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Case report

Prolonged remission of longstanding systemic lupus erythematosus after autologous bone marrow transplant for non-Hodgkin's lymphoma

JA Snowden, WN Patton, JL O'Donnell, EE Hannah and DNJ Hart

South Island Bone Marrow Transplant Unit, Christchurch Hospital, Christchurch, New Zealand

Summary:

We describe a patient with longstanding steroid-dependent systemic lupus erythematosus (SLE) in whom clinical and serological remission was achieved following high-dose therapy and autologous bone marrow rescue for high-grade non-Hodgkin's lymphoma. However, 3 years later, autoimmune disease re-presented in the form of immune thrombocytopenia (ITP), which had not previously been a feature of the SLE, necessitating reintroduction of steroid immunosuppression. Relapse of SLE is most likely, although *de novo* ITP post-BMT is also a possibility. The case suggests that severe longstanding autoimmune disease may be controlled by high-dose therapy and autologous stem cell reconstitution. However, further studies are required to determine the mechanism of re-emergence of autoimmunity and to evaluate optimal regimens and the potential value of such therapy in severe autoimmune diseases.
Keywords: systemic lupus erythematosus; autoimmune disease; autologous bone marrow transplantation

Remission from autoimmune disease can be achieved in animal models with myeloablative treatment and autologous, pseudoautologous or syngeneic bone marrow rescue.[1–3] Clinical observations suggest that autoimmune disease may response to intermediate doses of chemotherapy given either as specific treatment[4] or as treatment for co-existing malignancy.[5,6]

Resolution of autoimmune disease after allogeneic BMT is well reported[7,8] but it is unclear whether this effect is attributable to intensive immunosuppression or to the effects of allogeneic immune reconstitution. Data on patients with autoimmune disease following autologous transplantation is limited to one series.[9] In all of these patients there was early recurrence or persistence of autoimmune disease.

We present the case of a patient with longstanding systemic lupus erythematosus (SLE) who entered a prolonged clinical and serological remission following autologous bone marrow transplantation which permitted reduction and withdrawal of immunosuppressive medication until she developed immune thrombocytopenia 3 years post-BMT.

Correspondence: Prof DNJ Hart, Department of Haematology, PO Box 151, Christchurch Hospital, New Zealand
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Case report

The patient, a female Caucasian, presented in 1968 aged 28 with an inflammatory arthritis of the proximal interphalangeal joints and wrists, acrocyanosis, Raynaud's phenomenon, chest pains, fever, malaise and a facial rash which had been diagnosed as discoid lupus erythematosus by a dermatologist. Laboratory investigations showed an erythrocyte sedimentation rate (ESR) of 40 mm/h (Westergren), and LE cells were detected. A diagnosis of SLE[10] was made, prednisone therapy was commenced to good effect and she remained well on prednisone 10 mg daily.

In 1977, aged 40, she developed autoimmune haemolytic anaemia (AIHA) which responded to increased prednisone therapy. Thereafter, she resumed a maintenance dose of prednisone 10 mg daily and remained well. In 1990, reassessment revealed that she was well with normal clinical examination, full blood count, ESR, and renal function. However, her ANA titre was raised at 1/320 (speckled pattern) and her double-stranded DNA (dsDNA) antibody titre was marginally elevated at 9 IU/ml (NR 0–7 IU/ml). In view of her stable clinical condition an attempt was made to reduce gradually the dose of prednisone over the following months. However, between April 1991 and May 1992 she underwent a series of relapses which were treated with increased doses of prednisone. She was maintained on prednisone 10 mg daily between exacerbations.

In September 1992 the patient was referred to our Unit with right axillary lymphadenopathy, and histology of a lymph node biopsy showed high-grade lymphoblastic non-Hodgkin's lymphoma (B cell type). There were no 'B' symptoms. Computerised tomography body scan and lumbar puncture showed no evidence of disease elsewhere and a bone marrow aspirate and trephine biopsy were normal. Clinical staging was therefore IA. Other investigations showed haemoglobin 107 g/l, reticulocytes 368×10^9/l, blood film appearances of spherocytes and polychromasia, reduced haptoglobin, raised bilirubin at 29 mmol/l, raised

lactate dehydrogenase at 635 U/l (NR 30–460 U/l) consistent with ongoing AIHA. Total WBC, differential and platelet count were normal. Immunological studies revealed ANA antibody titre >1/1280 (speckled pattern), dsDNA 5 IU/ml, positive anti-ribonucleoprotein antibody (RNP), moderately raised anticardiolipin antibody (ACA) of 42 GPL (IgG phospholipid units, NR <10 GPL), with normal complement C3 levels but reduced C4 at <0.10 g/l (NR 0.13–0.42). Renal and liver function tests were normal.

She was treated with six cycles of the modified Magrath protocol (cyclophosphamide 1200 mg/m^2 day 1, doxorubicin 40 mg/m^2 day 1, vincristine 2 mg day 1, prednisone 40 mg/m^2 days 1–5, methotrexate 2760 mg/m^2 day 10, and a varying schedule of intrathecal cytosine arabinoside and methotrexate).

Significant complications included neutropenic sepsis responding to broad-spectrum antibiotics and mucositis. A bone marrow harvest was performed following recovery from the fifth cycle of chemotherapy which contained 1.1×10^8/l nucleated cells/kg and 1.2×10^4/kg CFU-GM. Controlled freezing was performed in dimethylsulphoxide and the cells were stored at −140°C.

In April 1993 the patient received consolidation using 'CBV'[11] (cyclophosphamide 1.8 g/m^2 days −6 to −3, BCNU 300 mg/m^2 day −6 and VP16 200 mg/m^2 days −6 to −4) followed by autologous bone marrow rescue. Early complications included neutropenic sepsis, which responded to broad-spectrum antibiotics, and delayed engraftment. By day +35 post-autologous marrow reinfusion neutrophils had risen to over 0.5×10^9/l but continued platelet transfusion was necessary until day +47 and occasional red cell transfusions until day +156. Further complications included: angular cheilitis which responded to anti-fungal therapy; culture positive oral herpes simplex which responded to acyclovir; and *Pneumocystis carinii* pneumonia at 5 months post-transplant which was successfully treated with intravenous pentamidine followed by chemoprophylaxis for a further year.

Three months post-autologous BMT, laboratory assessment showed a weak positive ANA titre of 1/80, dsDNA of 1 IU/ml, RNP negative by counter immunoelectrophoresis (CIE) and negative ACA and normal complement levels. At 1 year post-autologous BMT (April 1994) there was no clinical evidence of relapse of lymphoma or SLE. ANA, ds-DNA, RNP (by CIE) and ACA were negative and complement levels were normal. Prednisone was reduced 1 mg every 3 weeks and by November 1994 had been discontinued. The patient later reported vague symptoms of lethargy and some stiffness of the fingers without arthritis. Clinical examination was normal and disease markers were negative. The symptoms were attributed to steroid withdrawal. A trial of prednisone 10 mg daily relieved the symptoms and the dose was subsequently reduced more gradually without recurrence of similar symptoms.

By mid-1995, the patient was steroid independent and there was no subjective or objective evidence of recurrence of SLE or lymphoma. Laboratory investigations showed negative ANA, dsDNA, RNP (by CIE), ACA, direct Coombs' test, normal ESR and complement levels.

The patient remained well off steroids with no laboratory evidence of SLE until March 1996 when she developed isolated thrombocytopenia (platelet count 9×10^9/l). She had taken quinine for night cramps over the previous 3 months but tests for quinine-dependent antibodies were negative and she failed to respond after quinine withdrawal. There was no evidence of microangiopathic haemolytic anaemia, splenomegaly or lymphoma relapse. A bone marrow examination showed no infiltration with lymphoma and megakaryocytes were increased relative to the degree of thrombocytopenia implying peripheral platelet consumption and so a diagnosis of ITP was made.

She was treated with prednisone, initially 40 mg/day, and the platelet count gradually rose to 99×10^9/l, but following gradual steroid withdrawal (to 8 mg/day), it fell again to 29×10^9/l. Following three cycles of dexamethasone 40 mg/day for 4 sequential days, every 28 days, she continues on maintenance steroids. Her platelet count has now remained above 80×10^9/l for 3 months. At the time ITP developed immunological markers of SLE were negative, but subsequently in September 1996 (41 months post-ABMT) while on maintenance steroids the ANA became positive with an anti-centromere pattern. Other autoantibodies remain negative.

Immunological disease markers before, during and after chemotherapy and autologous bone marrow transplant are summarised in Table 1.

Discussion

Recent advances have significantly reduced the procedure-related mortality and morbidity of autologous blood and bone marrow stem cell transplantation[12] and it now seems reasonable to investigate its potential as intensified immunomodulation for severe autoimmune diseases. The above case suggests, in contrast to the report of Euler *et al*,[9] that significant remissions may be achieved with high-dose therapy and autologous rescue, although it is also important to address why the autoimmunity re-emerged.

The remission from SLE may have been achieved by several mechanisms. Firstly, the high-dose cytotoxic chemotherapy would have been markedly, if not totally myelo- and lympho-ablative. The preceding cyclic chemotherapy also provided significant immunosuppression, as reflected by the moderate improvement in the serological parameters. There may also have been a significant contribution from altered immune reconstitution that is known to occur following autologous transplantation.[13] Finally, the Magrath protocol chemotherapy given prior to the bone marrow harvest may have also been responsible for modulation of immune function and composition of the graft, a factor which may have influenced outcome. The mechanism of the autoimmune disease in our case deserved consideration. As immunological memory is considered to reside in T lymphocytes, recurrence of autoimmune disease could occur due to the persistence of T lymphocytes through high-dose therapy. This occurs as demonstrated by the mixed T lymphocyte chimerism found after allogeneic BMT in a significant proportion of patients.[14] The persistence of other cells important in SLE, such as monocytes and B lymphocytes,[15] may have been important. If persistence of autoreactive cells were to be the main factor in

Table 1 Immunological markers of disease activity before and after lymphoma therapy

Date in relation to ABMT	*ANA titre*	*dsDNA in IU/ml (NR 0–7 IU/ml)*	*ENA by CIE*	*RNP by haemagglutination*	*C4 in g/l (NR 0.13–0.42)*	*ACA in GPL (<10 negative)*
–24/12	>1/1280	6	Positive RNP	1/800–1600	<0.1	25
–7/12 Magrath protocol commenced	1/1280	5	Positive RNP		<0.1	42
Pre-CBV conditioning	1/320	1	Negative	1/200	<0.1	6
+5/12	1/80	0	Negative	1/50	0.31	6
+12/12	1/40	0	Negative		0.22	3
+31/12	Negative	0	Negative	1/50	0.24	5
+35/12		3	Negative	Negative	0.19	5
+39/12	Negative	0	Negative	Negative	0.16	3
+41/12	1/80 (anticentromere)	1	Negative	Negative	0.19	3
+44/12	1/80 (anticentromere)	1	Negative	Negative	0.21	2

relapse, then it is possible that longer remissions could be achieved with more effective ablative regimens. This might be achieved with different combinations of cytotoxic drugs, the use of cell-specific antibodies or repeated cycles of high-dose therapy and stem cell rescue. Alternatively, some form of maintenance immunomodulation may be necessary post-transplant. Alternatively, as suggested by animal data,[1] T cells contained within the bone marrow harvest may have been a source of relapse following reinfusion. The lower levels of T cells in a bone marrow harvest[16] may explain why the remission in this case was significantly longer than similar cases which received high-dose therapy followed by peripheral blood stem cell rescue.[9] Techniques are available for separating lymphocytes from haemopoietic progenitors and stem cells.[17] The degree of lymphocyte depletion achieved by various methods sufficient to prevent regrowth of putative autoreactive lymphocyte clones is not yet established, although experience from graft-versus-host disease suggests that harvests should be depleted to less than 10^5 T cells/kg.[18] However, the question of whether autologous graft manipulation can significantly prolong remission can only be answered in carefully constructed clinical trials.

Finally, the presentation of autoimmunity may have been a *de novo* event, perhaps due to a combination of an inherent susceptibility (MHC status or 'stem cell defect'[19]) and re-exposure to an environmental trigger. Such a mechanism of relapse would be difficult to prevent, especially if the environmental trigger were to be universal. The altered immune reconstitution, at the same time as possibly contributing to the lengthy remission from SLE, may explain why the autoimmune disease represented in a different way, ie with ITP and a positive ANA with a centromere pattern (in contrast to AIHA and ANA with a speckled pattern). Although it seems more likely that the re-presentation of this patient's autoimmunity is part of the 'kaleidoscope of autoimmunity' associated with SLE,[20] we cannot exclude late onset *de novo* ITP which has been previously described following autologous transplantation.[21] The recent establishment of an international registry of patients with autoimmune diseases undergoing high-dose therapy and autologous blood stem cell rescue should help to clarify whether this treatment modality offers promise for the future. Clinical trials should explore the safety and efficacy of different conditioning regimens and determine whether *ex vivo* graft manipulation, such as T cell depletion, can be justified by clinical endpoints.[22]

Note added in proof

On 18 April 1997, 4 years post-ABMT, lymphoma continues in remission with no clinical features of SLE. The platelet count has been $89–113 \times 10^9$/l since October 1996 following six courses of monthly dexamethasone which has now been discontinued. Maintenance prednisone has been reduced from 8 mg/day to 1 mg on alternate days over this period. The ANA is now 1/320 with other recent estimations of ACA and C4 being 2 and 0.18 g/l respectively. The DCT remains negative and haemoglobin, reticulocytes, WBC, LDH and bilirubin remain normal.

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