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Priapism Low-Flow Degree in Patient with Chronic Myeloid Leukemia (CML)

Dea Syafira Mahlevi[1], M. Noor Diansyah[2], Merlyna Savitri[3], Putu Niken Ayu Amrita[4], Pradana Zaky Romadhon[5], Ami Ashariati[6], Siprianus Ugroseno Yudho Bintoro[7]

[1]Department of Internal Medicine, Dr Soetomo General Academic Hospital, Surabaya, Indonesia

[2,3,4,5,6,7]Hematology Oncology Division, Department of Internal Medicine, Dr Soetomo General Academic Hospital, Surabaya, Indonesia

Email ID: Mahlevidea24@gmail.com

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ABSTRACT

Background: Chronic Myeloid Leukaemia (CML) is a type of cancer caused by disruption of haematopoietic stem cells. CML is a type of Myeloproliferative Neoplasm (MPN). CML is caused by a cytogenetic abnormality involving chromosome 9 and chromosome 22, known as Philadephia (Ph) Chromosome. Case report: A 25-year-old male patient has been diagnosed as Chronic Myelous Leukaemia (CML) for 2 years 2019. The patient has been tested for BCR-ABL1 Quantitative PCR with 63% (IS) results in 2019. Previously, the patient received imatinib but from 2019 to 2021 the patient did not take the medicine regularly. the patient came to the hospital to find that the penis had an erection for 6 hours continuously. Based on anamnesis, physical examination and supporting examination in the form of complete blood, peripheral blood smear, and intracavitary blood gas analysis, we diagnosed the patient with Chronic Myeloid Leukemia (CML) with accelerated phase accompanied by leukostasis manifesting priapismus (ischemic). As initial management, the patient was given rehydration therapy, imatinib mesylate, hydroxyurea, analgesics, Xanthin oxidase and leukoferesis. Leukoferesis was performed once. Priapismus in the patient reduced slowly during the 14-day treatment Conclusion: Reported a case of a patient with Chronic Myeloid Leukemia (CML) experiencing priapismus with a low flow degree that improved with the administration of imatinib mesylate, hydroxyurea, analgesics, Xanthin oxidase and leukoferesis. Leukoferesis was performed once. The patient's urologist performed intracavernous aspiration and distal shunting with the ebbehoj method.

Keywords: *CML, Priapism, Imatinib mesylate, aspiration intracavernous, distal shunting*

1. INTRODUCTION

Chronic Myeloid Leukaemia (CML) is a type of cancer caused by disruption of haematopoietic stem cells. CML is a type of myeloproliferative neoplasm (MPN). CML is caused by a cytogenetic abnormality involving chromosome 9 and chromosome 22, known as the Philadephia (Ph) Chromosome. The incidence of CML remains worldwide at 1-1.5 per 100,000 population. The incidence is higher in men than women, with a prevalence of 1.41. CML can cause hyperleukocytosis resulting in constitutional, cardiovascular, neurological and vascular symptoms (priapismus). (Höglund M. et al, 2015; Loscocco F. et al, 2019;) Priapismus is a prolonged erection (more than 4 hours) without sexual desire and often accompanied by pain. There are 2 types of priapismus namely, Ischaemic priapism and Non-priapism. Ischaemic (low-flow) priapismus is the most common type (95%) and is an emergency, caused by a veno-occlusion process, which manifests as penile rigidity. Priapismus is an emergency condition in the field of Urology that requires immediate treatment to prevent long-term complications. Delay in treatment will lead to persistent and prolonged dysfunction or priapismus. (Rodgjers R, 2012; Broderick GA, 2010).

The following is a case report of a patient with Chronic Myeloid Leukemia (CML) with leukostasis manifesting priapismus. The management in this patient used a combination approach of systemic therapy with intracavernous local therapy.

2. CASE

A man, Mr. AA, 25 years old, Javanese ethnicity, Islamic religion, lives in Sidoarjo, admitted to RSUD Dr. Soetomo Surabaya in Pandan Room 1 on 15 November 2021 with complaints of an enlarged and hardened penis.

Anamnesis:

History of Present Illness

The patient was referred from Ahmad Yani Islamic Hospital with complaints of an enlarged and hardened penis continuously for more than 6 hours. the penis enlarged and hardened suddenly. The penis feels painful, persistent pain. When the penis hardens and stiffens the patient only gives warm water compresses but does not improve. the patient said there were no previous complaints. The patient was taken to Ahmad Yani Islamic Hospital from TS urology to take action (Shunting Cavernosum). The patient was in MRS for 3 days and was evaluated but did not improve so was referred to Dr Soetomo Hospital. The patient said that in the last 6 months the stomach felt bulging. The patient did not have a cough, the patient also did not have a fever, the patient did not complain of excessive sweating at night. The patient was not found nausea and vomiting, the patient's appetite was good. The patient said there was weight loss for 1 year, the original weight was 65 kg, currently 50 kg. The patient's urination and defecation are within normal limits. Black stool is denied. The patient is still fully conscious, can communicate well, and does not experience disorientation of place, space, and time.

3. HISTORY OF PAST ILLNESS

The patient said he had been suffering from leukaemia since 2019, at the beginning of the patient's complaints he was found weak, fever and excessive sweating at night, decreased appetite and was also accompanied by weight loss. The patient had a molecular biology examination (BCR-ABL Quantitative PCR) on 26 December 2019 at the pramita laboratory with the results detected positive as much as 63%. The patient regularly takes Gleevec 4 tablets at night from December 2019 to June 2021. The patient stopped taking Gleevec because he was bored of taking the medicine and when taking the medicine the patient found it difficult to sleep. The patient has no previous history of hypertension, diabetes mellitus, thyroid disease and malignancy.

4. FAMILY HISTORY OF DISEASES

The patient's family has no history of similar diseases. Family history of hypertension, diabetes mellitus, thyroid disease and malignancy was denied.Patient Not yet married, patient lives with both parents. The patient is child the only one. Patient Work as expert partition. Patient Work since age 17 years. Patient daily life only exposed ray sun. Patient deny exposed radiation.

On physical examination, the general condition was found to be adequate with GCS 456. Blood pressure 110/80 mmHg, pulse 88x/min, regular rhythm, strong lift, normal amplitude, respiratory frequency 18x/min, axillary temperature 36.7 ^{o}C. Pain scale with Wong Baker face scale 5-6. Head and neck examination revealed anemic conjunctiva, no jaundice of sclera, no cyanosis or dyspnoea. There was no increase in jugular venous pressure and enlarged lymph nodes. Examination of the chest area was symmetrical movement, no retraction was found. In cardiac examination, S1 and S2 were found to be single, regular, no heart noise, gallop rhythm. On lung examination, vesicular breath sounds were obtained in both lung fields, neither ronki nor wheezing were obtained in both lung fields. Abdominal examination found normal bowel noise. On palpation of the abdomen, there was no tenderness, auscultation of normal bowel sounds. Lien palpable schuffner 3, hepar not palpable. Examination of the upper extremities found the acral warm, dry and red. There is no oedema. There is no lymph node enlargement. Lower extremity examination also found warm, dry and red acral. There is no oedema. There are no enlarged lymph nodes. Local examination of the genital area revealed an erect penis, palpably hard, with no discolouration of hyperemia, cyanosis, or pallor.

Laboratory examination at Dr. Soetomo Surabaya Hospital on 14 November 2021 showed results of 7.7 g / dL, HCT 21.6, MCV 21.6, MCH 32.6, Monocytes 6.7%, eosinophils 2.9%, basophils 4.6%, Lymphocytes 3.1, Leukocytes 525,750 /uL, Platelets 204,000 /uL, Reticulocytes 3. 47, ESR 5, LDH 953, PPT 17.7 sec, APTT 35.6 sec, CRP 1.46, Bun 6 mg/dL, SK 0.85 mg/dL, Sodium 142 mmol/L, Potassium 3.3 mmol/L, Chloride 106 mmol/L, Uric Acid 6.51, SGOT 27, SGPT 21, Bil D 0.17, Bil T 0.48, Alb 3.90, HbsAg reactive, anti HIV negative, Rapid Antibody Covid -19 negative. The results of peripheral blood smears obtained erythrocytes: Normochromic normocytic anisopoikilocytosis (microcytes, ovalocytes), polychromasia cells (+), normoblast (+), Leukocytes: The impression of increased numbers, obtained all stages of maturation of myeloid series cells without maturation gap with the proportion of myeloblasts 17%, promyelocytes 8%, myelocytes 30%, metamielocytes 19%, stab neutrophils (hypogranules) 14%, segment neutrophils (hypogranules) 22%. There were also eosinophils 5%, basophils 2% and lymphocytes 3%. Platelets: Normal count, giant platelet (-) Impression: Normochromic normocytic anaemia anisopoikilocytosis, leucocytosis with myeloblast 7%., with the conclusion that chronic phase CML is beginning to lead to an accelerated phase. Thoracic photograph shows Infiltrates in the right and left paracardial can be a manifestation of CML, there is pulmonary inflammation and cast does not appear abnormalities. BOF photo showed no abnormality. The patient was performed BGA Penis which showed ph 7.090, PCo2 90 mmHg, Po2 27 mmHg, HCO3 27.3 mmHg, BE -2.5 mmol / L, the patient was also performed doppler ultrasound on the penis with the results visible flow in corpora cavernosa There was no arteriovenous fistula picture on this examination with the conclusion suspicious of low flow priapism. Urology Department Consultation: Aspiration and irrigation were performed and surgery was performed using the percutaneous distal shunting method on 14 November 2021.

From clinical manifestations, laboratory and radiological results, the patient was diagnosed with Priapismus degree low flow post shunting on November 11, 2021 + CML accelerated phase + Normochrome Normositer Anemia (Hb 7.7) + Leukostasis

(WBC 525,750) + Hypokalemi (3.3). the patient is bedridden in the hospital by getting diet High Calorie High Protein 2100 kcal / day.

5. COURSE OF DISEASE:

On the first day of treatment (15 November 2021), the patient was still found to have an erection and the penis was painful with a pain scale of 5-6. On examination of the external genitalia, an Erectile Hardness Score (EHS) 4 was obtained with the description that the penis is completely hard and fully rigid, there are shunting sutures at 9 o'clock and 3 o'clock in the glans penis, DK 16 Fr 2 way is attached. the patient received a High Calorie High Protein 2100 kcal / day, 500 ml infusion in 24 hours, the patient received a PRC transfusion of 2 kolf per day. Gleevec 400 mg tablets at night, KSR tablets 3x600 mg tablets. Urology procedure was performed percutaneous distal shunting (ebbehoj method).

On the third day of treatment (17 November 2021), the patient still obtained a penile erection and felt pain with a pain scale of 5-6. On examination of the external genitalia, there is no change, an Erectile Hardness Score (EHS) 4 is obtained with edema. The patient underwent leucapheresis for 2 hours with no complications. The patient received Gleevec 400 mg tablets at night and Hydrea 2000 mg tablets at night. Urological action was performed proximal shunting and necrotomy. On the sixth day of treatment (20 November 2021), the patient still had penile erection but the pain was less, appetite was good, urination and defecation were within normal limits. From the examination of the external genitalia, Dk 16 Fr was attached, crustal tissue was seen on the shaft of the penis. Erectile Hardness Score (EHS) obtained score 3 with the description that the penis is hard enough for penetration but not completely hard. The patient did not get any change in therapy. The Urology department performed regular wound care and EHS evaluation.

On the tenth day of treatment (24 November 2021), the patient was found to have penile erection but less than usual, pain in the penis sometimes. From the examination of the external genitalia, Dk 16 Fr was attached, crustal tissue was seen on the shaft of the penis. Erectile Hardness Score (EHS) 2- 3 with the description (EHS 2) the penis is hard but not hard enough for penetration and (EHS 3) the penis is hard enough for penetration but not completely hard. The peripheral blood smear was found to be ERYTHROCYTES: Normochromic normocytic anisopoikilocytosis (microcytes, ovalocytes). Polychromasia cells (+), normoblast (+) LEUKOCYTES: Impression of increased number, all stages of maturation of myeloid cell series were found, without maturation gap, with the proportion of myeloblast 4%, promyelocyte 2%, myelocyte 6%, metamielocyte 8%, neutrophil (hypogranulous) stab 10%, neutrophil (hypogranulous) segment 61%, eosinophil 4% and basophil 5% PLATELETS: Normal count impression, Giant platelet (-) CONCLUSION: Anisopoikilocytic normochromic anaemia. Leucocytosis with myeloblast 4%. Conclusion: Suspected Chronic Phase CML. The Urology department performed regular wound care and EHS evaluation. On the fourteenth day of treatment (28 November 2021), the patient was not found to have erection of the penis, morning erection was still obtained, pain was reduced, urination and defecation were within normal limits. From the examination of the external genitalia Erectile Hardness Score (EHS), a score of 0 was obtained with the description that the penis does not enlarge. We plan to discharge the patient.

In addition to local penile clinical monitoring and complete blood examination, the patient was also monitored for urine production, uric acid and serum electrolyte examination to monitor the occurrence of tumour lysis syndrome. The patient's urine output averaged 1500-2000 cc in 24 hours and uric acid and electrolytes were within normal limits. The patient's serial laboratory examinations are shown in the table below.

Table 1. Laboratorium serial

Laboratorium	14/11	16/11	18/11	20/11	22/11	24/11	28/11
Hb	7.7	8.7	9.3	9.1	9.3	8.9	9.6
Hct	21.6	23.9	25.9	26.9	27.4	27.9	31.1
WBC (x1000)	525.750	533.320	516.720	439.430	326.400	222.310	60.600
Eo (%)	2.9	2.9	3.1	3	3.2	2.7	2.0
Bas (%)	4.6	5.4	4.4	5.5	5.6	5.9	7.6
Neut (%)	81.2	81.0	82.2	83.9	82.9	83.6	82.1
Lypmh (%)	3.1	6.3	3.3	3.3	4.9	5.5	10.5
Mono %	6.7	4.4	7.0	19.0	3.4	2.3	1.3
PLT (x1000)	204,000	212,000	208,000	221,000	236,000	315,000	412,000
LDH	953						

Sour tendon		6.51					7.6
Sodium	142	135	143				144
Potassium	3.3	3.0	4.0				4.2
Chloride	106	105	105				110
BUN	6			20			12
SK	0.85			0.99			0.94
Leukapheresis		(11/17)					

6. DISCUSSION

Chronic Myeloid Leukemia (CML) is a chronic leukaemia characterised by an increased number of leucocytes and all forms of granulocytes from mature to immature, where the dominant cells are myeloid cells. There is a specific abnormality in the karyotype of the Philadelphia chromosome. The diagnosis of CML is made by cytogenetic, or molecular identification of hematopoietic stem cells obtained through the process of reciprocal translocation between chromosomes 9 and 22 (BCR-ABL. (Ghane, 2019)

The 25-year-old patient, male, has been diagnosed as CML for 2 years (2019) with initial complaints of weakness, excessive sweating at night and accompanied by weight loss The patient has undergone BCR-ABL1 Quantitative examination with a result of 63% (IS) in 2019.

CML has 3 phases: chronic phase (CP), accelerated phase (AP), and blastic crisis (BP). Most (90%-95%) CML patients are in the chronic phase (CP-CML). Patients are categorised as < 10% blast cells in peripheral blood and bone marrow, accelerated phase when the blast cell count is ≥ 15% blast cells and ≥ 30% promyelocytes in peripheral blood, and blastic crisis phase when the blast cell count is > 20% in peripheral blood and bone marrow with common symptoms of anaemia and splenomegaly. Rare manifestations include bleeding (associated with low platelet count and/or platelet dysfunction), thrombosis (associated with thrombocytosis and/or leucocytosis), gouty arthritis, retinal haemorrhage and upper gastrointestinal ulceration. Leukostasis symptoms (priapism, dyspnea, drowsiness, loss of coordination, confusion) due to leukaemia cells settling in the blood vessels are rare in Chronic Phase (CP) although the white blood cell (WBC) count often exceeds 100 109/L. As for determining the prognosis before starting therapy for chronic phase CML patients with TKI, it is recommended to use the socal score and Hasford score. The socal score is determined based on age, spleen size, platelets and peripheral blood blast cell percentage. While the Hasford score is to evaluate the survival of CML patients treated with interferon- α (Baccarani et al., 2010; Hasford et al., 2011).

From the patient's history, there were complaints of a bulging stomach, it has been felt since the last 6 months. the patient also said that there was weight loss over the past 6 months, with the original body weight of 65 kg currently being 50 kg. the patient has regularly taken Imatinib Mesylate (Gleevec) 400 mg tablets at night since 2019, during treatment since 2019 the patient did not have any complaints, but the patient stopped taking the drug since June 2021. From the physical examination, it was found that the conjunctiva was anemic and schuffner's splenomegaly 3. From the laboratory results, leukocytosis was found (WBC 525,750). From the peripheral blood smear obtained from leukocytes, namely with the impression of increasing numbers, all stages of maturation of myeloid series cells without maturation gaps were obtained with the proportion of myeloblasts 17%, promyelocytes 8%, myelocytes 30%, metamielocytes 19%, stab neutrophils (hypogranules) 14%, segment neutrophils (hypogranules) 22%. Eosinophils 5%, basophils 2% and lymphocytes 3% were also found. Conclusion: Chronic phase CML that is starting to lead to an accelerated phase. The patient's socal score was 0.51 and Hasford score was 82.02.

In CML patients, hyperleukocytosis causes hyperviscosity and obstruction due to thrombus and microthrombus. Sexual stimulation causes an increase in parasympathetic nerve activity, which results in dilatation of arterioles and constriction of venules, so that inflow (blood flow to the corpora) increases while outflow (blood flow leaving the corpora) decreases. this leads to an increase in the volume of blood filling the sinusoid cavity and causes penile tension. Similarly, in the flaccid phase, there is contraction of the arterioles, contraction of the cavernous muscles, dilation of the venules to drain blood into the penile veins, and the sinusoid cavity decreases in volume. (R. Amini, 2017).

Priapismus is caused by impaired outflow mechanism (veno-occlusion) so that blood cannot exit the erectile tissue or increased arteriolar blood flow into the erectile tissue. Ischaemic priapismus is a persistent erection where there is decreased intracavernous blood flow. It is a type of compartment syndrome, with decreased venous flow leading to stasis, acidosis, and hypoxia. Ischaemic is an emergency case. It is present when there is no flow from the corpus cavernosus on doppler ultrasound of the penis and a corpus cavernosus blood gas analysis shows pH < 7.25, pO2 < 30 mmHg, and pCO2 > 60 mmHg. (Broderick GA, 2010)

At the time of presentation, the penis was found to be erect for 6 hours continuously. There was no previous history of trauma, sexual stimulation, or consumption of certain drugs before the erection. The patient also complained of pubic pain with mild intensity and almost continuous. There was no complaint of reddish, bluish, or pale colour change of the penis. From the examination of external genitalia, an erectile hardness score of 4 was obtained, an ultrasound doppler examination of the penis was performed, the results showed low flow in the corpora cavernosa, there was no arteriovenous fistula and also a Blood Gas Analysis (BGA) examination of the penis which showed ph 7.090, PCo2 90 mmHg, Po2 27 mmHg, HCO3 27.3 mmHg, BE -2.5 mmol/L. During the 2 days of treatment, the patient was found to have edema in the penis.

Once the diagnosis of ischaemic priapismus has been made, emergency management is required. In cases of ischaemic priapismus, aspiration of the corpus shows dark venous blood initially and should be continued until bright red oxygenated blood is aspirated. When aspiration is difficult due to increased blood viscosity in the corpus cavernosum, cold saline irrigation can promote evacuation of hypoxic blood. If the corporal aspiration procedure is unsuccessful, Percutaneous distal shunt (e*bbehoj* shunt) is performed by inserting a scalpel into the corpora cavernosa of the gland, followed by a 90° lateral rotation of the scalpel and then pulling it out. Delay in treatment within 24-28 hours may result in permanent damage and fibrosis, leading to persistent and prolonged problems of erectile dysfunction or priapismus. After 12 hours of priapismus, there will be trabecular oedema, and the penis looks oedematous at 24 hours, platelets adhere to the sinusoidal basement membrane, and after 48 hours, there is cavernous smooth muscle necrosis with sinusoidal thrombus and fibroblast proliferation. Ischaemia lasts 24-48 hours, causing endothelial and trabecular damage, with irreversible fibrosis and calcification, leading to erectile dysfunction. The main mechanism is the accumulation of leukaemia cells in the corpus cavernosum and dorsal veins of the penis. (Huang YC, 2003; Burnett AL, 2011; Song PH, 2013;)

At the beginning of the patient's arrival, EHS 4 was obtained, aspiration was carried out as much as ± 200 cc, an evaluation was carried out for 15 minutes the patient was still found to be erect. Irrigation with cold saline was carried out. After evaluation, the patient was found to have EHS 2-3. On the second day of treatment, the patient was found to have EHS 4 so that percutaneous distal shunting with the ebbehoj method was considered. On the third day of treatment, an erection was still obtained in the penis with EHS 4 and edema was also obtained in the penis, so percutaneous distal shunting with the ebbehoj method was again performed and necrotomy was also performed to obtain EHS 2. For the next action, only evaluate the erectile hardness score.

The principle of management of patients with leukostasis must be carried out immediately because it is included in medical emergencies. If there are signs of leukostasis, hydration, administration of imatinib mesylate, can be done simultaneously and leukaparesis can also be done. Initial treatment with adequate hydration. In addition to hydration, imatinib mesylate can also be given. Imatinib mesylate is a first-generation *Tyrosine Kinase Inhibitor* (TKI) used for the treatment of CML in the accelerated phase. Imatinib acts as a Transduction inhibitor (STI), which directly inhibits tyrosine kinase activity. The active form of this enzyme can lead to increased tumour cell proliferation and growth, induce anti-apoptotic effects, and promote angiogenesis and metastasis. (Liesveld and Lichtman, 2016).

In this patient, lekostasis was found, so immediate treatment was carried out, namely the patient received hydration by giving 1000 ml infusion in 24 hours. Previously the patient took Imatinib Mesylate (Gleevec) 1x400 mg tablets at night, so we continued the drug administration. Leukocyte counts are lowered in a short period of time by cytoreduction in the form of leukafaresis, which is indicated as a therapy for short-term leukocyte count control. Leukafaresis is carried out with the principle of separating and removing the number of leukocytes from other components, other components that are still needed are then flowed back into the body. Leukaparesis can reduce the peripheral leukocyte count by 20-50%. The main indication for leukaparesis is leukostasis. Some experts also perform leukafaresis in patients without symptoms of leukostasis and reduce the possibility of Tumor Lysis Syndrome (TLS). A study stated that leukaparesis can reduce mortality in the first two weeks, but cannot improve the long-term prognosis of patients. (Lange T, 2017).

In this patient, leukocytosis was still found with WBC (533,320) so that leukaparesis was performed once on day 3 of treatment, the patient did not get complaints during leukaparesis and after leukaparesis, the patient was given a complete blood test after leukaparesis with WBC (516,720). WBC decreased by only 16%. Imatinib mesylate and leukaparesis do not improve, a combination with hydroxyurea can be used. Therapy with hydroxuyrea is designed to achieve a slow decrease in leukocytes over several days to prevent tumor lysis syndrome. Hydroxyurea is a classic chemotherapy drug, which was used to limit leukocyte proliferation before the introduction of interferons and TKIs. Hydroxyurea is currently still widely used as a temporary treatment to reduce leukocytosis in CML, Hydroxyurea side effects can increase uric acid production and there are also minimal side effects, all of which are reversible when treatment is stopped. These include nausea and vomiting, anorexia, chills, body aches, flu-like symptoms, constipation, diarrhea, stomatitis, alopecia (hair loss), abnormal liver enzymes, abnormal creatinine and urea nitrogen. (Lange T, 2017).

On the 4th day of treatment, the patient still had leukocytosis after leukaparesis was performed and there was no significant decrease in leukocytes. The patient was still taking Gleevec 1x 400mg tablet at night so hydroxyurea 1x2000 mg tablet at night was considered. The patient experienced clinical improvement in the form of slowly reduced penile erection and also laboratory parameters, namely a decrease in leukocyte count. The patient was discharged on the 13th day of treatment,

previously evaluated with WBC 60,600 and uric acid 7.6 so Gleevec 1x400mg tablets at night and allopurinol tablets 1x100 mg at night were given.

7. CONCLUSION

A 25-year-old man was reported with a positive BCR-ABL result previously in 2019, the patient had a history of taking imatinib mesylate for 2 years but stopped in June 2021 who had continuous erections since 4 days before admission. Based on history taking, physical examination and supporting examination in the form of complete blood, peripheral blood smear, and intracavitary blood gas analysis, we diagnosed the patient with Chronic Myeloid Leukemia with accelerated phase accompanied by leukostasis manifesting priapismus (ischemic). As initial management, the patient was given rehydration therapy, imatinib mesylate, hydroxyurea, analgesics, Xanthin oxidase and leukoferesis. Leukoferesis was performed once. From the patient's urologist, intracavernous aspiration was performed and distal shunting was performed with the ebbehoj method. Priapismus in the patient decreased slowly. The patient was discharged on day 14 of treatment.

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