

Nefropatía membranosa asociada a leucemia linfocítica crónica

Chronic lymphocytic leukemia-associated membranous nephropathy

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Resumen

La leucemia linfocítica crónica (LLC) es una neoplasia de células B maduras caracterizada por una acumulación progresiva de linfocitos B monoclonales en la médula ósea, los ganglios linfáticos y el bazo. Aunque hasta el 90% de los casos de LLC presentan infiltración renal, la afectación renal generalmente permanece clínicamente no detectada. El síndrome nefrótico (SN) en la LLC es una complicación rara que ocurre en menos del 2% de los casos. Hasta la fecha, sólo hay 13 casos de nefropatía membranosa (NM) relacionada con LLC informados en la literatura. Presentamos a un hombre de 67 años que fue diagnosticado con LLC en 2011. No se inició ninguna terapia en ese momento. En 2016 presentó edema en sus extremidades inferiores; los resultados de laboratorio fueron, hemoglobina: 11.8 g/dl, urea: 63 mg/dl, creatinina: 2.02 mg/dl; excreción urinaria de proteínas: 10.25 g/24 h, proteínas séricas: 5.36 g/dl, albúmina sérica: 4 g/dl y glóbulos blancos: 19,600/mm³. Nos contactamos con el Departamento de Nefrología, se realizó una biopsia renal percutánea y se realizó un diagnóstico de MN. Además, estaba

presente una infiltración perivascular de linfocitos. La tinción inmunofluorescente reveló el depósito de IgG, IgM, C3 y C1q. El diagnóstico fue nefropatía membranosa tipo II secundaria a LLC. Se inició tratamiento con rituximab y ciclofosfamida (CYS) y el paciente ha alcanzado remisión de su LLC; La proteinuria ha mejorado con CYS por vía oral. El seguimiento actual de su caso es de 31 meses. De todos los casos en la literatura, nuestro enfoque de esta condición extremadamente rara es único, ya que evitamos el uso de fludarabina debido a su mielotoxicidad en pacientes mayores.

Abstract

Chronic lymphocytic leukemia (CLL) is a mature B cell neoplasm characterized by a progressive accumulation of monoclonal B lymphocytes in the blood, bone marrow, lymph nodes and spleen. Although up to 90% of CLL cases present kidney infiltration, renal involvement generally remains clinically undetected. Nephrotic syndrome (NS) in CLL is a rare complication that occurs in less than 2% of the cases. To date, there are only 13 cases

of CLL-related membranous nephropathy (MN) reported in literature. We present a 67-year-old male who was diagnosed with CLL on 2011; no therapy was started at that time. On 2016 he presented edema in his lower extremities; laboratory results were, hemoglobin: 11.8 g/dl, urea: 63 mg/dl, creatinine: 2.02 mg/dl; urinary protein excretion: 10.25 g/24 h, serum proteins: 5.36 g/dl, serum albumin: 4 g/dl and white blood cells: 19,600/mm³. We contacted the Nephrology Department, a percutaneous renal biopsy was performed and a diagnosis of MN was given. Furthermore a lymphocyte perivascular infiltration was present; immunofluorescent staining revealed deposition of IgG, IgM, C3 and C1q. The diagnosis was membranous nephropathy type II secondary to CLL. Treatment with rituximab and cyclophosphamide (CYS) was started and the patient has reached remission of his CLL; proteinuria has been improving with CYS orally. The current follow up of his case is 31 months. From all the cases in literature, our approach to this extremely rare condition is unique, as we avoid the use of fludarabine because of its myelotoxicity in older patients.

Introduction

Chronic lymphocytic leukemia (CLL) is a mature B cell neoplasm characterized by a progressive accumulation of monoclonal B lymphocytes in the blood, bone marrow, lymph nodes and spleen⁽¹⁾. Is the most common leukemia in adult in Western countries, accounting for approximately 25 to 30 percent of all leukemias in the United States. Its incidence is 100,000 population per year⁽²⁾.

Although up to 90% of CLL cases present kidney infiltration, renal involvement generally remains clinically undetected. Nephrotic syndrome (NS) in CLL is a rare complication that occurs in less than 2% of the cases⁽³⁾. The most common type of glomerulonephritis causing NS related to CLL is type I and II membranoproliferative glomerulonephritis (MPGN) (35.7%), while membranous nephropathy (MN) is less frequent, as well as minimal-change disease, focal segmental glomerulosclerosis, focal or diffuse proliferative glomerulopathy and amyloidosis⁽⁴⁾.

To date, there are only 13 cases of CLL-related MN reported in literature. We present another case and review the previously reported.

Case report

We present the case of a 67-year-old male who was diagnosed with CLL on 2011. His biopsy and bone marrow aspiration were consistent with a mature lymphocytic infiltrate (72%) in the bone marrow. The diagnosis was made by the presence of 11,000 lymphocytes/mm³, and a complete immunophenotype of CD19+, CD20+, CD45+, HLA-DR+, CD200+, CD23+, CD22-, CD5+, kappa-, BCL-6-, BCL-2-, lambda-, TDT-, CD34-, CD10-, CD103-, CD123-. This resulted on a Matutes score of 5, confirming the diagnosis of CLL. CLL-IPI score of 1 based on age, Binet A, B-2 microglobulin <3.5 mg/dl, IGHV unmutated (-) and TP53 mutation (-) indicated a low risk for the patient's condition. No therapy was started at that time, as he presented no symptoms nor biochemical or physical alterations. On 2016 in one of his control visits he presented edema in his lower extremities, physical examination showed no lymphadenopathy nor hepatosplenomegaly. He was admitted to the hospital in order to investigate his condition. Chest X-rays and abdominal ultrasounds were normal. Laboratory results were, hemoglobin: 11.8 g/dl, urea: 63 mg/dl, creatinine: 2.02 mg/dl; urinary protein excretion: 10.25 g/24 h, serum proteins: 5.36 g/dl, serum albumin: 4 g/dl, white blood cells: 19,600/mm³ (77% lymphocytes) and platelets: 140,000/mm³; the rest of the exams were normal. Serum and urine electrophoresis were performed and presented no monoclonal peak. The third (C3) and fourth (C4) components of complement were normal, antinuclear antibodies (ANA), perinuclear anti-neutrophil cytoplasmic antibody (pANCA) and cytoplasmic anti-neutrophil cytoplasmic antibody (cANCA) were negative. Hepatitis B, C and HIV serology were negative; the direct and indirect Coombs' test were negative and cryoglobulins were not detected in serum. A new bone marrow biopsy was performed in order to discard translocation of CLL into small lymphocytic lymphoma (Richter's transformation); the results were negative for the transformation and maintained the characteristics of the first hematological diagnose (CLL). We contacted the Nephrology Department and a percutaneous renal biopsy was performed. Twenty four glomeruli were evaluated; six of them were totally affected by hyalinosis. The rest (18) presented variable changes with segmental hyalinosis. In general, thickening of

the walls of the glomerular capillaries is seen, which appear rigid with a foaming appearance and spike projections. Furthermore a lymphocyte perivascular infiltration was present. Immunofluorescent staining revealed deposition of IgG, IgM, C3 and C1q. The diagnosis was membranous nephropathy type II secondary to CLL.

Because of this, the patient started treatment with a single dose of rituximab 250mg/m², and methylprednisolone 500 mg every 15 days with good response. On the next month, proteinuria levels decreased to 9.4 g/24 h, and WBC: 11,200/mm³. As both, proteinuria and WBC count decreased, we decided to increase the dose of rituximab to 1 g and to maintain methylprednisolone.

Two months later the patient had decreased proteinuria (8.04 g/24h) and WBC: 8400/mm³, however, because proteinuria was still present, 1 g of cyclophosphamide intravenous was added to the treatment, which achieved a decrease in urinary protein levels to 7.16 g/24 h.

After that, we decided to target the CLL with intravenous rituximab and oral cyclophosphamide (CYS) for 12 months, which decreased the levels of proteinuria to 1.8 g/24 h and WBC to 5300/mm³ with the regimen of 500 mg rituximab every three months associated to 100 mg oral cyclophosphamide daily, and it was decided to prolong the time of administration of rituximab to avoid adverse effects. Patient received the last dose of rituximab on January 2018 and maintains oral CYS 50 mg/day.

CLL has reached remission with rituximab and proteinuria has been improving with CYS orally. The current follow up of his case is 31 months.

Discussion

Renal impairment in CLL has been previously described in literature; however, the most common presentation of nephrotic syndrome in patients with CLL is caused by MPGN. MN, a common cause of NS in adults and the most common glomerulonephritis in carcinomas, is rarely associated with CLL⁽¹⁾.

To our knowledge, only 13 cases of MN in CLL have been reported in literature (Table 1). The mechanism of CLL-associated MN seems to be related with immunoglobulin and complement deposition on the glomerular basement membrane, even in the

absence of monoclonal component and complement consumption. The deposit of IgG and C3 translate to an immune process probably caused by the deregulation of humoral and cellular immunity that characterizes CLL. Other mechanisms may include autoimmunity due to T-cell dysregulation with the consequent production of autoantibodies that recognize renal epithelial cell structure, hyperglobulinemia and cytokine-induced altered glomerular permeability⁽⁴⁾. Lymphocytic interstitial infiltration occurs in up to 60% of the patients with CLL, 6/13 MN cases had lymphocytic infiltration. Renal failure with urinary presence of leucocytes is rare in MN, it is believed that CLL-associated interstitial nephritis caused this manifestation.

Recognition of neoplastic nature of lymphocytic infiltrate can be challenging. The monotonous appearance, size, shape and destructive nature of the cell population should prompt the examiner to perform additional work to confirm or discard the diagnosis. A series of immunohistochemical studies should be performed to establish the lineage, clonality and specific gene rearrangement of the cells⁽⁵⁾.

Most cases of MN in CLL show improvement of leukocytosis with the immunosuppression therapy, however, proteinuria is refractory in approximately half of the cases. Literature has shown that fludarabine or cyclosporine are an effective therapy for CLL-associated MN. However, further clinical evaluation is necessary to define the role of these drugs on this condition.

CLL first line treatment includes FCR (fludarabine, cyclophosphamide and rituximab). Studies suggest that regimens including these agents improve survival in younger patients. However FCR is not for everyone; in elderly and less fit patients fludarabine should be used with lower doses or even replaced or avoided because of its myelosuppressive potential. In addition to the utility of rituximab as a frontline agent for CLL, rituximab has a favorable toxicity profile both as a single agent and in combination with other drugs⁽⁶⁾. As our patient is 67 years old, we decided not to use fludarabine as evidence shows that myelotoxicity caused by this drug is more common in this group of patients.

Also, rituximab has been used as single therapy for secondary MN (including hematological diseases). In a systematic review by Bomback et. al, 16 cases

Table 1. Cases of MN in CLL

						Glomerular lesions				Outcome	
Ca-se No.	Ref.	Age/ Sex	Creat (mg/dL)	Protei-nuria (g/24 h)	Com-ple-ment	Light mi-cros-co-py	IF	Electron mi-cros-co-py	Treat-ment	NS	CLL
1	8	64/M	NA	NA	NA	MN	NA	NA	CBL	Partial response	NA
2	9	61/M	NA	NA	NA	MN	IgG, C3, C1q	NA	CBL	Improve	Improve
3	10	64/M	Normal	8.5	=	MN	IgG, C3, C1q	NA	NA	NA	NA
4	11	57/F	NA	NA	C3,C4 =, CH50 ↓	Atypical MN	IgG, κ, comple-ment	Deposits	CBL + PSL	Improve	Improve
5	11	75/M	NA	NA	C3 =, CH50, C1q and C4 ↓	Atypical MN	IgG, IgM, κ, λ, comple-ment	Deposits	CBL	Improve	Improve
6	12	55/M	1.7	NA	CH50 ↓	Atypical MN	IgG, C3 κ	Fibrillary deposits	CHOP + CBL	Partial response	NA
7	13	82/F	NA	NA	C3, C4 and C1q =	MN	NA	Fibri-lary depo-sits	CPA + PSL, C-sA	No res-ponse	No res-ponse
8	14	NA/F	Normal	6.7	NA	MN	NA	Deposits	CPA + PSL, Fluda-ra-bine	No response, improve	No res-ponse, improve
9	3	72/M	0.8	5	NA	MN	NA	Deposits	CBL+ PSL	Partial response	Partial response
10	15	56/F	3.8	19.2	NA	MN	NA	NA	Fluda-ra-bine	Improve	Improve
11	4	73/M	3.2	4.3	C3, C4=	Atypical MN	IgG, C3, C1q, κ, λ	NA	COP	Improve	Improve
12	5	56/M	2.4	13	NA	MN + FSGS	IgG, C3, κ and λ	Deposits	NA	NA	NA
13	1	74/M	1.7	7	C3, C4 =	MN	IgG, IgM, C3, C1q and λ	NA	Fluda-ra-bine	Improve	Improve
14	Our case	67/M	2.0	10.25	C3, C4 =	MN	IgG, IgM, C3 and C1q	NA	Ritu-xi-mab + CYS	Partial response	Improve

Creat: creatinine; CBL: chlorambucil; COP: cyclophosphamide, vincristine, prednisone; CHOP: cyclophosphamide, adriamycin, vincristine, prednisone; PSL: prednisolone; CPA: cyclophosphamide; CsA: cyclosporine A; IF: immunofluorescence; FSGS: focal segmental glomerulosclerosis; MN: membranous nephropathy; NA: not applicable; CYS: cyclophosphamide.

with these characteristics were analyzed; 9 of them achieved complete remission (<0.3 g/24 h), and 5 met criteria for partial remission (<3.5 g/24 h). Just one patient had no response to rituximab⁽⁷⁾.

As for cyclophosphamide, different studies show that a daily oral dose of CYS (1.5-2 mg/kg) show better long term results in patients with MN, as it decreases the immunological state of this condition. Our patient received 100 mg/day during 15 months

with good results, however, the dose was decreased to 50 mg/day in order to avoid side effects.

From all the cases in literature, our approach to this extremely rare condition is unique, as we avoid the use of fludarabine because of its toxicity and decide to use rituximab and CYS with improvement in CLL and partial response in MN. However, more research is necessary in order to establish a specific therapy to this complication.

Conflictos de interés: Los autores declaran no poseer conflictos de interés.

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