EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 1
424-427
Year: 2021

CHRONIC MYELOID LEUKEMIA, ULCERATIVE COLITIS AND NEPHROTIC SYNDROME: WHAT IS THE RELATIONSHIP?

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DOI: https://doi.org/10.17605/OSF.IO/4CNJM

Article Received on 20/11/2020 **Article Revised on 10/12/2020** **Article Accepted on 31/12/2020**

ABSTRACT
Membranous nephropathy could be primary or secondary to variety of conditions. It is essential to differentiate the two, which is difficult at times, but necessary to plan the appropriate treatment. We are reporting a case of chronic myeloid leukemia (in loss of remission status) and ulcerative colitis (clinically in remission), who developed membranous nephropathy and presented with acute kidney injury. He was advised to be treated with rituximab elsewhere, for presumed primary membranous nephropathy. On our analysis, it appeared to be a case of membranous nephropathy secondary to chronic myeloid leukemia, and the treatment of the underlying disease resulted in remission of nephrotic syndrome.

KEYWORDS: chronic myeloid leukemia, nephrotic syndrome, membranous nephropathy, acute kidney injury, imatinib mesylate, rituximab.

INTRODUCTION
Renal involvement in cancer patients could be multifactorial right from the disease itself to the chemotherapy, supportive care or its side effects. These renal syndromes vary from paraneoplastic glomerulopathies, electrolyte disorders, urinary tract obstruction, lysozymuria, leukostasis, to infiltration of renal parenchyma. Enlarged kidneys on imaging and resolution of acute kidney injury (AKI) after therapy with systemic chemotherapy or radiation support the diagnosis of kidney infiltration.[1]

Chronic myeloid leukemia (CML) can cause glomerular disorders presenting as a late complication which tends to have a poor renal prognosis, with progressive kidney injury occurring in most patients.[2] Similarly, Ulcerative colitis (UC) can cause CML,[3] and renal involvement in inflammatory bowel disease could be nephrolithiasis, tubulointerstitial nephritis, glomerulonephritis and amyloidosis.[4]

We are presenting a case who was diagnosed to have chronic phase CML and UC, who developed nephrotic syndrome (NS) and resulted in AKI, 5 years after initial diagnosis. We have discussed possible cause and effect relationship among CML, UC and NS.

CASE
SN, a 35 years old male was diagnosed to have CML in March 2014 in chronic phase when he had presented with constitutional symptoms. However, he also had abdominal pain and diarrhea intermittently for 5 months. Colonoscopy with biopsy showed UC during this same admission (Histopathology: chronic active colitis, mild).

He was started on treatment for CML with Imatinib mesylate (IM) 400 mg which is a standard dose for adults. For UC, he was also started on Mesalamine and oral prednisolone (1 mg / kg) for 1 month. Steroid dose was adjusted as per symptoms.

He had good response to CML therapy as per the European Leukemia Network (ELN) norms of RT-PCR quantitation.

However, due to exacerbation of his underlying UC (bleeding), despite steroid therapy, he stopped IM on his own in 2016; He remained on variable doses of oral steroids till 2017 with no CML assessment or therapy, as the financial constraints prevented regular RT PCR and he was lost to follow up after May 2016 to Aug 2018. In Aug 2018, he presented with relapse, WBC count of 308,000. He was advised to start 2nd generation of Tyrosine kinase inhibitor (TKI) (Nilotinib) but he was unable to take the same and he re-started IM at the dose of 400 mg on his own.

In November 2018 three months prior to nephrology referral in our hospital, his Hb was 11.2, WBC 7000, Platelets 2.21000; suggesting a good control of CML and simultaneously he was in remission clinically for UC.

In December 2018, he started developing pedal edema leading to anasarca and recurrence of UC symptoms; so he stopped IM. His RT PCR was 14% indicating loss of remission status. He was diagnosed with NS in January 2019 and was treated at another hospital for breathlessness, oliguria, raised Creatinine (7.0 mg/dl) and proteinuria of 14 gm/day and was stabilized with hemodialysis. He underwent a kidney biopsy which showed membranous nephropathy (MN) with acute tubular necrosis (ATN). However anti-phospholipase A2 receptor antibody (PLA2RAb) staining on tissue and serum PLA2RAb tests were not done. PLA2RAb is a biomarker for the diagnosis of primary MN.

When we saw him for second opinion, he was dialysis dependent and had been advised injection rituximab (anti CD 20 antibody) for presumed primary MN. He had reasonable urine output and hence HD was discontinued and he was monitored closely. S. Creatinine levels decreased slowly, to 1.35 mg/dl and proteinuria to 1.2 gm/day. IM was initially added at a reduced dose of 100 mg/day in January 2019; diuretics were added for edema and angiotensin receptor blocker for proteinuria. Prednisolone was added at 1 mg/kg/day. IM was gradually increased to 400 mg/day, and 1 year later in February 2020 the RT PCR was 1.3%. At last follow up in November 2020, his renal function was stable and his CML and UC in remission.

DISCUSSION

Differentiating primary MN from secondary MN associated with malignancy or chronic inflammatory state can be difficult. Our suspicion for a secondary glomerular disease should be high in such patients who have presence of proteinuria or NS.[2]

Our patient had UC with CML at diagnosis and while he had an excellent response (MMR <0.1 IS % RT-PCR for BCR-ABL- method) within a year with IM therapy as per the ELN guidelines, he had to unfortunately abruptly stop the same due to exacerbation of the UC. Hence, at the time of renal manifestation, he had lost hematological and molecular response of the CML (Table 1).

His renal involvement was a late manifestation in this disease and it could have been multifactorial from tumorlysis syndrome (TLS) due to the high WBC count (as part of the disease recurrence), hypotension, urinary tract infection and dehydration. He had also taken NSAIDs as part of the ulcerative colitis treatment for pain relief.

So, what was the relationship of MN with CML or UC? Was this primary MN, or was it secondary to either CML or UC? Should he be subjected to rituximab for primary MN or treat his CML and expect MN remission (secondary MN). This case brings out multiple issues, which have been discussed below, for possible cause and effect relationship.

I. The question: Is this membranous nephropathy primary or secondary? And what would be the role of biomarker in the diagnosis of MN?

The characteristics of cancer-associated MN are unknown. A cohort of 240 patients with MN were studied, among them 24 had malignancy at the time of renal biopsy or within a year thereafter. The incidence of cancer was significantly higher in these patients than in the general population (standardized incidence ratio 9.8 [5.5-16.2] for men and 12.3 [4.5-26.9] for women).[5]

Primary MN is now considered a renal-limited autoimmune disease, with PLA2RAb identified in 70-80 % of patients of various ethnic groups and antibodies against thrombospondin type-1 domain-containing 7A (THSD7A) in 2% to 5% of patients.[6, 7]

PLA2R-Ab levels should drive the lines of treatment. As PLA2RAb positive cases will go in favor of primary MN, and may need immunosuppressive therapy.[8]

To differentiate primary v/s secondary MN, we asked for serum PLA2RAb level and staining of paraffin block for PLA2RAb, both of which was negative. Thus we have ruled out primary MN in this case to the extent of about 80%. Though it is not possible to differentiate primary versus secondary MN in such cases with 100% accuracy, our belief is that this was a case of MN secondary to CML and treatment of CML is the treatment of MN. It could be argued that UC was the cause of MN, but as stated, he was in clinical remission for UC and had loss of remission for CML. We treated him with IM, and as the renal function improved, increased the dose of IM, and his renal function as well as proteinuria improved further. Hence there was no indication to treat with rituximab as was advised elsewhere.

II. NS with CML

NS associated with CML is rare, described as Membrano-proliferative glomerulonephritis, MN, and Minimal change disease. Reports of NS in CML have mostly been the result of interferon-α therapy or hematopoietic stem cell transplants. Glomerular injury in CML has occurred in blast crisis and the chronic phase of malignancy, making an association with disease state difficult. The cause can only be speculated as infection related, autoimmune dysregulation, or deposition of disease-mediated immune complexes. However, given the very low incidence, the etiology remains poorly understood.[9] There is a case report of a patient who developed NS four years after diagnosed CML. Renal histology showed characteristic changes of MN. As per the authors' knowledge, this was the first reported case of MN associated with CML.[10]

The quantitative RT-PCR for BCR ABL IS % used for monitoring the response in our patient is depicted in Table 1. His rise in leucocyte count suggestive of relapse of CML was followed by development of MN and AKI. A study from France reported 1 patient of CML out of 24 patients with cancer associated MN, who had complete remission of nephrotic range proteinuria after treatment with chemotherapy without steroids or alkylating agents.[5]

III. UC, MN and Myeloid Leukemia

In a Swedish cohort of 27,559 patients with UC, approximately twofold increased risks for both AML and CML were reported. A US study of adult leukemia (*n* = 7924 AML and 2174 CML cases) using data from the Surveillance Epidemiology and End Results Medicare database reported a significant increased risk of AML (OR = 1.7), but not CML (OR = 0.7), associated with UC. Finally, a large 2011 Swedish study that linked the cancer and inpatient registries reported no association between AML and UC (OR = 0.8). Hence it is reasonable to presume that in our patient, UC had no relationship with CML,[11] however, another study from Patrick Walker's group of Arkansas reported on primary kidney biopsy findings in patients with inflammatory bowel disease, had 2 out of 83 cases of MN.[12]

There were issues related to drug IM and kidney in this case.

I. Renal Dose Adjustment for IM.

IM is a small molecule first-generation TKI created by the Philadelphia chromosome t (9, 22) abnormality in CML. The standard dose is 400 mg daily in adults with chronic phase CML**.** The mean exposure to IM in patients with mild and moderate renal impairment is increased 1.5- to 2-fold compared to patients with normal renal function, hence dose reductions are necessary.[13]

II. AKI due to IM

IM is known to cause AKI, the likely mechanism being direct tubular toxicity, rhabdomyolysis, Fanconi syndrome and TLS. Hypocalcemia and hypophosphatemia due to renal cause have also been reported.[14]

III. Chronic kidney disease (CKD) due to IM:

CKD has been described in patients on extended-duration IM, the mean decrease in estimated GFR was 2.77 mL/min/1.73 m^2 per year. Renal injury appears to be dose dependent, as higher doses have been associated with a higher incidence of tubular damage.[15]

CONCLUSION

Differentiating primary MN from secondary MN associated with malignancy can be difficult. Our suspicion for a secondary glomerular disease should be high in a patient with known cancer (CML in this case) or chronic inflammatory state (UC in this case), who has presence of proteinuria or NS. A secondary MN should not be missed as far as possible so that patient is not unnecessarily subjected to immunosuppressive agents.

Disclosure and Conflicts of Interest: None

Table 1: M BCR ABL IS count in our patient.

Time line	M BCR ABL IS count
2014, when CML diagnosed	99%
May 2016, Imatinib stopped (by patient)	0.118%
20.11.18	8.5795%
24.1.19	7.175%
12.6.19	13.7941%

REFERENCES

1. Abudayyeh A, Finkel K. Hematologic Disorders and Kidney Disease, Chapter 7, In: American Society of Nephrology Onco-Nephrology Curriculum, 2016.
2. Monga D, Jhaveri KD. Glomerular Diseases and Cancer, Chapter 6, In: American Society of Nephrology Onco-Nephrology Curriculum, 2016.
3. Katsanos KH, Vagias I, Tsianos VE, Vassou A, Tsianos EV. Chronic myelogenous leukemia in ulcerative colitis. Ann Gastroenterol, 2011; 24(1): 64.
4. Corica D, Romano C, Renal Involvement in Inflammatory Bowel Diseases. Journal of Crohn's and Colitis, 2016; 10(2): 226-35.
5. Lefaucheur C, Stengel B, Nochy D, Martel P, Hill GS, Rossert J. Membranous nephropathy and cancer: Epidemiologic evidence and determinants of high-risk cancer association. Kidney Int, 2006; 70(8): 1510-17.
6. Du Y, Li J, He F, Lv Y, Liu W, Wu P, Huang J, Wei S, Gao H. The diagnosis accuracy of PLA2R-AB in the diagnosis of idiopathic membranous nephropathy: a meta-analysis. PLOS ONE, 2014; 9(8): e104936. doi:10.1371/journal.pone.0104936.
7. Tomas NM, Beck LH Jr, Meyer-Schwesinger C, Seitz-Polski B, Ma H, Zanher G, Dolla G, et al. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med, 2014; 371: 2277–87.
8. Bomback A, S, Fervenza F, C. Membranous Nephropathy: Approaches to Treatment. Am J Nephrol, 2018; 47 Suppl 1: 30-42.
9. Randy L. Luciano and Ursula C. Brewster. Kidney Involvement in Leukemia and Lymphoma. Adv. Chronic Kidney Dis, 2014; 21(1): 27-35.
10. de Faria JB, Alvs MA, Pedrini H, Alves Filho G. Nephrotic syndrome caused by membranous glomerulonephritis associated with chronic myeloid leukemia. AMB Rev Assoc Med Bras, 1991; 37(1): 47-49.
11. Johnson KJ, Blair CM, Fink JM, Cerhan JR, Roesler MA, Hirsch BA, et al. Medical conditions and risk of adult myeloid leukemia. Cancer causes & control, 2012; 23(7): 1083–89.

12. Ambruzs JM, Walker PD, Larsen CP. The Histopathologic Spectrum of Kidney Biopsies in Patients with Inflammatory Bowel Disease. CJASN, 2014; 9(2): 265-70.
13. Novartis ® prescribing information 2018.
14. Barta VS, Uppal NN, Pullman JM, Levy AT, Jhaveri KD. Acute Tubular Injury Associated with Imatinib. Journal of nephro-oncology, 2017; 1: 57-61.
15. Umit M, Haznedaroglu I. Discontinuation of Imatinib Mesylate could Improve Renal Impairment in Chronic Myeloid Leukemia. Open Med (Wars), 2019; 14: 22-24.