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Priapism in lymphoproliferative disorders: A systematic review

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REVIEW ARTICLE

Priapism in Lymphoproliferative Disorders: A Systematic Review

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Abstract

Priapism is defined as a persistent penile erection lasting more than 4 h. We searched the literature for reviews, case reports, and series for patients with lymphoproliferative disorders who developed priapism. The search involved all the lymphoproliferative disorders included in the revised 2016 World Health Organization classification of lymphoid neoplasms including chronic lymphocytic leukemia, multiple myeloma, Waldenström macroglobulinemia, and lymphomas. A total of 16 articles were found. The search included cases up to 4th January 2021. Priapism was seen most commonly as the first manifestation of lymphoproliferative disorders, rarely seen after treatment or after diagnosis.

Keywords: Lymphoproliferative disorders, Leukemia, Lymphoma, Priapism, Male fertility, Multiple myeloma

1. Introduction

The lymphoproliferative disorder is a group of heterogeneous disorders characterized by monoclonal or oligoclonal lymphoid cell proliferation resulting in dysregulated immune function [1]. They include several hematologic diseases like chronic lymphocytic leukemia, hairy cell leukemia, plasma cell myeloma, various types of lymphomas, and mature T-cell and NK-cell neoplasms. The main presentation of these disorders is usually related to infection, bleeding, anemia, bone pain, or disease-specific complications like or organomegaly. Priapism is a prolonged penile erection, generally lasting longer than 4 h. In adults, it is commonly seen as a complication of drug use. In hematologic disorders, priapism is well mentioned in association with anemias, most commonly sickle cell anemia [2] and less frequently thalassemia [3]. Moreover, it is mentioned in association with chronic myeloid leukemia and essential thrombocythemia [4,5]. Priapism in hematologic disorder is most likely the result of venous obstruction from microemboli/thrombi as well as hyperviscosity due to an increased number of circulating blood cells. Additional congestion can be aggregated by mechanical pressure from the abdominal veins draining the spleen or infiltration of the sacral nerves or the central nervous system by leukemic cells [6]. Increased production of cytokines and adhesion molecules by malignant cells results in endothelial cell activation and leads to increased sequestration of cells in the microvasculature [7]. Long-lasting priapism more than 24−48 h may result in varying extents of irreversible fibrosis with endothelial and trabecula destruction of the erectile tissue and subsequently in permanent erectile dysfunction. Priapism adversely affects the quality of life and erectile function; therefore, it is considered a urologic emergency [8]. In this review, we try to see how common priapism is and to understand its pathophysiology in lymphoproliferative disorders.

2. Methods

We searched the English literature (Google Scholar, PubMed, and SCOPUS) for original

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articles, reviews, case series, and case reports using the terms "priapism" and "multiple myeloma", "priapism" and "Plasma cell myeloma", "priapism" and "lymphoma", "priapism" and "Waldenström macroglobulinemia", "priapism" and "lymphoproliferative neoplasm." All articles documenting priapism associated with lymphoproliferative disorders were included. Gray literature were excluded. The search included articles up to up 4th January 2021.

3. Results

A total of 16 article were included Fig. 1. The search showed that the most frequent lymphoproliferative disorder associated with priapism was lymphoma ($n = 8$), followed by multiple myeloma (MM; $n = 6$), and then chronic lymphocytic leukemia ($n = 2$). There were no reports regarding the occurrence of priapism with other lymphoproliferative disorders, such as Waldenström macroglobulinemia (WM) and hairy cell leukemia. Priapism in lymphoma was mostly seen with diffuse large B-cell type ($n = 6$; Table 1 describes the lymphoma), and with undifferentiated lymphoma and well-differentiated lymphocytic lymphoma. This distribution is reasonable as diffuse large B-cell lymphoma is the most common type of lymphoma [1]. The histologic subtypes of large B-cell lymphoma were not described in the reports. The most common

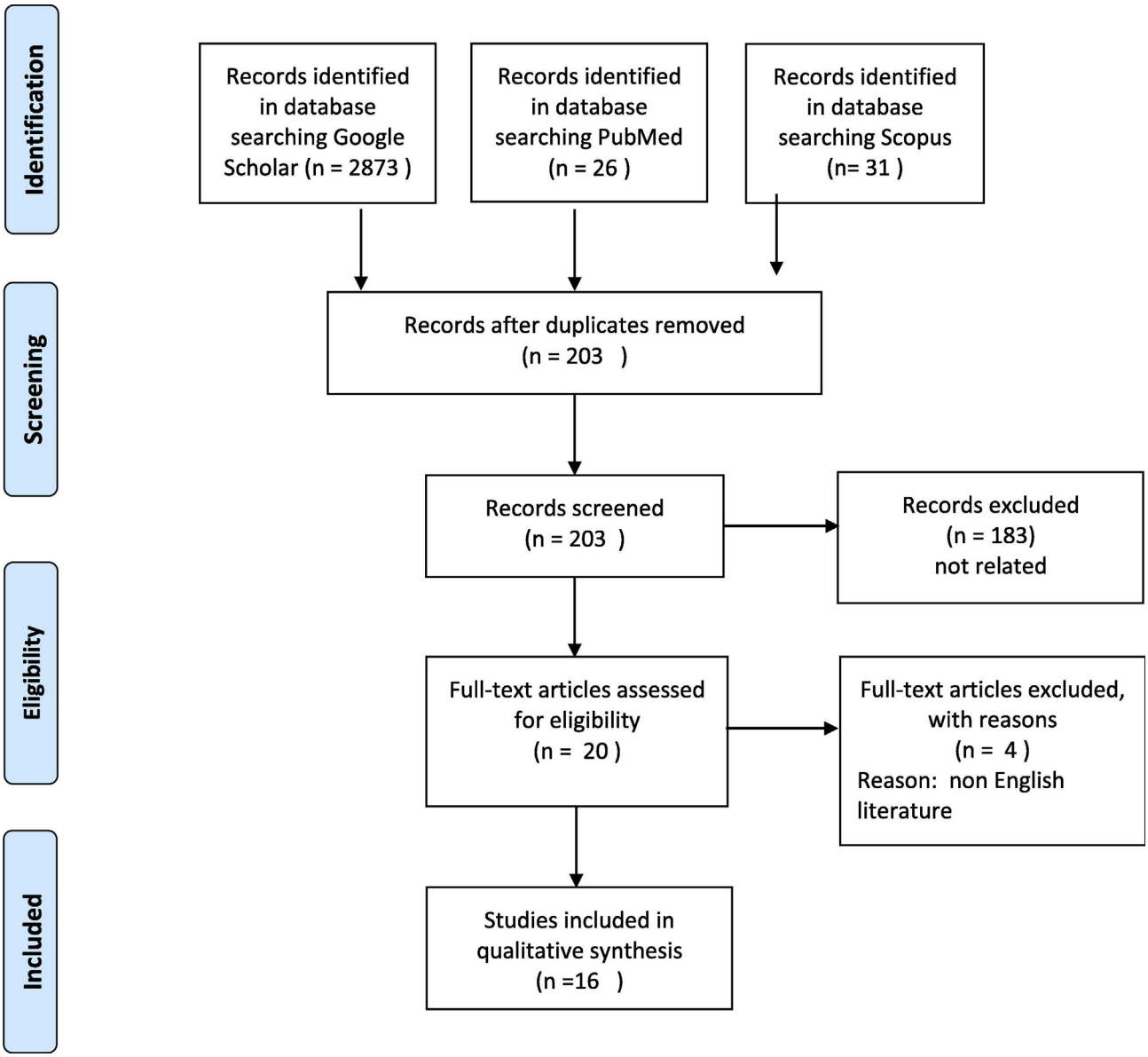

Fig. 1. The PRISMA flow diagram detailing the search of articles involving patients with lymphoproliferative disorders who developed priapism.

Table 1. Baseline characteristics of patients with lymphoma who developed priapism.

Lymphoma	Stage	Age (yr)	Priapism from onset to presentation to the hospital	Type of priapism	First presentation or previously diagnosed	WBC (×10^9/L)	PLT (×10^9/L)	HB (g/dL)	Lympha-denopathy	Splenomegaly/ hepatomegaly, below costal margin (cm)	Priapism treament/ improved with (required to relieve)	Medications for priapism	Aspiration and irrigation	Leukapheresis	Radiation therapy	Shunt	Outcome/ impotence
Penilelymphoma, diffuse large B-cell non-Hodgkin's [33] lymphoma	IV	48	1 month	Painless	First presentation	N/A	N/A	N/A	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Died 3 months later
Large B-cell lymphoma of the penis [34]	IV	76	N/A	ischemic	First presentation	3.3	128	10.1	No	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lymphoma of the penis, diffuse large B-cell lymphoma [35]	IIE	67	2 months	ischemic	First presentation	3	134	13.1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No ED
Lymphoma of the penis, diffuse large B-cell lymphoma [36]	III-IV	78	2 weeks	Painless, high flow	First presentation	Normal	Normal	Normal	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Diffuse, large-cell type stage II malignant lymphoma of B-cell origin [37]	II	50	6 months	Painless	First presentation	N/A	N/A	N/A	No	No	Shunt	Anticoagulation	Yes, failed	No	No	Yes	Developed ED
Undifferentiated lymphoma (stage CNS and hepatomegaly) [38]	N/A	20	N/A	N/A	First presentation	4.9	315	HCT 32	Yes	Liver 4 cm	N/A	N/A		N/A	No	No	Died 5 months later lymphomatous infiltration of the sacral spinal roots.
Well differentiated lymphocytic lymphoma [39]	N/A	76	2 weeks	Painless	First presentation	N/A	N/A	N/A	Yes	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Diffuse large B-cell lymphoma, lymphoma of the penis [40]	N/A	N/A	N/A	Painless partial priapism	First presentation	N/A	N/A	N/A	N/A	N/A	LMWH and folic acid	N/A	N/A	N/A	N/A	N/A	N/A

Note: ED = erectile dysfunction; HB = hemoglobin; HCT = hematocrit; LMWH = low-molecular-weight heparin; N/A = nonapplicable; PLT = platelet; WBC = white blood cell.

lymphoma stage at presentation for patients of lymphoma who developed priapism was stage IV ($n = 5$) and stage II ($n = 2$); others had no documentation or clear clue to the stage. One patient had a history of treated chronic myeloid leukemia [35]. MM was associated with priapism in six patients (Table 2 describes multiple myeloma and chronic lymphocytic leukemia). All of them were above the age of 40 years, consistent with the general MM patients (median age: 66 years) [9]. Two patients had a penile amputation, one had erectile dysfunction, and erectile dysfunction was not addressed in the other three. The most common subtype of MM-associated priapism was immunoglobulin (Ig)G in three patients, IgA in one patient, and lambda light chain in one patient. The mean time to presentation in MM was 50.6 h, excluding one patient with 9 months of stuttering priapism. All patients with MM had priapism as the first presentation, except one patient [30] who developed it after receiving the first cycle with bortezomib and thalidomide. Four patients had ischemic type of priapism, and two had the stuttering type one of them had priapism recurrent in 9 month duration [27]. The treatment modalities received is seen in Tables 1 and 2.

4. Discussion

Priapism can be classified as ischemic (low flow), which is the most common type, and nonischemic (high flow) [10]. Priapism can occur in recurrent short episodes lasting less than 4 h, called stuttering priapism [10]. The pathogenesis of ischemic priapism involves disturbed nitrous oxide (NO) and cyclic guanosine monophosphate (cGMP) signaling mechanisms [11,12]. High-flow priapism is rare and typically occurs following trauma or the creation of a fistula that increases the flow of oxygenated blood [10]. In hematology, priapism is more frequently seen with sickle cell anemia [2], less commonly associated with myeloproliferative neoplasms [4], and infrequently reported with lymphoproliferative disorders.

Lymphoma was the most common lymphoproliferative neoplasm to be associated with priapism. All the reported lymphoma patients were of non-Hodgkin type, mostly diffuse large B-cell lymphoma. Lymphoma patients with priapism were elderly, with the reported mean age of 59.2 years, which is close to the median age at presentation (64 years) for the general patients with diffuse large B-cell lymphoma [13]. Generally, lymphoma patients have normal white blood cell (WBC) count, and the reported patients had normal blood count in the peripheral blood. Normal blood count means that priapism etiology in lymphoma is not related to increased circulating blood cells or increased viscosity. Instead, an infiltration of the perineal nerves and pelvic organs by the malignant cell is the primary mechanism, as demonstrated in the autopsy of the priapism with the undifferentiated type [39]. This is supported by the fact that most of the lymphoma presenting with priapism have evidence of penile involvement or penile tissue infiltration (penile lymphoma) in five patients. This explains the reason why non-Hodgkin lymphoma, rather than Hodgkin type, is more frequently reported with priapism, as non-Hodgkin lymphoma is more likely to have extranodal involvement.

Moreover, Burkitt lymphoma, which is characterized by extremely high tumor burden, had not been reported with priapism, favoring that priapism in lymphoma is not related to the cell count or tumor burden but rather related to local infiltration. The sporadic type of Burkitt lymphoma is rare—2.2 cases per million persons per year in Europe [14]; however, Burkitt lymphoma is more common in Africa (the endemic type), and also no reports were available. This could distinguish the priapism in lymphoproliferative disorders from myeloid neoplasm, where increased circulating blood cells play a vital role in explaining the pathogenesis of priapism. Surprisingly, priapism in lymphoma is more of a painless type; it was reported to be painless in five patients. The painless high-flow priapism is uncommonly seen with hematologic disorders; the ischemic type is predominant [4]. The reason why some patients with lymphoma had painless priapism and others had painful priapism is not clear; this may be due to local infiltration of the nerves which may affect the pain fibers.

The second reported lymphoproliferative disorder was MM. Thrombosis in MM is not uncommon, particularly for patients on chemotherapy with dexamethasone [15]. Patients with MM are at risk of developing thrombotic events due to hypercoagulable state secondary to elevated factor VIII levels, acquired activated protein C resistance [16], and defective fibrinolysis [17]. However, venous thromboembolism in MM appears to behave differently than thrombosis in solid organ tumors, as thrombosis has not been proven to affect the prognosis in MM patients [18]. This different pathogenesis of thrombosis in MM could explain the finding that priapism in MM and lymphoproliferative disorders as general is not related to thrombosis and hypercoagulable state, but rather to local infiltration. Interestingly, the monoclonal gammopathy of unknown significance (MGUS), an early stage that proceeds the full-blown MM, was found to have a

Table 2. Baseline characteristics of patients with multiple myeloma and chronic lymphocytic leukemia who developed priapism.

Hematologic disease: PRV CLL MM…	Age (yr)	Priapism from onset to presentation to the hospital	Type	WBC (×10^9/L)	PLT (×10^9/L)	HB g/dL	Lympha-denopathy	Spleno-megaly	Priapism treament/ improved with (required to relieve)	Medications for priapism	Aspiration and irrigation	Leukapheresis/ plasma exchange	Irradiation	Shunt	Outcome/ impotence
MM IgG [25]	60	26 h	Stuttering	10.5	N/A	9.4	N/A	N/A	Plasmapheresis	None	No	Yes	No	No	Died of progressive disease ED N/A
MM IgG kappa [26]	63	3 days	Ischemic	N/A	N/A	N/A	N/A	N/A	Plasma exchange	N/A	N/A	Yes	N/A	N/A	N/A
MM IgA lambda [27]	61	14 h	Stuttering	Normal	Normal	10.6	N/A	N/A	Aspiration, irrigation, intracavernosal phenylephedrine injection, shunting	Terbutaline sulfate	Yes	No	No	Yes	N/A
MM IgG lambda [28]	44	3 days	Ischemic	42	180	11	N/A	N/A	Aspiration, plasmapharesis × 7.	None	Yes	Yes	No	No	Penile autoamputation
MM, lambda [29]	44	4 days	Ischemic	9.7	N/A	10	N/A	N/A	Aspiration, irrigation, phenylephedrine injection, shunt creation	Phenylephrine inj	Yes	No	No	Winter T	Partial penectomy
MM, stage 3 [30]	66	1 day	Ischemic	N/A	N/A	N/A	N/A	N/A	Aspiration, irrigation, shunt, bilateral cavernotomy	None	Yes	No	No	Yes	ED
CLL [31]	55	3 days	Ischemic	92	140	11	N/A	Yes	None	No	No	No	No	No	N/A
CLL [32]	54	7 h	Ischemic	434	91	8.7	Yes	Yes	Aspiration, phenylephedrine injection, leukapheresis	Phenylepherine inj	Yes	Yes	No	No	ED

Note. CLL = chronic lymphocytic leukemia; ED = erectile dysfunction; HB = hemoglobin; MM = multiple myeloma N/A = nonapplicable; PLT = platelet; WBC = white blood cell.

higher risk of thrombosis despite having lower level of circulating monoclonal immunoglobulin [19]. More surprisingly, the risk was higher with monoclonal spike of IgG or IgA than with IgM [19] despite the fact that IgM has stronger association with hyperviscosity than IgG or IgA. However, there are no reports of priapism in MGUS.

The normal serum viscosity is between 1.4 and 1.8, and M protein in MM can raise serum viscosity. In MM and WM, serum viscosity usually does not correlate precisely well with patients' symptoms, but most patients develop hyperviscosity symptoms when serum viscosity is >6 centipoise [20,21]. Most reports did not comment on the serum viscosity measurements of the patients with MM.

Waldenström macroglobulinemia is a plasma cell descries that has lymphoplasmacytic lymphoma picture in the bone marrow and produces monoclonal IgM in the blood. Patients usually present with constitutional symptoms, organomegaly, or features related to hyperviscosity [22]. Despite the known hyperviscosity in WM [22], no cases were reported in association with priapism. The absence of reports may be because WM is much rarer than MM. The annual incidence of MM is around seven per 100,000 annually [23] versus three per million people annually for WM [24]. Second, besides the few cases, there is probably underreporting of the priapism in these patients.

Such absence of reports in a condition with known hyperviscosity like WM makes the understanding of priapism more complex. This suggests that hyperviscosity or the increase in a cell line is not a major mechanism in the development of priapism in lymphoproliferative disorders as was observed in patients with high circulating blood count in essential thrombocythemia and chronic myeloid leukemia. Moreover, as in lymphoma patients, the WBC count is usually normal, making the proposed mechanism that eventually disturbs the final common pathway of altered NO cGMP balance different in lymphoproliferative disorders from other hematologic diseases.

In chronic lymphocytic leukemia, priapism was seen in two patients. Both had priapism as the initial presentation of their disease (Table 1).

Unfortunately, most of the reports had no clear documentation regarding the final effect on erectile dysfunction. However, in the reports of MM, two out of seven patients had a penile amputation, one had erectile dysfunction, and one died from disease progression. In lymphoma, data were more deficient. Additionally, there were little data regarding the presence or absence of organomegaly, which is proposed to raise the intraabdominal pressure and enhance the venous congestion and subsequent occurrence of the priapism.

In conclusion, priapism is an uncommon manifestation of lymphoproliferative disorders. The mechanism of priapism in lymphoproliferative disorder is different from that in myeloid disorders, not related to hyperviscosity. It generally occurs at the usual age of the specific disease. Despite the few reports in lymphoproliferative disorders, many patients ultimately had penile amputation or developed erectile dysfunction. This had a drastic effect on the quality of life; therefore, prompt diagnosis and rapid management are necessary to preserve erectile function.

Authors' contributions

All authors contributed to the writing, editing, and approval of the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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