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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.

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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. 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.

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/m² on day 1 and 10 mg/m² 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, histol-
ogical 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 au-
topsy 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. Immunohis-
tochemical staining using monoclonal antibodies
against hepatitis B surface antigen (HBs) (Dako, Co-
penhagen, Denmark), cytomegalovirus (CMV) anti-
gen (Dako, Copenhagen, Denmark), and early CMV
antigen (Chemicon, Temecula, California, US) was
done by standard avidin-biotin technique.

Histological grading was based on the classifica-
tion of Lerner et al.\(^2\) In essence, for cutaneous GVHD,
grade 1 disease is characterised by vacuolar degenera-
tion of the basal epidermis; grade 2 by apoptosis of
basal epithelial cells; grade 3 by severe basal cell de-
generation with bulla formation; and grade 4 by denu-
dation 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 data-
base 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 in-
testinal GVHD, grade 1 is defined as diarrhoea amount-
ing 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 clini-
cally, but three skin biopsies were negative. The
patient's skin rash eventually subsided without spe-
cific treatment. Of the 27 patients with clinical evi-
dence of acute GVHD involving the skin, 20 (74%)
had clinical features suggestive of GVHD affect-
ing 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 clini-
cally 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 con-
firmed in eight. Eight of the 16 patients suspected clini-
cally 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 remain-
der, 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 in-
festation was the cause of the diarrhoea, not GVHD.

Infections
Infections were diagnosed in 14 patients. Five pa-
tients had viral hepatitis; three had disseminated
CMV infection involving the lungs, adrenals, in-
testines, 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 candid-
iasis involving the lungs and ileum (one found at
autopsy); one had Pneumocystis carinii pneumonia;
and another had bacterial pneumonia. All five pa-
tients with histological evidence of hepatitis were
chronic HBs carriers. Clinical, serological, and his-
Table 1. Clinical and histological gradings in cutaneous graft-versus-host disease

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<td>Total</td>
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*ND = Not done

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

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<tr>
<td>Total</td>
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*ND = Not done

tological investigations did not indicate any other specific causes for the hepatic 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 and is distinctly lower in oriental populations. A study from Taiwan reports a low incidence (9.1%) of moderate to severe GVHD in HLA-matched BMT patients. 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). 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. It is known, however, that Chinese (at least, Hong Kong Chinese) have less HLA-polymorphism than Caucasians. 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 contributed 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, radiation, and in some patients with disseminated malignancy.

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. 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 diarrhea, 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. 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.

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. 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.

Infection is a significant cause of morbidity and mortality after BMT. 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.

References