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Case Report

Hemophilia and Renal Failure: Diagnostic and Therapeutic challenges in a Sub Saharan Africa Setting

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ABSTRACT

Hemophilia is an X-linked genetic hemorrhagic disease, which results in a deficiency of coagulation factor VIII or IX. Its management is based on the substitution of Coagulation Factor Concentrates (CFCs) with different protocols.

The life expectancy of patients living with hemophilia has been considerably improved by the availability of these CFCs. Thus, chronic diseases (age-related co-morbidities, viral infections) are emerging in this population and can potentially be complicated by renal failure, making management more difficult.

We report the case of a 26 years old patient with moderate hemophilia A and diagnosed with stage 5D chronic kidney disease (CKD). Due to the risk of hemorrhage, kidney biopsy could not be performed. Hemodialysis was prescribed with a CFC prophylaxis protocol encadring the placement of the central venous catheter and preceding each hemodialysis session.

This case illustrates the diagnostic and therapeutic difficulties of renal failure in hemophiliacs in a Sub Saharan Africa setting. It also highlights the risk factors of CKD and dialysis modalities in this field.

Keywords: Hemophilia; Coagulation Factor Concentrates; Chronic Kidney Disease; Prophylaxis

List of abbreviations: CFC: Coagulation Factor Concentrate; **CKD:** Chronic Kidney Disease; **ABR:** Annual Bleeding Rate; **APTT:** Activated Partial Thromboplastin Time; **GFR:** Glomerular Filtration Rate; **HIV:** Human Immunodeficiency Virus; **HCV:** Hepatitis C Virus; **HBV:** Hepatitis B Virus; **rFCVIII:** recombinant Factor Concentrate VIII; **FVIII:** Factor VIII; **FIX:** Factor IX

Introduction

Hemophilia is an hereditary hemorrhagic disease with recessive transmission carried by the X chromosome. It is characterized by partial or complete deficiency in factor VIII or IX, respectively hemophilia A and B. Its prevalence is estimated at 1/10000 births, with hemophilia A representing 80 to 85% [1]. The severity of the disease is correlated with the degree of factor deficiency, distinguishing three clinico-biological forms.

It is manifested by prolonged bleeding, which may occur spontaneously or induced. In most cases, this bleeding is localized in the joints and muscles.

Hemophilia is managed by substitution of the deficiency factor with treatment on demand and prophylactic treatment. This treatment is not devoid of complications, particularly infectious complications that have been controlled with the advent of recombinant factors. However, the prevalence of immunological complications is increasing, making it difficult to manage these patients.

Moreover, with the improved availability of Coagulation Factor Concentrates (CFCs) and, above all, diagnostic and therapeutic progress, the life expectancy of hemophiliacs has improved significantly, particularly in developing countries [2].

Other co-morbidities (diabetes, hypertension, kidney disease) have been observed in this population. These pose new challenges in management [3], especially in Sub Saharan Africa where diagnosis and care of Hemophilia are less accessible [4].

The risk factors for CKD in this population are numerous, including hypertension, transfusion-transmitted infections, hematuria, and nephrotoxic drugs.

We report here the difficulties in the management of stage 5D chronic kidney disease (CKD) in moderate hemophilia a patient.

Case Report

This is a 26 years old man with moderate hemophilia a diagnosed at the age of 5 years. The circumstances of the diagnosis were a prolonged mouth bleed secondary to a dental avulsion, an isolated prolongation of APTT at 112.6 s and a factor VIII level of 3.5%.

The patient is the third of a family of 5 children including 3 hemophiliac boys and 2 conductive. He is under treatment on demand and his annual bleeding rate (ABR) were 15/year.

Progressively, the patient presented a hemophilic arthropathy of the left ankle at the age of 25 years and we have not yet noted any immunological complications.

He had several episodes of hematemesis in 2018 that prompted an upper gastrointestinal endoscopy which revealed a bulbar gastric ulcer. It was treated by proton pump inhibitor and antibiotics and a healing was obtained at the control digestive endoscopy in April 2019.

These episodes of gastro-intestinal bleeding had resulted in persistent iron deficiency anemia requiring several red blood cell transfusions. Renal function was still normal at this time.

The clinical follow-up was regular and the blood pressure measured at each consultation were normal. In December 2019, he suddenly presented intense headache with tinnitus, dizziness and vomiting. Clinical examination revealed an anemic syndrome and systolic-diastolic hypertension grade I at 140/90 mmHg. Biologically, there was severe impairment of renal function with a glomerular filtration rate (GFR) of 2.15 ml/min/1.73 m^2 (Table 1). Other paraclinical parameters are summarized in Table 1. The diagnosis of stage 5D CKD by chronic tubulo-interstitial nephropathy was made.

Paraclinical parameters	Results
Hemogram	WBC = 8.6 G /L
	Hb = 6,3 g/dl VGM = 83,8 fl
	TCMH = 27,5 pg CCMH = 32,89 g/dl
	PLQ = 147 G /L Retic : 1,99% = 45.6 G / L
Blood electrolytes	Natremia = 134 mmol/l
	Kalemia = 5,5 mmol/l
	Chloremia = 106 mmol/l
Kidney function	Urea = 2,67 g/l
	Creatininemia = 2,45 mmol/L
	GFR = 2,15 ml/mn/1,73 m^2
Phosphocalcic balance	Calcium = 92,6 mg/l
	Phosphoremia = 58,7 mg/l
24 H-Proteinuria	1,59 g/24H
Addis count	Leukocytes = 225000/mm^3
	Red blood cells = 101100/mm^3
	Cylinders (-), Crystals (-)
Kidney echography	Kidneys of normal size
	Hyperechoic renal cortex with loss of hepato-renal gradient, absence of dilatation of the pyelocalicial cavities

Table 1: Summary of paraclinical examinations

According to the etiological investigation, there was a history of self-treatment by non-steroidal-anti-inflammatory drugs and traditional medicine. Viral serologies (HIV, HCV, HBV) were negative. Kidney biopsy could not be performed because of the very high risk of hemorrhage. The patient was put on hemodialysis with multidisciplinary management (hematologists and nephrologists).

The placement of the tunnel central venous catheter was encadred by the administration of factor VIII: rFCVIII 50 IU/kg 1H before the surgical procedure, then continued for 3 days after the procedure. The post-operative follow-up was simple, without hemorrhagic complications.

He performed two hemodialysis sessions per week, each preceded by the administration of rFCVIII at 25 IU/kg 1H before dialysis. Anticoagulation of the extracorporeal dialysis circuit to prevent the occurrence of clots was systematically prescribed during dialysis sessions which took place without major incidents.

Discussion

This case exposes a stage 5D chronic kidney disease (CKD) in moderate hemophiliac A. CKD is a comorbidity with an increasing incidence in hemophiliacs. No CKD case was reported in the previous 140 hemophilia cohort followed from 1995 to 2012 in the same setting [5].

A retrospective study analyzing the medical records of 3,422 hemophiliacs living in the United States from 1993 to 1998 found an incidence of 1.4% [6]. However, more than half of these patients were HIV positive.

More recently, studies have shown that the potential number of hemophilia patients with kidney disease is increasing [7].

CKD is not a specific complication of hemophilia; however, there are many risk factors for renal impairment in hemophiliacs.

The increased life expectancy of hemophiliacs has changed the clinical history of these patients with the onset of age-related co-morbidities [7]. Hypertension is common in adult hemophilia patients. For example, in a 2016 European study of 532 hemophilia patients over 40 years of age, 45% of the patients had hypertension and 5.3% of the patients in this cohort had stage 3 or higher CKD [8].

Blood pressure checks were routinely performed at regular consultation in our patient and were still normal before occurrence of CKD.

The current prevalence of blood-borne viral infections (particularly HIV and HCV) in adult severe hemophiliacs is high [9] and exposes these patients to renal complications (glomerulonephritis in particular) and treatment complications (tubule toxicity).

Hematuria may also be another risk factor for renal damage in hemophiliacs. Acute renal injury secondary to tubular obstruction and cortical necrosis following hematuria treated with antifibrinolytic agents has been reported [10,11].

Finally, as reported in the general population, drug nephrotoxicity is also a risk factor for renal impairment in hemophiliacs.

Given the multitude and diversity of risk factors for the development of CKD in hemophiliacs, it remains difficult to establish a causal relationship. Thus, the etiological diagnosis often relies on presumptive anamnestic, clinico-biological and histological arguments. In our patient, tubulo-interstitial damage due to nephrotoxic drugs is suspected. Thus, it is important to take preventive measures like education of patients but also improving knowledge level among health care professionals [12].

The diagnosis of renal disease in this field may be limited by the feasibility of renal biopsy. The risk of hemorrhage is particularly high, especially in hemophiliacs who have developed inhibitors. Renal biopsy in hemophiliacs has been rarely reported [8,13].

At the 5D CKD stage, hemodialysis and peritoneal dialysis may be performed, with respective advantages and disadvantages. Hemodialysis has the advantage of being performed in a hospital setting with qualified personnel who can limit hemorrhagic and infectious complications.

The central vascular approach for dialysis requires the prophylactic administration of CFCs. Different preoperative protocols have been proposed, but it can be retained that the preoperative antihemophilic factor level (FVIII or FIX) must be 100% and substitution therapy must be continued daily for at least 3 days after the procedure, maintaining the level at 50-100% [14]. In our patient, we opted for this protocol with satisfactory results.

It is recommended that these hemophiliacs with CKD be placed on a continuous prophylactic treatment protocol to minimize the risk of hemorrhage associated with hemodialysis. The most commonly used dose is 25-40 IU/kg CFCs 3 times a week [15].

Our patient was placed on tertiary prophylaxis with a dose of 25 IU/Kg twice a week. However, transplantation remains a feasible treatment option, especially in patients without inhibitors, provided it is accompanied by adequate supplementation.

According to this case, we recommend a regular screening of renal function in the hemophiliacs, at least once a year. Primary prevention of CKD in hemophiliacs will be done essentially by avoiding identified risk factors: avoiding self-medication, taking NSAIDs and traditional drugs, effective management of comorbidities that may be complicated by renal disease.

This case report highlights the diagnostic and therapeutic particularities of renal failure in hemophiliacs. It also highlights the identification of risk factors for chronic kidney disease and the challenges of replacement therapy in this area, particularly in sub-Saharan Africa where access is limited.

Conclusion

The management of CKD in hemophilia, from diagnosis to replacement therapy, is complex and requires comprehensive and multidisciplinary expertise. Kidney biopsy is possible, but remains limited by the risk of hemorrhage. Dialysis remains the only indispensable treatment in the absence of a transplant.

Primary prevention through the management of risk factors has become a new management challenge. Better access of CFCs in sub-Saharan Africa will improve the management of this particular comorbidity.

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