Introduction
Lupus nephritis (LN) is a serious complication of systemic lupus erythematosus (SLE). Despite modern induction therapy of proven efficacy, LN can still be associated with treatment failure. SLE is associated with a higher incidence of both hematological and solid organ malignancies, including cervical carcinoma which creates a paradox on how malignancies must be addressed therapeutically in the context of autoimmunity.[1,2]

Here we report an unexpected complete remission (CR) of a class IV LN following chemoradiotherapy of cervical carcinoma allowing the long-term discontinuation of immunosuppression.

Case Report
Clinical details
A 45-year-old female presented with polyarthralgia, alopecia, oral ulcers, photosensitivity, swelling of feet, vomiting, and decreased urine output. On examination, she had a blood pressure of 140/80 mm Hg, pallor, pedal edema and malar rash. Her investigations revealed serum creatinine (S.Cr) of 6.36 mg/dL, anaemia (Haemoglobin 5.1 g/dL), leukopenia (total leucocyte count 2500 cells/cmm), and thrombocytopenia (platelet count 58000 cells/cmm). Furthermore, urine examination showed microscopic haematuria with dysmorphic erythrocytes, albuminuria of 1.4 g/24 h, and a serum albumin (S. alb) of 2.68 g/dL. Serological investigations showed ANA 3+ diffuse pattern, positive anti-ds DNA, and normal complements. Her Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI- 2K) score was 22. She was initiated on hemodialysis and three intravenous (IV) methylprednisolone pulses of 1 g each followed by oral steroids of 1 mg/kg were given. Following normalization of platelet counts, renal biopsy was performed. On light microscopy, there were 20 glomeruli, of which one was globally sclerosed. Four glomeruli showed cellular crescents, four fibrocellular crescents, and four fibrous crescents. Underlying tufts showed segmental variable mesangial hypercellularity and matrix expansion. Five glomeruli showed segmental endocapillary proliferation. Tubules showed patchy interstitial fibrosis.
and tubular atrophy of 30%. Patchy acute tubular injury, interstitial edema, patchy tubulitis, and mild peritubular capillary dilatation and margination were also seen. Blood vessels showed hypertensive changes. Direct immunofluorescence showed granular C1q 2+ positivity in mesangial area and capillary loops. A diagnosis of class IV LN according to ISN/RPS classification was made with a modified NIH activity score of 8/24 and chronicity score of 6/12 [Figure 1].

Treatment and follow-up

After initial IV methylprednisolone pulses followed by oral steroids of 1 mg/kg, she was started on high dose monthly IV cyclophosphamide (IV CYC; 1000 mg/m²), along with hydroxychloroquine 300 mg and angiotensin receptor blockers. At the end of 6 months, she achieved a partial remission with a S. Cr of 1.9 mg/dL, proteinuria of 890 mg/24 hours, S. alb of 3.5 g/dL. Maintenance therapy with mycophenolate mofetil (MMF) 1 g in two divided doses and low dose steroids (wysolone 5 mg) was started. At the 8th month, she had a proteinuric relapse with a proteinuria of 1.7 g/24 hours, S. alb of 3.3 g/dL, and a S. Crt of 1.4 mg/dL for which MMF dose was increased to 1 g twice daily and wysolone was continued at 10 mg per day. Patient continued to have proteinuria. At 18 months, she had a S. Cr of 1.2 mg/dL, S. alb of 3.2 g/dL, and proteinuria of 1.2 g/24 hours; was planned to start on tacrolimus in addition to MMF and steroids. Meanwhile, she developed bleed per vagina for which she underwent a cervical biopsy and radiological evaluation: she was diagnosed with squamous cell carcinoma of cervix stage IIB. MMF was withheld in view of the underlying carcinoma and low-dose-steroids (5 mg) were continued. She received 4 cycles of radiotherapy @ 46 Gy/23 fractions for 4.5 weeks with concurrent chemotherapy with a radio-sensitizing dose of cisplatin 40 mg/m² *4 weeks followed by 2 cycles of Intracavitatory brachytherapy of 9 Gy/fraction. After two months of concurrent chemotherapy and radiotherapy, the patient went into CR with a proteinuria <500 mg/24 hours, S. Cr 1.04 mg/dL, S alb 4.2 g/dL, negative anti-DsDNA, and normal complements. The patient was continued on low dose wysolone (5 mg) along with hydroxychloroquine and angiotensin receptor blockers. She is currently 5 years post-diagnosis and continues to be in CR with low dose steroids with a SLEDAL-2K score of 0, normal complements, negative anti-ds DNA and also has no active disease of carcinoma cervix. The complete clinical course is depicted in Figure 2.

Discussion

Here we report a patient with SLE with Class IV LN who received induction with NIH regimen followed by maintenance with MMF. She developed a proteinuric relapse for which she re-induced with MMF to which she failed to achieve remission. Post-diagnosis of carcinoma cervix IIB, she received concurrent chemoradiotherapy following which she went into CR of LN despite being on just low dose steroid.

SLE patients have increased risk for both hematological malignancies like non-Hodgkin’s lymphoma, and solid tumors in lung, liver, vulvar/vaginal, and thyroid.[1] SLE patients with long-term use of immunosuppression have also been observed to have a higher prevalence of low-grade and high-grade cervical intraepithelial lesions (CIN) in comparison with those without long-term use of these agents; one series reported an overall 3-year incidence of CIN of 25% in IV CYC treated patients.[2] A dose relationship was observed between cumulative IV CYC exposure and CIN; every 1 g corresponded to a 13% increased risk of CIN. The cumulative dose of IV CYC received in our patient was 6 g which is less likely to have increased risk of carcinoma cervix.

Initially, the patient did not go into CR despite being on adequate immunosuppression. However, subsequently with the chemoradiotherapy for carcinoma cervix, she achieved a CR that was sustained for the next 5 years. We hypothesize that the remission of the lupus activity can be explained by the effect of either radiotherapy or cisplatin-based chemotherapy, or a combination of both.

Figure 1: Renal biopsy. a. Globally sclerosed glomerulus (PAS, 400x). b. Partial cellular crescent, mild to severe mesangial matrix expansion, hypercellularity, hypertensive change in blood vessels (PAS, 400x). c. Circumferential fibrous crescent, sclerosed tuft (PAS, 400x). d. Glomerulus with mild mesangial matrix expansion, variable GBM thickening (right), (PAS, 400x). e. RBC casts (arrow), acute tubular injury (H&E, 400x). f. Thyroidization of tubules, interstitial fibrosis with tubular atrophy (PAS, 200x). g. DIF: granular deposits in glomerular capillary wall and mesangium for antisera of C1q (2+), 400x.
SLE patients have lower serum TGF-β1 levels than healthy individuals which are associated with increased disease severity, especially renal damage. TGF-β1 is an important negative regulator of B cell differentiation and proliferation, and it also inhibits cytotoxic T lymphocyte, while promoting peripheral T Regulatory cells. Hence, TGF-β1 is a powerful immunosuppressive cytokine that plays a dual role during the development and progression of immune-mediated inflammatory diseases, including SLE. In fact, it is shown that addition of TGF-β1 and IL2 to peripheral blood mononuclear cells from SLE patients reverses the upregulated IgG production. Radiotherapy is known to increase TGF-β1 levels. For cancer patients with SLE, the release of TGF-β1 as a result of radiation therapy could be beneficial to the underlying SLE. However, there have been no reports in the literature of remission of SLE with radiotherapy. Furthermore, there has been a concern of use of radiotherapy in SLE patients as these patients have increased risk of developing acute and chronic toxicities albeit moderate, presumably due to increased radiosensitivity leading to the additive damage to the microvasculature.

Cisplatin is an alkylating agent that directly damages DNA thereby disrupting its replication and transcription, inducing cancer cell apoptosis. In addition, cisplatin is seen to have immunological effects as well. Platinum compounds can modify the immune response during both the induction and the effector phase leading to immunogenic cell death. We hypothesize that the use of cisplatin could have contributed to the remission. Topoisomerase I inhibitor irinotecan was shown to reverse LN and prolonged survival of NZB/WF1 mice by inducing single-stranded DNA breaks, inhibiting renal cell apoptosis, and preventing subendothelial deposits of IgG. A study in murine lupus model also found that paclitaxel, an antimicrotubule agent, was beneficial in the suppression of autoimmunity by reducing the anti-dsDNA antibody titer and prolonging survival. Animal experiments indicated that murine LN treated with fludarabine, a fluorinated purine analog that inhibits DNA synthesis had a more significant reduction in renal pathology compared with LN treated with CYC. A patient with chronic lymphocytic leukemia and steroid-resistant SLE achieved durable remission after administrating fludarabine. There have been case reports of long-term remission of SLE activity and disappearance of clinical symptoms following removal of coexisting ovarian dysgerminoma along with post-operative melphalan for six weeks. Thus, chemotherapy with cisplatin may have played a role in controlling SLE activity, though it may be difficult to explain a sustained remission with just low dose steroids in our case.

In conclusion, we report an unexpected association between CR of a class IV LN and chemoradiotherapy of cervical carcinoma allowing the discontinuation of immunosuppressive medications, the effect of which could be attributed to either the radiotherapy or cisplatin, or a combination of both.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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