

# Rhabdomyosarcoma of the Gluteus Maximus – Case Report, Review of Literature and Emerging Therapeutic Targets

## Rhabdomyosarkom gluteus maximus – kazuistika, přehled literatury a terapeutické cíle

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### Summary

**Background:** Rhabdomyosarcoma is an uncommon mesodermal cancer, which predominantly affects the young population. Common sites of primary disease include the head and neck region, genitourinary tract and the extremities. Less than 25% of the cases of rhabdomyosarcoma are metastatic at presentation. Embryonal and alveolar are the most common histological subtypes of rhabdomyosarcoma. Literature about rhabdomyosarcoma located in the gluteal region is sparse. **Case:** We present a case of a 3-year-old child with alveolar rhabdomyosarcoma arising from the gluteal region. The metastatic workup was negative. We determined the tumour to be of intermediate risk and managed the patient with systemic chemotherapy consisting of cycles of vincristine, actinomycin D and cyclophosphamide, along with local treatment (wide-margin excision and radiotherapy). No recurrence was observed in the follow-up period. **Conclusion:** Management of alveolar rhabdomyosarcoma of the gluteus maximus requires a multipronged approach consisting of systemic chemotherapy, local surgery and radiotherapy. Long-term surveillance is imperative in children for early identification and management of relapses and treatment-related adverse effects. Several biological agents and small-molecule inhibitors targeting the signalling and growth pathways of rhabdomyosarcoma are in the pipeline, which hold promise for personalised therapy in the future. However, due to the rarity and molecular heterogeneity of the tumour, integrating these novel agents with the existing therapy would be a challenge.

### Key words

rhabdomyosarcoma – buttocks – chemotherapy

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## Souhrn

**Východiska:** Rhabdomyosarkom je méně častý mezodermální nádor, který postihuje zejména mladou populaci. K častým místům výskytu primárního onemocnění patří oblast hlavy a krku, urogenitální trakt a končetiny. Méně než 25 % případů rhabdomyosarkomu je při prvním výskytu metastatických. Nejčastějšími histologickými podtypy rhabdomyosarkomu je podtyp embryonální a alveolární. Literatura o rhabdomyosarkomu vyskytujícím se v gluteální oblasti je minimální. **Případ:** Popisujeme případ tříletého dítěte s alveolárním rhabdomyosarkomem vzniklým v gluteální oblasti. Metastatické vyšetření bylo negativní. Nádor jsme určili jako středně rizikový a pacienta jsme léčili systematickou chemoterapií sestávající z cyklů vinkristinu, aktinomycinu D a cyklofosfamidu souběžně s lokální léčbou (excize s širokým okrajem a radioterapie). V období následného sledování nebyla pozorována žádná recidiva. **Závěr:** Léčba alveolárního rhabdomyosarkomu glutei maximi vyžaduje rozsáhlejší přístup, který se skládá ze systémové chemoterapie, lokálního chirurgického zákroku a radioterapie. U dětí je naprosto nezbytné dlouhodobé pozorování z důvodu včasné identifikace a léčby relapsů i nežádoucích účinků souvisejících s léčbou. Přípravuje se několik biologických látek a malomolekulárních inhibitorů cílených na signální a růstové dráhy rhabdomyosarkomu, které jsou příslibem budoucí personalizované léčby. Avšak z důvodu vzácnosti a molekulární heterogenity tohoto nádoru bude integrace těchto nových látek se stávající léčbou obtížná.

## Klíčová slova

rhabdomyosarkom – hýždě – chemoterapie

## Introduction

Rhabdomyosarcoma is the most common soft-tissue sarcoma afflicting children and adolescents. It is attributed to around 5% of all paediatric cancers [1]. Common affected sites include the head and neck region, genitourinary tract, retroperitoneum and, to a lesser extent the extremities [2]. The most common histological variants encountered are the embryonal and alveolar subtypes. Alveolar rhabdomyosarcoma with a size greater than 5 cm has a poor prognosis [3]. In this report we describe a case of alveolar rhabdomyosarcoma affecting the left gluteal region in a 3-year-old child. We



**Fig. 1.** Alveolar rhabdomyosarcoma present at the left gluteal region of a 3-year-old child.

also briefly discuss the emerging therapeutic agents in the pipeline.

## Case presentation

A 3-year-old child presented with a mass in his left gluteal region which had been enlarging gradually for 4 months. History revealed that the swelling was initially painless but had become painful after 2 months for which he had been prescribed painkillers and antibiotics. There was no history of trauma, fever, weight loss or chronic cough. None of the close family members had similar swellings. The general examination was unremarkable. On local examination, a 12 cm firm, tender mass was palpable (Fig. 1). No lymphadenopathy was present. Routine blood investigations did not reveal any abnormalities. Magnetic resonance imaging (MRI) showed a heterogeneous hyperintense infiltrative lesion arising from the gluteus maximus. An incisional biopsy was made. The histological examination was suggestive of the alveolar subtype of rhabdomyosarcoma. High resolution computed tomography (HRCT) of the chest, bilateral bone marrow biopsy and bone scan were negative for metastasis. The patient was referred to a higher cancer centre where he received neoadjuvant chemotherapy consisting of vincristine (V), actinomycin D (A) and cyclophosphamide (C), followed by wide-margin excision of the tumour mass. Radiotherapy was provided before the initiation of chemotherapy and on the 9<sup>th</sup> week post-chemotherapy. Post-operatively the pa-

tient is receiving chemotherapy cycles of VAC. The patient is responding well to chemotherapy without major adverse effects and without relapse/recurrence.

## Discussion

Rhabdomyosarcoma is a relatively rare mesodermal cancer with an estimated annual incidence of 4.3 cases per one million people younger than 20 years of age [1]. Common sites of the primary disease include the head and neck region, genitourinary tract and extremities [2]. Literature about rhabdomyosarcoma located in the gluteal region is sparse. Most cases of rhabdomyosarcoma are sporadic in nature, but there have been associations with familial syndromes such as neurofibromatosis and Li-Fraumeni syndrome [3]. The presence of familial syndromes in our patient was eliminated through detailed history and examination.

As previously mentioned, the two major histological subtypes of rhabdomyosarcoma are embryonal and alveolar. Our patient had been afflicted by the alveolar subtype as histological examination showed the presence of distinct alveolar architecture with aggregates of small round undifferentiated cells separated by dense hyalinized fibrous septa [3,4]. The alveolar subtype accounts for 15–20% of all cases, typically occurs in the second decade of life, has a higher propensity to metastasise and is usually located in the extremities [5].

Around 80% of all cases of the alveolar subtype are caused due to trans-

locations t(2;13)(q35;q14) or t(1;13)(p36;q14), which lead to the formation of chimeric transcription factors (PAX3-FKHR or PAX7-FKHR, respectively). These transcription factors cause cell proliferation, angiogenesis and other cancerous changes [3,4]. As our patient did not have enough resources, we could not proceed with mutational analysis for genotype-phenotype correlation.

Most medical centres employ imaging studies such as CT scan or MRI of the primary tumour to determine the size and possible involvement of surrounding vital organ structures [2]. Less than 25% of the cases of rhabdomyosarcoma are metastatic at presentation [5]. The lungs (40–50%), bone marrow (20–30%), bones (10%) and lymph nodes (10–20%) are the most common metastatic sites [2,5]. The metastatic evaluation in our patient was negative.

The prognostic factors which suggested a poor outcome in our patient were the unfavourable site of the primary tumour (buttock), the unfavourable histopathological subtype (alveolar) and the large diameter of the tumour (> 5 cm). The prognostic factors suggesting a positive outcome in our patient were the age (children aged between 1–9 years have a better prognosis), the absence of metastasis/lymph-node involvement and the good response to chemotherapy [2].

As the tumour was invasive in nature with a size greater than 5 cm and without any lymph node or metastasis, it was staged as T<sub>2b</sub>N<sub>0</sub>M<sub>0</sub> as per TNM (tumour, node, metastasis) classification [2,3]. Our patient was considered to be intermediate-risk and was provided with the VAC regimen, which is the frontline chemo-

therapy regimen for such patients [3]. The local treatment advised for our patient was radiotherapy and wide-excision of the tumour, following which the VAC regimen was continued.

Incorporating other anticancer agents into the VAC backbone such as ifosfamide, etoposide, carboplatin, irinotecan and vinorelbine in order to improve the outcome rates requires further clinical trials [2]. New molecular targets being explored include inhibiting tyrosine kinase receptors such as epidermal growth factor receptor (erlotinib, gefitinib), platelet derived growth factor receptor (olatumab, dasatinib, pazotinib, sorafenib), vascular endothelial growth factor receptor (sunitinib, apatinib) and anaplastic lymphoma kinase receptor (crizotinib, ceritinib) [6]. Monoclonal antibodies against insulin-like growth factor 1 receptor (cixutumumab, R1507, BMS-754807) have shown promise in early phases of clinical trials [4,6]. Cyclin-dependent kinase inhibitors (palbociclib), and mouse double minute 2 homolog-tumour – tumour protein p53 interaction inhibitor (MI-63) have shown some promise in phase I clinical trials [6]. The role of small GTP-ases family inhibitors (cetuximab, panitumumab, sorafenib), BRAF inhibitors (vemurafenib, dabrafenib) and mitogen activated protein kinase inhibitors (sorafenib, selumetinib, AZD8055) in reducing tumour growth is being explored in preclinical studies [4,7]. Other targets being explored include mammalian target of rapamycin kinase inhibitors (sirolimus, everolimus), phosphatidylinositol-4,5-bisphosphate 3 kinase inhibitors (temsirolimus, ridaforolimus), programmed cell death-1 receptor inhibitor (pembrolizumab) and polycomb-group

protein inhibitors (tazemetostat) [4,5,8]. Drugs targeting the PAX-FKHR fusion proteins (synthetic retinoid fenretinide, faspalisin) have been isolated, which need further evaluation [5]. Histone deacetylase inhibitors, survivin-responsive conditionally replicating adenovirus and V-ATPase inhibitors (esomeprazole) have been found to reduce cancer growth in preclinical studies [7].

## Conclusion

Alveolar rhabdomyosarcoma located in the buttock is an extremely rare entity. Management includes a multimodal approach consisting of systemic chemotherapy, local surgery and radiotherapy. Although several new molecules targeting rhabdomyosarcoma are in the pipeline, integrating them with existing therapy would be a challenge.

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