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CASE BASED REVIEW

Juvenile polymyositis associated with ureteral necrosis: a diagnostic and therapeutic dilemma—case report and review of the literature

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Abstract
We describe an 11-year-old girl, diagnosed with juvenile polymyositis (JPM), who developed right ureteral obstruction secondary to necrosis. We emphasize the dilemmas regarding optimal timing for surgical intervention and medical treatment. Vascular involvement, which could be a part of juvenile dermatomyositis, may also be a feature of JPM. We discuss the association between vasculopathy and ureteral necrosis and review the literature regarding similar conditions. Whether the ureteral necrosis is a specific feature of vasculopathy, or a result of visceral calcinosis, needs to be further explored.

Keywords Calcinosis · JDM · JPM · Juvenile dermatomyositis · Necrosis · Polymyositis · Stenosis · Ureter · Vasculopathy

Background

Juvenile polymyositis (JPM) is a rare condition that accounts for only 3–6% of childhood idiopathic inflammatory myopathies (IIM) [1]. Muscle weakness is an essential component of the diagnosis of JPM, as there is no skin involvement. Therefore, muscle biopsy is required according to the SHARE consensus-based recommendations for juvenile dermatomyositis (JDM) [2].

Visceral vasculopathy occurs in a minority of children with IIM. Currently, ureteral necrosis is listed under the visceral vasculopathic complications of dermatomyositis. Only a few reports of bilateral ureteral necrosis among dermatomyositis patients have been published [3–8]. To the best of our knowledge, ureteral necrosis related to polymyositis or JPM has not been described previously in the literature. We attempted to link between this rare phenomenon and the systemic disease, while emphasizing the dilemmas regarding optional treatment approaches.

Case presentation

An 11-year-old female was admitted to the pediatric ward following 2 months of bilateral limb weakness, paresthesia, nuchal pain, swallowing difficulties, and hypophonia, without any apparent skin lesions. Past medical history was unremarkable, except for maternal urolithiasis.

Physical examination revealed pallor, mild hepatomegaly, joint tenderness, and severe muscle weakness with a very low Childhood Myositis Assessment Scale (CMAS) score. Tendon reflexes were normal. Neuropathy was ruled out after neurological assessment. Nailfold capillaroscopy was normal. Electrocardiogram, echocardiography, pulmonary function tests, and chest radiograph were normal.

Laboratory work-up revealed elevated muscle enzymes (creatinine kinase up to 1752 μ/L, lactate dehydrogenase up to 1273 μ/L, aspartate transaminase up to 89 μ/L), with mildly decreased serum albumin, mild normocytic anemia, and thrombocytosis. Acute phase reactants were normal, and comprehensive infectious work-up was negative. Tuberculin skin test was negative (5 mm diameter). Myositis-specific antibody panel was negative. Urinalysis was normal.

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Magnetic resonance imaging scan directed to the quadriceps revealed diffuse myositis

Histopathological analysis of the biopsied quadriceps revealed perifascicular atrophy of striated muscles with capillary loss, and marked inflammatory infiltrates, mainly perimysial, perivascular, and perineural, composed of small CD20-positive B-lymphocytes, CD3-positive T-lymphocytes (CD4-positive cells more than CD8-positive cells), CD138-positive plasma cells, CD163-positive macrophages, a few eosinophils, and a few neutrophils. Fibrinoid necrosis or granulomas were not seen. These findings were compatible with inflammatory myopathy. As there was no skin involvement, JPM was diagnosed.

Treatment was initiated with intravenous methylprednisolone pulses. This was followed by oral prednisone and subcutaneous methotrexate.

Muscle strength improved. However, before completing 1 month of therapy, she began complaining of abdominal pain and returned for reevaluation. Abdominal sonography revealed moderate right hydronephrosis and mild dilatation of the middle and upper portions of the right ureter. A computed tomography scan without contrast media revealed a 3 × 16-mm cylindrical, hyperdense body within the distal right ureter (Fig. 1a, b). These findings were initially diagnosed as obstructive uropathy secondary to urolithiasis.

Laboratory work-up revealed mildly elevated creatinine and urea serum concentrations and elevated urinary calcium to creatinine ratio (0.3 to 0.37, normal < 0.2), but urinalysis was normal, without erythrocyturia. Some urine cultures yielded the growth of bacterial or fungal contaminants only. Conservative urolithiasis treatment was initiated.

As there was no clinical or sonographic improvement, primary ureteroscopy with laser lithotripsy was planned for stone evacuation. Direct ureteroscopy on the sixth day of hospitalization visualized a fluffy, white, necrotic mass obstructing the ureteral lumen. Ureterolithiasis was ruled out. A fragment of the tissue was retrieved for histopathological analysis. Retrograde ureterography showed extravasation of the contrast media at the level of the necrotic segment. A catheter and double-J stent were introduced to the kidney, bypassing the necrotic segment. A nephrostomy tube was inserted to facilitate drainage. Broad spectrum antibiotic treatment was initiated, and after short cessation, anti-inflammatory drugs were renewed.

Histopathology described the extracted tissue as collagenous, with smooth muscle fibers within. Necrosis with multiple calcifications was noted (desmin stain emphasized necrotic muscle fibers). Obstructing calcifications were noted within small blood vessels, but without vasculitis (Fig. 2a, b). Differential diagnoses included visceral vasculopathy, but also schistosomiasis. Although endemic in the patient's country of residence, serologic tests for schistosoma were negative.

Definitive surgical intervention was postponed until medical therapy was completed. Six doses of monthly intravenous immunoglobulin (IVIG) were added due to severity of the visceral disease. Subsequently, right ureteroneocystostomy was performed after 2 months. The distal affected ureter was resected, and the proximal healthy ureter was anastomosed to the bladder; a ureteral stent was temporarily inserted to protect the anastomosis. The nephrostomy tube was extracted.

Pathology report of the resected ureter revealed moderate, acute, and chronic inflammatory infiltrates within the ureter wall, urothelial erosions, and superficial granulation tissue; degenerated smooth muscle fibers within the muscularis propria, some of which were infiltrated with lymphocytes and plasma cells; and multiple calcifications within the lamina propria. Fragments of gross calcifications were also noted. Similar calcifications were seen in other parts of the ureter (Fig. 3a). Obstructing calcifications were again noted within small blood vessels (Fig. 3b). Following normal recovery, she was discharged on post-operative day 4.

At 24 months postoperative follow-up, the patient was in complete remission under methotrexate treatment, with normal CMAS score. She had no urinary complaints, except one hospitalization due to *Escherichia coli* pyelonephritis, proximal to the operated ureter. Hydronephrosis had resolved on ultrasound scan, and no apparent skin lesions or calcinosis cutis were ever documented.

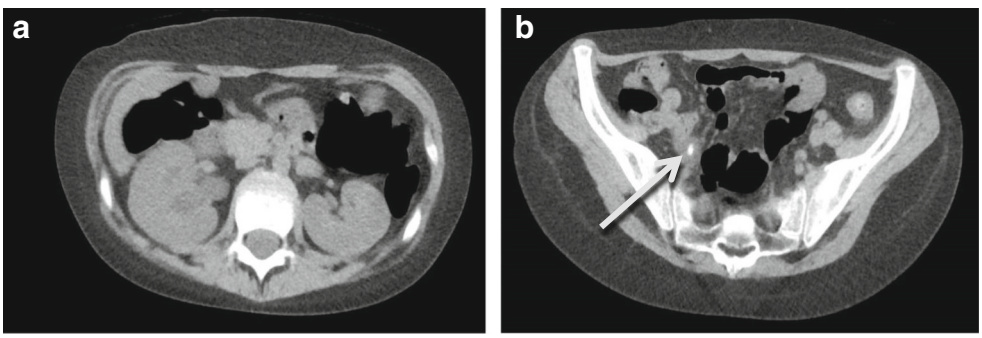

Fig. 1 **a** (left), **b** Abdominal CT scan findings: moderate dilatation of the right renal calyces (a) and renal pelvis, and a cylindrical, hyperdense body within the distal right ureter (arrow, b)

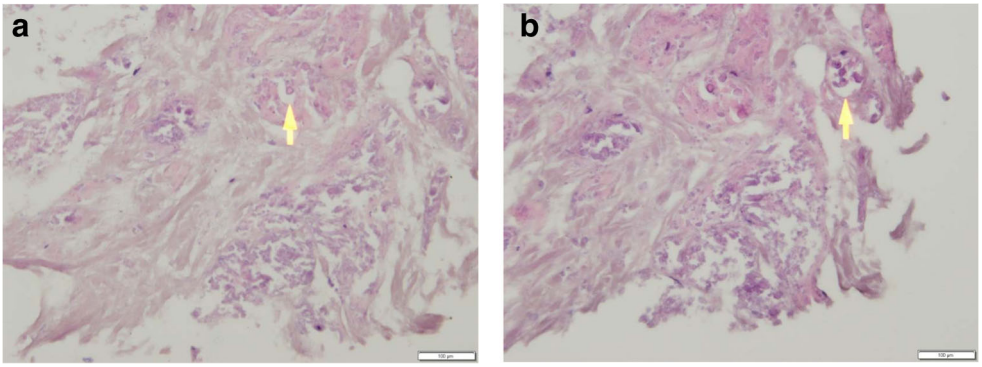

Fig. 2 **a** (left), **b** Histopathological analysis of the extracted fragments from the perforated ureter: necrotic collagenous tissue with smooth muscle fibers and calcifications (**a**), some of which were located within small vessels, as an obstructing mass (arrow, **b**)

Discussion

To the best of our knowledge, ureteral necrosis, a probable vasculopathic complication related to dermatomyositis and JDM, has not been described previously among patients with polymyositis or JPM.

Although symptoms related to muscular inflammation are similar, many aspects of JPM and JDM differ. Patients with JPM tend to be older than patients with JDM, with onset in preteen or teenage years (about the age of 12 years), and there is a significantly lower proportion of Caucasian patients with JPM compared with JDM [9]. JPM patients tend to present with higher creatinine kinase levels, more myalgia, and more severe illness. Cardiac involvement occurs among approximately 30% of JPM patients. Microscopic pathological findings differ from JDM and include frequent endomysial CD8+ T cell infiltrates in affected muscles [10]. Both are considered autoimmune disorders. JPM patients frequently have myositis-specific and myositis-associated autoantibodies, particularly anti-tRNA synthetases (anti-synthetases), especially anti-Jo1, anti-signal recognition particle (SRP), and anti-Pm-Scl autoantibodies. In one study, anti-SRP antibodies, which were found in JPM patients only, were also the most frequent autoantibodies present in JPM patients (18.2%) [9]. Pathogenesis relies on excess type I interferon production and downstream immune cellular activation and vasculopathy [11]. Visceral vasculopathy is a rare complication. It usually occurs soon after the onset of the disorder. It is a sign of poor outcome, associated with a higher mortality rate [12]. It seems that ureteral necrosis is a result of visceral vasculopathy, although the pathogenesis is obscure and the presence of multiple calcifications within tissues may be related to the pathogenesis of the typical calcinosis related to these diseases.

A combination of prednisone and methotrexate is considered the proven therapy for JDM [13]. The use of second- and third-line agents varies considerably among physicians and depends strongly on prognostic factors [12, 14, 15].

In order to address the many dilemmas this case presented, a multi-disciplinary team involving rheumatologists, urologists, and a nephrologist collaborated. Pros and cons of early vs. delayed intervention for definitive repair of the ureter, as well as surgical risks, were discussed. Some favored immediate surgery, because the procedure was simpler and would minimize the immune-suppressed patient's exposure to possible infectious agents while catheterized. Those in favor of delaying the operation found the risk of operating on tissue with uncertain pathology and healing potential too high. The final decision was to delay surgery for 2 months, while adding IVIG to enhance treatment.

We searched PubMed, Medline, and Scopus regarding the possible relation between inflammatory myopathies and uropathy. Using the keywords polymyositis, dermatomyositis, ureter, ureteral, necrosis, calcinosis, obstructive uropathy, and urolithiasis, only a few reports were found [3–8], all relating to female patients with dermatomyositis (Table 1). All but one were 9 to 11 years of age when ureteral calcinosis, stenosis, or necrosis was discovered. All patients complained of abdominal or flank pain, with or without fever or gross hematuria, and

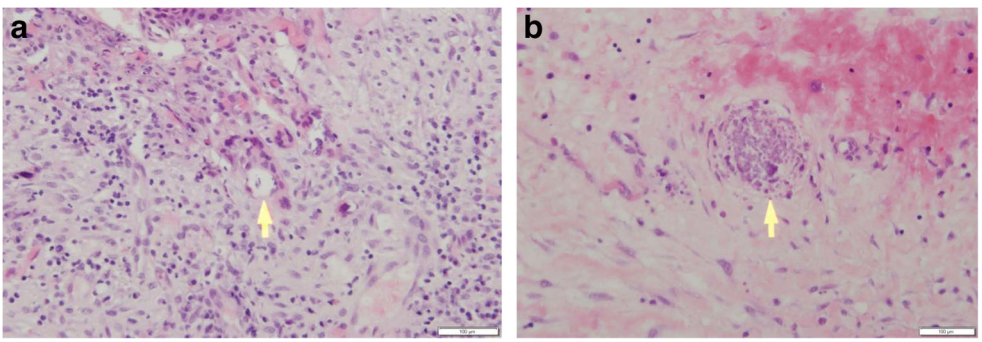

Fig. 3 **a** (left), **b** Histopathological analysis of the biopsied urinary bladder during uretero-neocystostomy: calcifications were noted within the bladder wall, accompanied by a few giant cells of foreign body (**a**). Calcifications were also located within small vessels, as an obstructing mass (arrow, **b**)

Table 1 PubMed and Medline search results and included and excluded articles

PubMed/Medline search terms	Number of articles found	Articles included (reference #)	Articles excluded	Reasons for exclusion
Polymyositis / dermatomyositis + ureter + necrosis	2	References [5, 6]	0	–
Polymyositis / dermatomyositis + ureteral + necrosis	4	References [3–6]	0	–
Polymyositis / dermatomyositis + ureteral + calcinosis	1	Reference [7]	0	–
Polymyositis / dermatomyositis + obstructive + uropathy	1	–	1	Obstructive anuria due to extrinsic ureteral compression in a patient with dermatomyositis and disseminated sigmoid colon adenocarcinoma
Polymyositis / dermatomyositis + ureter + obstruction	3	References [4, 8]	1	Obstructive anuria due to extrinsic ureteral compression in a patient with dermatomyositis and disseminated sigmoid colon adenocarcinoma
Polymyositis / dermatomyositis + urolithiasis	4	Reference [4]	3	Articles related to calcinosis cutis, urolithiasis due to corticosteroid treatment, and dermatomyositis among a patient with cystinuria

were finally diagnosed with bilateral ureteral lesions within months after dermatomyositis was diagnosed. All patients were treated with immunomodulatory drugs when symptoms began; corticosteroids were always included. Imaging studies helped diagnose the ureteral lesions, which may mimic calculi obstructing the ureters. The calcified ureteral necrosis was similar to that found within other visceral lesions, such as mesocolonic plaques discovered during abdominal surgery [5]. "Post-operative complications and prognosis depended on preoperative status; principally, whether urinary leakage was present, but also on severity of the systemic disease and on the immunosuppressive therapy regimen."

Diagnosis of ureterolithiasis in this clinical setting should be addressed with skepticism. Management should focus on the systemic condition, and treatment of ureteral obstruction should be limited to temporary drainage with a nephrostomy tube. Insertion of a ureteral stent may potentially aggravate the diseased ureter. After adequate medical therapy, repeat imaging is mandatory to determine whether surgery is needed and, if so, to plan the appropriate surgical approach.

In conclusion, calcified ureteral necrosis may be a feature of visceral vasculopathy, related to both JDM and JPM. The mechanism is obscure, and the presence of calcifications within visceral tissues might suggest the pathogenesis of the typical calcinosis related to these diseases. On the other hand, it is important to emphasize that the ureteral necrotic process was independent of calcinosis cutis and appeared early. Although rare, any patient diagnosed with new-onset inflammatory myopathy should be treated cautiously, if such a process is suspected. The level of suspicion should be higher with younger patients (when urolithiasis is uncommon), when time since diagnosis of the inflammatory myopathy or onset of the specific treatment is short, when associated pain is limited, or when laboratory work-up does not exactly match other diagnostic options.

If possible, delaying surgical treatment until the systemic disease is well controlled seems logical. Whether ureteral necrosis is a specific feature of vasculopathy needs to be explored, as well as additional treatment options for this complicated visceral disease.

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Compliance with ethical standards

Ethical standards This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

The patient's parents provided informed consent to publish their daughter's case anonymously.

Disclosures None

References

1. Stübgen JP (2017) Juvenile dermatomyositis/polymyositis and lymphoma. J Neurol Sci 377:19–24
2. Enders FB, Bader-Meunier B, van Royen-Kerkhof A et al (2017) Consensus-based recommendations for the management of juvenile dermatomyositis. Ann Rheum Dis 76:329–340
3. Grossiord A, Lacert P et al (1978) A case of bilateral ureteral necrosis in dermatomyositis in a child. Annals de Medicine Interne 129(1):1–3
4. Bléry M, Lacert P, Touboul A (1978) Lithiasis and bilateral necrosis of the ureters occurring during dermatomyositis. A definite entity or a coincidence? J Radiol Electrol Med Nucl 59(4):279–282
5. Le Guillou M, Richard F, Küss R et al (1980) Bilateral ureteral necrosis in a child with dermatomyositis. Eur Urol 6(3):190–191
6. Borrelli M, Prado MJ, Arap S et al (1988) Ureteral necrosis in dermatomyositis. J Urol 139(6):1275–1277

7. Duarte JD, Denes FT, Salum AM (2006) Ureteral calcinosis in juvenile dermatomyositis: successful precocious surgical management. International Brazilian J Urol 32(5):574–577
8. Huang KH, Hsieh SC, Chen J et al (2007) Dermatomyositis associated with bilateral ureteral spontaneous rupture. J Formosan Med Association 106(3):251–254
9. Gerami P, Sontheimer RD et al (2007) A systematic review of juvenile-onset clinically amyopathic dermatomyositis. Brit J Dermatol 157(4):637–644
10. Shah M, Rider LG et al; with the Childhood Myositis Heterogeneity Collaborative Study Group (2013) The clinical phenotypes of the juvenile idiopathic inflammatory myopathies. Medicine (Baltimore) 92(1):25–41
11. Rider LG, Nistala K (2016) The juvenile idiopathic inflammatory myopathies: pathogenesis, clinical and autoantibody phenotypes, and outcomes. J Int Med 280:24–38
12. Rider LG, Lindsley CB, Miller FW (2016) Juvenile dermatomyositis. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn LR (eds) Textbook of pediatric rheumatology, 7th edn. Elsevier, Philadelphia, pp 351–383
13. Ruperto N, Pistorio A et al; Oliveira S, for the Paediatric Rheumatology International Trials Organisation (PRINTO) (2016) Prednisone versus prednisone plus ciclosporin versus prednisone plus methotrexate in new-onset juvenile dermatomyositis: a randomised trial. Lancet 387(10019):671–678
14. Rider LG, Miller FW (2011) Phenotypes as clues to deciphering the clinical presentations, pathogenesis, and treatment of the idiopathic inflammatory myopathies. JAMA 305(2):183–190
15. Moghadam-Kia S, Aggarwal R, Oddis CV (2017) Biologics for idiopathic inflammatory myopathies. Curr Opinion Rheumatol 29(6):645–651