 mg
was administered. A CT scan performed 3 months later
showed a dramatic progression of the disease. Addition-
ally, mutations of c-Kit and PDGFR-α and PDGFR-β were not
confirmed in a subsequent biopsy specimen. Owing to the
deterioration of the patients’ general status, second-line
chemotherapy consisting of ifosfamide 3 g/m² IV with
deterioration of the patients’ general status, second-line
confirmed in a subsequent biopsy specimen. Owing to the
patient died.
continued due to disease progression, and in January 2009 the
disease. After 8 cycles, ifosfamide treatment was discon-
status (PS 80%), returned to work despite disseminated
radiological improvement. The patient, in a good general
ifosfamide unexpectedly resulted in symptomatic and
apy was also unsuccessful, whereas the re-administered
the patient received 2 cycles of ecteinascidin. This ther-
2 cycles and evident progression of right lung metastases,
er, due to progression in the right lung, retreatment with
in a good general
no response. Instead, palliative reirradiation decreased
bazine, cisplatin and ifosfamide was attempted, with
A third-line chemotherapy including doxorubicin, dacar-
bazine, cisplatin and ifosfamide was attempted, with
no response. Instead, palliative reirradiation decreased
dysphagia, chest pain and dyspnoea. Three months lat-
er, due to progression in the right lung, retreatment with
ifosfamide was started. Because of haemoptysis after
2 cycles and evident progression of right lung metastases,
the patient received 2 cycles of ecteinascidin. This ther-
apy was also unsuccessful, whereas the re-administered
ifosfamide unexpectedly resulted in symptomatic and
radiological improvement. The patient, in a good general
status (PS 80%), returned to work despite disseminated
disease. After 8 cycles, ifosfamide treatment was discon-
tinued due to disease progression, and in January 2009 the
patient died.

Discussion
Malignant peripheral nerve sheath tumour belongs to
the group of invasively growing soft tissue sarcomas with
poor prognosis, high metastatic potential and limited
radio- and chemo-sensitivity [15]. Incomplete resection,
large tumour size, location (axial vs. peripheral), lymph
node metastases, high-grade (G3), primary or recurrent
disease and NF1 mutations are predictive for early meta-
static spread [7, 16–18]. In the largest reported series of
patients, only negative surgical margins (R0) and no histo-
ry of irradiation remained significantly related to survival
in multivariate analysis, including tumour size, grade and
location, NF1 mutation, mitotic rate, necrosis and histolog-
ical subtype [7]. Adjuvant radiotherapy delivered in a total
dose of less than 60 Gy does not improve the outcome
significantly, whereas intraoperative brachytherapy seems
to increase survival [7]. The reported 5- and 10-year surviv-
al rates are, respectively, 34% and 22%, despite aggressive
local treatment. The risk of recurrence is high. Optimal
therapy of locally advanced or disseminated MPNST has
not been established. Palliative chemotherapy induces
a response in about one-third of patients and its impact
on survival is unknown. According to the results of the
largest analysed group of 175 MPNST patients treated in
12 different clinical trials, only PS and the use of doxorubi-
cin and/or ifosfamide are significant with regard to overall
and progression-free survival [19]. The median survival of
patients with NF-1-related or axial tumours does not ex-
ceed 12 months [1, 7].

Malignant peripheral nerve sheath tumour shows ex-
pression of at least one of the five somatostatin receptors –
sst4 (in 32% of cases) and sst2 (in 15% of cases) [14]. This
may suggest a beneficial role of somatostatin receptor
alogues in the diagnosis and treatment; however, their
usefulness has not been verified. Another possible area of
investigation includes PDGFRB or EGF, or cMet pathways
in both NF1-related and sporadic tumours, although data
on such treatment efficacy are inconclusive [1, 11].

To conclude, more effective therapies are needed in
MPNST, particularly in locally advanced and disseminated
disease. Despite relative chemoresistance, systemic treat-
ment provides a good palliation to some patients. Better

Fig. 1A. The CT scan of the patient showing giant recurrent tumor in
the left thoracic cavity, chest wall, and right hydrothorax

Fig. 1B. The CT scan of the patient showing multiple right lung me-
tastases
knowledge of the molecular features of these tumours may provide the basis for the newly targeted agents.

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References


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