Alveolar rhabdomyosarcoma in an adolescent male patient – case report and current perspectives

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Abstract
Alveolar rhabdomyosarcoma (RMS) is a common pediatric malignant mesenchymal tumor, representing half of soft tissue sarcomas and approximately 5% of all cancers. We present the case of an adolescent male patient treated in our Department for a tumoral mass located in the middle third of the forearm. Magnetic resonance imaging (MRI) and angiography–computed tomography (angio-CT) showed a large mass located in the muscles of the anterior compartment of the forearm. Surgical treatment consisted of tumor ablation including segmental resection of the radial and ulnar arteries and of the median nerve, followed by saphenous autograft vascular bypass. The treatment plan was based on tumor type, histological grading (high), age, tumor size greater than 5 cm, unfavorable location, postoperative tumor, node, metastasis (TNM) stage II, presence of microscopic tumoral tissue in the margins of the resected piece, lymph node metastases (N1) and bone metastases (M1) found on positron-emission tomography (PET)–CT according to the German soft tissue sarcoma study (CWS)-IV 2002 protocol. The chemotherapy used Carboplatin and Topotecan. Survival was less than two years after the initial presentation. Adolescent extremity masses should raise suspicion to exclude serious malignancy. Despite early diagnosis and use of multimodal therapies, alveolar RMS prognostic remains unpredictable.

Keywords: alveolar rhabdomyosarcoma, male individual, upper limb.

Introduction
Rhabdomyosarcoma (RMS) is a malignant tumor originating from mesenchymal tissue. RMS represents about 50% of all soft tissue sarcomas in pediatrics and approximately 5% of all childhood cancers. RMS is more frequent in the male population with almost two thirds of cases being diagnosed in children less than six years old [1].

In pediatrics, it represents the third most frequent extracranial solid tumor after the neuroblastoma and the Wilms tumor (nephroblastoma). Soft tissue sarcomas represent less than 1% of all malignancies in the adult population and RMS represents only 3% of soft tissue sarcomas [2].

The 2013 World Health Organization (WHO) classification of RMS describes four main subtypes: the alveolar rhabdomyosarcoma (ARMS) and its solid variant, embryonal rhabdomyosarcoma (ERMS) including two histological subtypes: the botryoid and pleomorphic cell rhabdomyosarcoma (PRMS) [3]. The first two subtypes are the most common subtypes of RMS encountered in children and adolescents. ERMS is more frequently observed in the first decade of life, while ARMS has a higher prevalence in the 10–25 years of age group [2].

In adults, the histological distribution is also different from children. Adults have more of PRMS not otherwise specified subtypes [3, 4].

The aim of our study was to highlight the aggressivity of ARMS in young male, given the fact that it raises diagnostic and therapeutic challenges for both disease control and preservation of function.

Case presentation
A 17-year-old young male patient (T. PD) was admitted in the Department of Plastic and Reconstructive Surgery of the Timișoara County Hospital, Romania (Observation Sheet No. 32193/2014) for a tumoral mass of the right forearm.

The medical history revealed no significant comorbidities relevant to the current situation. The patient affirms first noticing the mass approximately three months prior. It had an insidious onset and enlarged during the time from identification to presentation. The local examination identified a voluminous, palpable...
mass, located in the anterior compartment of the middle third of the forearm, with the approximate dimensions of 7/8 cm and firm consistency (Figure 1). The underlying skin seemed unaffected. Distal to the lesion radial pulse was present and there was no apparent sensory or motor deficit.

Magnetic resonance imaging (MRI) and angiography–computed tomography (angio-CT) showed a large mass located in the muscles of the anterior compartment of the forearm. Compared with the surrounding tissues, it had iso-signal in T1 and intense hyper-signal in T2, with visibly increased vascularity, diffuse restriction and high gadolinium deposition (Figures 2–4).

The extemporaneous biopsy was highly suspicious of a RMS.

**Figure 1 – Voluminous, palpable mass, located in the anterior compartment of the middle third of the forearm, with the approximate dimensions of 7/8 cm and firm consistency.**

**Figure 2 – MRI analysis: (a) T1 coronal; (b) T2 sagittal; (c and d) ADC map; (e) T1 coronal with contrast enhancement. The radial and ulnar arteries are dislocated by the tumoral mass. MRI: Magnetic resonance imaging; ADC: Apparent diffusion coefficient.**

**Figure 3 – Postoperative control MRI: T1 axial (a), T2 sagittal (b), and T1 sagittal with contrast enhancement and subtraction (c). We can see restoration of the right radial and ulnar arteries through bypass using venous graft from the right saphenous vein. MRI: Magnetic resonance imaging.**
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Thus, extensive surgery within safety margins was performed, consisting of tumor ablation including segmental resection of the radial and ulnar arteries and of the median nerve (Figure 5), followed by restoration of the radial and ulnar arteries through bypass using a saphenous graft collected from the right calf. The continuity of the muscle–tendon complex was achieved by attaching the flexor tendons of the fingers to the remaining muscle masses. Postoperatively, the patient received antibiotics, anticoagulants, analgesics and muscle relaxants. After discharge, the patient continued treatment with antiaggregant medication.

Histopathological (HP) and immunohistochemistry (IHC) exams performed on the resected tumor mass established the diagnosis of high-grade (G3) ARMS, tumor, node, metastasis (TNM) stage pT2bN1 LV1R1.

The patient continued the treatment in the Pediatric Oncology Clinic. The therapy was based on tumor type (ARMS), histological grading (high), age over 10 years old, tumor size greater than 5 cm, unfavorable location, postoperative TNM stage II, presence of microscopic tumoral tissue in the margins of the resected piece, lymph node metastases (N1) and bone metastases (M1) found on positron-emission tomography (PET)-CT (Figure 4). Given these conditions, the treatment was decided according to the German soft tissue sarcoma study (Cooperative Weichteilsarkom, CWS)-IV 2002 protocol. The first line of chemotherapy (Carboplatin and Topotecan) was administered for two sessions with good tolerability. After the first session of chemotherapy, the patient was diagnosed with bone marrow aplasia, severe thrombocytopenia and neutropenia. The patient was admitted in our Department, where he received treatment with repeated infusions of Carboplatin, Topotecan and granulocyte-colony stimulating factor (G-CSF). The cytostatic therapy with Carboplatin and Topotecan was continued for two more session. The patient survived for less than two years after the initial presentation.

**Histological analysis of the tumoral mass**

The macroscopic appearance of the surgically removed piece revealed its size of 13.7/9.2/6.3 cm, and consisted of muscular tissue, including a tumoral formation about 6.6/4/4.2 cm, with an overlying fragment of skin approximately 5.5/5.1 cm (surface flap) (Figure 5). The tumoral surface has an irregular outline, slightly polycyclic, whitish and firm elastic consistency. The tumor was macroscopically located at only 0.1 cm from the deep resection margin (in the central area).

The microscopic exam of both the needle biopsy and surgical resection piece revealed a proliferative malignant tumor consisting of small cells (Figure 6), arranged in alveoli (Figure 7) and solid nests of various sizes, with a row of cells adherent to the stroma, and the center ones discohesive. Tumor cells were generally small, but variable in size, round-oval, with reduced eosinophilic cytoplasm. Group of cells with broader cytoplasm have eccentric nuclei described as hyperchromatic, round-oval or kidney-shaped, some with irregular outline with nucleoli; dispersed rare
anaplastic cells with bizarre nuclei, greatly increased in volume, multilobulated, binucleated and multinucleated-like, frequent mitoses, some atypical and numerous apoposes (Figure 8), micro-outbreaks of tumor necrosis and hemorrhage; the nests of tumor cells are bounded by a conjunctive-vascular stroma of variable representation, with hyaline areas; the tumor infiltrates and incorporates striated muscle fibers (Figure 9), dense connective and adipose tissues, nerves, blood vessels, some with thick walls; images of vascular invasion; positive resection margin in some areas; one lymph node with extensive metastatic involvement.

IHC was performed to validate the HP exam, using myogenin (Myf4) (clone LO26, Novocastra, ready-to-use dilution, enzymatic antigen retrieval), high-sensitive marker for RMS and desmin (clone D33, Cell Marque, 3:1 dilution, enzymatic antigen retrieval) for the myogenic tumoral components. Desmin and myogenin are significant to perform a correct RMS diagnosis, based on our case on the immunohistochemically-positive expression of the tumor for desmin (Figure 10), with diffuse intense nuclear staining for Myf4 (Figure 11). Based on the aspects visible in the Hematoxylin–Eosin (HE) staining and the IHC results, the patient was diagnosed with ARMS pT2bN1 LV1R1.
Discussions

We present a case of a young adolescent with insidious onset of serious disease. The tumoral mass had an aggressive and rapid evolution. The local growth pattern was invasive but did not interfere with normal function prior to surgery. Acute complications, such as compartment syndrome, have been reported [5].

RMS is commonly observed in head and neck regions, genitourinary tract (non-bladder/prostate) and extremities. The ARMS and ERMS are characterized by different primary sites. ERMS is frequently described in the head and neck, genitourinary, and retroperitoneal areas, while the ARMS is mostly located on the trunk and in the deep soft tissues of extremities [2,3].

From the standpoint of prognosis, our patient was within the published risk groups. The favorable primary sites of RMS are the orbit, head/neck (non-parameningeal), bile duct region and genitourinary (non-bladder/prostate) regions, while all others areas are classified as unfavorable. The favorable locations point-out a better five-year survival rate compared with the unfavorable areas [1,4]. Children and adolescents diagnosed with localized RMS have similar five-year overall survival rates and five-year progress free survival rates. While the presence of metastases at the moment of diagnosis has a negative impact on these predictions concerning both age groups, adolescents with metastatic RMS have a worse survival compared with children. When compared with children, adolescents also have a higher frequency of unfavorable RMS type, lymph node involvement and metastases [6,7].

In our case, the 17-year-old boy did not present any particular symptoms, unlike other reported cases where RMS was associated with a heterogeneous associated symptomatology, which may affect the diagnosis consistency [8,9]. There were also reported distinct RMS which were present in the same time in different places of the body [10,11].

The histological appearance of our case was unambiguous, with a high correlation with the immunohistochemical study. Anti-desmin and anti-Myf4 antibodies positive immunoreaction in the tumor sustain the HP exam.

ARMS is usually a highly cellular tumor. Its cells are organized in nests and sheets separated by variably prominent fibrous septa. Commonly, the sheets and nests present a central loss of cellular cohesion that creates an alveolar-like aspect. The cells are medium sized, relatively monomorphic with hyperchromatic nuclei with or without small nucleoli and minimal cytoplasm with frequent mitoses. Rhabdomyoblasts are more frequently encountered in embryonal subtype. They are round- or oval-shaped cells, less frequent elongated, densely eosinophilic with hyperchromatic nuclei. Multinucleated wreath-like cells are observed occasionally, while clear cells and anaplasia are observed rarely. The solid variant of ARMS has a similar cytomorphology with the conventional type. It is composed of sheets of small round cells without the alveolar pattern [3,12]. Histologically, RMS is comparable to fetal striated muscle and expresses various myogenic regulatory genes.

Similarities continue to the aspect of cellular arrested state during development of normal skeletal muscle more than malignancy. Currently, drug resistance and metastases are the most common means of therapy failure. The targeting of epigenetic pathways may be the future. New drugs like inhibitors of tyrosine kinases, histone deacetylases, mammalian target of rapamycin (mTOR) pathway or fibroblast growth factor and transcriptional targeting viruses can be new resources in the treatment or RMS [3,13,14].

Surgery in the upper arm and especially elbow area presents numerous challenges [15–17]. We consider that the therapy has to be closely related to survival rates of RMS. Even though the upper limb is not weight bearing, the functional requirements are just as high [18–20]. Future advancements in biomarkers may contribute to early diagnosis, better outcomes and easier follow-up.

Conclusions

Adolescent extremity masses should raise suspicion to exclude serious malignancy. Despite early diagnosis and use of multimodal therapies, RMS prognostic remains unpredictable, because its aggressivity. New therapeutic approaches are necessary to improve survival rate.

Conflict of interests

The authors declare that they have no conflict of interests.

References


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