Title	The pathology of bone marrow transplantation in Hong Kong Chinese
Author(s)	Shek, TWH; Ng, IOL; Chiu, EKW; Chan, KW
Citation	Hong Kong Medical Journal, 1996, v. 2 n. 2, p. 133-137
Issued Date	1996
URL	http://hdl.handle.net/10722/53404
Rights	Hong Kong Medical Journal. Copyright © Hong Kong Medical Association.

The pathology of bone marrow transplantation in Hong Kong Chinese

TWH Shek, IOL Ng, EKW Chiu, KW Chan

The pathological lesions found in 68 successfully engrafted patients with human leucocyte antigen-matched sibling-related bone marrow transplants were reviewed retrospectively. Twenty-six (38%) patients had acute graft-versus-host disease, which was slightly less than that reported in Caucasians. Skin was a constant site of involvement (100%), followed by the gastrointestinal tract (74%) and liver (59%). There was a 74% correlation between the clinical and histological grading of cutaneous graft-versus-host disease, while that of the gastrointestinal tract was lower at 60%. Cytomegalovirus colitis was found on histological examination of two patients clinically thought to have graft-versus-host disease. Histological evidence of infection, which included viral hepatitis (n = 5), disseminated cytomegalovirus infection (n = 3), disseminated aspergillosis (n = 2), systemic candidiasis (n = 2), *Pneumocystis carinii* pneumonia (n = 1), and bacterial pneumonia (n = 1), was present in 14 patients. In addition to graft-versus-host disease and infections, there was a case of veno-occlusive disease of the liver. Histological examination is important in distinguishing graft-versus-host disease from infection and other complications in bone marrow transplantation.

HKMJ 1996;2: 133-137

Key words: Bone marrow transplantation; Pathology; Graft vs host disease; Opportunistic infections; Immunosuppression

Introduction

Queen Mary Hospital (QMH) is a major referral centre for the treatment of haematological and lymphoid diseases in Hong Kong. Bone marrow transplantation (BMT) began at QMH in May 1990. Acute graft-versus-host disease (GVHD) is one of the commonest complications of BMT and usually commences within two to 10 weeks of transplantation.[1] Other side effects of BMT are also very common and frequently alter the clinical course and management of these patients. In this study, we examined the pathology of surgical and postmortem specimens from Chinese patients after BMT, with emphasis on the clinicopathological correlation between the grading of acute GVHD.

The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong:
Department of Pathology
TWH Shek, MB, BS, FRCPA
IOL Ng, MD, MRCPath
KW Chan, MB, BS, MRCPath
Department of Medicine
EKW Chiu, MB, BS, MRCP
Correspondence to: Dr TWH Shek

Materials and methods

From 1 May 1990 to 30 September 1992, 79 human leucocyte antigen (HLA)-matched sibling–related bone marrow transplantations (BMTs) were performed at QMH. All patients were HLA-A, -B and -DR identical to their respective donor sibling. Sixty-eight of 79 patients survived beyond 21 days and were successfully engrafted. Sixty patients had haematological or lymphoid malignancies, four had thalassaemia major, three had severe aplastic anaemia, and one had severe combined immunodeficiency disease. Their ages ranged from 10 months to 44 years (mean, 27 years). Six patients were children, four of whom had thalassaemia major (ages, 4, 5, 6, and 11 years), one had severe aplastic anaemia (age, 7 years) and one had severe combined immunodeficiency disease (age, 10 months).

A combination of methotrexate (MTX) and cyclosporin (CSP) was used for GVHD prophylaxis. The dosage of MTX was 15 mg/m^2 on day 1 and 10 mg/m^2 on days 3, 6, and 11. The dosage of CSP was 1.5 mg/kg and was given intravenously every 12 hours from day 1 to day 50. After this, CSP was given orally

and the dosage was reduced by 5% every week until day 180, when CSP was discontinued. Whole blood CSP trough levels were measured weekly and the dose adjusted to maintain a level between 100 and 300 ng/mL. In patients with clinical evidence of GVHD, histological confirmation was made in at least one target organ. Once confirmed, specific treatment for GVHD was initiated.

The slides of non-bone marrow biopsies and autopsy specimens of all patients (when available) were reviewed. Autopsy was performed on six patients. Haematoxylin and eosin stain was performed in every case, and Masson trichrome, Gram, Ziehl-Neelsen and Grocott stains were done if necessary. Immunohistochemical staining using monoclonal antibodies against hepatitis B surface antigen (HB_S) (Dako, Copenhagen, Denmark), cytomegalovirus (CMV) antigen (Dako, Copenhagen, Denmark), and early CMV antigen (Chemicon, Temecula, California, US) was done by standard avidin-biotin technique.

Histological grading was based on the classification of Lerner et al.[2] In essence, for cutaneous GVHD, grade 1 disease is characterised by vacuolar degeneration of the basal epidermis; grade 2 by apoptosis of basal epithelial cells; grade 3 by severe basal cell degeneration with bulla formation; and grade 4 by denudation of the epidermis. For intestinal GVHD, grade 1 shows apoptosis of crypt cells; grade 2 shows partial destruction of crypt(s); grade 3 has total destruction of crypt(s); and grade 4, denudation of the epithelium. If a patient had more than one specimen from the same organ, the grading was based on the highest grade.

Clinical data were retrieved from the BMT database file to assess the degree of correlation between the clinical and pathological gradings of GVHD in the skin, intestinal tract, and liver. Clinical grading was made according to that proposed by Thomas et al.[1] In essence, grade 1 cutaneous GVHD is defined as the presence of a rash involving less than 25% of the total body surface area; grade 2 as 25% to 50%; grade 3 as more than 50%; and grade 4 as desquamation. For intestinal GVHD, grade 1 is defined as diarrhoea amounting to 500 to 1000 mL per day; grade 2 as 1000 to 1500 mL; grade 3 as more than 1500 mL; and grade 4 as diarrhoea with pain and ileus.

Results

Graft-versus-host disease

Clinical evidence of acute GVHD was found in 27 (40%) of 68 successfully engrafted patients, of whom 26 (38%) had histological evidence of the disease. The exception had cutaneous GVHD clinically, but three skin biopsies were negative. The patient's skin rash eventually subsided without specific treatment. Of the 27 patients with clinical evidence of acute GVHD involving the skin, 20 (74%) had clinical features suggestive of GVHD affecting the gastrointestinal tract and 16 (59%) involving the liver. Fifteen showed clinical features of GVHD involving the skin, gastrointestinal tract, and liver, simultaneously. All patients suspected clinically of having cutaneous GVHD had skin biopsy, and in 26 the clinical diagnosis was confirmed histologically.

Ten of the 20 patients with intestinal GVHD had rectal biopsies taken and histological GVHD was confirmed in eight. Eight of the 16 patients suspected clinically of having hepatic GVHD had liver biopsies and four showed histological evidence of GVHD. None of the patients showed histological evidence of GVHD in the gut or liver without having histological evidence of skin involvement.

Correlation between clinical and histological gradings

Of the patients with clinical or histological evidence of cutaneous GVHD, the clinical and histological gradings were identical in 20 (74%). In the remainder, the histological grading was one grade higher than the clinical one in four patients, and one grade lower in three (Table 1). As for intestinal GVHD, in the 20 patients suspected clinically of having this, rectal biopsies were performed in 10. The clinical and histological gradings were identical in six (60%). In two of the remaining four patients, the histological grading was lower than the clinical one by two grades in one, and by one grade in another (Table 2). In the remaining two patients, CMV infection was the cause of the diarrhoea, not GVHD.

Infections

Infections were diagnosed in 14 patients. Five patients had viral hepatitis; three had disseminated CMV infection involving the lungs, adrenals, intestines, and kidney (all were found at autopsy); two had disseminated, invasive aspergillosis involving the lungs, stomach, small intestine, and brain (both were found at autopsy); two had systemic candidiasis involving the lungs and ileum (one found at autopsy); one had Pneu*mocystis carinii* pneumonia; and another had bacterial pneumonia. All five patients with histological evidence of hepatitis were chronic HB_S carriers. Clinical, serological, and his-

Table 1. Clinical and histological gradings in cutaneous graft-versus-host disease

Clinical grading	Histological grading						Total
	ND*	0	1	2	3	4	
0	41	0	0	0	0	0	41
1	0	1	14	3	0	0	18
2	0	0	0	4	0	0	4
3	0	0	0	2	1	0	3
4	0	0	0	0	1	1	2
Total	41	1	14	9	2	1	68

*ND not done

Table 2. Clinical and histological gradings in intestinal graft-versus-host disease

Clinical grading	Histological grading						Total
	ND*	0	1	2	3	4	
0	48	0	0	0	0	0	48
1	2	0	2	0	0	0	4
2	4	2	1	2	0	0	9
3	2	0	0	0	1	0	3
4	2	0	0	1	0	1	4
Total	58	2	3	3	1	1	68

*ND not done

tological investigations did not indicate any other specific causes for the hepatitic picture, and the diseases were interpreted as likely to be reactivation of the hepatitis B virus.

Two patients had CMV infection of the large intestine, although clinically, they were thought to have GVHD of the gut. For both patients with disseminated aspergillosis, the diagnosis was made only at autopsy. The two patients with candidiasis were diagnosed by oesophageal biopsy. In the patient with *Pneumocystis carinii* pneumonia, the diagnosis was made by bronchial alveolar lavage. Skin biopsy did not result in the diagnosis of untreated systemic or localised infection.

Other diseases

Besides GVHD and infections, one patient developed veno-occlusive disease of the liver. Another patient had a recurrence of a previously treated gastrointestinal lymphoma, but none of the 68 patients developed secondary malignancy.

Discussion

The incidence of GVHD after BMT has been reported to be approximately 50% in Caucasian patients[3,4] and is distinctly lower in oriental populations.[5-7] A study from Taiwan reports a low incidence (9.1%) of moderate to severe GVHD in HLA-matched BMT patients.[5] Two studies from Japan also report a low incidence of GVHD in HLA-matched BMT patients (21% for grade II to IV GVHD; 28% for chronic GVHD).[6,7] Our results show incidences of 40% and 38% for clinical and histological GVHD, respectively, slightly lower than that in Caucasians.

The lower incidence of GVHD in oriental patients is intriguing. Graft-versus-host disease after BMT between siblings matched for the major histocompatibility complex develops presumably as a result of differences in the minor histocompatibility antigens between the donor and recipient.[8] It is known, however, that Chinese (at least, Hong Kong Chinese) have less HLA-polymorphism than Caucasians.[9] This may contribute

to the lower incidence of GVHD in Chinese. On the other hand, variations in the incidence of GVHD may be due to differences in the criteria used in the clinical and histological documentation of GVHD. This is particularly so because diagnostic histological changes may not be present in the early stages of the disease, and the changes of GVHD are similar to those produced by cytotoxic drugs and irradiation.

Involvement of the skin was present in all patients with GVHD in the present study. The easy accessibility of skin for clinical examination and the relatively less traumatic biopsy procedure undoubtedly contribute to its high rate of detection. Moreover, it showed a very high rate (96%) of clinicopathological correlation, as far as the diagnosis was concerned. Nevertheless, the clinical and pathological gradings differed in seven (26%) patients. It is, however, important to note that the histological features of mild cutaneous GVHD are not pathognomonic and similar changes may be observed in reaction to a variety of drugs, including cytotoxic agents,[10] radiation,[11] and in some patients with disseminated malignancy.[12]

Graft-versus-host disease may affect any part of the gastrointestinal tract but the rectum is most extensively studied because of its relative accessibility. As with the skin, the basic abnormality in acute rectal GVHD is selective epithelial damage.[13] Our results show an 80% correlation between the clinical and histological diagnosis of intestinal GVHD. It is important to note that two patients had CMV infection that was initially misdiagnosed as intestinal GVHD, on clinical grounds alone. This was a serious mistake because the treatments for the two are completely different and incorrect treatment is potentially fatal.

Infections, especially CMV infection, have to be vigorously excluded in any BMT patients with diarrhoea, and histological examination of the colorectal mucosa should be performed to ascertain the underlying cause. Furthermore, histological examination is important in assessing the response to treatment in patients with GVHD. It has not, however, been proven that examination of these biopsies would add any predictive value in the response of these patients to treatment for GVHD.[14] In addition, post-BMT reactivation of CMV has previously been identified as one of the significant risk factors for the development of acute GVHD in Chinese patients, although it is not certain whether CMV activates GVHD or vice versa.[15,16]

Graft-versus-host disease of the liver usually presents as non-specific liver function abnormality. The microscopic changes are also non-specific and include lymphocytic infiltration of the portal tracts, bile duct epithelial atypia, eosinophilic degeneration, and patchy centrilobular necrosis.[17] However, it is noteworthy that other pathological conditions, such as viral hepatitis C and CMV infection, may show similar histopathological changes. In the liver, reactivation of viral hepatitis is a known risk in hepatitis B virus carriers and patients who develop hepatitis after transplantation have a worse prognosis.[18]

Infection is a significant cause of morbidity and mortality after BMT.[19] Our data only includes those patients with tissue diagnosis of the infection, but there should have been more patients with infections diagnosed on microbiological grounds. Disseminated CMV infection, disseminated candidiasis, *Pneumocystis carinii* pneumonia, and invasive aspergillosis were evident in our patients. Most of these infections, with the notable exception of invasive aspergillosis, can be diagnosed antemortem. At present, antemortem diagnosis of invasive aspergillosis appears difficult and autopsy still plays an important role in its diagnosis.[20]

References

1. Thomas ED, Storb R, Clift RA, et al. Bone marrow transplantation. N Engl J Med 1975;292:832-43, 895-902.
2. Lerner KG, Kao GF, Storb R, Buckner CD, Clift RA, Thomas ED. Histopathology of Graft-vs.-Host Reaction (GvHR) in human recipients of marrow from HLA-matched sibling donors.Transplant Proc 1974;4(4):367-71.
3. Sloane JP. Graft-versus-host disease: a histological perspective. Blood Rev 1990;4:196-203.
4. Sloane JP, Norton J. The pathology of bone marrow transplantation. Histopathology 1993;22:201-9.
5. Chen PM, Fan S, Liu CJ, et al. Complications of bone marrow transplantation in Chinese. Hematol Bluttransfus 1990;33:712-4.
6. Morishima Y, Morishita Y, Tanimoto M, et al. Low incidence of acute graft-versus-host disease by the administration of methotrexate and cyclosporin in Japanese leukemia patients after bone marrow transplantation from human leukocyte antigen compatible siblings: possible role of genetic homogeneity. Blood 1989;74:2252-6.
7. Fuji H, Hiketa T, Matsumoto Y, et al. Clinical characteristics of chronic cutaneous graft versus host disease in Japanese leukemia patients after bone marrow transplantation: low incidence of mild manifestation of skin lesions. Bone Marrow Transplant 1992;10(4):331-5.
8. Santos GW, Hess AD, Vogelsang GB. Graft-versus-host reactions and disease. Immunol Rev 1985;88:169-92.
9. Hawkins BR, Serjeantson SW, Higgins DA. Distribution and co-occurrence of MHC class I, II, and III markers in southern Chinese: implications for autoimmune disease. Dis Markers 1988;6:237-45.

10. Sale GE, Lerner KG, Barker EA, Shulman HM, Thomas ED. The skin biopsy in the diagnosis of acute graft-versus-host disease in man. Am J Pathol 1977;89:621-36.
11. LeBoit PE. Subacute radiation dermatitis: a histologic imitator of acute cutaneous graft-versus-host disease. J Am Acad Dermatol 1989;20:236-41.
12. Holmes RC, Cooper CB, Black MM, Jurecka W, McGibbon DH. Syndrome resembling graft-versus-host disease in a patient with disseminated carcinoma. J R Soc Med 1983;76:703-5.
13. Sale GE, Shulman HM. The pathology of bone marrow transplantation. New York: Masson, 1984.
14. Sviland L, Pearson AD, Green MA, et al. Prognostic importance of histological and immunopathological assessment of skin and rectal biopsies in patients with GVHD. Bone Marrow Transplant 1993;11:215-8.
15. Chiu EW, Liang R, Lie A, Chan TK. Bone marrow transplantation in Hong Kong: the Queen Mary Hospital experience. J Hong Kong Med Assoc 1993;45:96-104.
16. Chiu EW, Yuen P, Chan TK. Bone marrow transplantation in Hong Kong. Bone Marrow Transplant 1994;13:713-5.
17. Sloane JP, Farthing MJ, Powles RL. Histopathological changes in the liver after allogenic bone marrow transplantation. J Clin Pathol 1980;33:344-50.
18. Chen PM, Fan S, Hsieh RK, et al. Liver disease in patients with liver dysfunction prior to bone marrow transplantation. Bone Marrow Transplant 1992;9:415-9.
19. Meyers JD. Infection in bone marrow transplant recipients. Am J Med 1986;81(1A Suppl):27S-38S.
20. Shek WH, Chan KL, Luk IS. Experience of invasive aspergillosis in Hong Kong. J Clin Pathol 1992;45:183.