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Radiotherapy-Resistant Pediatric Bladder Rhabdomyosarcoma: A Case Report

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Abstract

Introduction: Rhabdomyosarcoma (RMS) is a relatively rare type of malignancy originating from soft tissue. While RMS can manifest at any age, it is most commonly observed in children and toddlers. The primary approach to managing Rhabdomyosarcoma involves chemotherapy as the main modality, followed by surgery or radiation therapy in cases of residual disease or recurrence.

Case Presentation: In this report, the author will review a case of radioresponsiveness in pediatric bladder rhabdomyosarcoma. The patient underwent chemotherapy with cyclophosphamide-mesna, vincristine, and actinomycin. Following chemotherapy, a partial reduction in the mass was observed, after which the patients were treated with whole-bladder external radiation therapy. Post-radiation therapy evaluation revealed symptomatic relief but limited mass reduction.

Conclusions: Rhabdomyosarcoma in the pediatric bladder may exhibit characteristics of radioresistance, and radiation therapy provides symptomatic relief in locally advanced or metastatic cases.

Keywords : *bladder, pediatric, radiation, rhabdomyosarcoma.*

Introduction

Rhabdomyosarcoma (RMS) is a relatively rare malignancy originating from soft tissue, particularly skeletal muscle. RMS can manifest at any age but is most commonly observed in children and toddlers, with approximately 87% of patients being younger than 15 years.[1] Additionally, about 18-22% of these tumors arise from the genitourinary tract.[2] Multimodality therapy, including surgery, chemotherapy, and radiation therapy, is the standard treatment for bladder RMS.[3] The standard therapeutic modality for embryonal rhabdomyosarcoma involves a combination of surgery and chemotherapy, with surgery aiming for complete resection when feasible and also primarily limited to preserving micturition function.[4] Chemotherapy has been established as a crucial component in the treatment of rhabdomyosarcoma, with the combination of vincristine, actinomycin, and cyclophosphamide/ Ifosfamide being the standard regimen Radiotherapy also plays a significant role in the treatment of embryonal rhabdomyosarcoma, particularly in cases where complete resection is not feasible. For instance, in cases of rhabdomyosarcoma with residual disease following induction chemotherapy without an option for secondary resection, radiotherapy has been considered sufficient.[5] This article presents a case report on the radiation therapy of pediatric bladder RMS patients who underwent chemotherapy and radiation therapy at Dr. Sardito General Hospital in Yogyakarta, Indonesia. The focus is on the tumor response to radiation therapy.

Case Presentation

Clinical Presentation

A 3-year-old girl having trouble urinating to the extent that she is unable to urinate was admitted to Dr. Sardjito General Hospital in Yogyakarta, Indonesia. This issue is accompanied by the presence of fluctuating

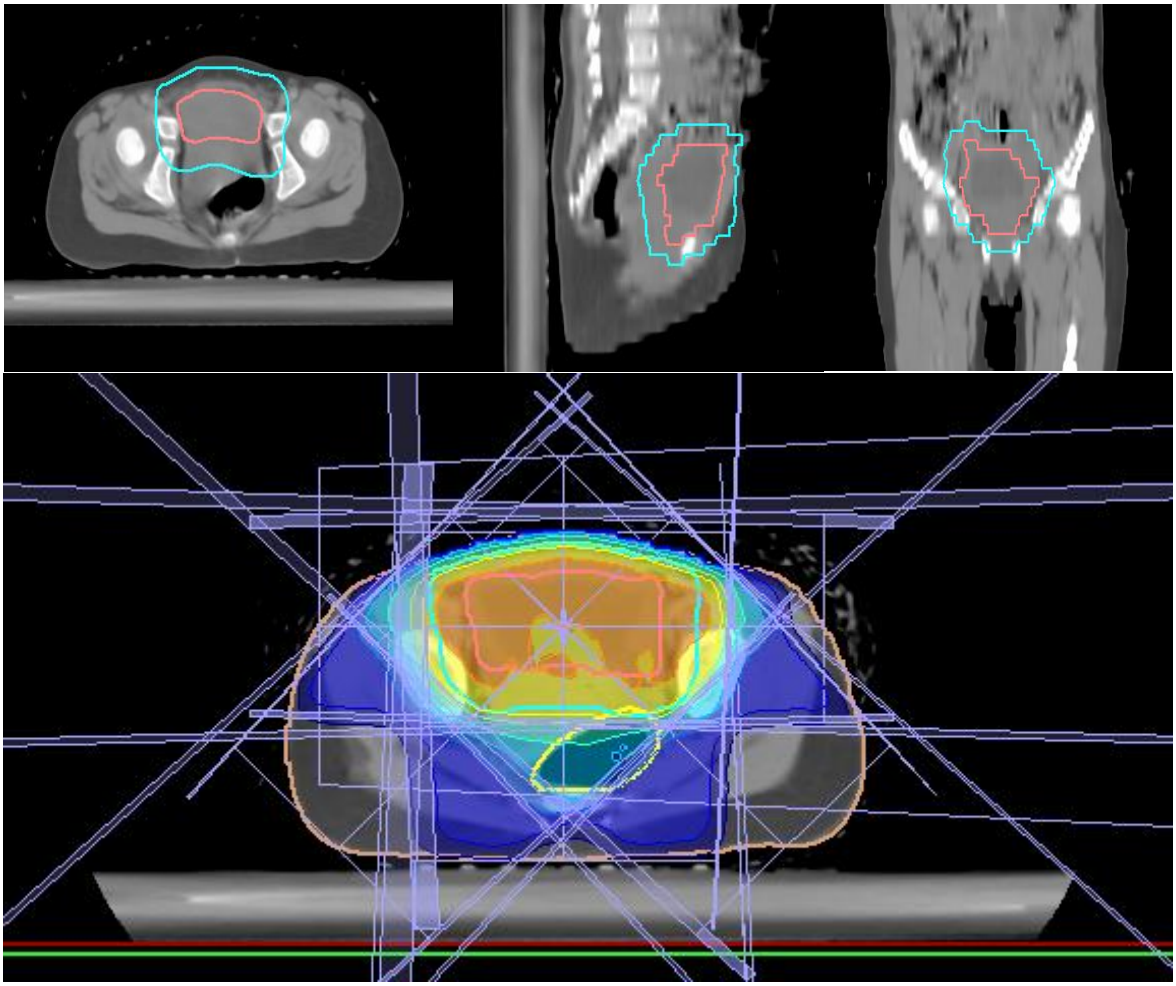

Figure 1. Target volume and dose distribution. The pink colour in the upper panel represents the Clinical Target Volume (CTV) which includes the mass in the bladder, the entire bladder, and the extension of the periurethral tissue. The light blue colour indicates Planning Target Volume (PTV).

lump from the urethra. During cystoscopy examination, a mass was identified in the bladder. The mass was inoperable, and biopsy was performed. The histopathological and immunohistochemical analyses of desmin and myogenin revealed the presence of embryonal rhabdomyosarcoma (RMS). On CT scan examination, lesions were observed on the bladder walls, displaying an irregular shape with indistinct boundaries. The lesion extends inferiorly (periurethral) and partially obstructs the bilateral vesicoureteral junction, leading to grade 2-3 bilateral hydronephrosis. Initially, the lesion appeared to be at a locally advanced stage; however, after performing a thorax CT scan, multiple small nodules suggestive of metastasis were observed in both lungs. Therefore, this case aligns with stage IV, based on the staging criteria of both TNM and the Intergroup Rhabdomyosarcoma Study Group (IRSG). The Risk Group Criteria categorize this case as High Risk.

The patient underwent chemotherapy with a regimen comprising cyclophosphamide-mesna, vincristine, and actinomycin. Upon evaluation at the 6th week of chemotherapy, the mass exhibited a reduction of 21% by size (partial response, according to RECIST 1.1). Following 13 cycles of chemotherapy, the assessment revealed a mass reduction of 32% from its pre-chemotherapy size (partial response, according to RECIST 1.1), and complaints related to voiding had significantly decreased. It was then, the decision to proceed with radiation therapy was made for the remaining mass.

Radiation Treatment

The patient underwent external radiation at the Radiotherapy Service of Dr. Sardjito General Hospital in Yogyakarta, Indonesia. CT simulation was conducted with intravenous contrast, involving preparation for bladder emptying, followed by the intake of 500 mL of drinking water before the simulation commenced. The

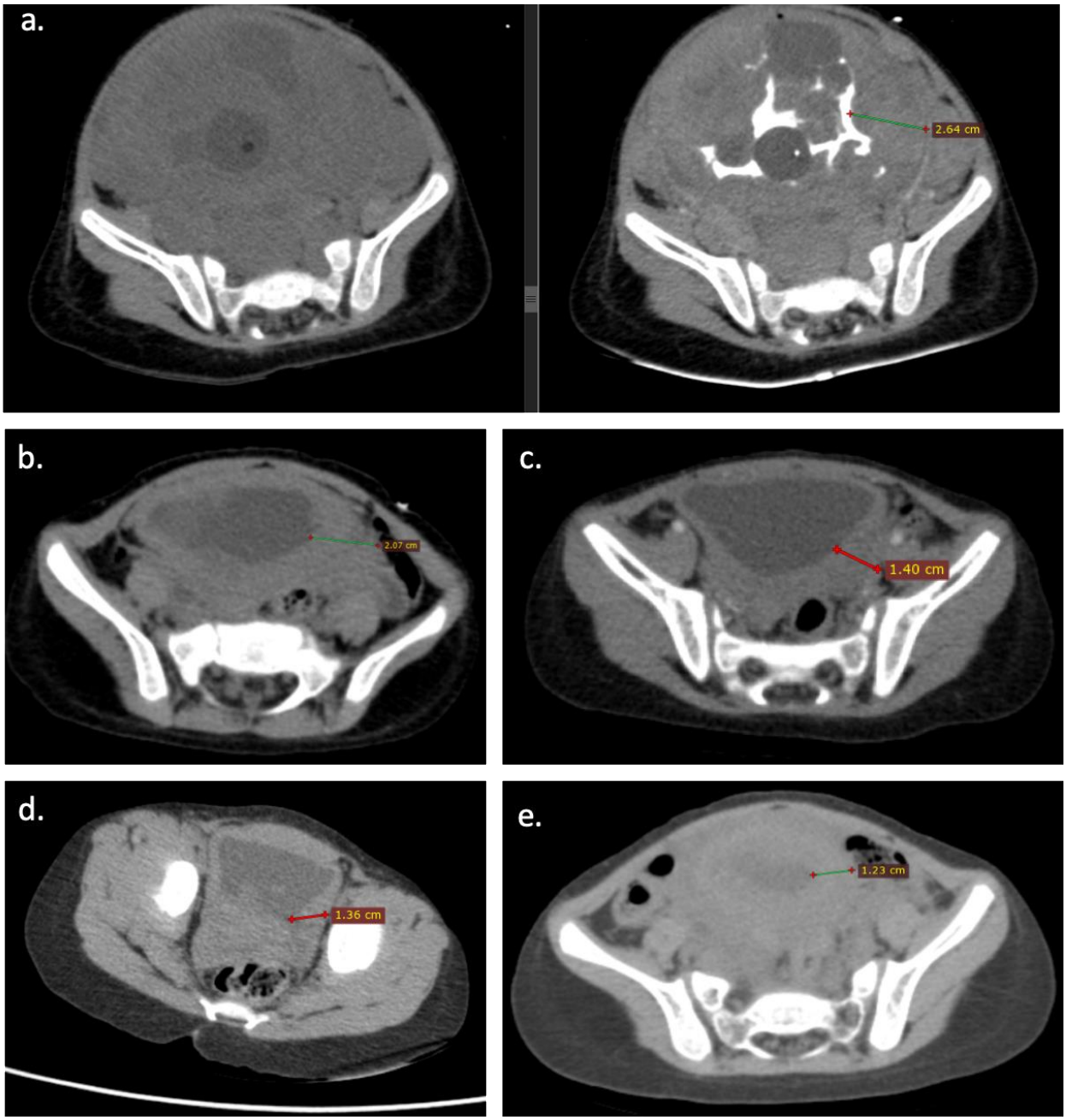

Figure 2. Multislice Computerized Tomography (MSCT) of the abdomen. (a) Before chemotherapy. (b) Durante chemotherapy. (c) After chemotherapy. (d) 1 Month after radiotherapy. (e) 6 months after radiotherapy.

radiation target volume encompassed the visible mass of the entire bladder. The prescribed dose was 38 Gy administered in 25 fractions. Intensity-modulated radiation therapy (IMRT) planning was carried out with a dose of 38 Gy distributed over 25 fractions (1.52 Gy per fraction). The therapy was administered using the LINAC Elekta over five fractions in a week.

Treatment Evaluation

During the course of external radiation administration, patients routinely consult with a radiation oncologist on a weekly basis to assess therapy outcomes and monitor side effects. Subsequent follow-up revealed a decrease in the lump in the pubic area and an improvement in symptoms, with no significant radiation side effects noted. However, upon post-radiation CT scan evaluation, it was determined that the reduction in mass was only 1% of the pre-radiation mass (stable response, according to RECIST 1.1). Clinically, it was also observed that the periurethral mass, which had decreased during radiation, exhibited regrowth after the completion of radiation therapy.

Discussion

The case described above illustrates an RMS that exhibited a partial response following

chemotherapy. Despite undergoing radiation, the reduction in the residual mass was not significant, indicating a stable response. This is indeed an uncommon occurrence for an embryonal RMS. Typically, RMS is a tumor that is relatively responsive to radiation. It falls within the histopathological group of "small round blue cells," which includes tumors like lymphoma, Ewing sarcoma, and neuroblastoma.[6] Tumors within this group typically demonstrate chemosensitive and radiosensitive properties.

The treatment of embryonal rhabdomyosarcoma varies based on its profile. For instance, radiation therapy is recommended for all patients except those with completely resected fusion-negative tumors.[7] Intermediate-risk patients, including those with fusion-positive tumors, typically receive radiation therapy regardless of the extent of resection. In the case of genitourinary RMS, except for paratesticular tumors, the standard care usually involves neoadjuvant chemotherapy followed by radiation therapy or a combination of chemotherapy and radiation therapy, with or without subsequent excision.[8] Additionally, a wide range of radiotherapy doses have been used, ranging from 36 Gy up to 55.8 Gy, using 1.5 to 1.8 Gy per fraction daily.[9] In our patient, the dose of 1.52 Gy per fraction was administered, taking into account the stage IV tumor and the patient's condition. Nevertheless, the young girl with a centralized bladder tumor extending to periurethral tissue and potentially affecting the uterus and genitalia, was treated accordingly.

Recent radiobiological findings by Petragnano et al. highlight the radioresistance of RMS.[10] This resistant type of RMS tends to be more aggressive and prone to have metastases. The RNS-RR tumor cell line was reported to have increased capability to detoxify reactive oxygen species and repair DNA through various non-homologous end-joining and homologous recombination pathways.[10] These cells resist arrest in the G2/M phase after radiation, facilitating easier repopulation post-radiation. The study also identified TGF-β, MIF, CCL2, CXCL5, CXCL8, and CXCL12 as key regulators in the immune evasion process of cancer cells in RMS. These results showed that RMS can develop intrinsic or acquired radioresistance through diverse mechanisms.

In the context of RMS, numerous factors have been reported to influence treatment responsiveness. For example, a previous study that examined Fusion genes involving forkhead box protein O1 (FOXO1) in alveolar RMS patients reported that Fusion-positive alveolar RMS was associated with a higher hazard ratio of 2.6 thus affecting survival.[11] Moreover, the standard chemotherapy regimen for rhabdomyosarcoma in Europe still involves ifosfamide, vincristine, and actinomycin D with cases of renal compromise, cyclophosphamide is often used along with vincristine and actinomycin D (VAC), a regimen also employed in North America confirming better treatment regimen for RMS affecting renal, similar to that observed in our study.[11] Despite rhabdomyosarcomas being recognized as chemosensitive tumors, a previous study in embryonal rhabdomyosarcoma patients who received radiotherapy as part of their initial therapy demonstrated a significant improvement of approximately 10%, with very high-risk patients also experienced a boost in 3-year event-free survival.[3] This finding prompts a role of radiotherapy in improving RMS patients outcome. In our case, there was a temporary amelioration of symptoms during the radiation process. However, upon cessation of radiation, tumor regrowth occurred, suggesting a more active post-radiation repopulation characteristic. Ultimately, the patient was scheduled to undergo chemotherapy again, as the response in chemotherapy was superior to radiotherapy. Nevertheless, this highlights that RMS exhibits radio-resistance characteristics, and radiation therapy provides symptomatic relief in RMS, particularly in pediatric embryonal RMS.

There are some limitations to our report. The assessment of symptoms in the patient was not conducted in this study and may need to be evaluated in the future for a more reliable comparison before and after treatment. Additionally, detailed data on grading, histological, and other immunohistochemistry findings were not available due to the limited sample obtained from the biopsy.

Conclusion

The case we reported indicates that embryonal RMS in the pediatric bladder might demonstrate radioresistance characteristics, but radiation therapy still plays a role in providing symptomatic relief. This

observation aligns with various previous studies illustrating the radioresistance of RMS through multiple mechanisms. Nevertheless, the extent of this radioresistance requires further substantiation through additional research, encompassing both *in vitro* investigations and larger-scale clinical studies.

Conflicts of Interest

The authors declare no competing interest in this study.

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