

Priapism as a Rare Presentation of Chronic Myelogenous Leukemia

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Abstract

Background: Priapism is a rare complication seen in one to five percent of adult leukemic patients. The word 'Priapism' is related to Priapus, the Greek and Roman God of procreation whose symbol was an erect phallus.

Clinical Presentation: The patient is a 22-year-old male with no known co-morbidities presenting with one month intermittent, unstimulated, painful penile erection with no other associated symptoms which resolves spontaneously, until nine hours prior to admission when symptoms recurred and persisted. Patient had no history of trauma and no drug intake.

Physical Findings: Patient was awake, in pain and tachycardic. There was note of pallor and splenomegaly. The penis was erect, firm, swollen and tender with superficial venous engorgement. The rest of the physical examination was unremarkable.

Laboratory Work Up: Complete blood count showed anemia and leukocytosis. Peripheral blood smear revealed markedly increased white blood cells with predominance of mature and immature cells belonging to granulocytic series. There was splenomegaly on ultrasound. Genetic testing showed an abnormal male karyotype of 46 chromosomes including translocation (9;22).

Treatment: Corpora cavernosa aspiration was done. Terbutaline was given. Patient was started and maintained on hydroxyurea and presently enrolled in Imatinib study.

Outcome: There was resolution of priapism after the corpus cavernosa aspiration and initiation of hydroxyurea and the white blood cell count had decreased after initiation of hydroxyurea.

Keywords: Priapism; Low-Flow Priapism; High-Flow Priapism; Chronic Myelogenous Leukemia

Clinical Presentation

Chronic myeloid leukemia (CML), also known as chronic myelogenous leukemia, is a type of cancer that starts in certain blood-forming cells of the bone marrow. In CML, a genetic change takes place in an early (immature) version of myeloid cells — the cells that make red blood cells, platelets, and most types of white blood cells (except lymphocytes).¹⁶

This is a case of a 22-year-old male, single, Filipino with no known co-morbidities admitted due to sustained penile erection. History started one month prior to admission when patient experienced intermittent spontaneous, unstimulated penile erection lasting for approximately two to three hours associated with penile pain occurring two to three times per week and resolves spontaneously. There was no other

associated symptom such as penile discharge, fever, dysuria, and hypogastric pain. No consult was done until one day prior when patient had increased episodes of penile erection. Patient consulted a family physician and treated as having urinary tract infection. The patient was given cotrimoxazole and mefenamic acid which afforded temporary relief. Nine hours prior to admission, patient experienced sustained, unstimulated, painful erection prompting consult at a local hospital. Terbutaline 0.5 cc SC was given and the patient was advised transfer to a tertiary hospital.

The patient had no family history of hematologic disorders and malignancy. He denied recent sexual intercourse, trauma, and illicit drug use and was not maintained on any medications. He is a non smoker and an occasional alcoholic beverage drinker. Review of systems revealed no history of bleeding tendencies.

On physical examination, patient was awake and in pain with a blood pressure of 100/60 mmHg, pulse of 120 beats/minute, respiration of 20 breaths/minute and was afebrile. There was splenomegaly on abdominal examination. The penis was erect, firm, swollen and tender with superficial venous

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engorgement. The rest of the physical examination was unremarkable.

On admission, the patient was hydrated with normal saline solution. Diagnostics done were complete blood count which showed anemia (hemoglobin of 10.7 g/L and hematocrit of 32.7%) and leukocytosis of 185,750/mm³ with differential count of 41% segmenters; 0.01% lymphocytes; 0.03% eosinophil; 0.03% monocytes; 0.02% basophil; 0.12% bands; 0.02% blast cells; 0.18% myelocyte; 0.02% promyelocyte and 0.16% metamyelocyte. Peripheral blood smear showed slightly microcytic normochromic red cells, platelets slightly decreased, marked increased granulocytes mast shift to the left predominant white blood cells are myelocyte, metamyelocytes, bands, nucleated RBC seen, occasional blast cell seen, promyelocyte seen, occasional lymphocytes seen, blast cell 9.0%. There was an increased reticulocyte count. Protime and partial thromboplastin time were within normal levels. Whole abdominal ultrasound showed splenomegaly. Urinalysis was normal. Medications started were Paracetamol and Morphine for pain, and Diazepam. Patient was admitted under the service of a hematologist and was referred to a urologist who started him with terbutaline 5.0mg tab and he was scheduled for aspiration of blood of corpora cavernosa under sedation. Impression was low flow priapism probably secondary to a hematologic disorder, to consider chronic myelogenous leukemia.

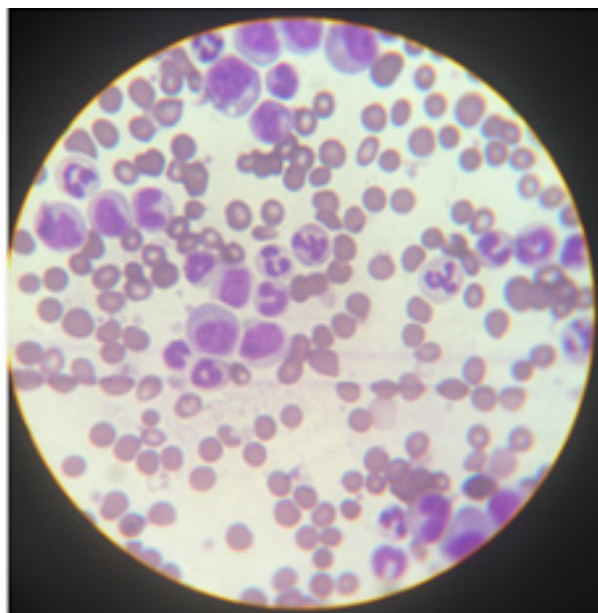


Figure 1: Peripheral blood smear showing marked increased granulocytes; presence of immature

On the first hospital day, the patient still had penile erection but with decreased penile pain. Vital signs were stable. He underwent corpora cavernosa aspiration (Winter procedure) under spinal anesthesia.

He was then given hydroxyurea 500mg capsule tid, allopurinol 300mg tablet bid and prednisone 20mg tablet tid. The patient's erection and penile pain gradually resolved. Repeat CBC prior to discharge showed decreased WBC count of 173, 510 mm³ with 40% segmenters; 0.05% lymphocytes; 0.02% eosinophil; 0.05% monocytes; 0.01% basophil; 0.10% bands; 0.02% blast cells; 0.15% myelocyte; 0.03% promyelocyte and 0.19% metamyelocyte.

Further work up showed hypercellular marrow with trilineage hematopoiesis, marked granulocytic hyperplasia, mild to moderate myelofibrosis (WHO MF Grade 1-2) on bone marrow biopsy. Genetic testing showed an abnormal male karyotype of 46 chromosomes including translocation (9;22) (Philadelphia chromosome) with breakpoints at bands 9q34 and 22q11, typically found in CML confirmed by gross G banding.

BCR/ ABL FISH ASSAY showed nuc ish 9q34(ABLx3), 22q11(BCR x3), (ABL con BCR x 2); 75 (67.57%) BCR/ ABL fusion genes were detected in 111 informative interphase cells analyzed. Hydroxyurea was adjusted and was maintained on 500mg capsule bid. Medications include ferrous sulfate tab od and allopurinol 300mg capsule od. Repeat CBC on follow up of the patient after two weeks showed hemoglobin of 14.2 mg/dL; white blood cell count, 16,700; segmenters, 69; lymphocytes, 30; eosinophils, 1; and platelet count, 262,000. He was then started on Imatinib 400mg/day. There was no recurrence of priapism after the procedure.

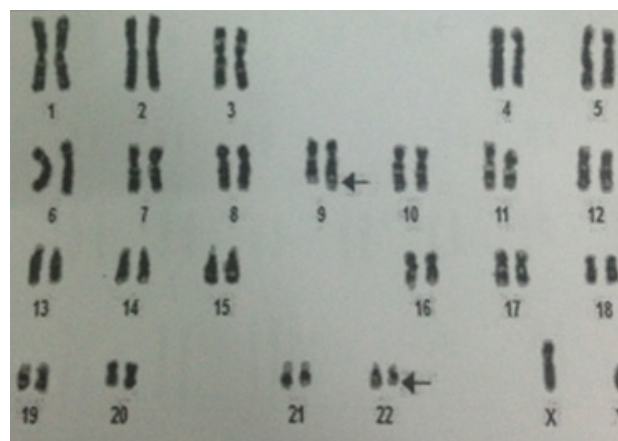


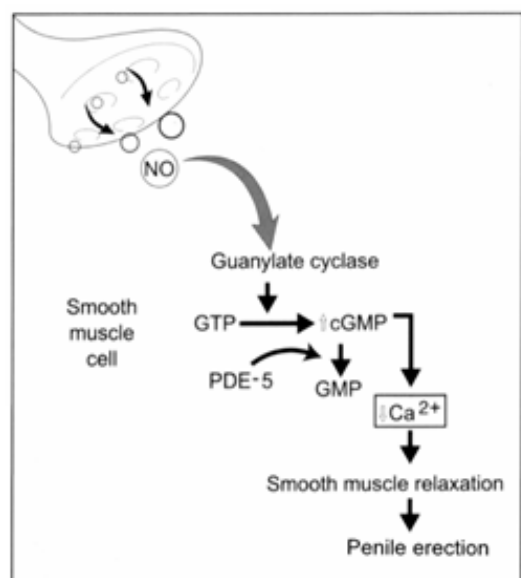
Figure 2: Genetic testing, abnormal male karyotype of 46 chromosomes including translocation (9;22)

Discussion

Priapism is defined as a persistent and prolonged penile erection without sexual stimulation and failure to subside despite orgasm.⁵ Most common presenting feature of CML is raised white cell count i.e.

hyperleukocytosis. The American Urology Society divides priapism into two subtypes. The most common, ischemic (veno-occlusive, low-flow) priapism is a nonsexual, persistent erection characterized by little or no cavernous blood flow and abnormal cavernous blood gases (hypoxic, hypercarbic, and acidotic). The corpora cavernosa are rigid and tender to palpation. Patients most often report pain. Ischemic priapism is an emergency because irreversible cellular damage occurs if treatment is not administered within 24 to 48 hours. It will result in long-term complication of erectile dysfunction or predisposition to frequent, prolonged priapism. This is the type present in our patient. Another subtype is the non-ischemic (arterial, high-flow) priapism, a nonsexual, persistent erection caused by unregulated cavernous arterial inflow. Cavernous blood gases are not hypoxic or acidotic. Typically, the penis is neither fully rigid nor painful. Antecedent trauma is the most common etiology and usually does not require emergent treatment.⁵ A detailed history and thorough physical examination, gas analysis of the blood within the corpora cavernosa and penile doppler ultrasound study can distinguish high-flow and low-flow priapism which is necessary due to the urgency of the latter.¹¹

For a patient having a painful erection with full rigidity of the penile shaft and with no history of trauma or manipulation, the consideration was a low-flow priapism, hence, an emergency urology referral.



Internal smooth muscle relaxation during erection depends on nitric oxide resulting in a Ca^{2+} efflux. This facilitates blood flow into the corpora cavernosa, obtaining and maintaining penile erection.

Figure 3: Physiology of normal erection (Lifted from the American Urology Society)

Penile erection is a complex neurovascular event involving the interaction of three physiological systems:

the Central Nervous System, the Peripheral Nervous System and the penile arterial and trabecula smooth muscle. Erection requires relaxation of trabecula smooth muscle that results in an increased compliance of the sinusoids and arterial wall as well as dilatation of the arterioles and arteries. Expanding sinusoids results in the compression of the subtunical venous plexuses sited into the trabecula network reducing venous outflow. Stretching the tunica albuginea encloses the emissary veins between the tunica layers leading to a decreased venous outflow. The smooth muscle relaxation during erection depends upon the promotion of calcium efflux which is mediated mainly by nitric oxide, which activates the enzyme guanylate cyclase. This cytoplasmic enzyme increases formation of the second messenger, cGMP. Elevated levels of peripheral cGMP in turn promote the efflux of calcium ions from the cavernosa smooth muscle cells. This induces muscle relaxation, facilitates blood flow into the corpora cavernosa, and helps obtain and maintain penile erection.

Under physiological conditions, the process of the penile detumescence is mediated by efferent sympathetic pathways. Adrenergic sympathetic nerves release norepinephrine, which acts on adrenoceptors in penile smooth muscle. This results in reduced arterial inflow, diminished lacunar space volume and accelerated corporeal venous outflow. The flaccid state of the penis is maintained by contraction of penile smooth muscle cells mediated by the intracellular accumulation of calcium ions, which is mainly effected by noradrenergic stimulation of alpha 1 - adrenergic receptors. The more common low-flow or veno-occlusive priapism results from persistent obstruction of venous outflow from the lacunar spaces. Eighty to ninety percent (80-90%) of clinically presented priapism are low-flow disorders.¹¹

The stepwise approach to priapism has been recommended, starting with corporeal aspiration of blood and irrigation with non-heparinized saline as a first line therapy especially in low-flow priapism wherein the goal is to increase the outflow of cavernous blood. This is followed by intravenous injection of vasoconstrictive agent and possible shunting.¹¹ The patient underwent this procedure and there was slight resolution of symptoms. Such urgent treatment is not always necessary in cases of leukemic priapism because of the generally poor prognosis of most cases of leukemia.¹²

The most common etiology of priapism are the following: drugs (psychotropics, antihypertensives, anticoagulants, sildenafil, ethanol, cocaine, and marijuana); hematologic (Sickle cell disease, leukemia, thalassemia) and spinal cord injury.⁵ As drugs and trauma were ruled out, a hematologic etiology of priapism was considered, although, only about 20

percent of cases of all priapism are related to hematological disorders.⁵

Work-up done to the patient showed anemia and leukocytosis on CBC and splenomegaly on whole abdominal ultrasound. Peripheral blood smear showed normocytic, normochromic red blood cells. Platelets are adequate in number while white blood cells are markedly increased in quantity with predominance of cells belonging to granulocytic series, many of which are young and immature. There was no noted sickle shaped cells. With this, a leukemic origin is highly considered. The incidence of priapism in adult leukemic patients is about one to five percent and leukemia is frequently associated with painful priapism.^{9,10}

Priapism as a result of hematologic malignancy is most likely caused by venous obstruction from microemboli/thrombi as well as hyperviscosity caused by the increased number of circulating leukocytes in mature and immature forms. Many studies have shown that a WBC count greater than $100.0 \times 10^9/L$ is a major contributor of an elevation of the whole-blood viscosity.

In our case, the WBC count on admission is $185,750/mm^3$. The four mechanisms of priapism in leukemia are:

- Venous congestion of the corpora cavernosa resulting from mechanical pressure on the abdominal veins by the splenomegaly
- Sludging of leukemic cells in the corpora cavernosa and the dorsal veins of the penis
- Infiltration of the sacral nerves with leukemic cells
- Infiltration of the central nerve system.

For this case, sludging of leukemic cells in the corpora cavernosa and the dorsal veins of the penis is the pathophysiology of priapism.

Because of the relatively rare occurrence of leukemic priapism and the small number of case series, there is no standard treatment protocol. The initial goal of therapy is relief of priapism (decompression of the penis within 24 hours) as there is incidence of impotence following this condition. A study cited 35% and 60% impotence rates for patients priapistic for five days and 10 days, respectively. Management of the underlying disease is as important as the initial therapy. Hydroxyurea can be given in chronic myelogenous disease to slow progression of the disease by inhibiting DNA synthesis in the S phase. Imatinib, a tyrosine kinase inhibitor, is the initial treatment of choice for the majority of patients with CML. It inhibits cellular proliferation and produces a 92 to 98% decrease in CML colony growth in vitro.¹²

With the combined urologic therapy and oncologic treatment, the patient recovered with no recurrence of priapism. There was noted cellular response in

the patient. The latest WBC count decreased to $16,700/microL$, with no immature granulocytes and platelet count of $262,000/microL$.

In cases of hematologic malignancy, controversy has existed regarding the optimal treatment of leukemic priapism. Earlier series of case reports show successful detumescence with local radiation therapy, open surgical shunting, or combination of the two treatments.¹²

More recent literature has focused on the use of cytoreductive modalities such as chemotherapy or combination chemotherapy and leukapheresis.

Chemotherapy or radiotherapy may first be attempted.¹³

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 therapies¹¹. 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 CML¹⁴. Imatinib at a dose of 400mg per day is still the gold standard first-line treatment for CML.¹³

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 trial.

Conclusion

The importance of prompt diagnosis and treatment of priapism cannot be overemphasized, as there is a definite, irreversible complication. Studies have shown that the longer the tumescence phase, the higher the risk of erectile dysfunction and impotence. Management does not stop with the relief of priapism but more important is the work-up and management of the underlying disease, in this case, CML. Priapism is an uncommon presentation in CML.

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