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The evolving management of a rare lymphoproliferative disorder: T-cell prolymphocytic leukaemia

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Figure 1. Facial erythema and periorbital oedema at presentation
38x55mm (300 x 300 DPI)

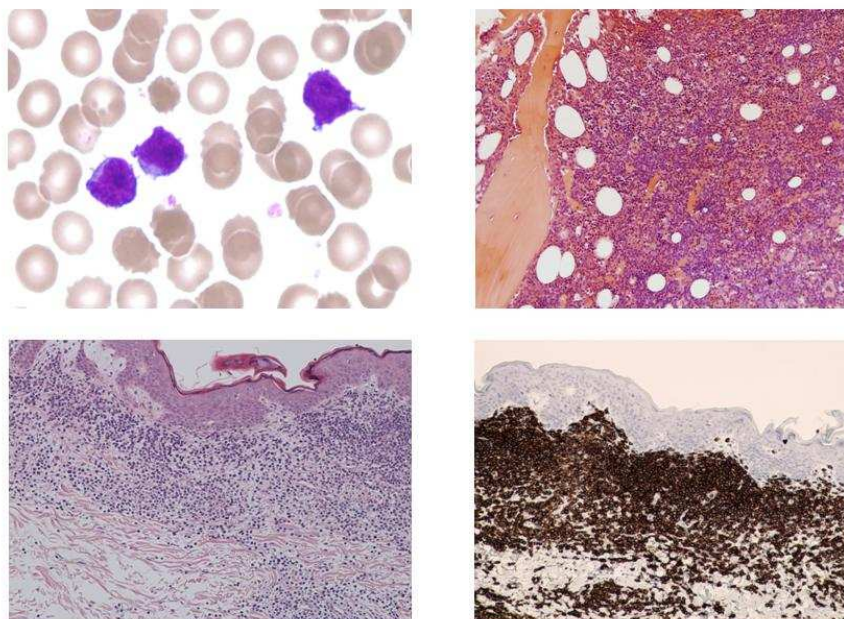


Figure 2. Peripheral blood, bone marrow trephine and skin biopsy showing typical polymorphocytic infiltrate
254x190mm (96 x 96 DPI)

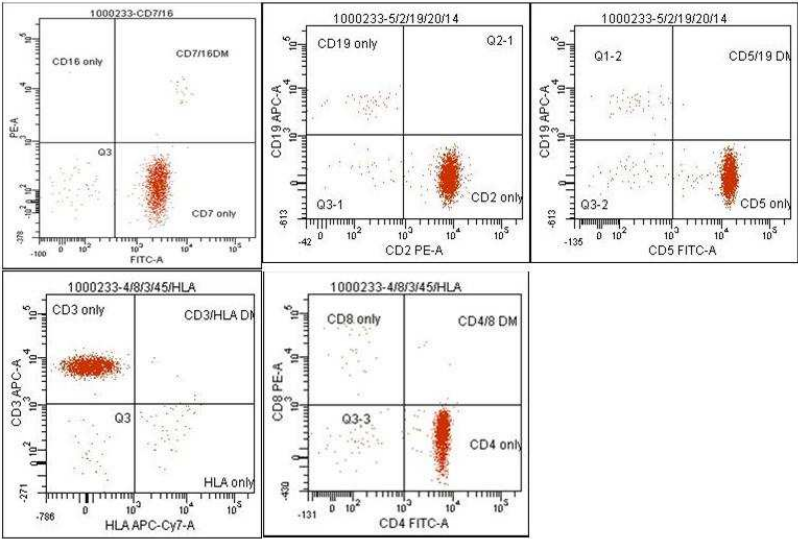


Figure 3. Flow cytometry plots showing positivity for CD7, CD2, CD5, CD3 and CD4
254x190mm (96 x 96 DPI)



Figure 4. Complete resolution of facial erythema and periorbital oedema following treatment.
37x50mm (300 x 300 DPI)

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The evolving management of a rare lymphoproliferative disorder –T-cell prolymphocytic leukaemia.

A 62-year-old woman presented with a 6-week history of facial swelling, periorbital oedema, generalised itch and a thickening of the skin over her neck, chest and abdomen. She did not report any systemic symptoms. She had no significant past medical history and took no regular medications.

On examination she had marked facial oedema and erythema most marked in the peri-orbital area (Figure 1) with thickened and fissured skin over upper chest, forearms and abdomen.

Full blood count showed Hb 130g/L, WBC 64.4 x 10⁹/L and Platelets 300x10⁹/L. Serum LDH was 1487u/L (NR <240). Blood film (Figure 2, top left) showed a population of small lymphoid cells with high nuclear/cytoplasmic ratio, infrequent nucleoli and prominent cytoplasmic blebs.

Bone marrow trephine was diffusely infiltrated with similar cells (Figure 2, top right).

Flow cytometry showed these cells to have a mature phenotype with pan T positivity (CD2, CD3, CD5 and CD7 +ve, TdT and DR -ve). The cells were CD4 positive, CD8 negative (Figure 3).

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3 **Skin biopsy of the affected areas showed a dense T cell infiltrate**
4 **expressing CD3 and CD57 at the dermoepidermal junction but without**
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6 **epidermotropism (Figure 2, bottom left and right respectively).**
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12 **A T cell gene receptor rearrangement was identified in the neoplastic**
13 **population. Standard cytogenetics were normal but FISH studies**
14 **identified an 11q22 deletion at the ATM gene locus. CT of chest and**
15 **abdomen showed mild splenomegaly and diffuse low volume**
16 **lymphadenopathy. The diagnosis was small cell variant T cell**
17 **prolymphocytic leukaemia (T-PLL).**
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29 T-PLL is a rare haematological disorder. In the largest series published, of 78
30 patients, the median age at presentation was 69 years with a male/female
31 ratio of 1.33¹. T-PLL tends to present with a leukaemia, hepatosplenomegaly,
32 lymphadenopathy and skin lesions. Skin lesions can be generalized or local
33 maculo-papular rashes or nodules². Occasional erythroderma has been
34 described as well as periorbital oedema³. Classically skin biopsies show a
35 dermal lymphoid infiltrate involving preferentially the appendages but always
36 sparing the epidermis². Blood profiles show a high WBC count with atypical
37 prolymphocytes on morphological examination. These appear as medium
38 sized cells with a high nucleo-cytoplasmic ratio, moderately condensed
39 chromatin and a single prominent nucleolus. Cytoplasmic blebbing is a
40 prominent feature. T-PLL cells show a post-thymic phenotype (TdT-ve,
41 CD2/3/5/7 +ve). Abnormalities involving chromosome 14, 8 and 11q are
42 typically found on cytogenetic analysis^{1, 4, 5}. 11q deletions often involve the
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ATM gene locus. ATM gene is often mutated in patients affected by the genetic debilitating neurological illness called ataxia-telangiectasia (A-T). Patients with A-T have biallelic inactivation of the ATM gene and show an increased tendency to develop a number of solid tumours but in particular lymphoid malignancies and particularly T-PLL⁶. ATM appears mutated also in a large number of sporadic T-PLL as a result of both sequence mutations and structural changes of the chromosome 11q region⁶⁻⁷. It appears to function as a tumour suppressor gene and is involved in the downstream activation of p53. ATM inactivation effects in tumorigenesis may be either direct, by enhancing cell proliferation and inhibiting apoptosis or indirect, by enhancing genome instability. Normal ATM, acting via p53, appears to have a pivotal role in DNA repair following sporadic, cytotoxic or radiation damage. P53 dysfunction leads to impaired DNA repair and increased susceptibility to carcinogens and also refractoriness to standard chemotherapies. It is a common finding in haematological malignancies refractory to therapy⁸. T-PLL responds poorly to standard therapies and the frequent occurrence of ATM mutations and disruption of the p53 tumour suppressor pathway might partly explain this finding⁹.

Treatment with subcutaneous alemtuzumab was commenced with rapid dose escalation to 30mg 3 times per week. The treatment was well tolerated but had little impact on her skin and lymphocytosis. After 2 weeks she was changed to intravenous alemtuzumab 30mg 3 times per week. Her WBC normalised and her skin symptoms and facial oedema resolved by week 6 (Figure 4).

At week 10 bone marrow aspirate showed 0.1% T-PLL cells using CD3/CD57 double marking. The plan was to complete 12 weeks of alemtuzumab and to consolidate with an early autologous or allogeneic stem cell transplant. By the beginning of week 12, however, the patient developed new erythematous and raised skin lesions affecting mainly her abdomen and chest. Biopsy confirmed relapse of T-PLL. Repeat CT imaging showed resolution of all previous lymphadenopathy with a normal liver and spleen. Repeat bone marrow trephine was morphologically normal.

In view of the disease progression in the skin she proceeded to receive second line chemotherapy with a combination of gemcitabine, cisplatin and methylprednisolone (GEM-P). Following three cycles there was only partial resolution of her skin lesions. As her disease was still limited to the skin we elected to use total skin electron beam therapy (TSEB) in an attempt to achieve complete remission of her skin lesions without systemic toxicity. She received a total dose of 1500 cGy in five fractions and achieved a complete response in her skin lesions.

T-PLL historically carried a dismal prognosis with a median survival of 7.5 months¹⁻⁵. Response rates have improved significantly since the introduction of the monoclonal antibody alemtuzumab¹⁰⁻¹³. Alemtuzumab, a humanised anti-CD52 monoclonal antibody, triggers complement mediated lysis and antibody-dependent cytotoxicity of CD52 expressing cells. Both normal and malignant lymphocytes express CD52: expression is higher on T cells than B

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cells. This explains not only the clinical efficacy of alemtuzumab in T PLL but also its immunosuppressive effects through T lymphocyte depletion. Alemtuzumab treatment requires close monitoring of the patients for signs and symptoms suggestive of an opportunistic infection. Regular monitoring for cytomegalovirus (CMV) reactivation by polymerase chain reaction (PCR) viral load quantification in peripheral blood in CMV total antibody positive patients is currently recommended. Pre-emptive treatment with intravenous ganciclovir in patients with a rising CMV viral load is also advocated¹⁴⁻¹⁶.

Up to 60% of patients treated with alemtuzumab achieve a complete remission with a median survival in responding patients of 16 months. Some patients have achieved a durable CR of up to 45 months¹⁷. It is notable that although subcutaneous alemtuzumab was well tolerated in the case described it appeared relatively ineffective compared to the intravenous route of administration. Recent studies have shown that intravenous alemtuzumab is more effective than subcutaneous alemtuzumab when treating T-PLL patients¹⁸ therefore supporting this finding in our patient. It is therefore advisable that intravenous administration should be used in this group of patients.

The patient achieved a complete remission following alemtuzumab therapy but quickly relapsed within the skin. We elected to use TSEB therapy. In contrast to conventional radiotherapy, electron beam therapy delivers radiation predominantly to the skin via low-energy electrons generated from linear accelerators. Therefore visceral exposure is minimized. It has been used successfully in the treatment of various cutaneous T-cell lymphomas¹⁹

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3 although there is little published experience in treating T-PLL. The use of
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5 TSEB allowed us to proceed with the transplant procedure. Finally the pattern
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7 of expression of cell surface markers can be used to monitor minimal residual
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9 disease (MRD) in T-PLL. MRD monitoring, used to quantify CD3/CD57 co-
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11 expressing cells, confirmed the complete blood and bone marrow response.
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13 This justified the use of skin directed therapy, with GEMP and TSEB, prior to
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15 the transplant procedure.
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25 **Given the aggressive nature of this disease we felt that an allogeneic**
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27 **stem cell transplant was indicated. As she had no sibling match we**
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29 **elected to proceed with a T cell depleted reduced intensity volunteer**
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31 **unrelated donor allograft. Her donor was 10/10 HLA-matched at high**
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33 **resolution, young, male and CMV low risk. The conditioning regimen**
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35 **consisted of fludarabine 30mg/m² for 5 days, melphalan 140mg/m² as**
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37 **single dose and alemtuzumab 20mg daily for 4 days. Graft versus host**
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39 **disease (GVHD) prophylaxis was with ciclosporin (CSA) alone. The**
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41 **patient tolerated the procedure well and engrafted promptly. Post**
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43 **engraftment she developed grade 2 acute GVHD, presenting with fever**
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45 **and extensive skin involvement. Unfortunately, CSA induced**
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47 **microangiopathic haemolysis and thrombocytopenia necessitating**
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49 **discontinuation of calcineurin inhibition but her GVHD did respond**
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51 **promptly to methylprednisolone and mycophenolate mofetil (MMF).**
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53 **However, at day 60 she developed a post-transplant lymphoproliferative**
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55 **disorder with lymphadenopathy and rapidly rising EBV viral load. This**
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resolved with 2 doses of rituximab 375mg/m² and rapid cessation of her immunosuppression. She remained well, with grade 1 skin GVHD, controlled with topical steroids, until nine months post transplant when she developed progressive chronic GVHD of skin and GI tract. This required extensive ongoing treatment with photopheresis, budesonide, MMF and steroids. Throughout she maintained 100% donor chimerism in lymphoid and myeloid compartments. Repeat skin and GI biopsies, bone marrow examination and CT scanning confirmed ongoing remission of T-PLL. Sadly, she developed an invasive fungal infection and died at eleven months following her transplant.

Both autologous and allogeneic stem cell transplant have been employed as consolidation therapy in T-PLL. Although autologous transplant is simpler to deliver it is not curative, as all patients eventually relapse^{17, 22}. Prolonged survival has been described after allogeneic transplant but the transplant related mortality is high when using full myeloablative conditioning²⁰⁻²². There are currently little published data on the use of reduced intensity conditioned allogeneic transplant in T-PLL; although the limited information that is available supports a GvL effect²³. In the case described the procedure was effective in eradicating the disease but the patient eventually succumbed to treatment related complications. While reduced intensity transplants are associated with lower morbidity and mortality rates, compared to standard myeloablative transplants, thus allowing their use in older patients²⁴, GVHD is still a frequent complication: the risk being higher in older patients and in patients undergoing volunteer unrelated donor transplants, as in our case²⁴⁻²⁵.

In addition, in T-PLL, in common with similar lymphoproliferative disorders, successful disease control is often likely to be inextricably linked to chronic GVHD, particularly if the skin is involved in the initial disease process^{23,26}. Even with these caveats reduced intensity conditioned allogeneic transplantation remains an attractive option in the management of selected T-PLL patients. Further studies are needed to clarify which patients will benefit and to develop transplant strategies that more effectively and safely harness the potent GvL effect while minimising toxicity.

T-PLL is a rare disease. The outlook has improved significantly since the introduction of alemtuzumab but treatment outcomes are still poor in the majority of patients. A multidisciplinary approach using the experience of haematologists, radiotherapists and transplant physicians is essential if long term survival is sought.

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