Extensive Chronic Graft-versus-host Disease of Skin Successfully Treated with Thalidomide

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Abstract
Thirty years female underwent allogenic peripheral blood stem cell transplantation for chronic myeloid leukaemia –chronic phase. She developed grade II acute skin graft-versus-host disease (GVHD) which was treated with cyclosporine and a short course of steroids. She developed extensive chronic GVHD of the skin and liver three hundred days post-transplant. She was managed with the standard immunosuppressants with partial response of liver dysfunction but no response of skin lesions. She showed a good response to therapy with resolution of skin lesions after treatment with thalidomide.

INTRODUCTION
Chronic Myeloid Leukaemia poses a major challenge to treating physicians even today. In the transplant era post transplant graft-versus-host disease (GVHD) is a constant worry for a successful outcome. Chronic GVHD occurs in 30-60% of marrow or blood derived haematopoietic stem cell allograft recipients surviving beyond day 100. It is a major cause of morbidity and mortality and is directly or indirectly responsible for death in over half of the patients who experience treatment related mortality. Patients with leukaemia who are alive and well 2 years after an allograft have a significantly higher risk of continued treatment related mortality, and poorer survival in the presence of chronic GVHD requiring immunosuppressants. This results from a number of factor as including infections and secondary malignancies. In our patient we describe the complication of chronic GVHD, which did not respond to the standard available immunosuppression but eventually responded to Thalidomide.

CASE REPORT
A 30 years female married with two children, resident of Amritsar; presented in Mar 2002, with abdominal swelling. Clinically she had massive splenomegaly and elevated blood counts (TLC > 100 000). Hematological workup confirmed a diagnosis of Chronic Myeloid Leukemia in chronic phase (CML-CP) with no other co-morbid conditions. Cytogenetic study revealed 100 % Philadelphia positivity in the metaphasis studied.

Allogeneic peripheral blood stem cell transplantation (PBSCT) (harvested in HAEMONETICS MCS 3p machine) was done on 27 May 2003 with a cell dose of 5 x 10^8 nucleated cells/kg; donor was HLA identical elder sister. She had an uneventful peri-transplantation period. She successfully engrafted on day 11 and was supported with RBC transfusion and single donor platelets for anaemia and thrombocytopenia respectively, which developed post conditioning. Conditioning was done with Busulphan (16 mg /kg body wt) and Cyclophosphomide (120 mg/kg). She received Cyclosporine A with Methotrexate as GVHD prophylaxis.

Post PBSCT patient had febrile neutropenia, which was managed with broad-spectrum antimicrobials (Teicoplanin, cefiprome, liposomal amphotericin). She also developed grade II acute skin GVHD (biopsy confirmed), which was treated with cyclosporine and a short course of steroids.

She was thereafter put on prophylactic therapy with septran (for *Pneumocystis carinii* pneumonia), penicillin (for Gram-positive bacterial organisms) and acyclovir (for herpes). She was discharged in a clinically stable condition with no evidence of any GVHD or sepsis.

She was stable until January 2004 when she developed cholestatic jaundice 230 days after PBSCT. This was associated with history of weight loss of 10 kgs over 6-8 weeks, multiple oral ulcers and herpes zoster lesions over lower abdomen, which was successfully managed with IV Acyclovir. She also developed wide spread violaceous to hyperpigmented maculopapular xerotic skin lesions bilaterally symmetrical involving face, trunk and extremities on a background of yellowish skin discolouration.

Palms and soles examination revealed similar
dry, lusterless with vertical thinning and reduced density. There was no evidence of any sclerodermatous changes. Mucosal biopsy taken from the oral cavity showed extensive infiltration by plasma cells and findings. Oral mucosa showed erosions with patchy hyperpigmentation over buccal mucosa and tongue. Conjunctival mucosa was dry. Nail plate dystrophy with acronydia of great toenails was found. Scalp hair was

Fig. 1: Icterus

Fig. 2: Mucosal Ulcer

Fig. 3: Wide spread violaceous to hyperpigmented maculopapular xerotic skin lesions bilaterally symmetrical involving trunk and extremities on a background of yellowish skin discolouration.

Fig. 4: Oral Mucosal Biopsy: Higher power view showing eosinophils and lymphocytes infiltrating the blood vessels (H&E x 400)

Fig. 5: Skin Biopsy: Ulcerated epithelium with dense mixed inflammatory cell infiltrate (H&E x 100)

Fig. 6: Oral Mucosal Biopsy: Subepithelial fibrosis with scattered inflammatory cells (H&E x 100)
lymphocytes. Skin and mucosal biopsy both were suggestive of chronic GVHD.

Serial complete blood counts, coagulation profile was normal. Work up for collagen diseases and direct Coomb’s test were negative. Viral markers for hepatitis were negative (HBsAg, Anti HCV, HBV DNA, HCV RNA, IgM Anti HEV, IgM Anti HAV).

Ultrasound abdomen revealed mild hepatosplenomegaly. Serial LFT showed total bilirubin between 15.6 to 35 mg% with direct component between 06 to 15mg%. Serum transaminases were also raised with ALT between 200-490 U/L, AST between 55-310 U/L.

Serial Alkaline Phosphatase reached a maximum of 1005 U/L. There was no evidence of hemolysis or Septicemia. Her liver biopsy was done which revealed features suggestive of chronic GVHD.

She was treated with methylprednisolone (1Gm IV OD x3 days.) followed by oral Prednisolone (40 mg PO/ D for 10 days and tapered thereafter since there was no improvement. It was replaced with mycophenolate (500 mg twice daily) for 4 weeks but without any response. Cyclosporine (2.5mg/kg/d) was then added, following which there was partial improvement of her liver functions with alkaline phosphatase coming down to 325 U/L, however there were no improvement of the skin lesions. Mycophenolate was then stopped and Thalidomide (100mg PO) was started 300 days post transplant. Patient showed marked improvement over a period of 8 wks with resolution of the xerotic skin lesions and the maculopapular lesions involving the face, trunk and extremities. Oral mucosal lesions also improved. The patient was maintained on Thalidomide and Cyclosporine.

**DISCUSSION**

Randomised and non-randomized trials have shown a significantly shorter period of aplasia using PBSCT compared to bone marrow (BM) in allogenic stem cell transplantation, and PBSCT allografts reduce the requirements for platelets and antibiotics. There are conflicting reports whether PBSCT allografts are more likely to reduce or increase transplant related mortality (TRM), however a few prospective trials have indicated that there is a significantly higher incidence of extensive chronic GVHD among recipients of PBSCT as compared to BM. On the other hand PBSCT seems to result in a stronger GVL effect with a subsequent reduced relapse rate but without a significant impact on the leukaemia free survival and the over-all survival (OS).3

The treatment of chronic GVHD is difficult. Cyclosporine, prednisolone and azathioprine have been the main agents used with variable success rates. Alternative drugs have been found to be useful in certain situations.

Thalidomide was developed as a sedative-hypnotic drug but the development of severe foetal malformation led to withdrawal of its use from clinical practice. Its diverse effects on the immune system and the cytokine cascade resulted in continuous exploration of the drug in various disorders.4 Initial data revealed it to be effective in acute GVHD, and subsequent human data showed it to be effective in acute as well as chronic GVHD.5 Studies have shown that it controlled chronic GVHD in a proportion of patients with haematological malignancies without increasing relapse, perhaps in some way secondary to its antimalignancy activity along with its anti-inflammatory and immunomodulatory property.3 This is potentiated when used in combination with cyclosporine and prednisolone. The efficacy and potential of thalidomide as a single agent in the treatment of GVHD is undefined. Drug intolerance is an important factor resulting in early discontinuation of therapy; its analogues such as CC5013 may improve response rates through better tolerance.6

In our patient introduction of thalidomide caused a dramatic improvement in the skin lesions.

**REFERENCES**


