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Cyclophosphomide Induced Recurrent Urinary Tract Infection and Pancytopenia in Lupus Nephritis Patient

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ABSTRACT

Lupus nephritis occurs about 30-40% of adult with Systemic Lupus Erythematosus and associated with increased morbidity and mortality. Focal and diffuse proliferative forms of lupus nephritis are known to progress to chronic renal failure unless treated by immunosuppressive drugs. Lupus nephritis remains a major cause of deaths among patients of Hispanic and African-American ethnicity. Generally renal involvement is more common in blacks, Indians and Chinese, with less prevalence Caucasians and Arabs. Cyclophosphamide and glucocorticoids are considered to be the standard care for the patients with proliferative lupus nephritis. Intravenous Cyclophosphamide use is limited due to its potentially severe toxic effects. Here we report a case of Cyclophosphamide induced recurrent occurrence of Urinary Tract Infection and Pancytopenia in lupus nephritis patients and it was treated by using the Mycofenolate Mofetil and Prednisolone.

Keywords: Lupus Nephritis, Systemic Lupus Erythematosus, Cyclophosphamide, Urinary Tract Infection and Pancytopenia.

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INTRODUCTION

Systemic lupus Erythematosus (SLE), which is a prototypic inflammatory autoimmune disorder characterized by abnormalities in T and B cell function, with broad spectrum of clinical presentations encompassing almost all organs and tissues[1]. Amongst several complications involved in SLE; renal complication is most severe and is termed as Lupus Nephritis (LN). Lupus Nephritis, if left untreated often leads to poor survival rate[2,3]. LN can occurin 40-80% of pediatric patients and up to 60-70% in adult patients and it can be even higher during the end stages of the diseases[3,4]. The prevalence of SLE and treatment response varies based on age, gender, location, and race/ ethnicity. LN is especially common in black and Hispanic patients in the United States, Hispanic patients have increased disease activity, and 6-year survival rate is only 50%[5,6]. LN is classified into 6 types by the International Society of Nephrology and the Renal Pathology Society. Class 1 nephritis as a normal glomeruli by light microscopy but with mesangial immune deposits by immune fluorescence; Class II as mesangial immune deposits with mesangial hypercellularity; Class III as focal glomerulonephritis involving 50% of glomeruli with subdivisions for active and sclerotic; Class IV nephritis as diffuse glomerulonephritis with 50% of total glomeruli affected; Class V as a membranous lupus nephritis; and Class VI as advanced stage lupus nephritis with 90% global glomerulosclerosis[7]. Intravenous Cyclophosphamide (IV CYC) is widely used in the treatment of proliferative LN (Class III and IV). Recently low-dose IV CYC (500mg/day, bi-weekly for 3 months) followed by Azathioprine (AZA) or Mycophenolate Mofetil (MMF) has been exhibit effects similar to those of a high dose of IV CYC regimen but with fever complications such as infection, bone marrow suppression, alopecia, hemorrhagic cystitis and malignancy, ovarian failure when compared to that of high dose IV CYC regimen[1, 8, 9].

Case Report

A 48-years old woman was admitted in the on February, 2015 with complaints of fever for last two and half months, 8-10 episodes of vomiting, cough and with symptoms of urinary tract infection. The patient is normotensive, non-diabetic, non-smoker and has no family history of ischemic heart disease. She is known case of hypothyroidism (under regular treatment), SLE (under irregular treatment), and has a past history (6 years ago) of Pulmonary Koch's under regular ATT therapy. On physical examination: Her body temperature was of 104Fahrenheit, the patient's pulse was 115 beats/minute and BP was 110/70mmHg, no icterus, pallor, clubbing, cyanosis or edema. CVS: S1, S2 normal, no murmur. Respiratory: normal breath sounds, no

added sounds. Patient is conscious and oriented to time, place and person, her abdomen was soft without tenderness or hepatosplenomegaly on palpation. The laboratory investigations revealed a serum albumin of 2.6mg/dl, serum. Cr was of 2.7mg/dl, Blood Urea Nitrogen is 56mg/dl, autoimmune screening was positive for Anti-Nuclear Antibodies (titre1:670) Anti-Double-Stranded DNA is positive (60IU/l) and Complement C3 level of 113mg/dl (normal: 85-160mg/dl) and C4 level is 75mg/dl (normal: 12-38mg/dl). Anti-Cardiolipin Antibodies (IgG, IgM and IgA) and Anti-Phospholipid (IgG) showed positive. Whereas, lupus anticoagulants was found to be absent. Hematological parameters revealed White Blood Cell(WBC) count- 44.5 x 10^3/µl (Neutropils 52%, Lymphocytes 14.5%), Platelet count of 55000/µl, and Hemoglobin level of 9.5mg/dl, Red Blood Cells(RBC) of 3.8mil/µl, Erythrocyte Sedimentation Rate(ESR) of 25mm/h. A renal biopsy of patient showed class IV lupus nephritis. Based on a diagnosis of Active Lupus Nephritis, she was treated with 1000mg (15mg/kg/day) of IntraVenous Methyl Prednisolone for 3 days and 500mg of IntraVenous Cyclophosphamide and Norfloxacin 400mg. She was discharged from hospital on a maintenance dose of oral Prednisolone of 1mg/kg/day and norfloxacin 400mg BD. She again presented to the hospital after a week of discharge with complaints of fever, Hematuria, burning micturation and vomiting. She was admitted in emergency ward and her Hematological and biochemical parameters revealed; Hemoglobin 6.9mg/dl, White Blood Cell count 3500/µl, Platelet count of 30000/µl, Erythrocyte Sedimentation Rate is 35mm/h. Urine analysis showed 4+ albumin, 45-50 RBC/HPF, 55-60 WBC/HPF, 3-5 granular cast and 4-5 hyaline casts/ HPFblood culture was sterile and urine culture showed 10,000 colonies/ml of Klebsiella Pneumonia. Mantoux test was negative and X-ray of chest showed bilateral pleural effusion, BloodUrea Nitrogen was 65mg/dl and Serum Cr was4.8 mg/dl. Her liver function test revealed, total serum protein w 4.6g/dl, Albumin 2.6g/dl and globulin 1.3g/dl, SGPT was 36U/L, SGOT was 29U/L, bilirubin direct 0.45, and total Bilirubin is 1.19mg/dl. Her LDL was found to be 765 U/L (normal: 141-247U/L), Her serumelectrolyte showed sodium 142mmol/L, potassium 4.55mmol/L, chloride 4.2mmmol/L and bicarbonates 6.6mmol/L. Her blood glucose level and arterial blood gases were normal. Serological for HBV, HCV and HIV were negative. The serum levels of fibrinogen degradation products and D-dimers were also found to be elevated to > 6500ng/ml (normal: less than 500ng/ml), her haptoglobin and ferritin level also found to be elevated to 410mg/dl(normal: 41-165mg/dl) and 349.3ng/ml (normal: 13-150ng/ml) respectively. Based on assessment she was diagnosed as Cyclophosphamide induced Urinary Tract Infection and Pancytopenia. Later she was admitted in Intensive Care Unit and treated with Meropenem 1gm every 8h,Mycofenolate

Mofetil 1gm twice a day, and Prednisolone 60mg orally once a day. She was treated with INJ. ESPOGEN 4000IU (Erythropoietein), Neucobal forte (methyl cobalamine) Caps. Zevit (multivitam supplement), Febuxostat 80mg once a daily, Thyronorm 25/50mg OD. After two days of treatment her blood culture showed Klebsiella pneumonia resistant to Meropenem, hence, the patient'sregimen was changed to Colistin (colistimethate) 1million unit along with Meropenem 1gm BD, dose was adjusted according to her creatinine clearance.After two days of Mycofenolate Mofetil treatment her hematological and renal function test showed improvement. A summary of the laboratory parameters during hospital admission was shown in Table 1. The patient condition improved gradually after 10 days of therapy. Erythropoietin was gradually discontinued after 8 sessionsand Prednisolone dose was tapered to 15mg/day without relapsing Pancytopenia. After seven days of treatment with Meropenem and Colistin her culture test showed no growth of Klebsiella pneumonia, hence, the antibiotic therapy was discontinued gradually. After 15 days, she improved remarkably, with a normalization of her Platelet count, Hemoglobin, WBC, RBC and other Hematological and renal parameters and she was discharged without any symptoms.

Table 1: A Summary of Clinical Course of Patient

PARAMETERS	26/2	27/2	28/2	1/3	3/3	5/3	7/3	10/3
PLATELETS(thou/ml)	30000	30000	35000	48000	63000	85000	97000	120000
RBC(mil/µl)	3.0	2.07	2.80	3.5	3.8	4.0	4.1	4.6
WBC(mil/µl)	4200	4600	6070	5700	6000	6200	6800	6800
HB(mg/dl)	4.9	5.5	8.7	8.2	8.5	8.9	9.1	9.4
Sr.CR(mg/dl)	4.8	3.6	2.7	3.2	3.8	2.1	2.0	1.5
BUN(mg/dl)	56	64	63	51	47	35	28	26
LYMPHOCYTES (%)	08	-	14	-	25	-	28	38
MONOCYTES (%)	1	-	1	-	1.5	-	1.8	2.3
EOSINOPHILS (%)	03	-	04	-	03	-	05	05

RESULTS AND DISCUSSIONS

Treatment of patients with severe lupus nephritis usually comprises of induction phase and maintenance phase. The current accepted standard of care for treatment of proliferative lupus nephritis is monthly high dose intravenous cyclophosphamide and corticosteroids for induction. This regimen was developed by US National Institutes of Health in 1970 and 1980. Longer duration of cyclophosphamide therapy associated with fewer relapses and better outcomes. Several meta-analyses showed that increased exposure to high dose of cyclophosphamide is associated with significant adverse drug effects like increased infection risk, sterility, secondary malignancy and bone marrow diseases[1, 4].The study conducted by L. Bono et.al,. showed that

the lupus nephritis patients treated with cyclophosphamide develops severe bacterial infection (sepsis) in 32 patients out of 110 patients[10]. Our case report highlights a rare but serious complication of Cyclophosphamide induced recurrent urinary tract infection and Pancytopenia in patient with recently diagnosed class IV nephritis, which is treated by using the Mycophenolate Mofetil (MMF). The study conducted by Castro-sanata et al., shows urinary tract infection developed in 80% patients with low dose and 25.6% with standard dose therapy[11]. The study conducted by Gerald B. Appel et al., reported 17 patients develops UTI infection due to IVCYP[5]. The study conducted by Manuel Mirandal et al., shows that 17 patients develops UTI out of 25 patients due to treatment delay with IVCYP in patients with proliferative lupus nephritis[12]. Although the strains are resistant to Meropenem, the combination treatment of Meropenem and Colistin is recommended due to synergistic or additive effect might be influenced by ability of Colistin to disrupt the bacterial outer membrane and increase its permeability for Carbapenems therefore stop the cross linkage of the newly synthesized polymers[13]. MMF is a relatively new immunosuppressive agent initially used in solid organ transplantation with selective inhibitory effects on activated T and B lymphocytes. MMF is a prodrug, depletes guanosine nucleotides through the inhibition of inosine-5'-monophosphate dehydrogenase acting preferentially on T- and b-lymphocytes[14]. Chan et al., says that MMF has been considered as an important alternative agent for the treatment of refractory lupus nephritis with better outcomes and fever side effects[15]. The study conducted by the Zahra et al., shows that MMF appears to be effective and very safe as a maintenance therapy in lupus nephritis patients with fewer side effects as compare to cyclophosphamide[16]. The Ginzler et al. conducted a study in 140 patients who had class III and IV lupus nephritis treated with oral MMF (1-3g per day for 24 weeks) compared with IV pulse cyclophosphamide shows less severe infections with better outcomes[17].

CONCLUSION

Our case report illustrates the occurrence of Pancytopenia and urinary tract infection following; administration of cyclophosphamide in patients with lupus nephritis. It highlights the need for an early detection and appropriate intervention, to restore the quality of life of the patients'.

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