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LETTER TO THE EDITOR

Use of rituximab in combination with high-dose methotrexate in the treatment of primary central nervous system lymphoma in a mycophenolate mofetil treated patient with lupus nephritis

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To the Editor,

Several studies have suggested that immunosuppression and several autoimmune and chronic inflammatory conditions such as rheumatoid arthritis (RA), Sjögren's syndrome (SS) and systemic lupus erythematosus (SLE), are associated with an increased risk of developing malignant lymphomas [1]. While NHL developing in patients with rheumatoid arthritis and Sjögren's syndrome has been fairly well described [2–5], NHL developing in patients with SLE is much less common and understood.

A 20-year-old female with a history of lupus nephritis on MMF presented following a seizure. She was diagnosed with stage 1 PCNSL, and was started on Rituximab, Methotrexate, Vincristine and Procarbazine. She developed status epilepticus and recurrent seizures during the seventh cycle. MRI brain showed disease progression, and treatment was changed to two courses of salvage CYVE chemotherapy (Cytarabine, Etoposide). She attained near complete remission and went on to receive high-dose Thiotepa, Busulfan, and Cyclophosphamide with autologous peripheral stem-cell rescue (APSCR).

She experienced numerous infective complications while receiving salvage CYVE chemotherapy. These included grade IV neutropaenic fever, fungaemia (*Candida glabrata)* and septicaemia (Methicillin-resistant *Staphyloccocal aureus*, *Klebsiella pneumoniae*).

On day+1 of APSCR, the patient developed grade IV hypertension and altered mental state. An urgent CT brain showed the classical appearance of posterior reversible encephalopathy syndrome (PRES). She was electively intubated to protect her airway and control blood pressure. Other significant complications following high dose chemotherapy included BK virus-associated haematuria, fungaemia (*Candida glabrata*) and Stevens-Johnson Syndrome. The patient was discharged from hospital after a five month stay. Unfortunately, three months post-discharge, an MRI brain confirmed disease progression and she passed on a month later, eight months after the initial diagnosis.

Ekström-Smedby et al. reported a 2.7-fold increase in the risk of lymphoma in patients with SLE [1]. Recently, several authors have reported occurrence of PCNSL in SLE patients [6–9]. Our patient is the fourth case report in the literature. Of importance, three of these patients had prior exposure to MMF [6,9]. MMF has not previously been shown to be associated with secondary malignancies and was thought to have activity against lymphoma [9]. Nonetheless, as MMF is relatively new, it is important to review its safety in long-term use.

In immunocompetent patients, systemic chemotherapy incorporating high-dose methotrexate [10,11] is routinely used, and Rituximab is increasingly incorporated. Rituximab may be particularly useful here as it has the potential to target both lymphoma and SLE. As such, we opted for a regimen that contained both Rituximab and high-dose methotrexate [12]. MMF was also discontinued. Although our patient tolerated the regimen relatively well, she experienced early disease progression. In contrast, O'Neill BP reported better outcomes in four patients

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with autoimmune conditions who developed an EBV-associated central nervous system (CNS) lymphoproliferative disorder after treatment with MMF [7]. All four patients improved after MMF withdrawal and administration of Rituximab. The optimal induction regimen remains to be determined.

For immunocompetent patients with relapsed or refractory PCNSL, Soussain et al. reported encouraging results with an intensive approach incorporating HDC and APSCR [13]. To the best of our knowledge, there is no available published data describing this approach in SLE patients with relapsed CNS lymphoma, although autologous stem cell transplant is an option in patients with SLE [14]. However, the substantial infectious complications suffered by our patients and the short progression-free interval raise the question of its feasibility.

Our patient also developed PRES, a rare neurological complication, shortly after HDC. A low index of suspicion should be considered if PCNSL patients with underlying SLE present with the typical presentations of seizures, headaches, loss of vision and altered mental function [15]. Prompt recognition is important so that reversibility can be achieved.

This case report profiles a patient with systemic lupus erythematosus (SLE) who developed primary central nervous system lymphoma (PCNSL) to highlight treatment dilemma, the various haematological, neurological and infectious complications encountered in the management of an immunocompromised host with lymphoma, and to draw attention to the safety issues of mycophenolate mofetil.

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