Successful treatment of refractory angioimmunoblastic T-cell lymphoma with thalidomide and dexamethasone

Angioimmunoblastic T cell lymphoma (AITL) is a peripheral T-cell lymphoma characterized morphologically by lymphadenopathy with a polymorphic infiltrate, marked vascular and follicular dendritic cell proliferation. Patients usually present with advanced disease and the overall prognosis is poor. While intensive chemotherapy has been shown to induce complete remissions in 50-70% of patients, the majority of patients subsequently relapse. Herein we report the case of a 32 year old man with AITL who was refractory to conventional chemotherapy, but achieved a remarkable sustained response to treatment with thalidomide and dexamethasone. Thalidomide may be an effective therapeutic agent against AITL, and given the poor prognosis of AITL, prospective clinical studies with either thalidomide or one of the thalidomide analogues are warranted.

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Angioimmunoblastic T cell lymphoma (AITL) is a peripheral T-cell lymphoma characterized morphologically by lymphadenopathy with a polymorphic infiltrate, marked vascular and follicular dendritic cell proliferation.[1,2] Patients usually present with advanced disease with a polyclonal gammopathy, as well as features of immune dysregulation. The overall prognosis of patients with AITL is poor, and while intensive chemotherapy has been shown to induce complete remissions in 50-70% of patients, the majority of patients subsequently relapse.[3,4] More recently, there have been reports of successful therapy of AILT using various immunomodulatory and immunosuppressive agents.[5-8] Herein we report a case of AITL who was refractory to conventional chemotherapy, but achieved a remarkable sustained response to treatment with thalidomide and dexamethasone. A 32 year old male presented with a two month history of lethargy, weight loss and pyrexia. Clinical examination revealed bilateral posterior and anterior cervical lymph nodes as well as inguinal and axillary lymphadenopathy. Haematological and biochemical investigations were normal and there was no paraproteinaemia. Biopsy of a right axillary lymph node showed features of AITL. The lymph node architecture was completely effaced by a polymorphic infiltrate comprising numerous small-medium sized atypical lymphocytes with pale cytoplasm, scattered transformed blasts, numerous eosinophils and plasma cells. There was a moderate degree of vascular proliferation. Vast majority of the lymphoid cells were CD3+ CD4+ T-cells with scattered CD20 and CD79a B-cell aggregates (Figure 1A-C). CD10 staining and *in situ* hybridisation for EBV mRNA (EBER) was negative. Computer tomography (CT) scanning revealed axillary, subcarinal, paratracheal and paraaortic lymphadenopathy but no hepatosplenomegaly. A bone marrow aspirate and trephine biopsy were normal. He received 6 cycles of standard 3-weekly CHOP chemotherapy (Cyclophosphamide 750 mg/m^2, Vincristine 1.4 mg/m^2, Doxorubicin 50 mg/m^2, Prednisolone 100 mg/m^2) with additional intrathecal methotrexate as CNS prophylaxis. There was partial resolution of lymphadenopathy however repeat axillary lymph node biopsy showed persistent disease. The patient declined high dose salvage therapy and he therefore received the PMitCEBO regimen (Mitoxantrone 7 mg/m^2, cyclophosphamide 300 mg/m^2, etoposide 150 mg/m^2, vincristine 1.4 mg/m^2, bleomycin 10 mg/m^2), with concurrent weekly Alemtuzumab 30 mg iv. After an initial partial response, night sweats and lymphadenopathy recurred after 6 weeks and he went on to receive Dexamethasone 40 mg po daily for 4 days every 3 weeks along with Thalidomide 100mg po daily. The B symptoms and lymphadenopathy reduced over 6-8 weeks and dexamethasone was discontinued. A CT scan performed after 4 months showed residual small volume lymphadenopathy, which completely resolved on restaging 4 months later. The patient is in clinical and radiological remission 28 months after commencing Thalidomide, and he remains on Thalidomide as maintanence therapy.

Figure 1. A. There is effacement of the normal lymph node architecture by a mixture of small and large lymphoid cells, eosinophils and prominent blood vessels. **B.** Immunohistochemical staining shows the majority of lymphoid cells stain strongly for CD3. **C.** Immunohistochemical staining for CD20 demonstrates residual lymphoid follicles that have been mostly replaced by the malignant infiltrate. **D.** Lymph node biopsy following first course of thalidomide and dexamethasone shows much of the tumour has been replaced by collagen, with residual foci of tumour seen within the lymph node.

AITL accounts for up to 1-2% of all Non-Hodgkin's lymphomas. The median age of presentation is in the sixth to seventh decade, and majority of patients present with stage III-IV disease.[1,2] Response to combination chemotherapy has been poor in comparison to other lymphoid disorders.[3,4] Siegert et al have previously reported on a multicenter non-randomised study which showed complete remission (CR) was obtained in half of the patients treated with either single agent prednisolone or conventional combination chemotherapy and prednisolone4. Despite the favourable remission rate obtained with chemotherapy, there remained a high relapse rate with only very few long-term survivors. More recently, Schetelig et al published findings of an EBMT-based survey of 29 patients (median age: 53 years, range 20-60 years), which demonstrated that consolidation with an autologous stem cell transplantation following high dose chemotherapy can induce long term remissions, with a 5 year disease free survival of 37%9, and may be a feasible therapeutic option in a subgroup of patients. Thalidomide acts through inhibition of TNF·, VEGF (vascular endothelial growth factor), IL-6 and NFkB, and has been shown to have immunomodulatory properties on both T-cells and NK-cells10. Both thalido-

mide and its analogues are being increasingly used in the treatment of multiple myeloma. Thalidomide has also been used in various refractory lymphoid disorders, albeit with minimal response.[11] In contrast, in vivo and in vitro studies have supported a possible basis for the use of thalidomide in patients with AITL. VEGF-A expression is increased in lymphoma cells and endothelial cells in AITL.[12] Increased levels of IL-6 have also been reported in lymph node mononuclear cells of patients with AITL.[13] Indeed, Dogan et al have recently reported a patient treated with single agent thalidomide as first line therapy for AITL who achieved a complete remission.[7] In addition, Strupp et al previously reported two heavily pretreated and refractory AILT patients who achieved a transient partial remission with thalidomide.[8] To our knowledge, this is the first case of refractory AILT treated with thalidomide and dexamethasone achieving a durable complete remission. There is mounting evidence to suggest that thalidomide may be an effective therapeutic agent against AITL, and certainly the side-effect profile of thalidomide compares favourably with that of conventional therapy. Given the poor prognosis of AITL, prospective clinical studies with either thalidomide or one of the thalidomide analogues are warranted.

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