SUPER SELECTIVE EMBOLIZATION AND ETOPOSIDE ISOFOSFAMIDE CHEMOTHERAPY ON A PEDIATRIC BLADDER EMBRYONAL RHABDOMYOSARCOMA: A CASE REPORT

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ABSTRACT

Objective: *This study reports our experience in managing pediatric ERMS cases treated with super-selective embolization and chemotherapy.* ***Case(s) Presentation:*** *We present a case report about a 2-year-old boy with urinary retention. The complaint began with a history of urination difficulty that has not improved with urethral catheter insertion, thus percutaneous cystostomy was performed. However, a mass appeared in the cystostomy wound.* ***Discussion:*** *The biopsy result confirmed the diagnosis as a bladder embryonal rhabdomyosarcoma. Afterward, the patient was treated with super-selective embolization in both of internal iliac artery branches and it succeed to omit the bleeding symptom and growth of the suprapubic mass. The chemotherapy regimen (Etoposide, Mesna, and Ifosfamide) was administered subsequently for 2 cycles and it showed a satisfactory result in form of the reduction of obstruction symptoms and mass volume.* ***Conclusion:*** *Our case report shows that super-selective embolization and Etoposide Isofosfamide chemotherapy can provide adequate local control in a pediatric patient with bladder ERMS.*

Keywords: *Embryonal rhabdomyosarcoma, etoposide, isofosfamide.*

ABSTRAK

Tujuan: *Studi ini melaporkan pengalaman kami dalam menangani kasus ERMS pediatrik yang diobati dengan embolisasi super-selektif dan kemoterapi.* ***Presentasi Kasus:*** *Laporan kasus ini melaporkan seorang anak laki-laki berusia 2 tahun yang mengalami sulit buang air kecil. Keluhan diawali dengan riwayat kesulitan buang air kecil yang tidak membaik dengan pemasangan kateter uretra, sehingga dilakukan tindakan sistostomi perkutan. Namun, muncul benjolan di area luka sistostomi tujuh hari setelah tindakan.* ***Diskusi:*** *Hasil biopsi menunjukkan bahwa benjolan tersebut merupakan rabdomiosarkoma embrional kandung kemih. Pasien kemudian menjalani embolisasi super-selektif pada kedua cabang arteri iliaka interna untuk menghentikan perdarahan dan menghambat pertumbuhan tumor di daerah suprapubik. Setelah itu, pasien mendapat kemoterapi dengan kombinasi obat Etoposide, Mesna, dan Ifosfamide selama dua siklus. Hasil kemoterapi menunjukkan perbaikan klinis yaitu berkurangnya gejala obstruksi dan mengecilnya ukuran tumor.* ***Simpulan:*** *Kasus ini menunjukkan bahwa kombinasi embolisasi super-selektif dan kemoterapi Etoposide–Ifosfamide dapat memberikan hasil yang cukup efektif untuk mengendalikan penyakit pada anak dengan rabdomiosarkoma embrional kandung kemih.*

Kata kunci: *Rhabdomyosarcoma embryonal, etoposide, isofosfamide.*

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INTRODUCTION

Rhabdomyosarcoma is a type of tumor resembling skeletal muscle structure. The distinction between embryonal and other rhabdomyosarcoma subtypes is based on pathological findings showing a hybrid of round and spindle cells in a myxoid stroma.[1] An epidemiological study from Indonesia shows that rhabdomyosarcoma is often found in pediatric patients aged 1-5 years.[2] However, another study showed that there were only 0.9% of bladder cancer patients in Indonesia who showed the results of pathology examination presented as rhabdomyosarcoma.[3] Multimodal therapy provides children with newly diagnosed rhabdomyosarcoma an estimated 47% to 62% five-year survival rates.[4,5]

Chemotherapy, radiotherapy, and surgery are common modalities used in ERMS

management. Local control of ERMS is a lsoperformed to help the success of multi modal therapy and minimize long-term complications. Previous studies indicate that local control is less successful in bladder rhabdomyosarcoma with masses ≥ 5 cm compared to smaller lesions, emphasizing the need to explore alternative treatment modalities for larger tumors.[6] Previous studies demonstrate that super-selective embolization achieves good outcomes in controlling bleeding, reducing tumor size, and alleviating obstructive symptoms.[7]

The rarity of bladder ERMS cases motivates urologists to develop and report various treatment modalities. However, limited literature discusses the use of super-selective embolization combined with chemotherapy in ERMS, resulting in restricted treatment options. Therefore, this study reports our experience in managing pediatric ERMS cases treated with super-selective embolization and chemotherapy.

CASE(S) PRESENTATION

A 2-year-old boy was complained by his parents about urinary retention. The patient initially experienced difficulty urinating and straining during micturition, which did not improve after urethral catheter insertion. As the complaints worsened, the patient was taken to a peripheral hospital and an open cystostomy was performed. Subsequently, a mass emerged from the cystostomy wound and enlarged seven days following the procedure. The patient was referred to our institution for further treatment. The parents are also complaining about bleeding and urine leaks from the suprapubic mass. The patient had no history of birth defects and previous mass on the abdomen. The patient also has no family history of malignancy.

On physical examination, the patient had a weight of 10 kg and a height of 82 cm. The patient came with normal vital signs. In the initial encounter, there was a solid mass on the lower abdomen that had a lobular shape with a diameter of 4 cm, supple, firmly bordered, and accompanied by redness on the surrounding skin (Figure 1a). From the laboratory examination, a complete blood count showed anemia with an Hb value of 9.3 g/dl, leukocytosis with a value of 18,290 / µl, and thrombocytosis with a value of 715,000. The urinalysis examination showed the presence of microscopic hematuria and leukocyturia. However, the kidney function examinations showed normal values with blood urea levels of 46.5 mg/dl and blood creatinine of 0.85 mg/dl. Albumin level, electrolyte examination, and coagulation study showed a normal value. An abdominal computed tomography (CT) scan with contrast revealed a mass that filled up the bladder with a size of ± 8.1 x 5.8 x 6.2 cm, which was dominant on the anterior side of the bladder, and it extended outwards the abdominal wall (Figure 2a). In addition, it also shown severe hydroureteronephrosis on both sides of the kidney. Multiple lymphadenopathies were found in perivesical, presacral, and right inguinal regions. The CT scan failed to show the boundaries between the bladder, prostate, and rectosigmoid, thus the pelvic MRI examination was carried out after a percutaneous nephrostomy (PNS) and biopsy was performed. MRI results show a clear boundary between the bladder and the rectosigmoid, and no metastatic disease in other organs, such as the prostate, liver, or spine. However, the mass invaded the abdominal muscles and skin. (Figure 2b).

Multidisciplinary discussion was conducted to ensure the appropriate plan for the patient. The diagnosis process begins with a tumor biopsy to establish the diagnosis of rhabdomyosarcoma. Biopsy result revealed a polypoid tumor structure lined by epithelial cells, with underlying tumor proliferation characterized by hypercellularity and a diffuse mixture of stellate, round, and spindle-shaped cells in a fibromyxoid background. At higher magnification, the tumor cells exhibited broad, round-centered eosinophilic cytoplasm resembling rhabdomyoblasts, accompanied by atypical mitoses (Figure 2c). An immunohistochemistry assay was also conducted, and the results showed the expression of desmin and myosin.An attempt was made to remove the suprapubic mass (Figure 1b). However, within seven days the mass regrew to its original size without any symptomp improvement (Figure 1c). In addition, percutaneous nephrostomy ware also conducted to treat the hydroureteronephroses occurred on both sides of the kidneys.

The treatment was continued with super selective embolization performed by radiology interventionist. This procedure was performed to relieve the symptoms of bleeding arising from the suprapubic mass. Embolization was done by clogging the branches of the internal iliac artery bilaterally with polyvinyl alcohol (PVA) and gel foam allowing devascularization of the bladder

(Figure 3a-d). The procedure showed a satisfactory result, the bleeding stopped after the embolization was carried out. In addition, the suprapubic mass reduced from 19 x 13 x 9 mm before embolization (Figure 1c) to 10 x 9 x 6 mm (Figure 1d) and the urine production in the urethral catheter began to appear. Subsequently, intravenous chemotherapy was administered as systemic therapy. The patient was administered Etoposide (100 mgm^2), Mesna (360 mg /m^2), and Isofosfamide (1800 mg/m^2).[8,9] A good clinical response was shown by the patient during the chemotherapy session. After the 2nd chemotherapy session, the size of the suprapubic mass was reduced to 9 x 7 x 3 mm (Figure 1e) and the urethral catheter was removed because the patient could urinate spontaneously.

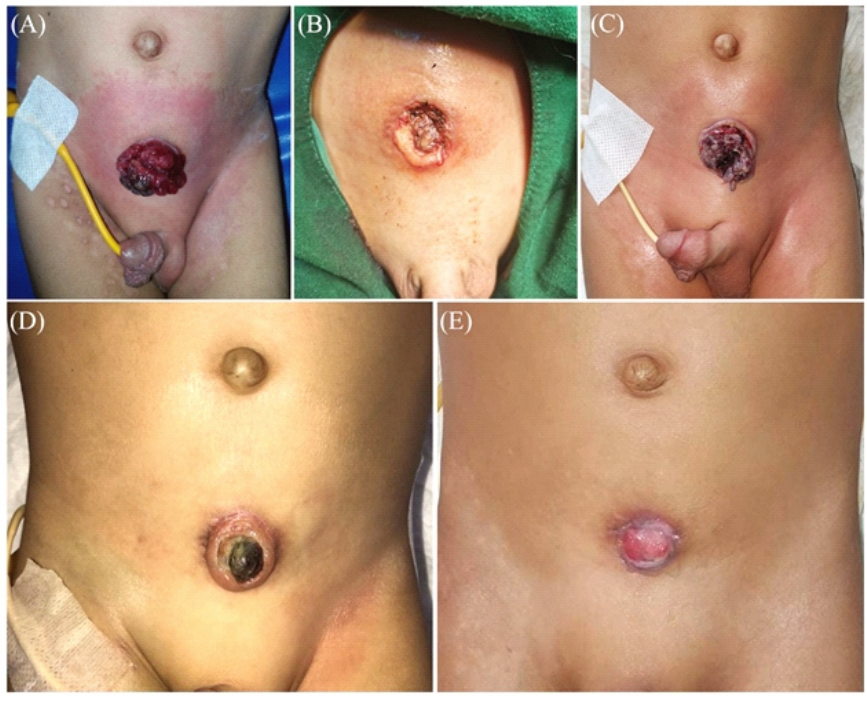

Figure 1. Clinical appearance of the suprapubic mass. a) the mass at the initial encounter; b) The mass after excisional biopsy; c) The mass 7 days after excision; d) The mass after embolization; and e) The mass after 2nd neoadjuvant chemotherapy session.

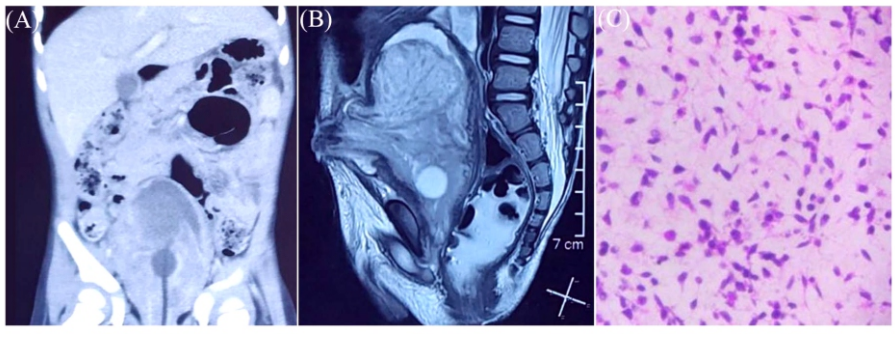

Figure 2. Radiology and histology examination results. a) The results of the abdominal CT scan showed a mass that fill the bladder; b) MRI results did not show rectosigmoid involvement and mass evisceration out of the abdominal wall; c) Anatomical pathology results showed an image of spindle, round, and stellate cells with a fibro myxoid base indicating embryonal rhabdomyosarcoma.

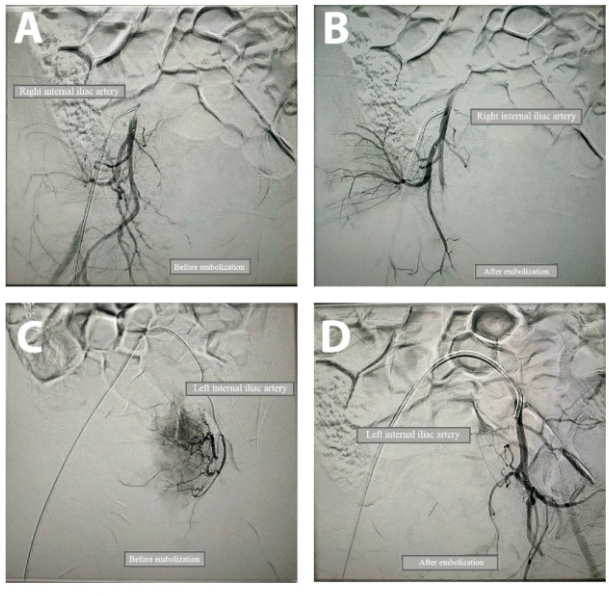

Figure 3. Digital subtraction angiography image between the prior and the results of super selective embolization.a) Images of bladder vascularies before embolization on the right side; b); after embolization on the right side; c) before embolization on the left side; and b); after embolization on the left side.

DISSCUSSION

Although cystostomy is relatively safe to be performed in acute urinary retention patient, some unforeseen complications, such as suprapubic masses growth, may occur. Several previous case reports reported the incidence of mass emerged from cystostomy wound with histopathological appearances as transitional cell carcinoma, squamous cell carcinoma, and rhabdo-myosarcoma.[10-12] The explanation for the pathogenesis of this condition is not clear yet, but some hypotheses involve irritation, local damage, and genetics as the cause.[12] The initial symptom can obscure the diagnosis when the cause of urinary retention is still indistinguishable through history taking and gross hematuria does not appear. In addition, physical examination cannot always show the presence of intrabladder masses, such as palpable masss in the suprapubic region, thus bladder ERMS have a high rate of misdiagnosis or delayed diagnosis.[12-13] However, our case presents a 2-year-old boy who had a history of acute urinary retention. The cause of acute urinary retention in children has an incidence rate of 8.48 per 100,0000 cases with many etiologies, but the most frequent case of acute urinary retention in children is mechanical obstruction, neoplasms are one of it.[13] Simple examinations such as ultrasonography (USG) can be considered to rule out anatomical abnormalities that can cause lower urinary tract obstruction in acute urinary retention case before invasive or semi-invasive procedures are planned to be performed.[14]

The management of the bladder ERMS includes multimodal therapies such as systemic chemotherapy, surgery, radiation therapy, or a combination of various modalities to achieve maximum local control of the tumor. In our case, the cancer infiltration to the abdominal muscles and skin made the radical cystectomy procedure difficult. Extensive excision of the skin and abdominal wall may be necessary, which increases the risk of postoperative complications and mortality.[15] Therefore, superselective embolization and chemotherapy were selected as treatment options. Although it has been introduced since 1973, the use of super selective embolization has not been widely discussed in the various guidelines for handling bladder ERMS and other types of bladder cancer. The reason behind it may be caused by inconsistent results from previous studies involving super selective embolization techniques on hematuria treatment in bladder cancer, the success rate ranged from 16% to 100% (Table 1).[16-17] However, our results are concordance with study conducted by Lei et al, which showed an improvement in bleeding symptoms and reduced mass size after devascularization of the branch internal iliac artery was performed.[7] In addition, our patients also showed improvement in obstruction symptom, but study on this subject was still not widely discussed. For example, Wang et al study discussed the improvement of obstruction symptoms after super selective metabolized was performed on prostate cancer patients. Mechanical obstruction can be relieved by the mass shrinkage, yet well-designed studies are needed to prove this hypothesis.[18] The side effects of embolization are also minimal. In our case, no complications such as gluteal pain or fever were observed after embolization. Unfortunately, super selective embolization has not been able to resolve the intrabladder mass that was present as the main problem.

Chemotherapy is a therapeutic option that used in the management of bladder cancer, especially in muscle invasion or metastasis case.

Table 1. Published systematic reviews discussing embolization to treat hematuria due to bladder cancer and other causes.

Author	Year	Number of study	Population	Outcomes of interest
Taha, et al	2018	27	Hematuria caused by bladder cancer, bladder mestastasis, radiation cystitis, and hemorrhagic cystitis	- Clinical success rate ranging from 43%100% - Post embolization syndrome reported in two studies (24% and 64%) and few studies reported minor complications - PVA usage as embolic agent reported in two studies, internal iliac artery targeted in 2 studies, and performed bilaterally in 5 studies
Chen, et al	2021	13	Hematuria caused by bladder cancer, bladder mestastasis, radiation cystitis, and hemorrhagic cystitis	- Pooled clinical succes rate is 80.9% (ranging from 16%-100%) - Reported major complication rate is 5.5% and minor complication rate is 31.8% - Most studies used PVA (38,6%) as an embolic agent, targeted the anteriordivision of the internal iliac artery (73,3%), and were performed bilaterally (81,1%)

Lymphogenous and hematogenous pathways of sarcoma make the malignant cells spread rapidly to the surrounding organs. The combination of cisplatin and gemcitabine chemotherapy is the first line commonly used on the case of bladder cancer, but the VAC (Vincristine, Dactinomycin, and cyclophosphamide) chemotherapy regimen is more commonly used in ERMS cases specifically.[9] However, alternative option was made because our institution did not have dactinomycin avalaible. Studies by Grier et al showed that the administration of Etoposide and Isofosfamidehad no difference in five year event free survival rate compared to VAC regiment in patients with Ewing's Sarcoma.[19] Studies by Miser et al also showed that 69.2% of cases of rhabdomyosarcoma had a complete or partial response with the administration of Etoposide, Mesna, and Isofosfamide. This regimen was able to reduce the tumor size in 34.7% of cases, as also observed in our patients. The study explained that side effects arising were tolerable, as follows neutropenia in 97% of patients, thrombocytopenia in 32% of patients, and fever in <1% of patients from the 124 study samples.[8]

There are some limitations in our report. First, the evaluation imaging cannot be shown because the patient expired before the evaluation was performed, so the case report is only able to compare clinical presentations chronologically. Second, radical cystectomy cannot be performed so the complete benefits of super selective embolization and neoadjuvant cannot be presented. We recognize that our case contributes meaningful insight to the limited literature on bladder ERMS. Opportunities for additional research in this area remain widely open. Well-designed research is needed to prove the benefits provided by the super selective embolization and chemotherapy administration on the treatment of ERMS.

CONCLUSION

The case report we presented shows that bladder ERMS is a rare case that requires complex management. The super selective embolization and Etoposide Isofosfamidechemotherapy regimen can provide benefits to relief obstruction symptoms and reduce the tumor volume in our patient.

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