TRANSFUSION ASSOCIATED GRAFT VERSUS HOST DISEASE

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Abstract

A 70-year-old man developed a skin rash with fever, vomiting and diarrhea ten days after partial gastrectomy for gastric adenocarcinoma which had metastasized to intra-abdominal lymph nodes and liver. Four days later a skin biopsy confirmed the clinical diagnosis of transfusion associated graft versus host disease. His condition deteriorated with jaundice, high liver enzymes, leucopenia and thrombocytopenia. He died 19 days after surgery.

Introduction

Graft-versus-host-disease (GVHD) is a well known complication of bone marrow transplantation. It is increasingly recognized that it can develop also in severely immunosuppressed patients after transfusion of non-irradiated blood or blood products[1-5]. It can also occur following transplacental transfer of maternal lymphocytes into an immunodeficient foetus. GVHD is classified into an acute and a chronic form. The acute disease appears within 100 days of transplantation whereas the chronic form is defined as persistent GVHD or that appearing more than 100 days after transplantation[5].

The principal target organs of acute GVHD are skin, gastrointestinal tract and liver, presenting clinically as anorexia, nausea or vomiting, skin lesions, jaundice, diarrhea and organomegally. Erythematous maculopapular rashes typically involve palms, soles and the upper part of the trunk, but may spread to the entire body leading to bullae formation and scold-like desquamation similar to toxic epidermal necrolysis.

Manifestations of chronic GVHD include skin lesions, chronic liver disease, intestinal involvement, generalized wasting and pulmonary insufficiency. The early lesions of chronic GVHD are often lichen planus-like and frequently involve oral mucosa. Later, a sclerodermatous picture develops[5].

Histologically, acute GVHD shows vacuolar degeneration of basal cells, altered polarity of the epidermal cells and single cell death in the form of apoptosis, dermal infiltrate of CD3+ and CD8+ T lymphocytes[6], and lymphoid cell exocytosis. Satellite cell necrosis of keratinocytes defined as an eosinophilic body associated with adjacent lymphocytes may be present[7]. As the disease progresses, clefts and spaces develop after necrosis of basal cells and acantholysis. Frank loss of epidermis, as seen in toxic epidermal necrosis, is seen in the most severe form of acute GVHD.

Early stages of chronic GVHD shows Lichenoid changes but the dermal infiltrate is usually less than that seen in idiopathic lichen planus. The late stage of chronic GVHD has a sclerodermatous picture with epidermal atrophy, sclerosis of the dermis and destruction of adnexal structures including the nerve endings. Eosinophilic bodies and hydropic degeneration of the basal layer may or may not be evident at this stage. Cytopathic and proliferative lesions of GVHD are also often seen in hair follicles[8] and sweat glands[9] and in underlying mucous glands of the lip[10].

Case Report

A 70-year-old Qatari man had distal partial gasterectomy for an infiltrating gastric adenocarcinoma. During surgery he had received two units of fresh, cross-matched, non-irradiated blood from healthy unrelated donors. One week post-operatively a subcutaneous haematoma developed at the incision site with fever of 38.5 C, anorexia, abdominal colic, vomiting and watery diarrhea.

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The preliminary clinical impression was wound infection and gastroenteritis. Repeated cultures of the wound swabs, blood, urine and stool did not grow any pathogen. Complete blood count, blood chemistry including urea nitrogen, creatinine, electrolytes and liver function tests, and chest X-ray were normal. Abdominal ultrasound showed liver metastases and enlarged perigastric and peripancreatic lymph nodes, but no evidence of sub-diaphragmatic collections. Kidneys, ureters and bladder were normal. The patient was put on hyperalimentation , palliative treatments and antibiotics, but the fever continued and his general condition continued to deteriorate.

On the 10th day post-op, an erythematous scaly macular rash developed on his face and trunk which, in two days, progressed to involve the extremities. Drug eruption was considered and the patient was put on alternative antibiotics. Liver function tests became abnormal with elevated alkaline phosphotase (195 U/l), SGOT (117 U/l), SGPT (142 U/l. He had leukopenia ($1.4 \times 10^3/mm^3$) and thrombocytopenia ($30 \times 10^3/mm^3$). A repeat ultrasound of the liver and biliary tract showed an ill-defined low echogenic area in the liver and chest X-ray suggested pleural effusions. Exfoliative erythroderma and watery diarrhea persisted.

On the 14th day post-op he was seen on consultation. A skin punch biopsy was taken from the right thigh. Histopathological findings (Figs. 1-5) included apoptosis of keratinocytes in the epidermis with lymphocytic exocytosis and satellitosis, degenerative changes of the basal zone and upper dermal lymphocytic infiltrate, confirming the clinical diagnosis of graft versus host reaction. Apoptoses with haematoxophilic debris were also present in sweat gland ducts (Figs. 4 & 5). Prednisolone therapy started, but the patient developed jaundice (Bilirubin 3.4 mg/dl), liver function deteriorated further (Alkaline phosphotase 847 U/l, SGOT 192 U/l, SGPT 360 U/l), diarrhea and leukopenia persisted, and he died on the 19th day after surgery.

Fig. 2: Multiple apoptosis in the epidermis shown at higher power.

Fig. 3: Convergence of lymphocytes around an apoptotic cell in early stage of satellitosis.
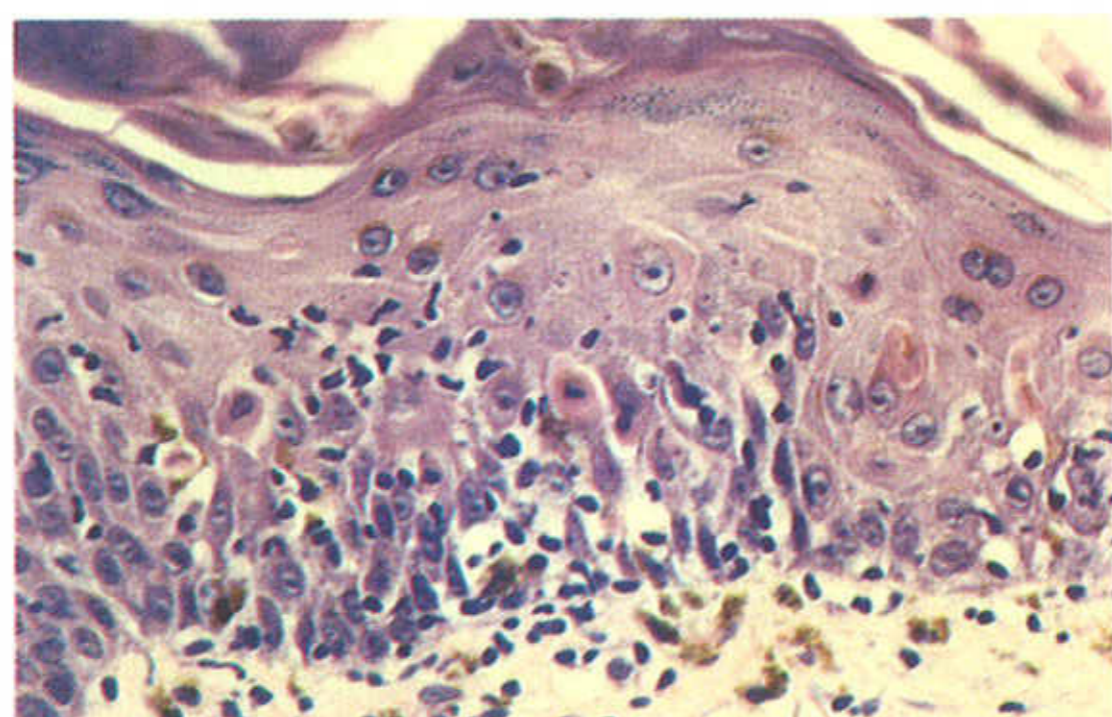

Fig. 1: GVHD: Degenerative changes in the basal zone with frequent apoptosis of the epidermal cells, abundant exocytosis of lymphocytes and satellitosis.
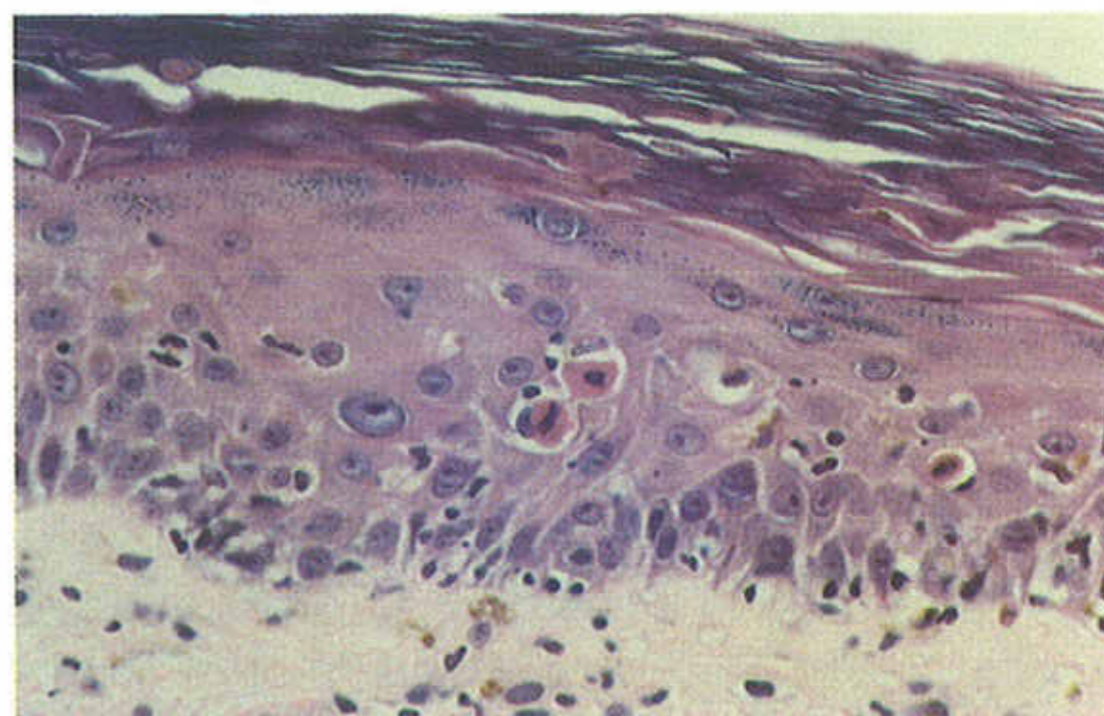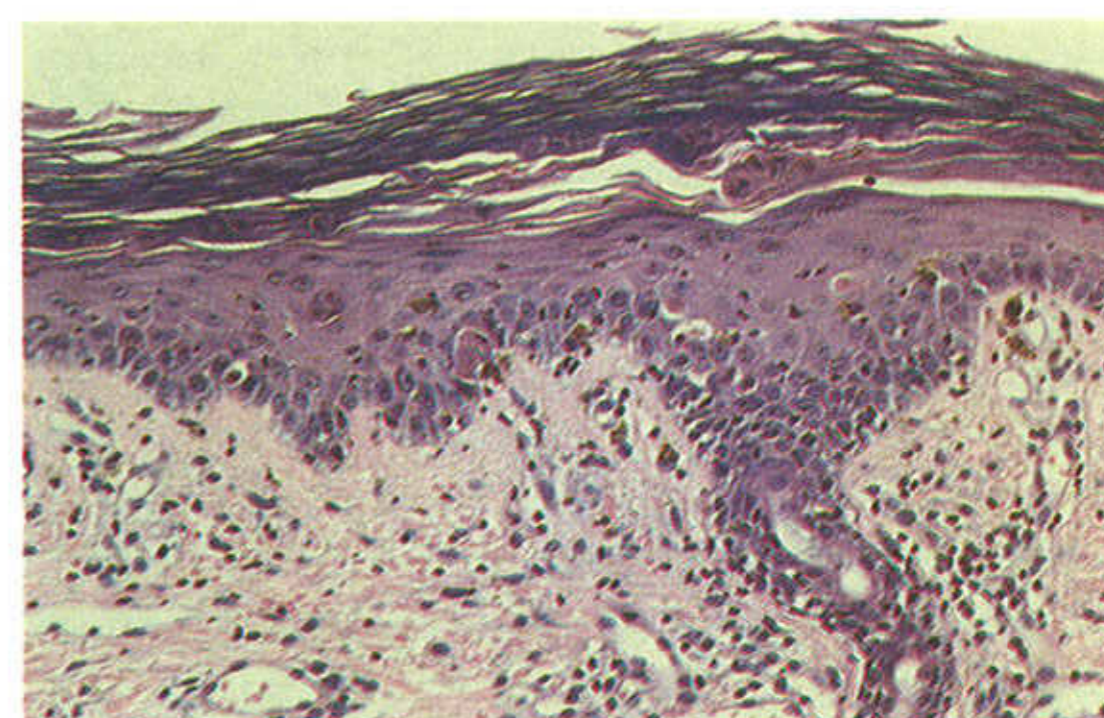

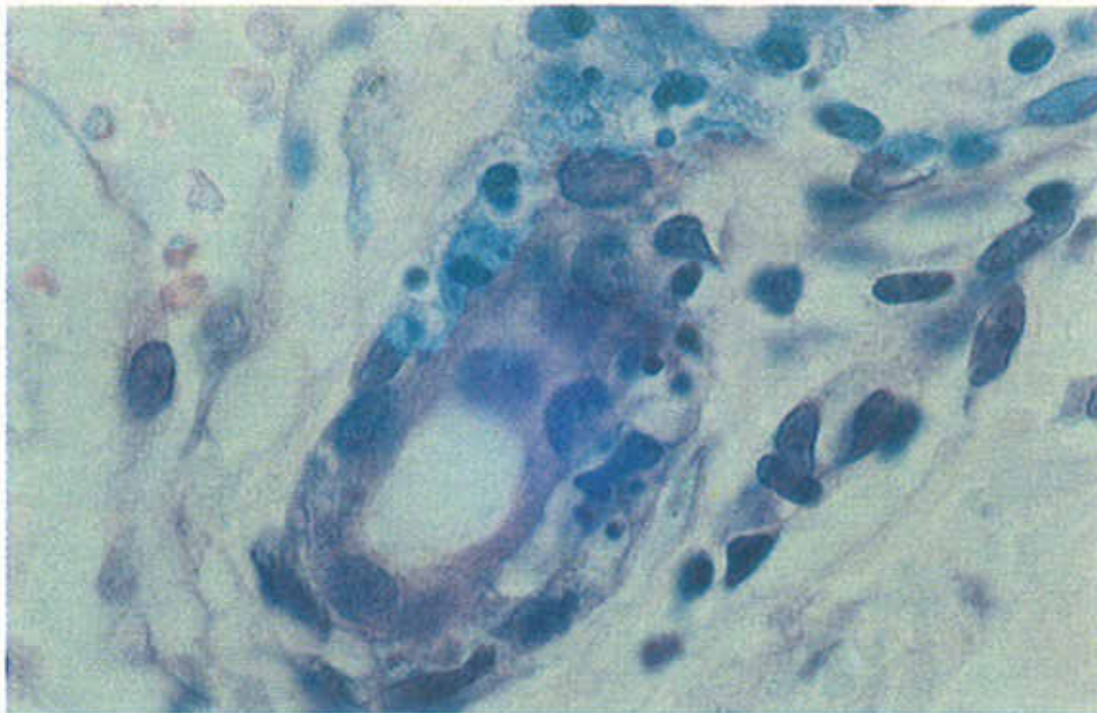*Fig. 4: GVHD: Involvement of the epidermis and a sweat gland duct.*

Fig. 5: *Apoptosis with haematoxophilic debris in the sweat gland duct shown at higher power.*

Discussion

Transfusion associated GVHD occurs in immunocompromized patients who receive non-irradiated blood or blood products containing immunocompetent donor lymphocytes. It presents almost exclusively as an acute illness days to weeks after transfusion (median of eight days), is almost invariably associated with bone marrow failure and has a rapidly progressive course with a mortality rate approaching 90 per cent (median 21 days survival)[11-19]. First reported in 1964, probably still goes unrecognized in a significant number of cases. Up to 1990, only thirty cases reported in patients with malignancies[2]. Recently, fatal GVHD has been reported in presumed immunocompetent hosts13 receiving fresh non-irradiated blood products: six cases following cardiac surgery,[20, 21] one case after cholecyctectomy[22] and one case post-partum[23].

Given the serious nature of the disease with its high mortality rate and inefficacy of almost all therapeutic regiments (corticosteroids, anti-thymocyte globulin, methotrexate and cyclosporine)[24, 25] it is vital to prevent it by irradiating blood before transfusion to patients who are at risk. Even one unit of non-irradiated blood contains enough lymphocytes to produce the disease. Whole blood, packed red cells, frozen deglycerolized red cells, buffy coat granulocytes harvested from healthy individuals or from patients with chronic myelocytic leukaemia , and pooled platelet concentrations all contain enough lymphocytes to be considered capable of causing GVHD. Fresh frozen plasma and cryoprecipitates have not been reported to cause the disease. Storage of blood does not eliminate the risk. Current leukocyte depletion techniques that use white cell filters may not be effective in prevention[24]. Prophylactic irradiation of blood or blood products is currently considered as the most effective way of preventing GVHD. The recommended doses of 1500 - 3000 rads apparently cause no impairment of red cells, granulocytes or platelet functions[26]. However, controversy continues because of the high costs involved and lack of well controlled studies demonstrating the over all usefulness of irradiating blood products[27].

Although it is generally accepted that GVHD is caused by donor T lymphocytes reacting to host histocompatibility antigens, the exact pathogenesis of the tissue damage is poorly understood[28]. Both in humans and in animal models of the disease GVHD is frequently seen in skin, liver, and gut, never in the brain, endocrine organs, and kidney, and rarely in skeletal muscle and heart. Moreover, certain cells are affected more than others: in the skin, these are tips of the rete-pegs[29], in the liver, the bile ducts, and in the gut, the neck of the gastric glands and the base of the crypts of Liberkuhn while enterochromaffin cells are selectively spared[30].

These inter- and intra-tissue differences can not be explained on histocompatibility antigen differences. It is suggested that the intra-epithelial T-lymphocytes become activated with release of lymphokines, which induces the expression of HLA-DR. Since all cells of the body which express HLA-DR are not affected, clearly additional factors are involved. Langerhans cells have been said to be required for the induction of GVHD because UV radiation causes both loss of Langerhans cells and inhibition of cutaneous GVHD[31]. However, GVHD can occur in situations where Langerhans cells have been depleted as a result of either total body irradiation or cytotoxic therapy. Further, Langerhans cells are not present in sweat ducts, which are a target in both acute and chronic forms of GVHD. It has, therefore, been suggested that only cells capable of proliferation are susceptible to acute GVHD. The observation of basal cells in the epidermis and in sweat glands (the only cells in which proliferative activity is evident) as the main targets of damage and destruction in acute GVHD support such hypothesis[9, 30, 31].

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