

## Chronic Myeloid Leukemia Presenting with Priapism

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### Abstract

Chronic myeloid leukemia is a chronic myeloproliferative neoplasm that usually presents with an elevated white blood cell count and an enlarged spleen. Presentation with priapism is rather exceptional and is usually caused by leukostasis due to hyperleukocytosis. Priapism in chronic myeloid leukemia is a medical emergency that requires local therapies, symptomatic treatment as well as specific measures aimed at rapid control of the leukemia in the form of cytoreductive therapy, early initiation of targeted therapy with tyrosine kinase inhibitors in addition to leukapheresis in order to decrease the elevated leukocytic count as quickly as possible. A young patient with chronic myeloid leukemia who presented with priapism to King Khalid University Hospital in Riyadh is presented. The diagnostic work up and the lines of management are discussed.

**Keywords:** Chronic myeloid leukemia; Priapism; Hyperleukocytosis; Leukapheresis; Tyrosine kinase inhibitors.

### Introduction

Priapism is a medical and surgical emergency that is characterized by prolonged and painful erection of the penis unassociated with any sexual arousal or desire. Approximately 50% of patients having priapism are at risk of impotence, despite appropriate therapy. If untreated, priapism may lead to penile necrosis and permanent erectile dysfunction [1-7]. Priapism can occur at any age. It has bimodal peak incidence with the first peak mainly occurring in children with Sickle Cell Disease (SCD) between 5 and 10 years of age and the second peak developing in sexually active adult males belonging to the age group 20 to 50 years. The incidence of priapism is 1.5 per 100,000 people. Priapism can either be idiopathic or secondary to several medical conditions (Table 1) [1-5,7]. Idiopathic priapism accounts for 64% of all cases of priapism. About 20% of cases of priapism are caused by hematological disorders [2,4,5]. In children, SCD accounts for 67% of cases while leukemia accounts for 15% of cases of priapism. The incidence of priapism in adult leukemia ranges between 1 and 5% [3-6]. In patients with leukemia, 50% of cases of priapism are due to Chronic Myeloid Leukemia (CML) and priapism is less common in patients with acute leukemia than in patients with chronic leukemia. Priapism can be classified into low flow type and high flow priapism (Table 2) [1,2,4,6].

### Case Presentation

On 11/06/2013, a previously healthy 38 years Saudi male was referred from a local hospital to King Khalid University Hospital (KKUH) for treatment of painful erection of his penis that had lasted for 30 hours. There was no history of trauma, intake of new medications, exposure to radiation, fever or chills but the patient gave history of weight loss of 20 kg over 6 months in addition to dragging sensation in the abdomen and malaise. There was no history of bleeding from any site, dyspnea, headache, blurring of vision, convulsions or loss of consciousness. On arrival to the emergency room, his vital signs revealed pulse: 109/min, blood pressure: 136/72 mmHg, respiratory rate: 20/minute and temperature: 36.7°C. The physical examination revealed conjunctival pallor, but no: external palpable lymphadenopathy, jaundice, ecchymoses, skin rashes or leg edema. Abdominal examination showed

no tenderness, impalpable liver and splenomegaly of 18 cm below the left costal margin. Examination of cardiovascular, respiratory and central nervous systems did not reveal any abnormality. The penis was erect, firm and tender with superficial venous engorgement. The testicles were bilaterally descended. Digital rectal examination revealed no enlargement or tenderness of the prostate. Complete Blood Count (CBC) showed white blood cell (WBC) count:  $378 \times 10^9/l$ , hemoglobin: 105 g/l, platelets:  $155 \times 10^9/l$ . Differential cell count revealed: 57% neutrophils, 15% metamyelocytes, 20% myelocytes, 2% promyelocytes and there were no blast cells on peripheral blood smear. Renal, hepatic and coagulation profiles were all normal. Uric acid was 429  $\mu\text{mol/l}$ , lactic dehydrogenase was 688 u/l.

As the patient presented with priapism and before obtaining the results of CBC, he was initially seen by urologists. Because of the prolonged duration of priapism, treatment was initiated by performing cavernosal aspiration and irrigation. Unfortunately, there was incomplete relief of the erection by the procedure. Then the patient was admitted to KKUH initially under care of urologists. Later on-call hematologists were consulted to see the patient. After reviewing his clinical findings, laboratory investigations and making sure that CML was the most likely cause of his priapism, he was commenced on intravenous fluids, allopurinol and cytoreductive therapy with hydroxyurea 4 g/day. Also, leukapheresis was initiated and the patient received a total of three sessions of leukapheresis. Bone marrow biopsy was performed and it confirmed the diagnosis of CML (Figures 1-4).

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Idiopathic: no cause is found		
Secondary:		
	a- Trauma to perineum or genitalia	
	b- Infection or inflammation:	Prostatitis
		Mumps orchitis
	c- Malignancy:	Infiltration of penis by cancer
	c- Central nervous system mediated	
	d- Drug induced:	Alcohol ingestion
		Phenothiazines
		Intravenous fat for parenteral nutrition
		Heparin
	e- Thromboembolic diseases:	Systemic lupus erythromatosis
		Protein C deficiency
	f- Hemoglobinopathies:	Sickle cell disease
		Sickle cell trait
	g- Hyperleukocytosis:	* Acute leukemia:
		acute lymphoblastic leukemia
		acute myeloid leukemia
		* Chronic leukemia:
		chronic myeloid leukemia
		chronic lymphocytic leukemia
	h- Hyperviscosity states:	Polycythemia rubra vera
		Multiple myeloma
		Waldenström's macroglobulinemia
	i- Miscellaneous causes:	Hemodialysis
		Amyloidosis

Table 1: Shows causes of priapism.

Type of priapism	Low flow (ischemic, venous) priapism	High flow (non-ischemic, arterial) priapism
Etiology and associations	<ul style="list-style-type: none"> <li>- Idiopathic</li> <li>- Drug induced</li> <li>- Neurologically mediated</li> <li>- Tumor infiltration</li> <li>- Hyperviscosity states: thrombophilia, hemoglobinopathies and hyperleukocytosis</li> </ul>	<ul style="list-style-type: none"> <li>- Trauma to perineum or genitalia</li> </ul>
Clinical manifestations	<ul style="list-style-type: none"> <li>- Painful and rigid erection.</li> <li>- Irreversible erectile dysfunction if condition persists longer than 24-48 hours.</li> </ul>	<ul style="list-style-type: none"> <li>- Painless erection at clinical presentation</li> <li>- Irreversible cellular damage and fibrosis are rare</li> </ul>
Pathogenesis and course	<ul style="list-style-type: none"> <li>- Intracavernosal blood sampling: acidosis and low oxygen tension.</li> <li>- Blockade of venous drainage from emissary venules causes intra-cavernosal blood stasis leading to accumulation of deoxygenated blood within the cavernous tissue thus causing trabecular interstitial edema and ultrastructural changes in trabecular smooth muscle. Functional transformation of these cells to fibroblast like cells ultimately causes cellular damage and fibrosis.</li> </ul>	<ul style="list-style-type: none"> <li>- Intracavernosal blood sampling: bright red oxygenated blood.</li> <li>- * Increased blood flow in arteries causes an increase in blood flow into cavernosal sinusoids thus overwhelming the venous outflow.</li> </ul>
Management	<ul style="list-style-type: none"> <li>- Local penile or systemic anesthesia: spinal anesthesia, circumferential penile block or subcutaneous local penile shaft block.</li> <li>- Intracavernosal instillation of a sympathomimetic agent e.g. phenylephedrine to induce detumescence.</li> <li>- Surgical shunt designed to divert blood away from corpus cavernosum is indicated in case of failure of the above measures.</li> <li>- Immediate aspiration and irrigation of the corpora cavernosa.</li> <li>- Anticoagulants and antifibrinolytic agents may be indicated.</li> <li>- <b>More common; actual medical and surgical emergency.</b></li> </ul>	<ul style="list-style-type: none"> <li>- Perineal trauma causes injury to internal pudendal artery and this establishes a fistula between cavernosal artery and corpus cavernosum thus ultimately leading to unregulated blood flow.</li> <li>- Treatment can be given on an elective basis.</li> <li>- <b>Less Common; not a medical emergency.</b></li> </ul>

Table 2: Types of priapism, their etiology, pathogenesis and management.

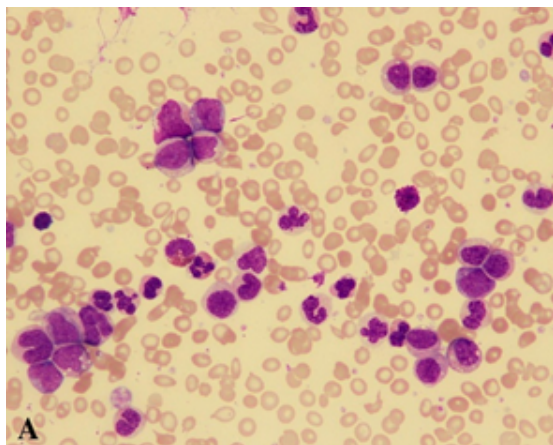
Cytogenetic analysis revealed the presence of Philadelphia chromosome and molecular studies confirmed the presence of BCR-ABL transcript, so the patient was commenced on imatinib 400 mg/day. Five days after admission, priapism resolved and his leukocyte count dropped to  $53 \times 10^9/l$ . Later on, the patient became asymptomatic, he remained stable clinically and his WBC count continued to drop which allowed discontinuation of hydroxyurea and allopurinol.

On 11/11/2013, the patient was discharged on imatinib 400 mg/day and he was given regular follow up appointments at the hematology outpatient clinic. Six months after starting imatinib therapy, the

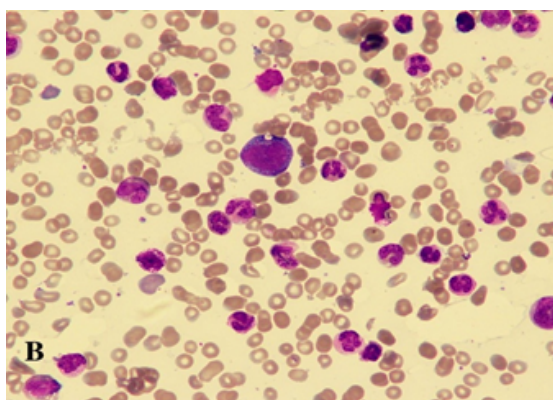
patient achieved major molecular response (MMR) of his CML. The patient was last seen on 11/23/2014. He was asymptomatic, his clinical examination showed impalpable spleen and his CBC was normal and his BCR-ABL taken 2 weeks earlier was negative. He was continued on imatinib, given new follow up appointment and was planned for a new molecular evaluation of his disease in 3 months.

## Discussion

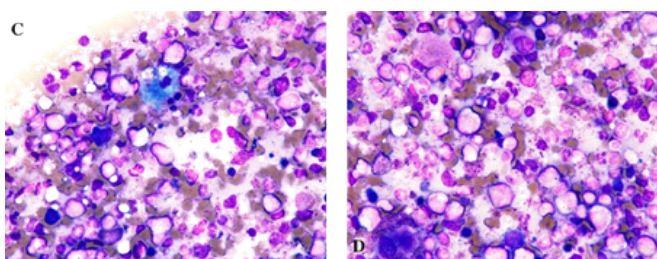
CML is a chronic myeloproliferative neoplasm, characterized by Philadelphia chromosome and results from clonal expansion of pluripotent hematopoietic stem cells containing the active BCR-



**Figure 1:** Peripheral blood smear showing: leukocytosis, neutrophils at different stages of maturation and prominent basophilia without evidence of dysplasia.



**Figure 2:** Bone marrow aspirate showing marked granulocytic proliferation with maturation pattern similar to that in the peripheral blood.



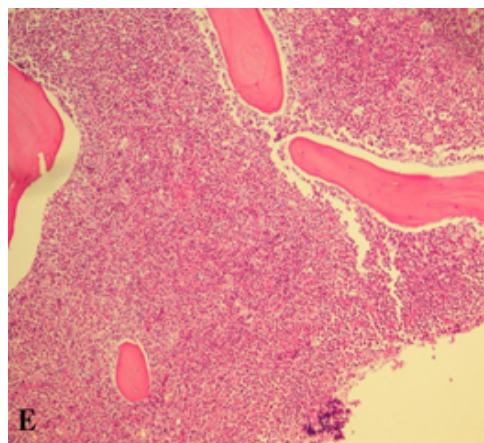
**Figure 3:** Sea-blue histiocytes are observed in the bone marrow aspirate. These histiocytes are secondary to increased cell turnover and they are derived from the neoplastic clone.

ABL fusion gene which is produced by a reciprocal chromosomal translocation between the ABL oncogene on chromosome 9 and the BCR gene on chromosome 22 [8-12]. The disease is often discovered accidentally when the patient presents with an elevated WBC count and/or an enlarged spleen. The most common clinical manifestations of CML are: anorexia, malaise, weight loss, sweating, bleeding episodes due to platelet dysfunction, abdominal fullness and pain or dragging sensation in the abdomen due to progressive enlargement of the spleen. Involvement of extramedullary tissues or sites such as liver, lymph

nodes and skin is generally limited to patients having progressive disease [10]. At times, patients may present with leukostatic complications of hyperleukocytosis such as thromboembolic phenomena, hearing loss or priapism [4,13-15].

Introduction of imatinib and other Tyrosine Kinase Inhibitors (TKIs) has radically improved the outcome of patients with CML and some other diseases with BCR-ABL expression [8]. Imatinib was the first TKI to be licensed for use in treating patients with CML in Chronic-Phase (CP) and its introduction was associated with substantial improvements in response and survival compared with previous therapies [11]. Imatinib was approved by the food and drug authority in the United States of America as first-line treatment for newly diagnosed CML in December 2002, following an International Randomized Study (IRIS) initiated in June 2000 comparing imatinib as a single daily dose of 400 mg to interferon plus cytarabine in newly diagnosed patients with CML in CP [16]. The IRIS study showed the outstanding effectiveness of imatinib and its superiority with respect to the rates of Complete Hematological Response (CHR), Major Cytogenetic Response (McyR) and Complete Cytogenetic Response (CcyR). However, imatinib at dose of 400mg per day is still the gold standard first-line treatment for CML [17]. If the patient has a suboptimal response whilst on imatinib therapy, shifting to a second generation TKI such as dasatinib or nilotinib is justified in order to have a more optimal response as these agents have shown higher efficacy in clinical trials in imatinib-resistant or intolerant CML patients compared to imatinib treatment [10,18]. Other therapeutic options in case of suboptimal response to imatinib include: (1) escalation of the dose of imatinib, (2) allogeneic hematopoietic stem cell transplantation (HSCT), and (3) the use of agents that are being evaluated in clinical trials.

Approximately 20-30% of patients with CML fail imatinib therapy and develop resistance to the drug. These patients require alternative therapies. Therefore, it is vital to identify high risk patients at presentation of CML and start them on appropriate alternative therapies as early as possible [10,19]. Patients with CML harboring specific mutations such as T315 I remain resistant not only to first line but also to second line TKIs and require additional third generation inhibitors such as ponatinib to overcome resistance induced by these point mutations [8,18]. In patients with CML having accelerated phase or blast cell crisis, therapeutic options are limited and survival



**Figure 4:** Bone marrow trephine biopsy showing 100% cellularity, increased megakaryopoiesis and granulopoiesis, prominent eosinophils without increase in blast cells.

is significantly shorter than that of patients with CP-CML even in the presence of powerful targeted therapies [20]. Allogeneic HSCT is still the only potentially curative therapy for CML and is the most valid therapeutic option that can be offered before the disease reaches the blastic phase [17].

In a comparative study, the rates of CcyR, MMR and Complete Molecular Response (CMR) in adolescents and young adults with CML treated upfront with TKIs were found to be lower than those in older patients but the overall survival was similar between the two groups. So, additional research in adolescents and young adults is needed to optimize CML treatment in this age group [21]. The aim of TKI therapy in patients with CML is to obtain ideal hematological, cytogenetic and molecular responses at certain and critical time points. Molecular monitoring of BCR-ABL transcripts by performing real time, quantitative, polymerase chain reaction has proven to be the most sensitive available method and has shown prognostic impact with regard to progression-free survival. The depth of response obtained with TKI therapy and the time to achieve this response are important in predicting the prognosis in patients with CML [17,20,22]. Careful and regular monitoring of CML patients on TKI treatment according to the European Leukemia Net CML guidelines and recommendations is of vital importance as timely and accurate monitoring is the key to optimizing patient management [18,20]. Excessive monitoring may have an economic cost, whilst failure to optimize TKI therapy may result in CML disease progression and death. Additionally, achievement of optimal responses and minimizing healthcare costs require full adherence of patients with CML to TKI therapy [23]. The patient presented achieved MMR 6 months after diagnosis and he achieved CMR 12 months after starting imatinib therapy.

Hyperleukocytosis is usually defined as having circulating blast cell count or WBC count exceeding 50 to 100 x 10<sup>9</sup>/l. Hyperleukocytosis is usually encountered at the presentation of acute myeloid leukemia, acute lymphoblastic leukemia, CML or chronic lymphocytic leukemia [14,24,25]. Hyperleukocytosis leads to leukostasis that may be complicated by: hearing loss, papilledema, cerebellar dysfunction, impairment of memory function, intracranial hemorrhage, respiratory depression or failure, acute renal failure and priapism [14,15,24,26-28]. Treatment of hyperleukocytosis and leukostasis includes: cytoreductive therapy with hydroxyurea, cyclophosphamide or cytosine arabinoside, and therapeutic leukapheresis.

Although priapism is a rare and a rather exceptional presentation in male patients with CML, physicians should be aware of this disorder in order to ensure timely management [1,2,6,13]. At times, CML presents with an unexpected emergency such as priapism and the diagnosis of CML can only be made retrospectively after obtaining results of laboratory investigations. Hyperleukocytosis in CML causes formation of leukocyte aggregates or leukostasis which leads to the formation of thrombi in small blood vessels that ultimately causes vascular obstruction [4,13]. In our patient, hyperleukocytosis caused leukostasis and possibly microthrombi in the cavernosal circulation which precipitated priapism. The following five pathophysiological mechanisms of priapism in CML have been postulated: (1) venous congestion of the corpora cavernosa resulting from mechanical pressure exerted by the enlarged spleen on the abdominal veins, (2) sludging of leukemia cells in the corpora cavernosa and the dorsal veins of the penis, (3) local infiltration of sacral nerves by leukemia cells, (4) central nervous system infiltration by leukemia, and (5) hyperleukocytosis causing elevation of whole-blood viscosity and this ultimately causing complication due to vascular obstruction [2,4].

In a patient presenting with priapism, the following are essential to make diagnosis of the cause of presentation: detailed history, through physical examination, appropriate laboratory investigations including CBC, differential cell count and peripheral blood film, cavernosal blood gas analysis and color duplex ultrasonography [6]. However, early intervention allows the best chance for full recovery. Currently, there are no standard protocols for management of priapism in CML patients and optimal management is still controversial. Old therapies reported in literature included: local radiotherapy, with or without open surgical shunting. New therapies include: (1) cytoreductive therapies with chemotherapeutic agents such as hydroxyurea, (2) leukapheresis in case of hyperleukocytosis, (3) allopurinol, hydration and symptomatic treatment, and (4) early initiation of TKI therapy with agents such as imatinib [3,7]. The patient presented was initially tried on local measures then he received: cytoreductive therapy in the form of high dose hydroxyurea, leukapheresis and TKI therapy in the form of imatinib, which allowed rapid reduction of the disease burden and rapid reversal of his priapism.

## Conclusion

Priapism is a rare presentation of CML. Once it is encountered, the diagnostic procedures should be performed urgently and the patient should be commenced on: cytoreductive therapy, TKI therapy and leukapheresis in case of hyperleukocytosis as soon as possible not only to control priapism, but also to prevent further complications.

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