

Urologic Management of Priapism Secondary to Chronic Myeloid Leukemia



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INITIAL PRESENTATION

A 27-year-old Caucasian male with a history of chronic myeloid leukemia (CML), diagnosed at age 19, presented to his local emergency department with a painful persistent erection of 9 hours duration. He reported a history of 2 prior episodes of painful erections unrelated to sexual activity over the last 2 months, with each episode lasting less than 4 hours. Although his CML had been managed long-term with Imatinib (Gleevec), on presentation he admitted to medication noncompliance with Imatinib over the past year. The patient additionally endorsed 15 pound unintentional weight loss over the last 2-3 months as well as waxing and waning tender subcutaneous nodules on his extremities. He was not in respiratory distress and denied other common symptoms of CML including fatigue, fevers, chills, shortness of breath, visual changes, easy bruising/bleeding, or abdominal pain. The patient was otherwise healthy and had no other pertinent medical or surgical history.

Physical examination revealed a fully erect penis with maximum rigidity without evidence of trauma or discoloration, and baseline penile pain exacerbated by palpation. The remainder of the examination was within normal limits without lymphadenopathy, rashes, or splenomegaly. The patient was afebrile and hemodynamically stable in the emergency department, but with laboratories notable for anemia with a hemoglobin of 8.8 g/dL and significant elevation of his white blood cell (WBC) count to 450,010/mm³ with 8% blasts, neutrophil count of 171,000/mm³, thrombocytosis to 509,000/mm³, and elevated uric acid to 11.4 mg/dL.

MANAGEMENT

The urology service was consulted and performed corporal body aspiration followed by intracavernosal injection of 1 dose of phenylephrine. The patient's priapism began resolving following this treatment, and he was subsequently transferred to our institution for further management of CML. Leukapheresis was considered for management of hyperleukocytosis, but ultimately this treatment was withheld as the patient did not exhibit signs of respiratory distress or neurologic deficits, both clinical manifestations of leukostasis that portend a worse prognosis.¹ Upon transfer the patient was initiated on intravenous fluids, hydroxyurea, and allopurinol as prophylaxis against tumor lysis syndrome, as well as acyclovir due to his immunocompromised status.

A bedside bone marrow biopsy was performed, which revealed 2% blasts, hypercellular bone marrow with granulocytic hyperplasia, and small megakaryocytes. Pathology did not reveal morphologic transformation to accelerated leukemia or blast crisis. Similarly, cytogenetic studies for BCR-ABL kinase domain mutation did not reveal clonal evolution, consistent with chronic phase CML. An ultrasound of the spleen was performed, revealing splenomegaly without infarct. During his hospital stay, the patient denied further penile swelling or pain and his leukocyte count down trended to 218,760/mm³ with 1% blasts.

The patient was discharged home on imatinib 400 mg daily, acyclovir 400 mg twice a day, allopurinol 300 mg daily, and hydroxyurea 500 mg daily. At his 1-week urology follow-up appointment, he reported complete resolution of priapism and return to baseline erectile function. He denied new complaints and his physical examination was normal. He was encouraged to continue his CML treatment regimen to prevent recurrent ischemic priapism. Further management was deferred to his outpatient oncologist.

Priapism is a medical emergency requiring prompt evaluation and management. It is defined as a persistent penile erection that continues for more than 4 hours beyond, or is unrelated to, sexual stimulation.² While the incidence of priapism in the general population is low, about

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1.5 cases per 100,000 person-years, its prevalence increases in certain pathologic conditions including sickle cell disease, leukemia, and spinal cord injury.³ Approximately 20% of priapism cases result from hematologic abnormalities, with the incidence of priapism due to leukemia comprising only 1%-5% of all cases.

Three types of priapism are described in the literature: ischemic, characterized by penile pain and low venous outflow; nonischemic, characterized by painless unregulated arterial inflow; and stuttering, characterized by recurrent episodes of ischemic priapism with intervening periods of detumescence.² Irreversible damage to the cavernosal smooth muscle and endothelium may result by 24-48 hours duration of ischemic priapism, resulting in fibrosis and erectile dysfunction. Treatment of priapism depends on the underlying etiology, however management of the compartment syndrome in ischemic priapism should not be delayed by diagnostic testing. Ischemic priapism accounts for 95% of priapism cases and can be determined through a thorough history notable for penile pain, physical examination, color duplex ultrasonography, and penile cavernous blood gases.^{2,3} Aspirated cavernosal blood in ischemic priapism is venous and hypoxic, demonstrating a pH <7.25, P_{O₂} <30 mm Hg, and P_{CO₂} >60 mm Hg. In contrast, aspirated blood in nonischemic priapism is similar to arterial blood, with a pH of 7.40, P_{O₂} >90 mm Hg, and P_{CO₂} <40 mm Hg.

Ischemic priapism treatment typically begins with diagnostic and therapeutic aspiration using a large bore (19 or 21 gauge) angiocatheter with or without saline irrigation.² Greater resolution of ischemic priapism and decreased rates of erectile dysfunction occur when aspiration is followed by injection of a sympathomimetic agent. Phenylephrine is recommended due to its selectivity and minimal side effect profile. Injections of 1 mL of phenylephrine (diluted with normal saline to a concentration of 100-500 µg/mL) should be prepared. One injection may be administered every 3-5 minutes until resolution of priapism, up to 1 hour, with careful monitoring of the patient's status on telemetry to avoid adverse systemic effects such as hypertension, headache, reflex bradycardia, and arrhythmia. Surgical measures such as a cavernoglansular shunt may be warranted after a trial of sympathomimetic injection or in cases of ischemic priapism lasting greater than 48 hours in duration. Nonischemic priapism is most commonly due to penile or perineal trauma leading to laceration of the cavernous artery.² These cases typically self-resolve with low risk of complications, but in cases that persist, selective arterial embolization of the cavernous artery may be an effective treatment.

Once treated, investigation of the underlying cause of priapism should proceed.² The patient should be screened for the use of drugs such as antidepressants, intracavernosal injections, and illicit drugs. A complete blood count with WBC differential may reveal abnormalities in the white blood cell count, reticulocyte count, or platelet counts that point to a blood cell dyscrasia or hemoglobinopathy. Suspected hemoglobinopathies should be

confirmed with hemoglobin electrophoresis to screen for sickle cell disease. A complete blood count and history of fatigue, weight loss, and anemia concerning for leukemia should be followed by the appropriate confirmatory test.⁴ A peripheral smear showing leukocytosis with all morphologically normal neutrophilic forms along with cytogenetic studies indicating the presence of the BCR-ABL1 fusion gene will establish CML. For chronic lymphoid leukemia, peripheral smear will demonstrate greater than $5 \times 10^9/L$ monoclonal B lymphocytes and flow cytometry confirms clonal proliferation. Acute myeloid leukemia and acute lymphoblastic leukemia both have characteristic morphologies on peripheral smear, with greater than 20% blast cells being required on bone marrow biopsy for diagnosis. Further subtyping may be confirmed using immunophenotyping and is beyond the scope of this report. In many cases, a cause may not be found, and in fact idiopathic priapism accounts for the majority of recurrent priapism cases.²

DISCUSSION

Presented by Dr. Drogo K. Montague

The proposed mechanism of priapism in CML is hyperviscosity of the blood caused by massive leukocytosis, or leukostasis, resulting in thrombus formation and corporal venous outflow obstruction. Additional mechanisms include venous congestion of the corpora cavernosa caused by compression of abdominal veins from splenomegaly, cell sequestration in the microvasculature due to increased cytokine production by the leukemia cells, and leukemic infiltration of sacral nerves.^{1,3} The patient described above had a known history of CML and presented with classic symptoms and physical examination findings of ischemic priapism. Treatment with corporal blood aspiration and phenylephrine yielded satisfactory results. Leukapheresis with or without cytotoxic therapy has been advocated as a treatment strategy in leukemia-induced priapism to reduce hyperviscosity.³ In addition, the American Society for Apheresis recommends therapeutic leukapheresis for symptomatic hyperleukocytosis (Grade IB), although this recommendation currently applies only to acute leukemias.⁵ This process involves the mechanical separation of white blood cells from circulating blood and returns the remaining filtered blood to the patient. However, leukapheresis is costly, requires close monitoring by trained personnel, and carries significant risks of bleeding and thrombocytopenia without clear evidence of long-term benefit.^{1,3} Typically, leukapheresis is reserved for patients who cannot tolerate immediate chemotherapy induction or suffer from neurologic/pulmonary sequelae of leukostasis including visual changes, gait imbalance, somnolence, and dyspnea.¹ These symptoms are associated with early death and are more rapidly reversed using leukapheresis. Here, prompt urological management

Table 1. Comparison of case reports of CML-induced priapism and treatment methods

First Author	Age	Time to Treatment	CML History	Management	Resolution	Erectile Dysfunction
Castagnetti 2008 ⁶	Case 1—9 Case 2—9 Case 3—9	Case 1—several days Case 2—4 days (stuttering) Case 3—9 hrs	First presentation	Case 1—Oncologic: hydroxyurea, leukapheresis Case 2—Oncologic: hydroxyurea Case 3—Oncologic: cyclophosphamide, leukapheresis	Y, 13 days to partial detumescence, complete resolution achieved by 20 days to 3 months	N
Gupta 2009 ⁷	12	2 days ^a	First presentation	Oncologic: hydroxyurea, imatinib	N, achieved resolution 2 days later with administration of terbutaline	—
Jameel 2009 ⁸	Case 1—21 Case 2—55	Case 1—8 hrs Case 2—12 hrs	First presentation	Case 1—Urologic: aspiration, epinephrine Case 2—Urologic: aspiration	Y	N
Veljković 2012 ⁹	16	Over 24 hrs	First presentation	Oncologic: hydroxyurea, leukapheresis	Y, after 13 hours	—
Villegas Osorio 2014 ¹⁰	Case 1—24 Case 2—29	Case 1—14 hrs ^a Case 2—6 hrs ^a	First presentation	Both cases—Urologic: aspiration, phenylephrine	Y	—
Ergenc 2015 ¹¹	18	3 days	First presentation	Oncologic: imatinib, leukapheresis	Y, after 3 hours	N
Shaeer 2015 ¹²	21	6 days	First presentation	Combined: aspiration, epinephrine, leukapheresis	N, at 3 month follow-up	Y, penile prosthesis implanted
Patil 2016 ¹³	22	8 hrs	Known CML, had stopped medications	Combined: aspiration, imatinib, blood transfusion	Y, at 1 month follow-up	—
Swapna 2017 ¹⁴	18	4 days	First presentation	Combined: aspiration, phenylephrine, penile irradiation, leukapheresis	Y, after 2 days	—
Becerra-Pedraza 2018 ¹⁵	52	6 days	First presentation	Urologic: aspiration, surgical shunt	Y	—

^a Patient reported at least 1 episode of priapism that spontaneously resolved prior to presentation.

and conservative management using hydroxyurea combined with prophylactic allopurinol was effective at reducing leukocytosis and treating the primary disease process without recurrence of priapism in the acute setting.

Priapism in CML patients is documented in limited reports and small case series. Current guidelines emphasize immediate treatment of the compartment syndrome in priapism prior to initiating treatment for the underlying cause.² Although important for preventing future episodes of priapism, diagnosis and management of a systemic etiology may be time-consuming and increases the risk of permanent penile injury. Although the management of CML presenting as priapism is multimodal with treatment options including oral cytotoxic agents and leukapheresis, the initial and immediate treatment strategy should focus on urological decompression of the compartment syndrome. Since our patient had a known history of CML, once a management strategy was established our team was able to initiate hydroxyurea promptly in the treatment course. A review of 14 case reports within the last 10 years of priapism in patients with CML was conducted, with 5 cases utilizing urologic treatment only, 6 cases implementing oncologic treatment only, and 3 incorporating combined urologic and oncologic approaches (Table 1). All but 1 patient presented with priapism as the first manifestation of CML, and all were in stable condition without respiratory distress or neurologic symptoms of hyperleukocytosis. Of the cases that incorporated oncologic intervention, 6 utilized leukapheresis with 4 as part of a purely oncologic approach in conjunction with cytotoxic drugs, and 2 reports in conjunction with urologic interventions. Of the remaining 8 cases, only 1 incorporated combined urologic and cytotoxic approaches, 2 used purely cytotoxic drugs, and the remaining relied solely on urologic treatment including 1 case that progressed to surgical shunting. Of note, all reported cases involving patients under the age of 18 utilized purely oncologic treatment, likely to avoid the invasiveness of penile aspiration or injection. Interestingly, patients undergoing leukapheresis experienced a longer time to resolution of priapism, usually greater than 12 hours, with both reports from Castagnetti requiring 13 days until initial detumescence and up to 3 months to full resolution.⁶ In contrast, all but 1 patient who underwent urologic intervention without leukapheresis reported resolution of priapism within an hour of treatment. This report by Patil et al was also the only 1 in the review utilizing a combined urologic and oncologic approach with cytotoxic agents without leukapheresis.¹³ Here we present a case of CML-induced priapism that was successfully treated in the acute setting using a combined urologic and oncologic approach that did not incur the risks and cost of leukapheresis. To our knowledge this is the first such case presented in the literature.

Importantly, our patient described 2 prior episodes of shorter duration unrelated to sexual stimulation, consistent with the diagnosis of recurrent or stuttering priapism. When seen in urology clinic for his follow-up appointment,

the importance of maintaining systemic therapy for CML was emphasized to avoid future episodes. With good WBC count control using cytotoxic agents, leukostasis can be avoided and it is unlikely that priapism will recur, which may explain why the majority of reports of CML-induced priapism occur in patients not on systemic therapy. Each episode of recurrent priapism carries the risk of cavernosal fibrosis and thus treatment should be aimed at prevention. An acute episode is managed following guidelines for ischemic priapism. Patients may be able to self-treat at home by being taught how to administer their own phenylephrine injections, typically a low-dose of 100 μ g at a time, up to 3 doses.² In addition to close control of the systemic disease, additional therapies have been studied for use in recurrent priapism. Testosterone supplementation for hypogonadal men, antiandrogens, 5 α -reductase inhibitors, gabapentin, and phosphodiesterase 5 (PDE5) inhibitors may reduce the frequency of priapism episodes and have been studied primarily for use in patients with sickle cell disease.^{2,3} However, these treatments require long-term use and their safety and efficacy has not yet been fully established.

Priapism is a rare but serious complication of CML leukostasis that can occur at any age, as a presenting symptom or as a result of discontinuing treatment. Management should be initiated promptly to prevent erectile dysfunction. In patients with a hematological disorder, initial treatment of the penile compartment syndrome should not be delayed by diagnostic testing and systemic therapy. We report the first known case of a patient with CML-induced priapism achieving early resolution using a combined urologic and oncologic approach without leukapheresis. Systemic therapy using cytotoxic agents is effective at maintaining priapism resolution and avoids the complications associated with leukapheresis.

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