UK. However, in the Black group anencephaly is 50% more common than spina bifida. It is possible to speculate that this might be a result of local factors, as it is contrary to findings reported from Natal.[3]

Recent data from Liverpool[2] indicate an appreciable decline in the incidence of NTDs over the last few years for which no single reason can be identified. Our figures for 1979 and 1980 were slightly lower than those for the preceding years, although not to a statistically significant extent; this may be due to the cyclical peaks and troughs previously recorded in association with NTDs.[4,5]

We intend to continue monitoring the incidence of NTDs in the Cape Town area so that a sound statistical basis can be established for decisions regarding the prevention and long-term management thereof.

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Jaundice following bone marrow transplantation

The problem of diagnosis

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Summary

Jaundice presented a major diagnostic and therapeutic problem in 6 out of 20 patients undergoing allogeneic bone marrow transplantation for severe acute aplastic anaemia or leukaemia in relapse. In the first 2 cases histological features of graft-versus-host disease were demonstrable in the skin but absent in the liver. In the 3rd case B-virus hepatitis was the most likely diagnosis, in the 4th cumulative cytotoxic chemotherapy was incriminated, and in the last 2 cases the jaundice was obstructive. These 6 cases illustrate the varied causation of jaundice in patients undergoing bone marrow transplantation, and emphasize that correct diagnosis is essential for rational management.

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Bone marrow transplantation is established as the preferred form of treatment for patients with severe acute aplastic anaemia and immunodeficiency disease whenever an HLA-identical and MLC-non-reactive donor is available. The role of this procedure in patients with acute leukaemia is less clearly defined, but it offers a definite therapeutic option even in patients who have relapsed and who have therefore usually received large doses of cytotoxic drugs, many of which are hepatotoxic. Despite careful matching between donor and recipient graft rejection may occur and patients therefore receive immunosuppressive therapy, which is associated with an increased risk of opportunistic infection, septicaemia and subsequent liver dysfunction. Jaundice may also be associated with the administration of antibiotics or follow the infusion of blood or blood products transmitting viral hepatitis.

Graft-versus-host disease (GVHD) is a unique process which occurs after a successful transplant in patients in whom donor lymphocytes mount an inflammatory reaction, predominantly against the skin, gastro-intestinal tract and liver of the recipient. Apart from the morbidity and mortality associated with this syndrome, it is a classic cause of hepatitis.

The management of jaundice depends upon its cause, and some of the diagnostic difficulties in the patient who has recently received a transplant are illustrated by our experience with 6 patients.

Transplantation procedure

The recipient is conditioned with high-dose cyclophosphamide for aplastic anaemia and with additional radiotherapy for relapsed leukaemia, using the protocol described by Thomas and

Storb of Seattle.[1] The patient is nursed in reverse isolation and receives such allogeneic white cell and platelet support, collected from the donor by continuous-flow centrifugation,[2] as is appropriate.

Marrow-rich blood is collected under general anaesthesia from the compatible donor, using multiple small-volume aspirations, infusing between 1,5 and 4,0 x 10^8 nucleated cells per kilogram, and adequacy of the graft is monitored by *in vitro* bone marrow culture.[3] Donors usually leave hospital on the same day.

Both donor and recipient are screened for hepatitis antigen and cytomegalovirus infection, and have a biochemical profile established on their first clinic visit. Methotrexate is administered after transplantation to try and reduce the incidence of GVHD. Hyperalimentation is given using a central venous cannula,[4] and supplementary trace elements, electrolytes and vitamins are provided until adequate absorption is re-established after transplantation.

Case reports

Case 1

A 24-year-old White man presented with a 3-month history of malaise, tiredness, and increasing shortness of breath on exertion. He had previously been well and had no past history of jaundice or any liver disease. On examination he was found to have a temperature of 37,8°C and multiple pustules over his back. There was no jaundice, and apart from pallor the remainder of the examination was negative.

Investigations revealed a haemoglobin concentration of 6,2 g/dl, a reticulocyte index of 0,9%, and a white cell count of 5,5 x 10^9/l with 61% neutrophils, 3% eosinophils and 36% lymphocytes. The platelet count was 34 x 10^9/l. Bone marrow aspiration and trephine biopsy findings fulfilled the morphological requirements for the diagnosis of aplasia.[5] Plasma protein, bilirubin and alkaline phosphatase values and liver enzyme levels were normal.

On 14 February 1978 the patient received a transplant of bone marrow from his HLA-identical, MLC-non-reactive brother. The initial postoperative course was uneventful except for streptococcal pharyngotonsillitis which responded promptly to antibiotics.

He made satisfactory progress with evidence of successful marrow engraftment, but 6 weeks after discharge the serum glutamic oxalo-acetic transaminase (SGOT) value was 231 IU/l (normal 10 - 50 IU/l), and 3 weeks later was higher than 300 IU/l. The aspartate transaminase level was 205 IU/l (normal 0 - 12 IU/l), and the total bilirubin level rose to 146 μmol/l (normal 9 - 17 μmol/l), of which 125 μmol/l was conjugated. The alkaline phosphatase level was 218 IU/l (normal 30 - 85 IU/l). The last dose of methotrexate had been given 10 days previously.

The patient complained of nausea and watery diarrhoea. On examination he was icteric but apyrexial. There were no stigmata of chronic liver disease and no hepatomegaly or splenomegaly. The haemoglobin concentration was 13,6 g/dl, the white cell count 4,7 x 10^9/l with 33% neutrophils, 14% lymphocytes, 34% eosinophils, 18% monocytes and 1% basophils, and the platelet count 245 x 10^9/l. Serum urea, creatinine and electrolyte levels were normal. The total protein level was 72 g/l, the albumin level 43 g/l, and the prothrombin index 93%. Radio-immunoassay for hepatitis B surface antigen was negative, as was the Paul-Bunnell test. There was no rise in cytomegalovirus titre.

A liver biopsy performed at this time revealed that the portal tracts contained inflammatory cell infiltrates, with eosinophils being fairly conspicuous. Several Councilman bodies were present and there were a few aggregates of Kupffer cells, indicating death of several hepatocytes together. Ballooning degeneration was not a feature. There was some evidence of regeneration. The architecture was preserved, and the limiting plates were intact. No cholestasis was evident. These features were thought to indicate drug-induced hepatitis, but GVHD and viral hepatitis could not be excluded.

The bilirubin and liver enzyme values slowly returned to normal, and during the 11 months following transplantation the alkaline phosphatase level rose to 940 IU/l.

The patient is now well, with a dry, rough, scaly rash on his neck and back. Biopsy revealed chronic GVHD (grade I) with hyperkeratosis, follicular plugging, atrophy of the epithelial layer, and vacuolar changes in the basal layer.

Comments. Despite full investigation, including liver biopsy, the pathogenesis of the hepatic disease remained uncertain. Drug-induced hepatitis, A-virus or non-A, non-B hepatitis and GVHD could all have accounted for the clinical and histological features. The patient had histological evidence of chronic GVHD in the skin, and the elevated alkaline phosphatase level is compatible with this diagnosis. Liver biopsy has not yet been repeated.

Case 2

A 16-year-old White youth was referred with a diagnosis of Fanconi's anaemia. In 1971 he had been treated with oxymetholone 50 mg/d, which was later decreased to 25 mg/d and subsequently increased to 100 mg/d towards the end of 1974. Prednisone 30 mg on alternate days was also added at this stage. In August 1978 he had been admitted with fever and jaundice, thought to be due to non-A, non-B hepatitis. Oxymetholone was also considered to be a possible cause of the hepatitis and was discontinued. Bone marrow transplantation was performed on 9 December 1978 with subsequent successful engraftment.

He was pyrexial for at least a week before the transplant, with spiking temperatures up to 39,5°C. Blood, urine, and stool cultures were repeatedly negative, although a throat swab revealed ß-haemolytic streptococci. Intravenous antibiotics used included co-trimoxazole, penicillin, metronidazole and tobramycin. Fever persisted, and on the 9th day after transplantation an extensive erythematous rash appeared which rapidly became bullous, resulting in desquamation, especially of the face, axillae, groin and buttocks. The rash was typical of acute GVHD and skin biopsy revealed the major changes to be in the epidermis, where there was spongiosis and early bullous formation with dyskeratotic cells (Civatte bodies). Although there were no lymphocytes in the dermis, the features were considered diagnostic of GVHD.

At the same time gastro-intestinal symptoms developed, including anorexia, nausea, and profuse diarrhoea of up to 6 litres a day. Hepatic involvement was evidenced by rapidly progressive jaundice and tender hepatomegaly.

Investigations revealed a haemoglobin concentration of 8,7 g/dl, a white cell count of 0,7 x 10^9/l, with only a few lymphocytes and monocytes present on the peripheral smear, and a platelet count of 14 x 10^9/l. Serum urea, creatinine and electrolyte levels were normal. Other values were as follows: serum total protein 52 g/l, albumin 31 g/l, total bilirubin 57 μmol/l, of which 47 μmol/l was conjugated, alkaline phosphatase 51 IU/l and SGOT 89 IU/l. The total bilirubin rose progressively to 508 μmol/l, of which 325 μmol/l was conjugated. The alkaline phosphatase level rose to 223 IU/l and the SGOT level to 163 IU/l, while the serum protein level fell to 34 g/l and the albumin level to 22 g/l. Cultures of the stool, urine and a throat swab were all negative.

Treatment of the GVHD included a single dose of vincristine 1,5 mg intravenously and intravenous methylprednisolone 100 mg/d. The patient received white cell support daily and blood transfusions for anaemia. Because of persisting pyrexia large doses of intravenous penicillin, carbenicillin, cloxacillin, tobramycin, metronidazole, amikacin, and amphotericin B were administered. His general state deteriorated. The skin rash was

severe and extensive and resembled a severe scald. He died on 8 January 1979.

Autopsy showed the skin to contain all the typical features of GVHD reaction with hyperkeratosis, parakeratosis, epidermal atrophy, and associated dyskeratotic cells throughout the epidermal layer. There was some increased collagen in the papillary dermis but no lymphoid infiltrate. On examination of the gastro-intestinal tract it was found that the small intestine was atrophic, this affecting mainly the lamina propria and superficial submucosa. There was a slight increase in collagen and the cells present were mainly fibroblasts, with occasional large mononuclear cells, lymphocytes and scanty plasma cells. There were focal areas of epithelial regeneration as well as widespread intramucosal haemorrhage. The submucosa showed some degree of oedema, with scattered mononuclear and plasma cells. The muscular layers were not affected. The colon showed similar features affecting the superficial layers, but in areas there was ulceration with pseudohyphae of *Candida* present in the exudate and also extending into the tissue. In the liver the most striking feature was predominantly centrilobular intrahepatic cholestasis. The architecture was preserved, and the portal tracts were of normal size and contained the normal population of cells. There was no bile duct reduplication. In the areas showing cholestasis there were bile plugs and occasional small bile lakes with occasional cells showing eosinophilic degeneration and necrosis. Bile was prominent in both parenchymal and Kupffer cells, although some of the Kupffer cells also appeared to contain haemosiderin. Some of the hepatocytes had a slightly glassy appearance.

Comment. The clinical picture was typical of GVHD and illustrates the difficulty of management, even when a firm diagnosis has been established. There was histological evidence of GVDH in the skin and gastro-intestinal tract, but the liver appearance was not typical.

Case 3

A 6-year-old Coloured girl was referred with the diagnosis of severe acute aplastic anaemia. She had been given prednisone 40 mg/d, and was now on maintenance doses of 5 mg on alternate days. Anabolic androgens (oxymetholone and mentenolone acetate) at a dose of 2 mg/kg had been ineffective. Parenteral gammaglobulin had been given on two occasions. In the past she had received repeated transfusions with fresh whole blood and platelets for anaemia and cutaneous bleeding. Clinical examination was negative apart from pallor.

Initial investigations revealed a haemoglobin concentration of 4 g/dl, a total granulocyte count of 0,2 x 10^9/l, and a platelet count consistently lower than 20 x 10^9/l. Bilirubin, liver enzyme, total protein, urea, and creatinine levels were normal. The cytomegalovirus titre was 1/64, and hepatitis B surface antigen was not demonstrable.

In April 1978 she underwent transplantation of bone marrow from a compatible sibling, which was uneventful apart from a single episode of septicaemia requiring intravenous antibiotics. Three months after transplantation total protein and albumin levels were normal and the alkaline phosphatase level was raised appropriately for her age, but liver enzyme values were found to be between 5 and 10 times normal. Radio-immunoassay for hepatitis B surface antigen was now positive. No specific treatment was given.

At approximately the same time a mild skin rash developed and biopsy showed epidermal atrophy, basal vacuolar changes, slight hyperkeratosis, and individual cell necrosis. No treatment for this was given and an insignificant rash persists. Liver enzyme values had returned to normal. Liver biopsy was refused.

Comment. While this patient has histologically proven cutaneous GVDH it is so mild as to require no treatment. The normal liver biochemical findings and the absence of gastro-intestinal tract symptoms, particularly in the face of a proven episode of hepatitis B antigenaemia, make viral hepatitis the most obvious diagnosis.

Case 4

This 18-year-old White girl presented with acute myelomonoblastic leukaemia in April 1976. Complete remission was induced with a combination of cytosine arabinoside and daunorubicin.[6] One year later she relapsed; remission was reinduced with TRAMPCO(L)[7] but she relapsed a second time 6 months later, and bone marrow transplantation was decided upon. The patient was then asymptomatic and physical examination was negative. Apart from 60% myeloblasts in the bone marrow all laboratory investigations, including liver function tests, gave normal results. Cytoreduction was undertaken with oral busulphan (1 mg/kg/24 h) and the epipodophyllotoxin VP 16-213 (200 mg intravenously daily on days −7, −6, −5 and −4). In addition she was conditioned with an intravenous infusion of cyclophosphamide 60 mg/kg/24 h on days −3 and −2, with special attention to fluid and electrolyte balance. After 1 day's rest 1 000 rad midline total-body irradiation was given from a cobalt source. The patient was then given hyperalimentation as well as anti-emetics; menorrhagia was controlled with conjugated oestrogens and hydroxy-progesterone.

The initial course was uneventful except for mild diarrhoea which responded promptly to codeine phosphate, and unexplained pyrexia managed with intravenous cephalothin, gentamicin and carbenicillin. Routine post-transplantation immunosuppression with methotrexate was given. By the 17th day after transplantation engraftment was documented, all support and antibiotic therapy was withdrawn, and the results of biochemical, hepatic and renal re-evaluation in anticipation of her discharge were normal.

On the 18th day tender hepatomegaly with ascites developed suddenly and liver failure progressed rapidly, leading to the patient's death within 3 days. Autopsy confirmed engraftment and revealed no abnormality apart from a grossly congested liver weighing 2 480 g. There was no obstruction to any of the large hepatic veins, and histological study revealed extensive centrilobular congestion with necrosis of the parenchyma. A narrow rim of haemosiderin-laden liver cells survived around the portal tract and small numbers of lymphoid cells were present in the sinusoids. Central veins showed minimal separation of the endothelial lining cells from the basement membrane by inflammatory cell infiltration, but no thrombi were seen. The details have been reported previously.[8]

Comment. The fulminating hepatic necrosis caused by the Budd-Chiari syndrome has been attributed to the cumulative hepatotoxic effects of the many cytotoxic drugs this patient received in the 18 months before transplantation. The additional radiotherapy could have contributed to the microvascular response, but this remains unproven. The possibility that the veno-occlusive disease might have been due to GVHD was discarded on the basis of normal skin and gastro-intestinal tract findings.

Case 5

A 22-year-old White man with acute myeloblastic leukaemia presented with a brief history of tiredness and malaise. Examination was negative except for a 1 cm splenomegaly. Initial investigation revealed a haemoglobin concentration of 12,5 g/dl, a reticulocyte index of 0,3%, a white cell count of 3,5 x 10^9/l with 11% neutrophils, 5% eosinophils, 1% basophils, 38% lymphocytes (some atypical), 6% monocytes, 3% promyelocytes, 5% myelocytes, 31% metamyelocytes, and a platelet count of 146 x 10^9/l. All biochemical values were normal.

Initial bone marrow aspiration biopsy was thought to show features of acute myeloblastic leukaemia. Treatment began with our standard three-drug regimen.[9] On day 10 a second bone marrow aspirate and trephine biopsy showed residual disease, and on review the diagnosis was changed to acute lymphoblastic leukaemia (L1-FAB classification).[10] This may well have accounted for the poor response to treatment. Remission was successfully induced with L-asparaginase, vincristine, adriamycin and prednisone. He was offered bone marrow transplantation once complete remission had been consolidated.

He was conditioned with cyclophosphamide and 1 000 rad total-body irradiation before the procedure. From the 5th day after transplantation he had a persistent mild diarrhoea, and on day 14 he developed a skin rash with histological features compatible with GVHD; treatment with prednisone was begun. A herpetic rash and mouth ulcers were treated with 5-deoxyuridine with some improvement. On day 24 he developed pyrexia associated with jaundice and abdominal tenderness with a palpable gallbladder but no hepatomegaly. Ultrasonography confirmed dilation of the gallbladder and proximal bile ducts. The total bilirubin level rose to 384 μmol/l, the conjugated bilirubin level was 327 μmol/l, the alkaline phosphatase level 264 IU/l, and the SGOT level 204 IU/l. His condition deteriorated rapidly, and just before his death *Salmonella* species were isolated from blood cultures.

At autopsy the gallbladder was found to be markedly distended, with dilation of the cystic and common bile ducts indicating recent obstruction. The whole of the mucosa of the common bile duct and cystic duct had sloughed and had impacted firmly, causing obstruction. No gallstones were observed.

On histological examination the bile duct was found to be entirely necrotic with extravasation of bile into the subjacent connective tissue, where fat necrosis had occurred. There was no evidence of inflammation and no fibrosis. The liver was markedly enlarged and histological examination showed a large number of bile infarcts, mainly situated around the central veins. The presence of bile plugs in the canaliculi were compatible with the obstruction. There was some periportal chronic inflammatory cell infiltration and hepatocytes were widely separated, some being nucleate. The skin showed widespread involvement with atrophy of the epidermis and papillary dermis with hyperkeratosis. There was a thick reticular dermis with foci of collagen necrosis with infiltrating histiocytes. The whole of the gastro-intestinal tract was extensively ulcerated.

Comment. The jaundice in this patient was obstructive and resulted from sloughing and impaction of the mucosa of the common bile and cystic ducts. The cause remains unknown, but it is our opinion that this reflects a change similar to that seen in the gastro-intestinal tract after mucosal destruction due to the cumulative effects of cytotoxic agents and superimposed radiotherapy. The acute GVHD in the period immediately after transplantation had responded dramatically to prednisone, and while the high-dose steroids may have effected the changes in the liver and the skin the findings in these two systems at autopsy were difficult to reconcile with this diagnosis. The changes in the gastro-intestinal tract were impossible to resolve, and would be entirely compatible with drug- and radiation-induced ulceration which appeared histologically to be in the process of recovery.

Case 6

A 12-year-old Coloured boy with proven severe acute aplastic anaemia was referred for elective bone marrow transplantation. Physical signs were limited to mild pallor. Peripheral blood and bone marrow samples showed features diagnostic of severe acute aplastic anaemia, but the biochemical profile was normal and tests for viral infection were all negative.

The patient underwent uneventful transplantation of bone marrow from an HLA-identical and MLC-non-reactive sibling, with engraftment established by day 12. Since the present protocol is examining the role of cyclosporin A[11] in the control of GVHD he was given this agent in a dose of 15 mg/kg body weight, and plasma levels were monitored regularly.

In the 3rd week after transplantation the patient became jaundiced, with rapid elevation of liver enzyme levels, conjugated hyperbilirubinaemia, and a rising alkaline phosphatase level. Cramping abdominal pains were present and examination showed the right upper quadrant to be tender. Ultrasonography revealed a large cystic mass occupying the anatomical situation of the gallbladder. An emergency surgical operation confirmed the presence of a sterile mucocele, which was drained. Otherwise the laparotomy revealed nothing abnormal. Bile could be milked through the common bile duct only with the greatest difficulty but no stones were demonstrated, and it was elected not to explore the common bile duct.

The patient tolerated the surgical procedure well; within 3 days bowel motility had returned and both skin rash and diarrhoea now became evident.

A liver biopsy specimen taken at operation showed only centrilobular liver cell necrosis of a focal nature, and there was no evidence of GVHD in the liver or in a skin biopsy.

The patient remained well clinically but the jaundice increased rapidly. In view of the known hepatotoxicity of cyclosporin A the dose was further reduced, and at the end of the 3rd postoperative week the drug was discontinued because the jaundice was deepening, and this drug was replaced by a corticosteroid (prednisone 1 mg/kg/24 h). The response was dramatic, and within 48 hours there was clinical and biochemical evidence of resolution of the hepatitis.

On the 28th day after transplantation the patient developed melaena and had a 2-litre haematemesis. Although liver enzyme and alkaline phosphatase levels were now normal, suggesting that cell necrosis and obstruction had been reversed, the prothrombin time was only 25% of normal. Further haemostatic evaluation showed the laboratory characteristics of severe hepatocellular dysfunction; treatment with fresh whole blood, cryoprecipitate, factor concentrates and platelet infusions returned the prothrombin time to normal. Bleeding from the gastro-intestinal tract settled within 6 hours.

During emergency resuscitation the patient had aspirated blood, and right lower lobe pneumonia was confirmed radiologically. Although only transiently hypotensive oliguria developed, the patient died of refractory cardiorespiratory failure later the same night.

Autopsy confirmed engraftment and consolidation of the right lower lobe. The major anatomical changes were confined to the abdomen. The liver was enlarged and bile-stained, the common bile duct was patent and the gallbladder healthy. There was extensive mucosal desquamation of the entire gastro-intestinal tract, this being maximal in the left colon and the rectum.

Histological examination showed necrotizing enterocolitis but no evidence of GVHD. The causation of this lesion, which contributed to his septicaemia, is unexplained. None of the other organs, notably liver and skin, showed any evidence of GVHD.

Comment. In this patient the postoperative jaundice could have occurred for any of three reasons. Firstly, there might have been transient obstruction to the common bile duct with mucosal oedema, as in the previous case. Whether the corticosteroids were instrumental in reducing the oedema and restoring patency to hepatic drainage is unknown. Secondly, the patient may have had GVHD with the maximum effects in the gastro-intestinal tract and the liver, skin changes being masked by the administration of cyclosporin A.[12] Alternatively, the jaundice might have been related to cyclosporin administration and its rapid reversal to withdrawal of the drug and commencement of a corticosteroid. During the pancytopenic period the patient was pyrexial and presumably septicaemic, although blood cultures were negative. It therefore remains a fourth possibility that the

liver disease may have been related to infection, in part at least. In support of this is the finding of gas in the pelvic retroperitoneum, but postmortem bacteriological investigation was not undertaken.

Discussion

Jaundice is common after bone marrow transplantation. The causes vary widely and successful management depends upon accurate diagnosis. However, these patients are often exposed to more than one well-recognized cause of jaundice both before and after transplantation.

GVHD is a clinical syndrome resulting from an acute inflammatory process mediated by donor lymphocytes and directed against antigens in the target organs of the host.[13] Up to 70% of patients may be affected, and two clinical variants have been recognized. The first is an acute or fulminating illness characterized by extensive skin involvement, voluminous diarrhoea and hepatitis. In chronic GVHD cutaneous involvement predominates and sclerodermatous features may develop, liver and gastro-intestinal tract involvement being less obvious. Both clinical and histopathological staging is possible.[14]

GVHD is a major barrier to the more widespread use of bone marrow transplantation, and while the incidence and severity may be decreased by histocompatibility matching and post-transplantation immunosuppression, both adequate prophylaxis and therapy are lacking.[15]

The hepatic component is characterized by hepatomegaly and jaundice. Elevated total and conjugated bilirubin, alkaline phosphatase and transaminase levels are characteristic biochemical features. Progression to liver failure may occur.

The histological diagnosis may be difficult but is aided when there is proven cutaneous involvement, since the latter characteristically precedes the hepatitis. Histologically there is degeneration and eosinophilic necrosis of the hepatic parenchymal cells, resulting in irregularity of the limiting plates and foci of hepatocellular necrosis of varying size within the liver lobule. Lymphocytes infiltrate the portal areas and may be observed adjacent to the necrotic hepatocytes, where macrophages will sometimes also aggregate. Kupffer cell hyperplasia and haemosiderosis occur, while the parenchymal cells show variable fatty change and may also accumulate iron. The most constant finding is that of degeneration and necrosis of the epithelium of bile ducts. Intrahepatic bile stasis is variable and often minimal. The epithelial lesion is most reliable in distinguishing hepatic GVHD from other types of hepatitis and is the basis for histological rating.[14] In a double-blind study in the dog the specificity of changes in the small bile ducts was confirmed, although it has been suggested that a viral infection may produce similar features.[16]

GVHD may also affect the small centrilobular and sublobular hepatic veins, giving rise to a Budd-Chiari syndrome with hepatic failure.[17] Histologically there is non-thrombotic obliteration of these small vessels by subintimal oedema and cellular infiltration with early fibrosis. The changes are most prominent in the small lobular veins, the lumens of which appear compromised to varying degrees by a collar of the oedematous tissue or reticulin. The incrimination of GVHD in this syndrome is complicated by the occurrence of an essentially similar picture in patients receiving intensive radiation or chemotherapy,[8] although there does not appear to be any correlation with the type of immunosuppressive regimen employed. This lesion is distinguishable from the classic Budd-Chiari syndrome by lack of involvement of the large hepatic veins and intrahepatic radicals of the inferior vena cava, and the absence of thrombi.

Viral hepatitis may be difficult to distinguish from GVHD and is a potential complication in transplant patients because of the multiple transfusions to which they are exposed. The findings of hepatitis B surface antigenaemia in one of our patients raises the possibility that in some of the other cases histological changes might have been due to non-A, non-B hepatitis or cytomegalovirus or hepatitis A infection. The points of contrast are destruction of the small bile ducts in cholangiolytic viral hepatitis, where this change may be severe, and ballooning degeneration of hepatic cells. In contrast, in GVHD there is eosinophilic necrosis of single cells or loss of small groups of hepatocytes, and prominent involvement of the bile ducts.

Differentiation from cytomegalovirus infection is often more difficult.

Extensive involvement of the liver and gastro-intestinal tract with cytomegalovirus is a common complication of GVHD, and the characteristic inclusion bodies in biopsy specimens from the liver and gastro-intestinal tract and a rising titre of cytomegalovirus antibodies confirm the presence of two processes without clearly delineating the contribution of each to changes in the liver.

Each of the 6 patients also had a clinical course compatible with drug administrations. Methotrexate produces dose-dependent hepatotoxicity. The histological features include parenchymal fatty change and necrosis, Kupffer cell proliferation, and portal tract infiltration. Hepatic fibrosis and cirrhosis occur with longer term therapy.[18] Furthermore, the hepatotoxicity caused by methotrexate increases when this drug is administered with other cytotoxic agents.[19]

In addition, amphotericin B may cause hepatocellular dysfunction and jaundice and occasionally acute liver failure.[20,21] The aminoglycosides are associated with mild increases in hepatic transaminase, alkaline phosphatase and bilirubin levels,[22] while the cephalosporins[23] may also alter liver enzyme and alkaline phosphatase levels.

More recently cyclosporin A has been used to suppress immune competence, primarily in an attempt to control GVHD.[11] This drug is known to be hepatotoxic, and in our last patient, histological examination of the liver demonstrated changes compatible with either viral or drug-induced centrilobular hepatic cell necrosis. The absence of any serological evidence of viral infection and the dramatic response to withdrawal of cyclosporin A and substitution of corticosteroids is interpreted as a reversal of drug-induced hepatitis. The lesson to be learned from this experience is that careful monitoring of plasma levels with radio-immunoassay and dosage adjustment may avert even transient episodes of this nature.

Septicaemia is known to cause jaundice,[24] and blood cultures need not be positive. Biochemical investigations reveal conjugated hyperbilirubinaemia with only a modest rise in serum alkaline phosphatase and transaminase levels. Histological examination of the liver shows mild-to-moderate bile stasis and nonspecific changes such as fatty infiltration and the presence of inflammatory cells in the portal tract. The difficulty is that many of the patients are pyrexial, organisms fail to grow from blood or other cultures, and more than one cause for jaundice is already present. The contribution of infection in the individual patient may therefore be difficult to define precisely.

Of great interest has been our experience with three recent patients in whom mechanical obstruction to biliary drainage resulted in jaundice following bone marrow transplantation. In one patient, not included in this report, jaundice, conjugated hyperbilirubinaemia and an acute abdomen necessitated emergency exploration in another hospital. Laparotomy was entirely negative apart from the presence of pigment stones in the gallbladder and one stone firmly impacted in the common bile duct. The postoperative course was uneventful and despite intensive studies an explanation for biliary stone formation has not been established. Two patients in this series presented with jaundice immediately after the transplant. We do not think that obstruction of the common bile duct by a mucosal cast (case 5)

has ever been reported before. The reason for the desquamation is not known, but it may reflect the same changes seen in the gastro-intestinal tract and is probably attributable to the high-dose cyclophosphamide and radiotherapy used to condition the patient. Whether the previous fulminating GVHD made any contribution must remain speculative, particularly since histological examination of the liver, skin and gastro-intestinal tract provided no evidence for that diagnosis at autopsy. Furthermore, examination of the desquamated mucosa showed only cell necrosis and oedema. The reluctance of the surgeons to undertake emergency surgery is understandable, but this should not have presented an insurmountable problem. In retrospect, exploratory laparotomy, confirmation of the lesion and an appropriate drainage operation might well have prevented the death of this patient.

This experience undoubtedly influenced management when a similar problem was encountered in our last patient. Although the operative risk was as great, he tolerated the surgical exploration well and drainage by cholecystostomy was effective. It is noteworthy that considerable difficulty was experienced in milking bile through the common duct. Notwithstanding the grave clinical condition of these patients, we have come to realize that this entity may be a previously unrecognized complication in the early transplant period; it would appear best managed by exploration of the common bile duct and T-tube drainage. In this patient the causation of the lesion is again uncertain, although there is no histological evidence of GVHD. The fact that the same changes (namely oedema and mucosal desquamation) were present throughout the gastro-intestinal tract, may explain the common bile duct lesion adequately.

Because jaundice after bone marrow transplantation is frequently multifactorial it poses major diagnostic difficulties. A differential diagnosis will often include acute or chronic GVHD, viral hepatitis, drug-associated liver disease and septicaemia. Less frequently the Budd-Chiari syndrome or mechanical obstruction of the common bile duct may be encountered. Rational therapy is only possible after accurate diagnosis and, as in the case of mechanical biliary obstruction, early diagnosis and surgical intervention are necessary. The increasing use of cytotoxic drugs, including new immunosuppressive agents such as cyclosporin A, emphasizes the need to be aware of these complications and the role of early liver biopsy in the histological diagnosis of GVHD.

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