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CASE REPORT

Ureteral stones due to systemic mastocytosis: diagnostic and therapeutic characteristics

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Abstract Urolithiasis is expected to cause a considerable complication in patients with systemic mastocytosis. The aim of the present report is to demonstrate that due to pathological activation and irritability of mast cells, special features in the diagnostic investigation and therapy of urolithiasis have to be considered in patients with systemic mastocytosis. The clinical presentation, diagnostic investigation and therapeutic procedure of urolithiasis in a patient with systemic mastocytosis are described. Urolithiasis may be a significant complication of systemic mastocytosis. Non-contrast CT is the main tool for diagnosing urolithiasis after a detailed history and clinical exam. Patients with systemic mastocytosis should receive a premedication composed of a glucocorticoid and H_1- and H_2-histamine receptor antagonists. An increased vulnerability of mucosal tissues is expected in patients with systemic mastocytosis that may limit the options of operative and postoperative therapy. Opioids should be used cautiously for analgesia in patients with systemic mastocytosis.

Keywords Urolithiasis · Systemic mastocytosis · Ureterorenoscopy · Analgesia

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Introduction

The term *systemic mastocytosis* is used for a heterogeneous group of disorders characterized by abnormal mast cell accumulation and pathologically enhanced release of mast cell mediators in almost all organs and tissues in response to trigger stimuli or spontaneously (for review, see [1]). Patients present a variable and often changing pattern of symptoms (such as pruritus, flushing, tachycardia, palpitations, light-headedness, dizziness, shortness of breath, nausea, diarrhea and headache) that depends on the tissue responses to released mediators from mast cells and on the local tissue mast cell burden. A subvariant form of systemic mastocytosis, the *monoclonal mast cell activation syndrome,* seems to be more common in everyday practice than previously thought [2–4]. Its diagnosis relies primarily on the recognition of the complex clinical picture of mast cell mediator-induced symptoms, because specific reliable laboratory biomarkers are still lacking.

The prevalence of urolithiasis in patients with systemic mastocytosis is unknown. Although so far there is only one case report on urolithiasis in a patient with systemic mastocytosis [5], it is to be expected that urolithiasis is not a rare complication in systemic mastocytosis for two reasons: (1) osteoporosis is a frequent symptom in systemic mastocytosis [6] due to the increased release of mast cell mediators [7]. It has been shown that osteoporosis is associated with

an increased risk of urolithiasis (for review, see [8]). (2) Osteoporosis is often treated by oral application of vitamin D and calcium. This treatment is known to increase the risk for urolithiasis (for review, see [9]). Accordingly, in mastocytosis support groups (e.g., https://listserv.surfnet.nl/scripts/wa.cgi?A0=masto-med) many patients report the occurrence of nephrolithiasis and urolithiasis.

Case report

A 50-year-old man presented to the emergency department with colicky abdominal and right-sided pain. Onset of pain had been approximately 2 h before presentation. The patient was known in our clinic to suffer from an aggressive form of systemic mastocytosis (tryptase in blood slightly increased; mast cell clusters in gastrointestinal biopsies; alterations in tyrosine kinase Kit outside codon 816; mast cell mediator release syndrome). The patient was on medication administered for a reduction of mast cell activity (prednisolone, cromoglycate, ranitidine, fexofenadine, ketotifen, ascorbic acid) and on drugs administered to reduce mediator-related symptoms (pantoprazol, montelukast, valsartan, α-liponic acid, vitamin D and calcium). Although the pain character resembled to a large extent what was periodically experienced by the patient due to the unregulated increased mast cell activation, the sudden onset of the pain after taking the morning pills with water and the increasing colicky form of the pain suggested an ureteral stone as its cause. Physical examination was unremarkable besides the pain in the right lower lateral abdomen. Sonographic examination showed a dilated right upper urinary tract. Many erythrocytes were found in the urine in the laboratory workup. A non-contrast CT scan was obtained, which depicted a 5-mm calculus at the right ureterovesical junction with hydronephrosis grade II. In order to reduce the increasing pain, meperidine (pethidine) 50 mg was applied intravenously. However, under injection, pain dramatically increased and mast cell mediator-related symptoms (flush, tachycardia, central nervous symptoms) occurred. Since the symptoms, which were likely to be due to degranulation of mast cells induced by meperidine, did not spontaneously resolve within 5 min, 100 mg prednisolone was given as a fast infusion. Under application of the glucocorticoid, the mediator-related symptoms vanished within a few minutes and the analgesic effect of meperidine appeared.

The patient was admitted to the urological service and started on an aggressive hydration regimen in an attempt to "flush" the stone by drinking 4 l water daily. Pain was controlled by intravenous application of metamizole. Since this therapy did not succeed within 24 h, an endourologic approach was selected. The patient was premedicated with 80 mg prednisolone, 60 mg fexofenadine and 150 mg ranitidine to prevent activation of mast cells induced by the operation stress [10, 11]. The procedure was performed under general anesthesia by ketamine and propofol which both have been shown to inhibit mast cell degranulation [12]. A 7-Charr semirigid ureterorenoscope was inserted. Intra-operative balloon ureter orifice dilatation was performed and the stone was retracted. Already discrete manipulation yielded a fast local reaction of the mucosa leading to a swollen right ostium. Analysis showed the stone to be a composition of Whewellit (30%), Weddellit (10%) and Carbonatapatit (60%). An indwelling double J stent was inserted. Postoperative pain control was achieved by metamizole. The JJ-stent was removed after 8 days. As long as the JJ-stent was inserted, urine was to a greater or lesser extent sanguineous and the patient reported a strong desire to void. Both symptoms vanished immediately after removal of the JJ-stent.

Discussion

Urolithiasis is a frequent cause of presentation to hospital. It has been estimated that approximately 122 of every 100,000 hospital admissions can be attributed to urolithiasis [13, 14]. The diagnosis of urolithiasis is largely dependent on analyzing the clinical presentation and physical examination. Pain is the most common symptom, especially when the stone passes into the ureter. As the calculus propels distally, the pain migrates in a parallel fashion. Stones in the upper ureter often produce flank pain, while calculi that have migrated to the lower ureter can masquerade as groin pain. Hematuria, either gross or microscopic, has also been attributed to urolithiasis. Dysurias, urgency and increased frequency of micturition are all potential signs and symptoms of patients suffering from urolithiasis. In patients with systemic mastocytosis, diagnostics of urolithiasis can be complicated by the fact that the unregulated release of mast cell mediators can induce similar symptoms and pain. Suspicion of urolithiasis is usually confirmed with radiologic tests, particularly, the non-contrast enhanced CT scan that renders accurate detection of size and location of calculi possible [15].

Management of urolithiasis depends on stone size and clinical symptoms. Stones can take a variable amount of time to pass spontaneously, particularly those measuring 4–6 mm [16, 17]. Therefore in patients with excruciating pain, operative intervention may become necessary. Ureterorenoscopy offers a minimally invasive yet highly efficacious approach to successful patient care. Ureterorenoscopy involves cannulation of the urethra and bladder. Once the ureteral orifices are identified, balloon catheters, stone baskets or grasping forceps can be introduced to facilitate

stone retrieval. One has to be aware that in patients with systemic mastocytosis, the urothelium may be highly vulnerable because of an infiltration with pathologically activated and irritable mast cells and/or an increased circulation of mast cell mediators. Shock wave lithotripsy may be applied in patients with systemic mastocytosis despite the risk that stone fragments may damage the highly vulnerable urothelium, if the stone is located in a position not suitable for ureteroscopy. Because of the increased vulnerability of the urothelium, ureteral stents should be removed as soon as possible. Opioids, in particular morphine, codeine and meperidine, should not be used for pre- and post-operative analgesia, since they have been shown to potently induce mast cell degranulation using complex sites of action [18, 19].

Conclusions

Urolithiasis may be a significant complication of systemic mastocytosis. Non-contrast CT is the main tool for diagnosing urolithiasis after a detailed history and clinical exam. Patients with systemic mastocytosis should receive a premedication composed of a glucocorticoid and H_1- and H_2-histamine receptor antagonists. An increased vulnerability of mucosal tissues is to be expected in patients with systemic mastocytosis that may limit the options of operative and postoperative therapy. Opioids should be used cautiously for analgesia in patients with systemic mastocytosis.

Conflict of interest statement No competing financial interests exist.

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