e - ISSN - 2349 - 8005

INTERNATIONAL JOURNAL OF ADVANCES IN CASE REPORTS

Journal homepage: www.mcmed.us/journal/ijacr

THROMBOTIC THROMBOCYTOPENIC PURPURA ASSOCIATED WITH RAPIDLY PROGRESSIVE LUPUS NEPHRITIS IN PREGNANCY – EFFICACY OF CYCLOPHOSPHAMIDE AND STEROID PULSE ALONE WITHOUT PLASMAPHERESIS: A CASE REPORT

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Article Info
Received 15/03/2015
Revised 27/04/2015
Accepted 02/05/2015

Key words:
Gitelman Syndrome, Hypokalemia, Hypomagnesemia

ABSTRACT
There are few reported cases in the literature of Thrombotic microangiopathy (TTP) associated with Systemic Lupus Erythematosus (SLE). We describe a case of Thrombotic Thrombocytopenic Purpura (TTP) which presented along with rapidly progressive lupus nephritis with edema, proteinuria, hypertension, thrombocytopenia, microangiopathic hemolytic anemia and progressive rise in serum creatinine from 1.4 mg/dl to 4.2 mg/dl over a period of 10 days in pregnant woman who was having 20 weeks of amenorrhoea who was successfully treated with pulse cyclophosphamide and pulse methylprednisolone, with patient normalizing her renal function. Further experiences are needed whether intensive and prompt treatment with pulse cyclophosphamide and corticosteroids will lead to favorable outcome in cases of TTP associated with SLE.

INTRODUCTION

Thrombotic Thrombocytopenic Purpura (TTP) is an unusual complication of Systemic Lupus Erythematosus (SLE). There are no randomized prospective studies of its treatment. The association of plasma infusions or plasma pheresis with steroids improves survival compared to steroids alone. The role of immunosuppression with cyclophosphamide and steroids alone without plasma exchange is uncertain, and that too in a patient who is pregnant. We report a case of TTP with SLE who was 20 weeks of Amenorrhea who came to us with rapidly progressive lupus nephritis who was successfully managed with pulse methyl prednisolone and pulse cyclophosphamide without the need for plasma exchange.

CASE REPORT

We present a case of pregnant woman of 20 weeks of amenorrhoea, with past history of abortion in first pregnancy at 4 months of amenorrhoea and hypertension in previous pregnancy. She came to us with history of puffiness of face, pedal edema and oliguria. On clinical examination she had pedal edema, puffiness of face and ascites with blood pressure of 160/90mm of Hg. Haemogram revealed Hb of 8.8 gm /dl, TC 5200 cells/cumm, platelet of 39700 cells/cumm. Reviewing her previous reports we found that her serum creatinine increased from 1.63mg/dl to 4.25mg /dl over a period of 10 days. Her urine showed Albumin of 2+, nil sugar, RBC – 20-30/hpfand, protein/creatinine (P/C) ratio of 6.2. Her both serum complement levels were decreased. C_3 <30.01mg/dl and C_4<6.0mg/dl. Her ANA (Anti Nuclear Antibodies) was strongly positive – 66.28 units, dsDNA+ (double stranded deoxy riboneucleic acid), Anti neucleosome++, and antihistone ++, her ultra sound report showed normal kidney size and echotexture with 20 weeks

of gestation and fetus with polyhydramnios. Her Urine output was 800ml in 24 hours.

In view of progressively increasing serum creatinine we suspected patient to have rapidly progressive lupus nephritis and treated the patient with pulse methyl prednisolone 1gm I.V. for 3 days. In view of rapid progressive renal failure, the patient was counseled about the poor outcome of pregnancy as she would require immune suppressive medication like cyclophosphamide. We counseled that patient may have fetal malformation and spontaneous abortions. After obtaining consent from the patient we went ahead with pulse cyclophosphamide therapy and give her 500 mg in 100ml 0.9% saline infusion and followed up the patient. Patient had spontaneous abortion after 15 days with no complications and her serum creatinine decreased to 3.1 mg/dl after 15 day and platelet count increased to 80,000 cells/cumm, we deferred biopsy of kidney and went ahead with our second dose of pulse cyclophosphamide of 500 mg. Patient had developed pyelonephritis after second pulse of cyclophosphamide and was treated with appropriate antibiotics after which we treated her with third pulse of cyclophosphamide 500 mg. Patient had improvement in both renal function with serum creatinine decreasing to 1.33mg/dl and rise in platelet count to 1.93 lakhs. We than went ahead with renal biopsy which was uneventful. The report of kidney biopsy which showed in light microscopy 18 glomeruli with 2 global Sclerosis, 5 showing segmental Sclerosis, cellular crescents in 2 and segmental tuft necrosis in 2, with mesangiolysis in 4 glomeruli. The Arterioles showed changes like fibrinoid change to circumferential medial thickening and intimal widening with medial hypertrophy. Immunofluorescence showed only mesangial deposits and peripheral deposits of $C_{1q.}$ The final report suggested Chronic Thrombotic Microangiopathy with Cresentric changes.

Seeing the beneficial effects of pulse Cyclophosphamide we continued 3 more pulse doses of Cyclophosphamide every 15 days monitoring WBC counts and then switched over to Azathioprine and prednisolone as maintenance regime. After 4 months of Azathioprine and prednisolone with initial pulse Cyclophosphamide of 3 gms initially her serum creatinine decreased to 1.25mg/dl and proteinuria of 1+ and urinary P/C ratio of 0.8. One year later on follow up her serum creatinine is 0.9mg/dl and urinary P/C ratio of 0.44, with Hb of 15.2 gm/dl and platelet count of 2.75lakh/cumm suggesting near remission.

Figure 1. Kidney biopsy showing Mesangiolysis in the centre

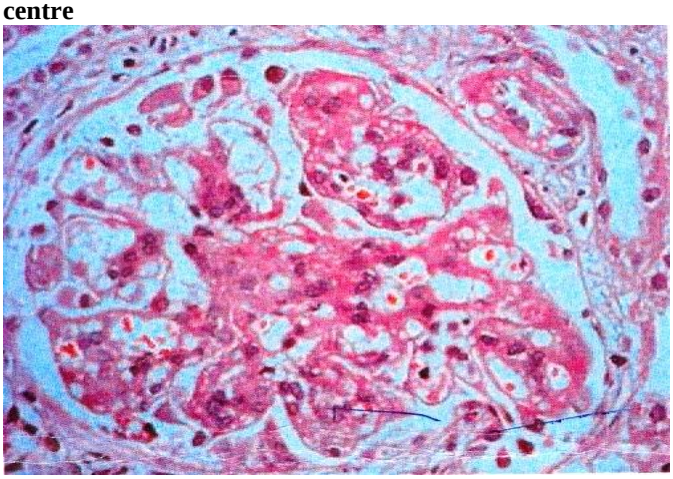


Figure 2. Kidney biopsy showing Segmental crescentic changes

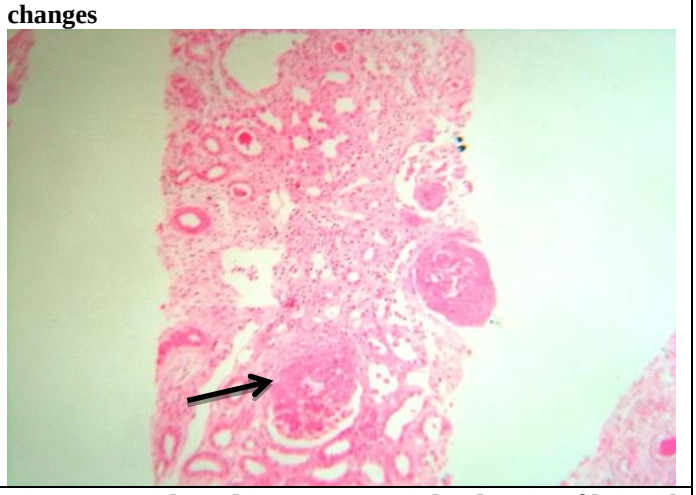


Figure 3. Kidney biopsy showing arterial medial hyperplasia

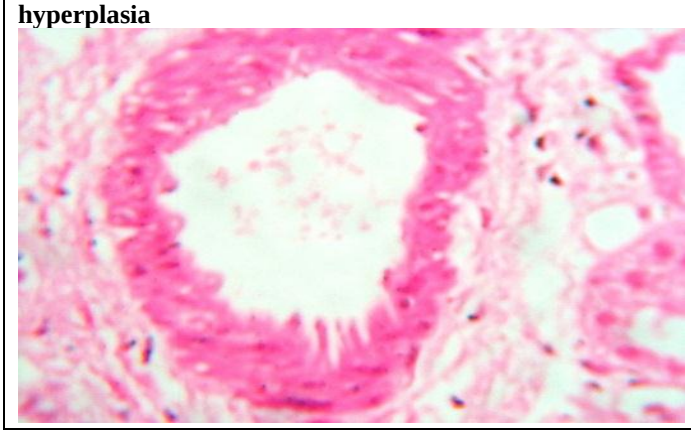
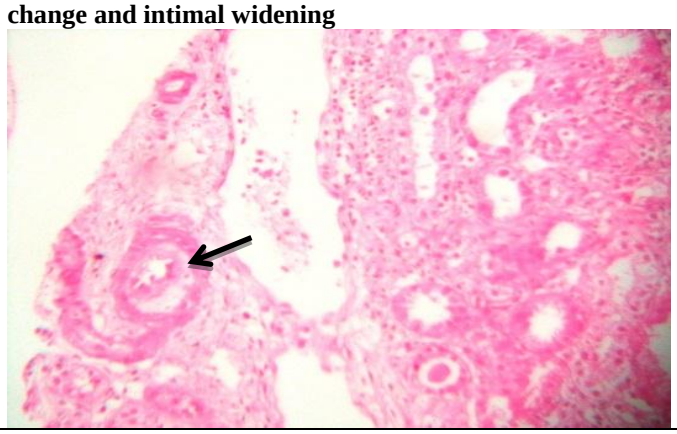


Figure 4. Kidney biopsy - Arteriole showing fibrinoid change and intimal widening



DISCUSSION

SLE is an autoimmune disease resulting from both genetic and environmental stimuli, with lupus nephritis occurring in almost 75% of cases of SLE any time during the course of the disease, with RPGN seen in 30% of lupus. SLE frequently occurs in women of child bearing age and pregnancy in patients causes exacerbation of disease in over 50% of patients [1] and flares occurs in all three trimesters and immediate post-partum. Patients are suspected to have lupus by history of fetal loss, as our patient had history of spontaneous abortion in previous pregnancy. The rate of fetal loss in all SLE patients in most series is 20-40% and may approach 50% in some series.[2,3] The association of thrombotic thrombocytopenic purpura (TTP) with Systemic Lupus Erythematosis (SLE) is rare. It is associated with high mortality and morbidity. Information about the risk factors and clinical outcomes is scant [4].

Our patient presented with clinical features of anaemia, thrombocytopenia, oliguria and progressive rise in serum creatinine from 1.63mg/dl to 4.25mg/dl over a period of 10 days with presence of proteinuria of 2+ , hematuria 20-30 rbc/hpf and strongly positive ANA, with decreased levels of complement C_3(C_3<30mg/dl) and C_4(C_4<6mg/dl) and dsDNA +. In view of these clinical features the first differential diagnosis of rapidly progressive lupus nephritis was made and we started with inj pulse methylprednisolone 1gm daily for 3 consecutive days. But as serum creatinine was persisting around 4.26mg/dl after 3 doses of methylprednisolone and patient was having 20 weeks of amenorrhea the decision to give immunosuppressive cyclophosphamide to the patient was made after obtaining the consent from the patient explaining the poor outcome to both mother and fetus in case the disease progresses to dialysis requirement. We started pulse cyclophsphamide 500 mg to the patient and followed up serum creatinine and urine output. Serum creatinine decreased to 3.1mg/dl after 15 days and patient had spontaneous abortion. This made us suspect that we were dealing with RPGN and we went ahead with 2 more pulse doses of cyclophosphamide, after which we got platelet count improved to 1.93 lakhs/cumm and serum creatinine of 1.33 mg/dl . After 3 pulse, biopsy was done which showed chronic thrombotic microangiopathy with cresentric changes and Immunoflorescence microscopy showed only patchy deposits of $C1_q$ which is not the usual case in any class of Lupus Nephritis of ISNRPS forms (International society of Nephrology and Renal pathology society consensus conference)(class 1-6) which generally has full house pattern on immunoflorescence microscopy.

We searched for the literature and found that Vasoo S et al [5] have reported that their patients had been refractory to plasmapheresis but responded to cytotoxic drugs. This was the scenario in our case, although we never tried plasmapheresis in our patient, as our primary diagnosis of rapidly progressive lupus nephritis was considered. Vasoo S. et al [5] have also found that their patient's disease activity had high and they had good and favorable response to cytotoxic drugs, as was our case who had high disease activity by clinical and laboratory parameters like low C_3 and low C_4, anaemia, thrombocytopenia and active sediments in the urine. Other literature search reveled that Perez-Sanchez L et al [6] reported two cases of TTP complicating SLE who did benefit from the use of cyclophosphamide, but these patients received plasma infusions and plasmapheresis and steroids in addition. But our patient responded without plasmapheresis to only steroids and cyclophosphamide which was a very rare event to happen in TTP.

We hypothesize that our patient had favorable response to cyclophosphamide as we had given it early during the course of disease when the disease activity was full even though we did not use plasmapheresis. Vaidya S et al [7] have reported two cases of TTP with SLE, one patient who was given cyclophosphamide early had a favorable response and other given late in the disease had poor response, but both patients received plasmapheresis. Our case is unique in that our patient responded only to cyclophosphamide and steroids without using plasma pheresis. Seeing the patients good response to first 3 bolus doses, we gave 3 more pulses of cyclophosphamide fortnightly to a total dose of 3 grams and started patient on Azathioprine as maintenance immunosuppression. After one year of follow up patient is having serum creatinine of 0.9 mg/dl and urinary P/C ratio of 0.44 which was the best response we could give her.

CONCLUSION

Thus we conclude that pulse cyclophosphamide therapy early in the course of TTP complicating SLE works efficatiously if patient's disease activity is high.

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