

Bladder granulocytic sarcoma in a child: case report and literature review

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ABSTRACT

Background. Granulocytic sarcoma (GS) is an extramedullary solid tumor composed of immature myeloid cells. GS has been associated with acute myeloid leukemia (AML), myelodysplastic syndromes or myeloproliferative diseases. Although GS can affect various tissues of the human body, it has rarely been reported in other soft tissues such as the breast, gastrointestinal, respiratory and genitourinary tracts. We report a pediatric case diagnosed with granulocytic sarcoma of the bladder and concomitant AML.

Case. A twelve-year-old previously healthy girl was admitted to the pediatric urology clinic with a ten-day history of hematuria and pollakiuria. Laboratory examinations revealed anemia, thrombocytopenia and neutrophilic leukocytosis. Bone marrow aspiration results were consistent with acute myeloid leukemia -FAB subtype M2-. Abdominal magnetic resonance imaging (MRI) showed an irregularly bounded 12 cm mass on the right side of the bladder. Transurethral resection (TUR) pathology was consistent with granulocytic sarcoma. After a multimodal treatment approach, complete remission was achieved.

Conclusions. Malignant bladder masses are rare causes of macroscopic hematuria in childhood. The diagnostic spectrum is wide, ranging from rhabdomyosarcoma to leukemia involvement. The bladder is a rare site of extramedullary involvement in pediatric patients with AML. Multimodal treatment should be considered on a per-patient basis.

Key words: acute myeloid leukemia, children, granulocytic sarcoma, bladder, treatment.

Granulocytic sarcoma (GS) is an extramedullary solid tumor composed of immature myeloid cells. Initially, it was named chloroma as a word originating from greenish color in the 1850s. GS has been associated with acute myeloid leukemia (AML), myelodysplastic syndromes or myeloproliferative diseases. More frequently than in adults, it is seen approximately 10 % concomitantly at the time of diagnosis of pediatric AML.¹⁻³ GS can be

seen as isolated extramedullary without bone marrow involvement at the time of primary diagnosis or relapse, can proceed to bone marrow involvement or occur later in the course of primary AML disease. Although GS can affect various tissues, the most frequent extramedullary involvement sites in children are; skin, central nervous system, gingiva, bone and, orbit.¹ It has rarely been reported in other soft tissues such as the breast, gastrointestinal, respiratory and genitourinary tracts.⁴⁻⁸ We report a pediatric case presented with hematuria, diagnosed with granulocytic sarcoma of the bladder and concomitant AML. To our knowledge, this is the 4th pediatric case of granulocytic sarcoma of the bladder in the

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Received 5th February 2020, revised 16th April 2020,
9th February 2021, 28th February 2021,
accepted 3rd March 2021.

literature. We presented this case due to its rare involvement site, and to discuss treatment modalities.

Case Report

A twelve-year-old previously healthy girl was admitted to the pediatric urology clinic with a ten-day history of hematuria and pollakiuria. Family history was unremarkable. Physical examination revealed no abnormality other than paleness. Vital signs were within normal limits. Laboratory examinations revealed anemia (hemoglobin 7.1 gr/dL), thrombocytopenia (platelet count 45.700/ μ l) and neutrophilic leukocytosis (white blood cell count was 20300/ μ l, the neutrophil count was 11000 / μ l, lymphocyte count was 6900/ μ l, respectively). The erythrocyte sedimentation rate was elevated (77mm/hr). Blood chemistry and coagulation parameters were normal with age-appropriate values. Urine analysis revealed three positive erythrocytes, three positive leukocytes and two positive protein with leukocyte esterase negativity. Pediatric hematology-oncology consultation was requested due to bicytopenia before cystoscopy. Peripheral blood smear revealed no abnormal cells. Bone marrow aspiration showed hypercellular marrow with leukemic infiltration; myeloid blasts with large cytoplasm and occasional granulation were 60% of bone marrow cells. Immunohistochemical studies demonstrated positive staining for

MPO, lysozyme, CD68, and CD33. Flow cytometry revealed high positivity for CD 13 and 33. Cytogenetic analysis revealed translocation t (8; 21). Consequently, acute myeloid leukemia -FAB subtype M2- diagnosis was established. Abdominal magnetic resonance imaging (MRI) showed a mass originating from the right side of the bladder wall, extending into the lumen, measuring 12 cm in diameter and presenting irregular, lobulated margins (Fig. 1a). Transurethral biopsy pathology showed malignant round cell tumor, immunohistochemical studies were consistent with granulocytic sarcoma (Fig. 2). The patient was started on MRC AML 2012 protocol chemotherapy.⁹ After 2 cycles of induction (ADE), bone marrow remission was achieved but pelvic MRI showed residual bladder mass despite marked regression (Fig. 1b). After 4 cycles of chemotherapy (2*ADE+ MACE+MidAC) bladder mass persisted. Transurethral resection was performed to clarify the content of the residual mass. Especially due to the special localization of the tumor, pathological evaluation of the mass was preferred before radiotherapy decision. Pathology results confirmed the diagnosis of granulocytic sarcoma. Radiotherapy was planned to the primary tumor location for local control. Bilateral oophoropexy was performed for fertility preservation. Radiotherapy was applied to the bladder region at the dose of 18 Gy in 10 fractions followed by one

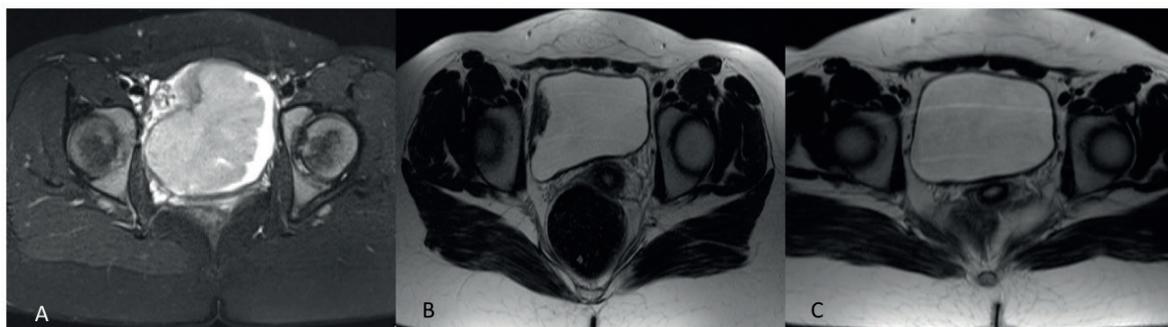


Fig. 1. (A) Initial MR image of bladder mass; T2 weighted fat saturated axial MR image shows hyperintense solid mass with lobulated contour, extending into the bladder lumen. **(B)** T2 weighted axial image reveals marked regression of the lesion after 2 cycles of induction chemotherapy and **(C)** total resolution after the end of the treatment.

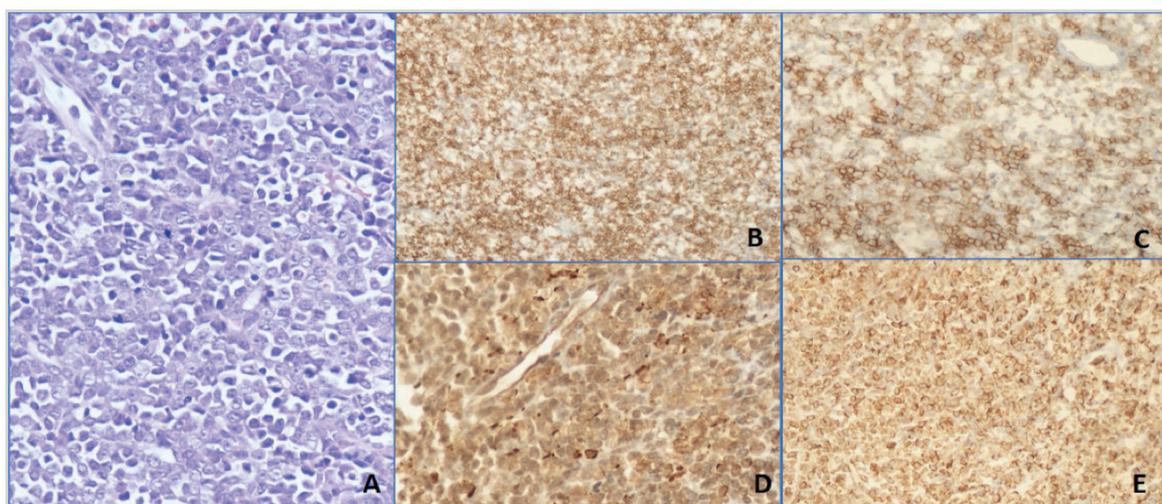


Fig. 2. Transurethral resection pathology: Bladder granulocytic sarcoma (A) Diffuse blastic cell infiltration is seen (H&E, 40X). Tumor cells were positive with CD117 (B), CD56 (C), CD68 (D) and myeloperoxidase (E).

course of chemotherapy (CLASP). At the end of the chemoradiotherapy, MRI showed total resolution of the bladder mass (Fig. 1c). Considering the incomplete response to treatment with persistence of extramedullary involvement at the end of induction and consolidation chemotherapy, she was stratified as high risk despite favorable genetic features of AML. Therefore hematopoietic stem cell transplantation (HSCT) was approved by the HSCT board. She went to allogeneic HSCT from HLA matched unrelated donor. She remains in complete remission for more than 5 years, outpatient follow up is ongoing. Informed consent for publication of this case was obtained from the children and the parents.

Discussion

Granulocytic sarcoma is an extramedullary solid tumor composed of myeloid lineage leukemic cells, which can be seen in the course of myeloid leukemia or myeloproliferative disorders. The molecular pathogenesis of the invasion and accumulation of immature cells in various tissues is not fully understood.¹⁰ It has been shown that invasive acute myelogenous leukemia cell lines have higher expression of matrix metalloproteinase 2-9, membrane type 1 metalloproteinase and tissue

inhibitor of metalloproteinase 1-2 compared to normal bone marrow cells and less invasive leukemic cell lines.¹¹⁻¹³ Higher expression of metalloproteinases was considered to be associated with the invasion and metastasis capacity of solid tumors.^{14,15} It also increases the invasion capacity of leukemia cells and is associated with extramedullary infiltration.^{11,16}

In the absence of bone marrow involvement, diagnosing GS can be challenging and requires clinical suspicion. Appropriate immunohistochemical studies are essential for differential diagnosis with non-Hodgkin lymphoma, small round cell tumors and undifferentiated carcinoma, especially for isolated GS.^{17,18} GS with skin involvement is mostly seen in M4 (myelomonocytic) and M5 (monocytic) subtypes of AML, while M2 (mature myeloblastic) is more common in patients with GS in other sites.^{1,2} The most common cytogenetic abnormalities are t(8;21)(q22;q22) and inv(16)(p13;q22), the latter is associated with extramedullary disease in abdominal sites.¹⁸ The evidence on the effect of extramedullary involvement on favorable genetic features and prognosis is inadequate. In a study of 84 adult AML patients with t(8;21) published in 1997, extramedullary involvement was shown to significantly reduce

survival.¹⁹ A population-based cohort study on 315 children with AML showed that the presence of extramedullary involvement, which corresponds to 23% of total cases, significantly reduced 5-year overall survival.²⁰

Despite extramedullary infiltration being relatively common in childhood AML compared to adults, there are a few case reports of bladder involvement in children.^{8,21-23} Other rare sites of GS in children are gallbladder, nasal and oral cavity, perineum, small intestine, colon, and testicles.^{7,24-28} It shows different signs and symptoms according to localization. Bladder involvement presents with hematuria, pollakiuria, dysuria, fatigue, pallor, urinary incontinence, urinary retention, suprapubic and flank pain. Obstruction and hydronephrosis can lead to acute renal dysfunction and decreased creatinine clearance.

There are a couple of pediatric cases of granulocytic sarcoma of the bladder in the literature (Table I). The first one was a 16-year-old boy who was previously diagnosed with AML, came with isolated bladder GS after bone marrow transplantation. He was treated with radiotherapy but progressed to AML and died.²¹ The second case was a 4-year-old previously healthy boy who was diagnosed with AML with bladder GS. The primary mass biopsy was not performed but there were myeloid blasts in the urine with flow cytometric examination.²² In this case, the presence of myeloid blasts in the urine suggests that leukemic cells may spread within the urinary system, likewise, they do in the cerebrospinal fluid. In this case, remission was achieved with chemotherapy alone. The last case was a 18 month-old previously healthy girl who was diagnosed with bladder GS concomitant with AML. She died with febrile neutropenia after the first cycle of induction chemotherapy.²³ Our patient who had newly diagnosed bladder GS concomitant with AML had achieved complete remission with 5 courses of chemotherapy, local radiotherapy, and allogeneic hematopoietic stem cell transplantation without serious toxicity.

GS should be treated as AML whether there is bone marrow involvement, or not. Even in isolated GS, progression to AML occurs without systemic therapy.¹⁰ Multimodal treatment must include combinations of chemotherapy and radiotherapy, surgery or hematopoietic stem cell transplantation on a patient-specific basis. A study from Children's Cancer Group (CCG) including 1832 newly diagnosed pediatric AML patients shows a higher survival rate in patients diagnosed with AML plus GS in the sites other than skin compared with AML plus skin involvement or isolated AML. In the multivariate analysis, other favorable prognostic factors were low initial leukocyte count, female gender and FAB M2 subtype. According to this study, local radiotherapy to tumor sites did not improve the outcome.² However, heterogeneity of the groups with and without radiotherapy constitutes an uncertainty for this result.

In a cohort of 38 adult and child patients with GS, the longest median survival rate with 109 months was observed in patients with genitourinary system involvement compared to other sites.²⁹ Local treatment with radiotherapy or surgery should be considered for patients with GS and concurrent AML in case of residual tumor despite bone marrow remission after induction chemotherapy likewise for patients with isolated GS as consolidation.^{10,30,31} Local treatment modalities can also be used as a part of the initial treatment, in case of a need for palliation and symptom relief or relapse, considering tumor size and localization.^{27,31} While lower doses less than 20 Gy are efficient, doses up to 30 Gy can be used for radiotherapy in children for extramedullary involvement of AML.²⁹ Gonad protective measures for fertility preservation should be considered before radiotherapy to the genitourinary region. Several studies show favorable results with allogeneic HSCT in adult patients with GS, pediatric data did not show a clear benefit for survival despite decreased relapse rates.^{9,32,33} For the decision of HSCT in children with AML, reclassification of high-risk patients based on both genetic features and chemotherapy

Table I. Characteristics of reported pediatric cases with granulocytic sarcoma of bladder.

Case	Age	Gender	Past medical history	Symptoms	Imaging	Mass biopsy	Bone marrow examination	Diagnose	Treatment	Bone marrow involvement	Outcome	Reference
1	12 yr	Female	Healthy	Gross hematuria, pollakiuria	Abdomen MRI: Irregularly bounded 12 cm mass extending from right side of bladder wall to lumen	Round cell malignant tumor IH: P positive for LCA, CD 56, MPO, CD 68, CD 117 and negative for desmin, TdT.	60 % myeloblasts AML (FAB M2)	AML Primary diagnose	5 course of chemotherapy (AML MRC12) Local radiotherapy Allogenic BMT	Concomitant with granulocytic sarcoma	CR	Present Case
2	18 mo	Female	Healthy	Bilateral orbital swelling, intermittent gross hematuria, fever, gum swelling	Abdomen CT: Polypoid mass lesions in bladder wall measuring 4 * 2.8 cm	Small-medium sized, round to oval tumor cells with high N: C ratio and collagenous stroma. IH: Positive for vimentin, CD34, CD99, CD44, CD117 and MPO and negative for desmin, tDt, CD3, CD4, CD8, CD10 and CD19.	60 % myeloblasts AML	AML Primary diagnose	Chemotherapy	Concomitant with granulocytic sarcoma	Died	Kumar et al. ²³
3	4 yr	Male	Healthy	A febrile syndrome, abdominal pain, pallor	Ultrasound: Solid, vascularized, heterogeneous, polypoid formation measuring approx. 8*6* 3.2 cm involving posterior bladder wall	Primary mass biopsy: Not performed Urine flow cytometri: Myeloid blasts	AML	AML Primary diagnose	Chemotherapy	Concomitant with granulocytic sarcoma	CR	Kaplan et al. ²²
4	16 yr	Male	AML- FAB M2 BMT	Gross hematuria	Ultrasound: Moderate hydrourteronephrosis on left side Cystoscopy: 30*20mm rounded mass at left ureteral orifice	Large, primitive mononuclear cells demonstrating variable cytoplasmic granule formation and nuclear maturation, positive granulocytic differentiation with naphthol ASD-chloracetate esterase and lysozyme	Hypocellular marrow with no leukemic infiltration (blasts 3.5%)	AML relapse	Local radiotherapy	2 months after treatment of granulocytic sarcoma	Died after bone marrow relapse	Cartwright et al. ²¹

AML: acute myeloid leukemia, BMT: bone marrow transplantation, CR: complete remission, IH: immunohistochemistry, MRI: magnetic resonans imaging, MPO: myeloperoxidase, CT: computed tomography, yr: year, mo:month.

response improves the outcome according to multicenter studies.^{34,35} However the effect of extramedullary tumor response to therapy on the risk groups is not clear. Clinical trials for molecular targeted therapies in selected patients are ongoing.³⁶

Malignant bladder masses are rare causes of macroscopic hematuria in childhood. Diagnostic spectrum is wide, ranging from rhabdomyosarcoma to leukemia involvement. The bladder is a rare site of extramedullary involvement in pediatric patients with AML. There is no current clinical consensus guideline for the treatment of this rare disease. Multimodal treatment including chemotherapy, radiotherapy, surgery, hematopoietic stem cell transplantation, and targeted therapies should be considered on a patient-specific basis.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: RT, SK; data collection: RT, ZB, ÖD; analysis and interpretation of results: RT, SK, TO, SA, ÖD, AÜ, DT, ZB, SÇK, AİÇ, ZK; draft manuscript preparation: RT, SK. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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