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Malignant nerve sheath tumors of the head and neck: four case studies and review of the literature

K. Hujala[1], P. Martikainen[2], H. Minn[3], and R. Grénman[1]

Departments of [1] Otolaryngology and [3] Oncology and Radiotherapy, Turku University Central Hospital, SF-20520 Turku, Finland
[2] Department Pathology, University of Turku, SF-20520 Turku, Finland

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Summary. Malignant peripheral nerve sheath tumors (MPNST) are very uncommon neoplasms. While the incidence of these lesions is estimated to be 0.001% in a general population, they make up 5–15% of all soft tissue sarcomas in the head and neck region. We present four cases of MPNST in the head and neck. Since certain difficulties were encountered in diagnosis, the importance of clinical evaluation is emphasized. The prognosis for these tumor patients is poor in spite of improvements in diagnostic and therapeutic modalities.

Key words: Malignant peripheral nerve sheath tumor – Head and neck – Positron emission tomography

Introduction

In contrast to the benign neurogenic tumors, in most cases schwannomas, malignant peripheral nerve sheath tumors (MPNST) are very uncommon in the head and neck region [3, 6, 28]. These neoplasms constitute 5–15% of all soft tissue sarcomas, of which the fibrosarcoma is by far the most common [2, 5, 14, 24].

MPNST can arise either de novo or from pre-existing neurofibromas. It is not our preference to use the term "malignant schwannoma" because a benign schwannoma rarely undergoes malignant change [6, 11, 17]. In addition to schwann cells these tumors can also be composed of fibroblasts and perineural cells in varying combinations [3, 21].

The head and neck region accounts for 8–19% of all MPNST cases [3, 8, 9, 12, 16, 18]. In most instances MPNST originate from the trigeminal nerve and its branches. Other possible sites are the sympathetic chain and brachial and cervical plexuses, as well as the cutaneous nerves and other cranial nerves [1, 16, 19]. A reported association of MPNST with von Recklinghausen's disease varies between 26% and 70% [9, 12, 18, 24, 26]. The individuals with known von Recklinghausen's disease have a 20–30% risk of developing MPNST [7].

The most common clinical sign of MPNST is a rapidly growing mass. While tumors are usually painless, some lesions have been associated with considerable pain. Depending on location neoplasms can cause paresthesia, muscle atrophy or weakness. When arising from a preexisting neurofibroma sudden onset of pain or rapid beginning of growth is highly suggestive of malignancy. The following case reports review our experiences in dealing with MPNST.

Correspondence to: R. Grénman

Case reports

Case 1

A 62-year-old female presented with a rapidly growing swelling in the left side of her neck. When increasing pain and weakness of the left forearm were experienced, medical care was sought.

On clinical examination a tumor was detected behind the sternocleidomastoid muscle in the lateral neck region. A fine needle aspiration was done and demonstrated possibly malignant mesenchymal cells. Positron emission tomography showed low uptake. An open biopsy was then performed giving a diagnosis of benign neurofibroma. Because of a strong clinical suspicion of malignancy a radical neck dissection was done. However, radicality of the surgery was unsatisfactory because of spreading of tumor towards the base of the skull along the cervical nerves. Histopathology of tissue specimen excised now showed poorly differentiated MPNST (Fig. 1a–c).

Postoperatively adjuvant chemotherapy with etoposide and ifosfamide was started but discontinued because of hematological side-effects. Thereafter external radiation therapy of 69/59 Gy was undertaken. At 1 year follow-up a lump was found deep in the neck. This was excised but histological examination proved to be only scar tissue. After 16 months follow-up the patients is free from disease.

Case 2

A 36-year-old female detected a growing mass in her left cheek associated with an increasing burning sensation. Ortopantomography examination revealed a destructive lesion in the alveolar wall be-

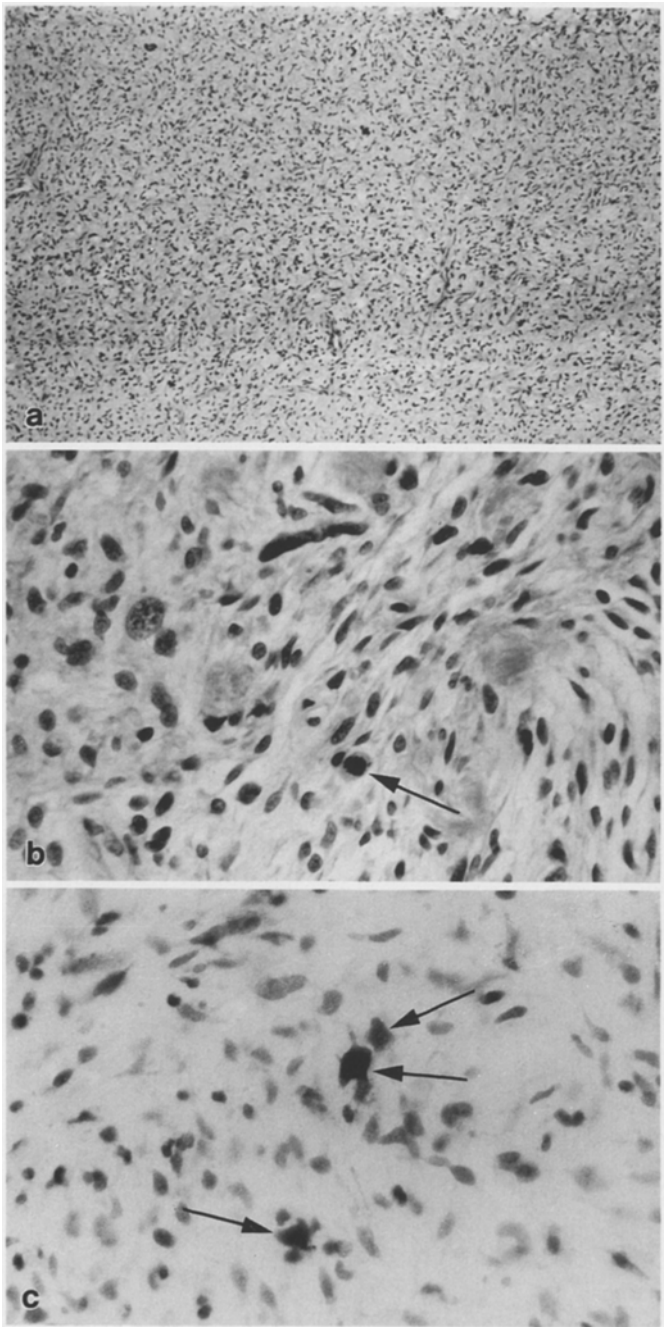

Fig. 1. a Histology of a malignant peripheral nerve sheath tumor (MPNST) in case 1. The tumor is cellular and composed of irregular spindle-shaped cells. Weigert van Gieson stain, × 75. **b** Histology of MPNST in case 1. Note pleomorphic nuclei and indistinct cytoplasmic borders. One mitotic figure is shown by the *arrow*. Weigert van Gieson stain, × 300. **c** S-100 immunoreactivity in case 1. The pleomorphic tumor cells show immunoreactive S-100 protein *(arrows)*. Toluidine blue counterstain of nuclei, × 470

tween the teeth 21–23. Open biopsy showed malignant tissue, which was believed to be either malignant melanoma or MPNST. Gamma imaging was abnormal.

Radical surgery was then undertaken and tumor was removed en bloc. Margins of resection were free from disease by frozen section examination. The extirpated alveolar process was replaced with free transplanted bone and periosteum from the tibia.

Local tumor relapse was detected at 2 months clinical follow-up. However, tumor growth was found to be so rapid that the patient's lesion was considered to be inoperable.

Radiation therapy to 66 Gy was then undertaken to the primary tumor area. The effect of this therapy was very short and disease continued to progress rapidly. The patient died 10 months after diagnosis. At this time, in addition to primary tumor, metastases were found in both lungs and in laryngeal soft tissues.

Case 3

A 41-year-old female farmer suffered from constant occipital headache, which was first treated as "tension" neck disease. A swelling appeared in the left side of her neck and an open biopsy revealed a proliferative myositis.

Because of a strong clinical suspicion of malignancy radical surgery was performed. The tumor was highly fixed to surrounding tissues and extended to the left pleura, which was opened intraoperatively. The opening was then closed and a pleural catheter placed. The tissue specimen showed poorly differentiated MPNST. Microscopically the completeness of the operation was found to be insufficient and postoperatively external radiation therapy to 65/58 Gy was given. Thirteen months after surgery local tumor recurrences were detected in the primary area and also in the former pleural catheter site.

Tumor was now judged to be inoperative and palliative chemotherapy was undertaken first with etoposide and ifosfamide and then cyclophosphamide, vincristine, adriamycin and dacarbazine. However, there has been no response to date and the patient is now terminal, 4 years after initial treatment.

Case 4

A 42-year-old male came into the ENT clinic at University Central Hospital because of prolonged symptoms of maxillary sinusitis. Clinical examination demonstrated a depression in the right infraorbital ridge. X-ray examinations were abnormal and sinus exploration was performed. A small tumor was found and was first diagnosed as a malignant neurofibroma; however, further tissue examination was considered controversial and definitive diagnosis of grade II MPNST was confirmed only after repeated open biopsies 6 months later.

Radical exentration of the orbit was done at this time, because disease had now spread into the orbit. Reconstruction was performed with free microsvascular transplantation of the iliac crest and latissimus dorsi pedicled flap. After 10 months follow-up, the patient has been free of disease.

Discussion

Imaging

In all cases conventional radiography was used and revealed bone destruction and inflammatory signs in cases 2 and 4. All patients were also examined with computed tomographic (CT) scans, which proved to be a reliable method for estimating the distribution of disease (Fig. 2). Ultrasonography examinations were used but did not reveal any additional information compared with CT.

Although not specified in the case reports, magnetic resonance imaging (MRI) was used in attempting to evaluate the extent of disease. The value of MRI was restricted in the estimation of soft tissue changes and was, in comparison to CT, more uncertain in determining bone invasion by tumor.

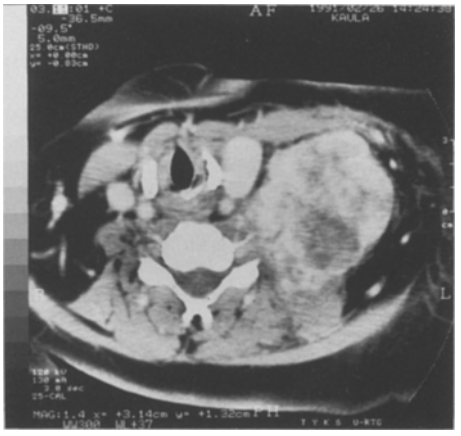

Fig. 2. CT scan of case 1 showing the wide expansion of tumor

In case 1 positron emission tomography (PET) imaging with [^{18}F]-fluoro-2-deoxy-D-glucose (FDG) and L-[^{11}C]-methionine showed a relatively diffuse and low uptake of both tracers (Fig. 3a, b). In case 2 gamma imaging with FDG and ^{99m}-Tc-hexamethylpropylene amine oxime showed a high uptake of both tracers.

Histology

MPNST is composed of spindle cells, with nuclei varying from elongate to round and plump and demonstrating hyperchromasia and various degrees of pleomorphism. Ultrastructural features are compatible with schwannian differentiation. The stroma can be fibrotic or myxomatous. Heterotopic elements are often seen in MPNST, mature islands of cartilage and bone being the most common. Skeletal muscle and mucin secreting glands have also been described and loci of hemorrhage and necrosis can be found.

Diagnostically MPNST make up a heterogeneous group, because they can resemble other sarcomas such as fibrosarcoma, monophasic synovial sarcoma, malignant fibrous histiocytoma, leiomyosarcoma or epithelioid sarcoma [10]. Sometimes the only distinguishing feature from other types of sarcomas is its origin from a nerve trunk [4].

In the last few years great advances have been made with immunohistochemical examinations. The antibody used in most cases is S-100 protein, which is found to be positive in 56–71% of MPNST cases [17, 21, 23, 27]. The problem in using these examinations is the overlap between immunohistochemical attributes of MPNST and other soft tissue sarcomas. When assessing multiple neural markers neuron specific enolase and myelin basic protein are used in most cases.

Several grading systems to classify MPNST are in use, with most having four categories. In general, classification is based on the stage of differentiation, polymorphism of cells and nuclei, mitotic activity, cellularity, presence of necrosis and pattern of growth.

Treatment and prognosis

Surgery is still the basis of therapy for MPNST [8, 13, 14, 16]. In general, tumor should be resected en bloc and as radically as possible. Additionally proximal nerve margins should be examined by frozen section to ensure that they are free from disease. Since lymph node involvement is very rare, radical neck dissection is uncommonly needed except for access to tumor [16, 18, 19].

In addition to surgical treatment, local radiation has been used to complete therapy. It has also been used in the treatment of local recurrences and in inoperable cases. High-dose radiation therapy has been reported to have favorable results in some cases and in improving 5-year survival [3, 13, 19]. The role of chemotherapy is still controversial [3, 24].

Overall prognosis of MPNST is poor and is based on tumor grading. Most grading systems have four categories, with each having a high prognostic value [2].

Five-year survival has been particulary poor for patients with von Recklinghausen's disease, ranging from 15% to 30% [12], while other patients have somewhat better prognoses ranging from 40% to 66% [8, 12, 18, 24, 26]. In the head and neck region, 5-years survival appears to be lower and has been from 15% to 34% [3, 12].

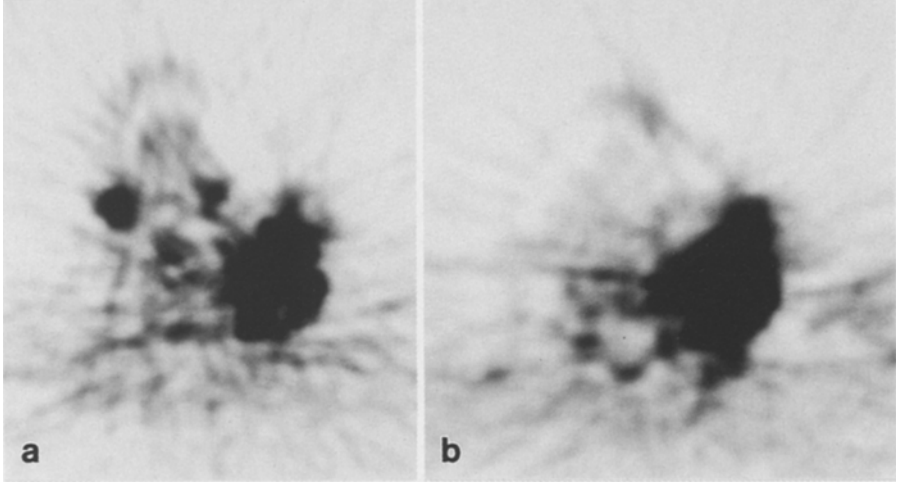

Fig. 3. a PET imaging of case 1 showing the low and diffuse distribution of L-[^{11}C]-methionine within tumor. The submandibular glands are also well visualized **b** PET imaging of case 1 with FDG shows a low and diffuse uptake of tracer in tumor

After primary surgery local recurrences have occurred in at least 50% of all cases [8, 16, 19]. Distant metastases appear in approximately 33% of the cases and are nearly always pulmonary [18].

Conclusion

Although MPNST is a rare lesion, it must be kept in mind when diagnosing fastly growing asymptomatic head and neck masses. Diagnosis can be difficult to make because of the heterogeneity of the histological appearance of tumor. Immunohistochemical studies have facilitated the confirmation of diagnosis by their greater specificity and sensitivity. However, on occasion the only feature still distinguishing MPNST from other sarcomas is its origin from a nerve trunk [4].

Tumor in our first case contained different histopathologcial findings. This tumor included areas that resembled a benign neurofibroma, making our fine needle aspiration and initial biopsy lead to a false-negative result. Although primary operation was not radical, our patient has lived 16 months free from disease. In this case high-dose radiotherapy has been advantageous. Our third case also contained a benign layer around malignant tumor, compromising our ability to make a correct diagnosis. As a consequence, we now recommend total extirpation of tumor to confirm a diagnosis when there is clinical suspicion of MPNST.

Malignant melanoma was considered an alternative histological diagnosis in our second case. Not until the whole resection block was examined was the neurogenic origin revealed. Melanocytic MPNST is a rare variant of the MPNST [20]. Additionally, it was difficult for us to determine tumor margins in this case, because of the presence of a thick scar tissue layer surrounding tumor and masking malignant cells.

Usually all sarcomas visualize well in PET imaging [15, 22], although there was low uptake of both tracers used in PET examination in our first case. This indicated low metabolic activity, even though final histological grading was as high as grade III-IV. The discrepancy between PET images and the high rate of mitoses may depend on the specific metabolic phenotype of tumor. It suggests that energy sources other than glucose, e.g. glutamine, must have been used as fuels for energy metabolism and tumor growth.

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