Treatment associated Mantle Cell Lymphoma with Cyclophosphamide therapy for Granulomatosis with Polyangiitis

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Abstract
We present a case of a 68-year-old woman who developed mantle cell lymphoma in the setting of long-term cyclophosphamide therapy and relapsing granulomatosis with polyangiitis (Wegener’s granulomatosis, GPA). Adverse outcomes associated with cyclophosphamide therapy are well documented; however, the development of non-Hodgkin’s lymphoma appears rare. Cumulative dose of cyclophosphamide (>36 g) is a significant risk factor in the development of serious long-term adverse outcomes and is particularly relevant to this case in which maintenance cyclophosphamide therapy was continued, following induction, for 2 years total, on account of patient preference. This case study will highlight the patient’s initial diagnosis, treatment response, relapse and subsequent complications of therapy.

Introduction
Cyclophosphamide therapy has long been used as both induction and maintenance therapy for systemic small vessel vasculitides such as granulomatosis with polyangiitis (GPA, formerly known as Wegener’s granulomatosis). This case highlights a rare instance of treatment-related mantle cell lymphoma, associated with long-term cyclophosphamide therapy in the setting of pulmonary GPA. The development of secondary malignancies with long-term cyclophosphamide therapy are generally well documented, and commonly include bladder transitional cell carcinoma, non-melanomatous skin cancers and hematologic disorders, typically acute myeloid leukemia (AML) [1]. Mantle cell lymphomas (or non-Hodgkin’s lymphomas, in general) are considered significantly less common than other hematologic complications (such as AML or myelodysplastic syndrome) associated with cyclophosphamide therapy. By describing and analyzing the circumstances around this case study, we gain some insight into risk factors for this rare, serious adverse outcome, and in turn may be used in counseling patients receiving maintenance therapy with small vessel vasculitides in respect to treatment options.

Case Report
A 68-year-old woman presented with intermittent chronic haemoptysis, shortness of breath, 3-kg weight loss and fatigue. Subsequently, she developed nasal sinus congestion, epistaxis, a diffuse maculo-papular rash and drenching night sweats. She was an ex-smoker, with a 20 pack year history.

A computed tomography (CT) scan of the chest demonstrated multiple nodular densities of up to 4 cm throughout both lung fields most marked in the left lower lobe. cANCA (anti-neutrophil cytoplasmic antibodies) titer was 160 with PR3-ANCA (proteinase 3 antibodies) of 27 U/L. CT-guided biopsy of one of the pulmonary lesions demonstrated granulomatous inflammation. These findings in conjunction with the clinical picture led to the diagnosis of GPA.
Treatment options were discussed, and induction cyclophosphamide commenced with high-dose prednisone. After 1-month therapy, the patient felt greatly improved, with resolving shortness of breath, no further night sweats and her epistaxis had ceased. Prednisone was weaned to 25 mg daily, and cyclophosphamide was up-titrated to 75 mg daily. After 3 months of treatment, the patient’s exercise tolerance and weight had returned to baseline. Surveillance for cyclophosphamide-associated complications was reassuring, with mild alopecia as the principal adverse effect.

Although alternative maintenance immunosuppression was strongly recommended, the patient expressed great reluctance to consider weaning cyclophosphamide. It was ultimately decided to cease prednisolone, and maintenance therapy was continued for 2 years with oral cyclophosphamide, without clinical relapse. Sixteen months following the completion of therapy, the patient presented with streaky mide, without clinical relapse. It was strongly recommended, the patient expressed great reluctance to consider weaning cyclophosphamide. It was ultimately decided to cease prednisolone, and maintenance therapy was continued for 2 years with oral cyclophosphamide, without clinical relapse. Sixteen months following the completion of therapy, the patient presented with streaky mide, without clinical relapse. It was strongly recommended, the patient expressed great reluctance to consider weaning cyclophosphamide. It was ultimately decided to cease prednisolone, and maintenance therapy was continued for 2 years with oral cyclophosphamide, without clinical relapse. Sixteen months following the completion of therapy, the patient presented with streaky mide, without clinical relapse. It was strongly recommended, the patient expressed great reluctance to consider weaning cyclophosphamide. It was ultimately decided to cease prednisolone, and maintenance therapy was continued for 2 years with oral cyclophosphamide, without clinical relapse. Sixteen months following the completion of therapy, the patient presented with streaky mide, without clinical relapse. It was strongly recommended, the patient expressed great reluctance to consider weaning cyclophosphamide. It was ultimately decided to cease prednisolone, and maintenance therapy was continued for 2 years with oral cyclophosphamide, without clinical relapse. Sixteen months following the completion of therapy, the patient presented with streaky mide, without clinical relapse. It was strongly recommended, the patient expressed great reluctance to consider weaning cyclophosphamide. It was ultimately decided to cease prednisolone, and maintenance therapy was continued for 2 years with oral cyclophosphamide, without clinical relapse. Sixteen months following the completion of therapy, the patient presented with streaky mide, without clinical relapse. It was strongly recommended, the patient expressed great reluctance to consider weaning cyclophosphamide. It was ultimately decided to cease prednisolone, and maintenance therapy was continued for 2 years with oral cyclophosphamide, without clinical relapse. Sixteen months following the completion of therapy, the patient presented with streaky mide, without clinical relapse. It was strongly recommended, the patient expressed great reluctance to consider weaning cyclophosphamide. It was ultimately decided to cease prednisolone, and maintenance therapy was continued for 2 years with oral cyclophosphamide, without clinical relapse. Sixteen months following the completion of therapy, the patient presented with streaky mide, without clinical relapse. It was strongly recommended, the patient expressed great reluctance to consider weaning cyclophosphamide. It was ultimately decided to cease prednisolone, and maintenance therapy was continued for 2 years with oral cyclophosphamide, without clinical relapse.

Evidence of cyclophosphamide-related malignancy in GPA began to emerge in the early 1990s with one study suggesting a 2.4-fold increase in risk of cancer in vasculitis patients treated with cyclophosphamide induction and maintenance therapy, when compared with matched controls. This was primarily driven by bladder cancer with a 33-fold increased risk [3]. Another large case series in 2002 generated up to 26 years of follow-up of 1065 Swedish patients diagnosed with GPA. The overall standardized incidence ratio (SIR) of malignancy in patients with GPA was found to be 2.0. Bladder cancer featured highly with an SIR of 4.8 [5]. In both of these series, an increased risk of lymphoma was noted, with 11-fold increase and SIR of 4.2, respectively. The Swedish study, with an SIR of 4.2, found seven of eight cases to be non-Hodgkin’s lymphoma.

In a study that has important implications for our case, cumulative dose of greater than 36 g of cyclophosphamide has been suggested as a significant risk factor for the development of malignancy, particularly bladder transitional cell carcinoma (SIR 9.5) and AML (SIR 59) [1]. While this is of particular significance with our patient who received cumulative dose well in excess of 36 g, it is interesting to note that this particular series of 293 patients did not identify an increased risk of lymphoma.

In summary, treatment decisions, particularly regarding maintenance therapy in those with systemic small vessel vasculitides such as GPA are complex and need to be tailored to individual patients. Long-term cyclophosphamide therapy, particularly with cumulative doses of greater than 36 g, is associated with increased risk of malignancy, particularly bladder cancer. While rare, there is some evidence to suggest the relative risk of secondary lymphoma is also significant. Regardless of treatment choice, this case demonstrates the need to maintain vigilant surveillance both during and following active treatment not only to monitor for disease relapse but to detect complications of therapy early.

**Discussion**

Previous literature suggests that non-Hodgkin’s lymphomas, such as mantle cell lymphoma is an exceedingly uncommon adverse effect associated with cyclophosphamide therapy. Options for maintenance therapy in GPA are varied, with azathioprine, cyclophosphamide and methotrexate all considered comparable options, with most evidence advocating for maintenance regimens to extend up to 24 months total [2]. The risk of relapse is significant, and in one series, relapse following remission occurred in 50% of patients who received standard cyclophosphamide and prednisone therapy [3]. Another study estimated the risk of relapse as high as 73% for patients with pulmonary involvement, high PR3 titers and disease of the upper respiratory tract, versus those without these features, who had a 26% relapse rate following standard therapy [4]. Relapse usually warrants further induction therapy; however, drug toxicities are an important consideration in the choice of agent.

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**Disclosure Statements**

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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