Priapism: presentation of rare haematological disease

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Abstract

Monoclonal gammopathies are conditions where abnormal amounts of immunoglobulins are produced by a clone developed from a single pro-germ cell. In some cases, monoclonal gammopathies may occur as a result of abnormal B cells, which have not yet developed into plasma cells. This type of gammopathy is seen in leukaemia or lymphoma. Hypergammaglobulinemia increases serum viscosity, being the most common cause of hyperviscosity syndrome. Symptoms of hyperviscosity usually appear when the normal serum viscosity of 1.4 to 1.8 cp reaches 4 to 5 cp, corresponding to a serum immunoglobulin M (IgM) level of at least 3 g/dL, IgG level of 4 g/dL, and an IgA level of 6 g/dL. Symptoms of hyperviscosity may include constitutional symptoms, bleeding and ocular, neurological or cardiovascular manifestations.

Several etiological factors have been associated with priapism. The main etiological categories are hematologic dyscrasias, neurologic conditions, nonhematologic malignancies, trauma, erectile dysfunction pharmacotherapy, pharmacologic exposure and idiopathic factors. Long standing priapism due to malignant lymphoma is a rare incident. We report a case of lymphoma with abnormal production of serum IgM (more than 5 g/dL) and priapism as the first clinical manifestation.

Key words: priapism, monoclonal gammopathies, hyperviscosity syndrome, lymphoma.

INTRODUCTION

Priapism is defined as a prolonged and persistent erection that is not associated with sexual interest or stimulus.[1] This situation is rare, and the causes and mechanisms are still not fully known. Epidemiological studies report an annual incidence of 0.5 to 1 case per 100.000 people.[2] There are many etiological factors that can lead to this dysfunction. The most important situations described are: hematological dyscrasias (10-30%), neurological disease (3%), nonhematological neoplasms (3-8%), perineal trauma (12%), and pharmacotherapy *(Table I)*, but in a third of cases, no etiology is found.[2] Secondary malignity of the penis is a rare clinical entity, despite the rich vascularization of this organ.[3] Of the hematological diseases, falciform anemia is the most frequently involved clinical entity (10-30%), followed by leukemia (3-15%), polycythemia, multiple myeloma and thalassaemia.

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The blood rheological properties determine its flow, especially in the capillaries, and its oxygen supply capacity. The viscosity depends on macro-rheological parameters: hematocrit, serum protein levels, especially fibrinogen and globulins, and also on micro-rheological parameters: level of aggregation and deformation capacity of the erythrocytes. Hyperviscosity syndromes can be observed in which the hematocrit count is high (polycythemia and pseudopolycythaemia), in conditions where there is an increase in serum proteins or alterations in their composition (especially hyperfibrinogenemia, increase in immunoglobulins or low levels of albumin), inflammatory syndromes, dysglobulinemias (Fahey syndrome), low body temperature (hypothermia), increase in aggregation capacity of the erythrocytes (shock, fat embolism) and reduced deformation capacity of the erythrocytes, whether congenital or acquired (drepanocytosis, renal insufficiency, hyperlipoproteinemia, thrombosis, and diabetes).[4]

Hypergammaglobulinaemia increases the serum viscosity and is the most important cause of hyperviscosity syndromes, generally in a context of multiple myeloma or Waldenström's macroglobulinaemia. In these cases, the hyperviscosity is the result of an increase in protein content, high molecular weight, abnormal polymerization and abnormal configuration of the immunoglobulins produced.[5]

TABLE I

Drugs that cause priapism[2]

Pharmacological group	Drugs
Antidepressants	Amitriptyline Bupropion Trazodone Fluoxetine Sertraline Lithium
Antipsychotics	Clozapine
Antihistaminics	Hydroxyzine Cimetidine
Psychotropics	Chlorpromazine
Antihypertensives	Clonidine Prazosin Hydralazine Propranolol Methyldopa
Diuretics	Hydrochlorothiazide
Hormones	Corticosteroids Testosterone
Anticoagulants	Heparin
Illegal drugs	Cocaine Alcohol

The symptoms of hyperviscosity occur when the normal serum viscosity of 1.4 to 1.8 cp increases to 4-5 cp, which corresponds to a serum level of immunoglobulin M of 3 g/dL, serum IgG of 4 g/dL and serum IgA of 6 g/dL.[5] Thus, the plasma viscosity is higher in the case of IgM production than that of IgA or IgG, due to the high molecular weight of the IgM in relation to the other paraproteins, its asymmetrical form, and its size (formation of pentamers).[6]

The increased viscosity results in a slowing of the blood flow, stagnation of the blood components, and as a result, ischemia.

The symptoms of hyperviscosity include general symptoms (fatigue, general malaise, weight loss), hemorrhages, and ocular, neurological and cardiovascular manifestations.[7] Hyperviscosity syndrome remains a clinical diagnosis, as there is no other method that enables us to evaluate the intrinsic viscosity, aggregation tendency, and other physical-chemical properties of the plasma proteins. Thus, evaluating the degree of severity of the hyperviscosity can be difficult, and there is a lack of adequate correlation with the laboratory values.[6]

The treatment is targeted at control of the underlying disease, seeking to prevent the production of abnormal protein.

CASE REPORT

We describe the Case Report of a male patient, aged 65, Caucasian, born in Setúbal, a worker at Secil (a local cement factory), admitted to the Urology Service in September 2006 with recurrent painful and persistent erections with evolution of around 3 weeks. In the first episode, the patient was submitted to decompression of the priapism at the Emergency Urology Service, and in the subsequent episode, he underwent surgical intervention: Winter's cavern glandular shunt. As priapism is considered a surgical and medical emergency, the opinion of the Internal Medicine specialist was requested in the evaluation of potential causes.

The patient's personal history included a history of thrombosis of the retina of the left eye 3 years previously, benign hypertrophy of the prostate, urolithiasis, Barrett's esophagus (endoscopy with biopsies in 2006) and recurrent aphthous stomatitis.

He reported no alcohol or smoking habits. Regular medication included Trimetazidine (Vastarel®), acetylsalicylic acid (Cartia®), Pentoxifylline (Trental 400®), and Omeprazol (Losec®), but included no drugs considered to cause priapism. The patient denied using medication for erectile dysfunction. From the family history, we emphasize that his father died of CVA and his mother died of colon neoplasm.

The patient had no fever, headaches, body weight loss or diaphoresis. The skin showed no lesions, lung auscultation was normal, no adenopathies, splenomegaly or hepatomegaly were felt on palpation. There was no pain on active or passive mobilization, or functional incapacity of the limbs.

In laboratory terms, on admission to hospital, normocytic-normochromic anemia of 11.1 g/dL (MCV 94.7 fL, MCH 32pg) was detected without alterations in the blood count. The remaining exams did not show any alterations (creatinine 1.2 mg/dL, urea 53, 5 mg/dL, ALT 31 U/L, AST 22 U/L, GGT 27 U/L, Alkaline phosphatase 65 U/L , Calcium 10 mg/dL, LDH 117 U/L, $Beta_2$-microglobulin 1.85 mg/L). During hospitalization the anemia worsened, with the appearance of leukocytosis with immature forms

TABLE II

Blood count of the patient in evolution

Blood count	9/2006	10/2006
Erythrocytes	3.5 3 x 10^6/µL	3.3 x 10^6/µL
Hemoglobin	11.1g/dL	9.5 g/dL
Hematocrit	32.8%	28%
MVC	94.7fL	94fL
MCH	32pg	32pg
Leukocytes	6.5 x 10^3/µL	16.9 x 10^3/µL
Neutrophils	41.6%	44%
Lymphocytes	41.9%	28%
Monocytes	11.6%	1%
Eosinophils	4.2%	3%
Basophils	0.7%	0%
Metamyelocytes		18%
Lymphoplasmocytes		6%
Other cells		6
Reticulocytes	1.8%	
Platelets	416 x 10^3/µL	369 x 10^3/µL

(metamyelocytes 18%, lymphoplasmocytes 6%) *(Table II)*.

The parameters of characterization of anemia did not show any alterations (serum iron 61µg/dL, ferritin 90 ηg/mL, vit B12 432 pg/mL, folic acid 3.5 ηg/mL, transferrin 198 mg/dL, TIBC 257 µg/dL). The serologies requested (Anti-HIV1/HIV2, AgHBs, Anti-HCV, HSV1/HSV2, VDRL) were negative, and anti-CMV and Anti-EBV were positive (IgG positive, IgM negative).

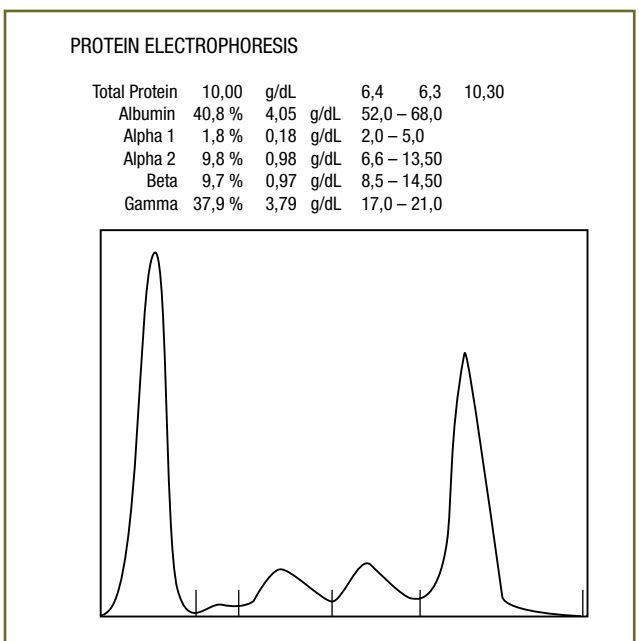
Protein electrophoresis revealed gammaglobulinemia of 3.79 g/L, with a monoclonal peak *(Fig. 1)*, having confirmed monoclonal gammopathy IgM κ by urinary and serum immunofixation (serum IgM 5270 mg/dL ; kappa light chains (serum) 3170 mg/dL and lambda light chains 208 mg/dL; kappa light chains (urine) 5.5 mg/dL and lambda light chains < 5.0 mg/dL), in conclusion: "a monoclonal band of moderate intensity corresponding to µ heavy chains and a monoclonal band of moderate equivalent intensity, corresponding to kappa light chains". Immunoglobulin A and G were within the normal limits.

Total PSA was 2.19 ηg/mL, free PSA 0.58 ηg/mL and free PSA/total PSA 0.26.

As image evaluation, radiographies of the cranium, shoulder and long bones were carried out, revealing no alterations.

CT of the chest, abdomen and pelvis did not reveal and alterations, except for a millimetric calculation in the lower caliceal group of the left kidney, without alteration of the ganglionary chains in the areas studied, and without hepatosplenomegaly. Upper digestive endoscopy confirmed the initial diagnosis (Barrett's esophagus).

Myelogram revealed normocellular bone marrow, M:E ratio 2:0, lymphoid series of 45% with a prevalence of morphologically mature lymphocytes and presence of some lymphoplasmocytes and plasmocytes series of 16% with some binucleated cells. In conclusion:.... "the alterations observed may be compatible with SLPC/monoclonal gammopathy". Immunophenotyping of the peripheral blood and bone marrow (10/2006) was suggestive of non-Hodgkin B-cell lymphoma, and no phenotypic alterations suggestive of pathogenic plasmacytes were observed. Cytogenic analysis (11/2006) confirmed the karyotype 46XY. No chromosome abnormalities were detected in the 30 metaphases analyzed, or deletion



Protein electrophoresis.

FIG. 1

TABLE III

Association of monoclonal gammopathy and other diseases[8]

Hematological	Lymphomas, chronic lymphoid leukemia, chronic myeloid leukemia, Acquired von Willebrand disease, antiphospholipid antibody syndrome, pernicious anemia, pure red cell aplasia, myelodysplasia, polycythemia vera, and Gaucher's disease
Rheumatological	Rheumatoid arthritis, systemic lupus erythmatosus, and myositis
Neurological	Peripheral sensomotor neuropathy, myasthenia gravis, chronic inflammatory demyelinating polyradiculoneuropathy, and ataxia telangiectasia
Dermatological	Lichen myxedematosus, Buschke's scleroedema, gangrenous pyoderma, necrobiotic xanthogranuloma, xanthomatosis plana, fungoid mycosis, and Kaposi's sarcoma
Immunosuppression	AIDS and post-transplant (associated with CMV)
Miscellaneous	Infection by the hepatitis C virus, Helicobacter pylori, chronic active hepatitis, primary biliary cirrhosis, type II acquired angioedema and post-silicone implant

of chromosome 13.

The definitive diagnosis was established after the bone biopsy (11/2006/IPO), which identified bone marrow with interstitial infiltration by lymphocytes with characteristics of the plasmocyte: CD20+, CD23, CD5- cells, but without plasmocytic differentiation antigens, which was compatible with non-classifiable low grade B-cell lymphoma.

The patient began chemotherapy with Cyclophosphamide 150 mg/m2 and Prednisolone 40 mg/m2 and the disease is now stable.

DISCUSSION

Monoclonal gammopathies are clinical entities associated with monoclonal proliferation of plasmocytes, also known as paraproteinaemias, dysproteinaemias or immunoglobulinopathies. They are characterized by the production and secretion of a monoclonal-immunoglobulin protein (Ig) or a fragment of Ig. Ig is comprised of two polypeptidic chains of the same class and subclass (IgG, IgA, IgD, IgE, IgM) and two light polypeptide chains of the same type (kappa or lambda).[8] The confirmation of the presence of monoclonal protein is essential to differentiate monoclonal gammopathies from polyclonal gammopathies, as the first are neoplastic or potentially neoplastic entities, while the latter are the result of inflammatory or infectious processes.

Electrophoresis of proteins should be used to detect monoclonal protein and immunofixation to characterize the heavy and light immunoglobulin chains. Electrophoresis of the proteins, in the case presented here, was the point of departure for the diagnostic process.[8] Observing monoclonal gammopathy, subsequently identified as IgM gammopathy, the initial diagnosis was targeted at confirmation of the multiple myeloma or Waldenström's macroglobulinaemia, although the differential diagnosis of this situation is very complex, and can also include gammopathy of indeterminate significance, lymphoproliferative diseases, amyloidosis, and the group of infectious, inflammatory and autoimmune diseases *(Table III)*.

Multiple myeloma (MM) is a dyscrasia of the plasma cells. It is an incurable disease, characterized by the proliferation of clonal plasmocytes, which produce and secrete monoclonal Ig or fragment of monoclonal Ig. The term multiple is used because the plasmacytoma is found in many places. The main characteristics are bone destruction, renal insufficiency, anemia and hypercalcemia. The etiology is unknown, but exposure to radiation, benzene and other organic solvents, insecticides and herbicides may be important. It constitutes 1% of all malignant neoplasms and 10% of hematological neoplasms. The average age on diagnosis is 66 years, and only 2% of patients are aged under 40 years. Bone pain is the most frequent clinical manifestation, present in around 60% of cases. Radiological alterations are detected in 79% of patients through conventional radiology. MM is characterized by the presence of more than 30% plasma cells, or less than 30% and more than 10%, in the presence of other criteria. In MM, the most common immunoglobulin is IgG (53%), followed by IgA (21%) and IgM. In myeloma, the existence of IgM monoclonal protein is a very rare situation (<0.5% of cases). Bone pain is the most common symptom in this type of myeloma, which is clinically different from the case described. The bone marrow is infiltrated by small plasmocytes, the levels of polyclonal

IgG and IgA are lower than in other subtypes, and there is a high level of translocation (11:14).[8,9]

Waldenström's macroglobulinaemia (WM) is a lymphoproliferative disease that is characterized by lymphoplasmocytary infiltration of the bone marrow and the synthesis of monoclonal IgM. It accounts for 2% of hematological neoplasms. Fatigue, weight loss, and neuropathy are the most frequent symptoms, adenomegaly is present in 20% - 40% of cases, and hepatosplenomegaly is also common. Hypercalcemia and symptoms of blood hyperviscosity commonly exist.[8,9]

Primary systemic amyloidosis (AL) is a rare pathology, characterized by the deposition of amyloid fiber (fragment of light chain of Ig) in the tissues. The organs most frequently affected are the kidneys, heart, liver and digestive tube. Although the central nervous system is not generally affected, complications of the peripheral nervous system are common. Bone marrow biopsy normally shows less than 5% of plasma cells. The amyloid substance is clearly identified in the biopsy of the organ involved. The symptoms are vague and are characterized by fatigue, weight loss and peripheral edemas.[8,9]

Monoclonal gammopathy of unspecified significance (MGUS) affects 2% of individuals aged between 50 and 70 years, and 3% of individuals are aged over 70. Around 15-20% of cases involve monoclonal cells with production of IgM. This syndrome is characterized by monoclonal proteins values less than 3 g/dl, less than 10% of the plasma cells in the bone marrow, with or without a small amount of Bence-Jones protein in the urine, absence of lytic bone lesions, and no anemia, hypercalcemia, renal insufficiency or any organic involvement. One of the great challenges facing clinical practice is to differentiate between MGUS and impairment of the organs due to other pathologies, such as: bone lesion by osteoporosis, kidney lesion by high blood pressure or diabetes or, as in our clinical case, priapism of other etiology. follow-up is essential, given the possibility of evolution to MM, AL, WM or lymphoproliferative disease.[8,9,10]

Plasmocyte leukemia, a rare variant of multiple myeloma, is defined by the presence of circulating plasmacytes at levels higher than 2000/mm3 and plasmacytosis higher than 20% of the total white blood cells. The most common clinical manifestations are asthenia, renal insufficiency, bone pain, splenomegaly and hepatomegaly.[8]

CONCLUSION

The diagnosis of monoclonal gammopathies is not always simple, and requires of the health professional a knowledge of the clinical characteristics, diagnostic criteria and prognosis of each variant, so that the patient can be treated accordingly.

Hyperviscosity secondary to lymphoma is a rare cause of priapism, and priapism is a complication that is only rarely observed in patients with lymphoma.[11] We find, in the literature, only one case of long-term priapism caused by lymphoma of the B cells.[11] ■

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