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Case report

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A child with a central nervous system relapse of a facial embryonal rhabdomyosarcoma

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Rhabdomyosarcoma (RMS) is the most common type of soft tissue sarcoma in children. There are two main types of RMS: embryonal and alveolar (having a worse prognosis). The treatment for childhood RMS is based on surgery, chemotherapy and radiation. In spite of very intensive therapy, 1/3 of patients suffer a relapse. The case report presents a child with facial embryonal RMS with an atypical central nervous system relapse; this, despite a comprehensive diagnostic process, was diagnosed during the autopsy.

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Introduction

Rhabdomyosarcoma (RMS) is the most common type of sarcoma among children, accounting for approximately 3–4% of childhood cancers [1]. According to the American Cancer Society there are 350 new cases in the USA annually, which means about 4.3/1,000,000 children and young people per year, with half of them occurring below 10 years of age, and boys being slightly more prone [1, 2]. There are two main subtypes of RMS: embryonal (*embryonale*) and alveolar (*alveolare*). The embryonal type is the most frequent with usual occurrence in children below 5 years of age with the primary location being the head, neck and urogenital system. RMS alveolare in turn, occurs more often among older children and teenagers, usually affecting the trunk and limbs [2]. The prognosis in RMS depends on many factors: histological subtype, the stage of the disease at the moment of diagnosis, the location and size of the baseline lesion, age and sex. The treatment for childhood RMS is complex, being based on chemotherapy and radiation; however the most important role is played by the possibility of a radical surgical resection of the primary tumour. Almost 90% of patients with a localised form of the disease, achieve remission during intensive treatment, and in 1/3 of cases, there is a relapse of the disease, most often within 2–3 years of the end of treatment [3]. Depending on the stage of the disease, for the very high risk group, the 3-year EFS (event free survival) curve is 30–40%, for the high risk group it is 50–55%, for standard risk 70–80% and for low — 90% [4].

The objective of this paper is to discuss an atypical picture of the recurrence within the central nervous system (CNS) in a child with facial RMS, which, in spite of extensive diagnostic process was confirmed as late as the post-mortem examination.

Case study

A 6-year-old patient (a girl) was admitted for treatment at the Department of Pediatric Oncology, Hematology and Transplantology, in Poznan University of Medical Science in February 2013 on account of facial embryonal RMS with metastases to the right submandibular lymph nodes, qualifying for the high risk group. The primary tumour infiltrated the nasal passages and ethmoid bones, as well as the left

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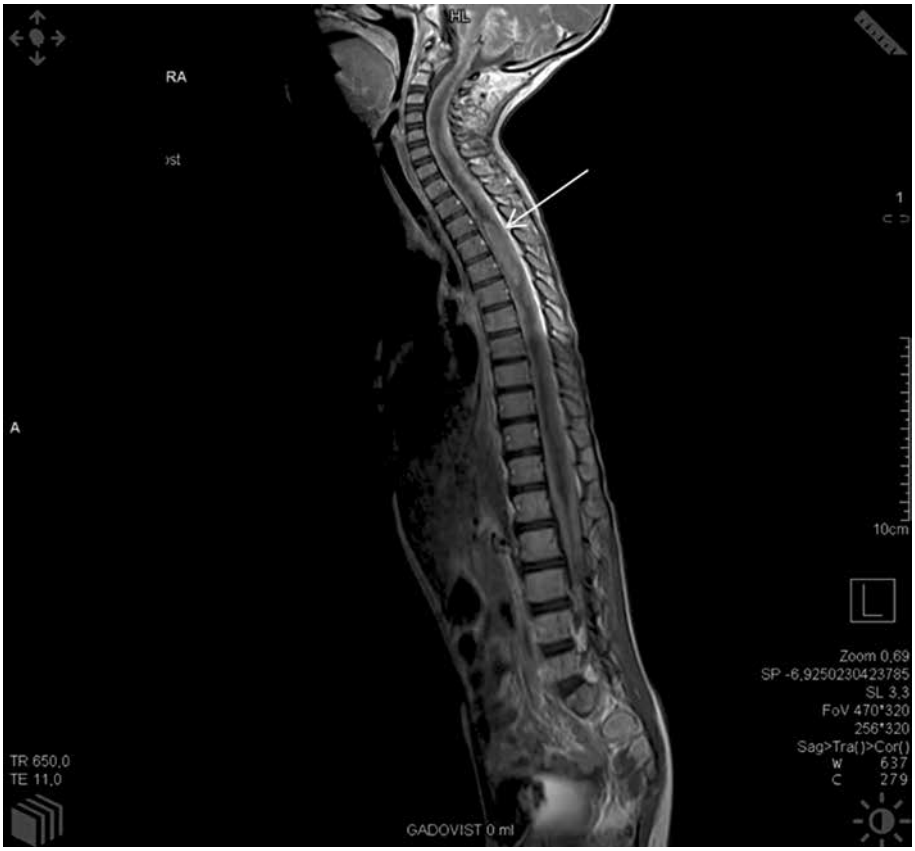

Figure 1. The MRI image of the spinal canal, longitudinal scan, with contrast agent, the enhancement of the spinal cord and meninges is visible

maxillary sinus and partly the sphenoid sinus; the tumour masses were also infiltrating the pterygopalatine fossa, covering the pharyngeal tonsils and peripharyngeal spaces. The child received treatment in accordance with the CWS 2006 therapeutic regimen, currently standard in Poland; it comprised 9 chemotherapy cycles, radiotherapy of the tumour bed (aggregate dose: 50.4 Gy), and surgical treatment consisting of the removal of the right submandibular lymph nodes [5].

In September 2013, upon completion of the first line of treatment, the MRI (magnetic resonance imaging examination) of the face and neck confirmed a complete remission of the disease.

In mid-November 2013, the patient was re-admitted to the Clinic on account of loss of appetite for 4 days, hypersalivation and weakening of the lower limbs. The significant abnormalities found upon admission were: ptosis on the left side, a decrease of muscular strength and disorders of the exteroceptive sensation in the lower limbs. In laboratory tests, no significant abnormalities were found.

During the following three days of hospitalisation, a gradually increasing paresis of the lower limbs and sphincter impairment was observed, as well as increased headaches and vomiting. Periodically the child was not responsive and drowsy. Given the above symptoms, a neuro-infection was suspected and wide-spectrum antibiotic therapy (Cetofaximum, Vancomycin, Ampicillin), anti-fungal (Fluconazolum) and anti-viral treatment (Acyclovir) were implemented. A diagnostic lumbar puncture was performed. The findings of the laboratory testing of CSF were the following: WBC 20/μL; protein 3084 mg/dl; glucose 34mg/dl. The culture of the CSF was sterile, and no presence of specific pathogens was confirmed in the PCR tests (*Enterovirus, HSV-1, HSV-2, EBV, CMV, Adenovirus, Aspergillus fumigatus, Candida albicans, Candida glabrata, Candida crusei, Listeria monocytogenes*). An MRI of the head, neck, face and spinal cord revealed the presence of extensive multilevel lesions: hyperintense lesions were seen on T2-weighted images. The oedema of the spinal cord was observed along its entire length. Upon administration of the contrast agent, heterogeneous enhancement of the spinal cord and strong enhancement of the meninges was observed (Fig. 1). A neurophysiological examination revealed axonal polyneuropathy and motor polyneuropathy without the involvement of the sensory fibres, which did not correspond to the paresis. Given the above symptoms, aseptic meningitis was suspected. The pulses of methylprednisolone were added, with a dose of 30 mg/kg/d for 5 days, resulting in a slight improvement of

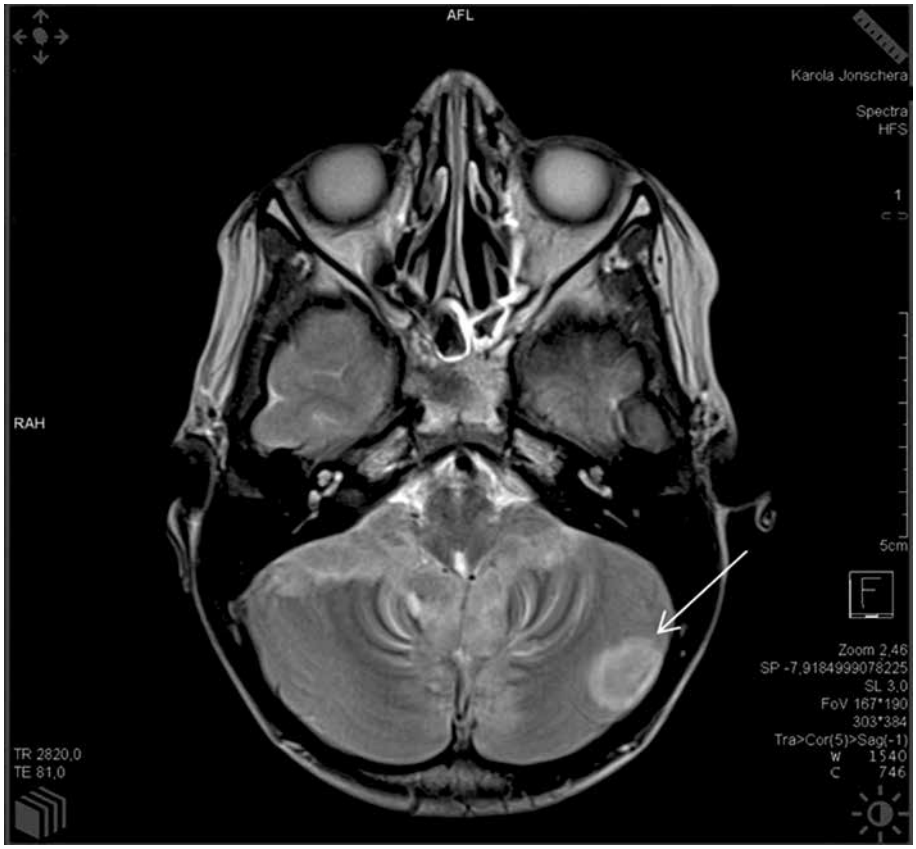

Figure 2. The MRI image of the head, transverse scan; T2-weighted image with the contrast agent, hyperintense foci in the cerebellum cortex are visible

the neurological condition of the child — the patient was logically responsive. During steroid therapy, no improvement in motor and sensory disorders or with regards to sphincter impairment was observed. After the reduction of the steroid doses, on the tenth day of hospitalisation a fast deterioration of the general condition of the patient occurred and, with regards to increasing bradycardia, as well as prolonged episodes of apnoea, the child was transferred to the ICU department in a serious condition; treatment with methylprednisolone was continued, yet without any improvement of the clinical condition of the girl.

Another MRI of the head and spinal cord (performed 10 days later) revealed a significant deterioration of the picture: numerous foci with an increased signal (T2-weighted and FLAIR images) in the cerebellar cortex, both in the hemispheres, vermis and tonsils, which suggested an acute cerebellar stroke (on DWI D1000 and ADC images). On the supratentorial images, the ventricular system was not dilated and not shifted, and no supratentorial ischaemic areas were found (Fig. 2). The CT (computed tomography) examination of the head (performed two days after the previous MRI examination) revealed lesions corresponding to the ischemic stroke of the cerebellum; an increased volume (oedema) of the cerebellum with some features of increased subtentorial compartment in the posterior fossa of the cranium, pressure on the medulla oblongata with a complete stenosis of the cisterns of the pons and cerebellar-spinal cisterns, as well as thickening and heterogeneous structure and density of the medulla oblongata. Moreover, the loss of corticomedullary differentiation in both brain hemispheres was found; a supratentorial dilation of the ventricular system and of the IV ventricle was observed. Around the lateral ventricles there were lesions corresponding to an active hydrocephalus (CSF leak). The brain CSF spaces and sulci were totally stenosed. Within the posterior fossa and brain stem, there was an image of diffuse, systemic lesions with heterogeneous density with no way of differentiating the brain structures — the anatomical distinctions were blurred. On the twelfth day of treatment, the pupils were fixed and non-reactive. In the following days, a further deterioration of the neurological condition was observed. On the 15th day of hospitalisation, the death of the brain stem was confirmed and the child was confirmed dead. The post-mortem examination revealed RMS metastases to the cerebellum, medulla oblongata, spinal cord and meninges; brain oedema; the foci of the ischemic necrosis of the brain; tonsillar herniation into the foramen magnum.

Discussion

The main cause of the failures of the treatment of soft-tissue sarcomas in children is relapse of the disease. Most frequently, relapses occur within 2 years from the completion of the treatment, and in the majority of patients, the relapse has a local character [3, 6, 7]. The prognosis, in the case of RMS is poor, and the probability of a general 5-year survival, depending on different factors, varies between 17 and 36% [3, 6]. The primary location of RMS in the area of meninges and face is burdened with an exceptionally high relapse rate, due to the impossibility of performing a total resection of the tumour. At the same time, the symptoms of the cancer are nonspecific, which might delay an early diagnosis resulting in a very high stage of clinical advancement at its baseline and the impossibility of carrying out radical surgery. In the described case, with regards to the total clinical and imaging remission achieved after the pre-surgical chemotherapy, no radical surgery was performed during the first line of treatment. The cause of the symptoms, which occurred 9 months after the diagnosis of the *embryonale* RMS of the face, was found, in the autopsy, to be the remission of the disease. The involvement of the central nervous system, atypical either for RMS or for other soft tissue sarcomas, occurs in 10% of patients with this diagnosis [8]. The lesions have usually a supratentorial location and solid type. The involvement of the spinal cord is very rare [9].

Evaluation of the symptoms presented by the patient should be performed with diagnostic methods such as a head and face MRI (for the exclusion of local relapse), an MRI of the central nervous system, and, further, laboratory tests, blood and CSF microbiology. The differential diagnostics should include neuro-infection, neurotoxicity resulting from chemotherapy, a relapse of the core disease and neurodegenerative diseases.

In the case of this patient, both the local and late relapse were definitely excluded in imagining tests, resulting in a diagnostic process for infectious and neurodegenerative diseases. Also, the implemented treatment was targeted towards a disease with an infectious aetiology. The administration of methylprednisolone pulses, which transitionally decreased the oedema of the brain and spinal cord and also limited inflammation, led to the alleviation of symptoms and the reduction of the protein concentration in CSF; this misled the doctors, apparently confirming their diagnosis of aseptic meningitis. The post-mortem examination showed that the enhancement of the MRI signal within the cord and meninges was already a manifestation of the cancer relapse.

Publications describe some isolated causes of the RMS relapse within the CNS, similar to this case, i.e. in a 4-year-old boy with orbital RMS whose relapse was accompanied by the symptoms of increased intracranial pressure and the presence of abnormal cells in CSF [10]. Some other described relapses within CNS concerned two patients with RMS primarily located in the chest, who underwent radical surgery and systemic and intrathecal chemotherapy [11]. Those patients died as a result of the diseases progression.

Taking into consideration the above case of an atypical RMS relapse within the CNS as well as the quoted examples from literature and given both the diverse clinical symptoms and equivocal imaging results in the patients with primary diagnoses of RMS, one must consider the relapse of the core disease as the first cause of the occurrence of neurological symptoms and, in order to confirm it, a biopsy of the lesion must be performed followed by a verification against histopathological criteria.

The abbreviations in the text:

RMS — rhabdomyosarcoma
EFS — event free survival, CNS — central nervous system
MRI — magnetic resonance imaging
CT — computed tomography
CSF — cerebro-spinal fluid

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