A case of a lethal febrile illness in a renal transplant patient presenting after a dental visit

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A 28-year-old man with type 1 diabetes mellitus and renal replacement by a cadaver kidney transplant presented with fever, swelling and pain in the right jaw following a tooth extraction.

His illness began at the age of 2 when he presented with an episode of diabetic ketoacidosis. After a year he was started on insulin therapy. The ensuing 18 years were relatively quiescent, save for progressive proliferative diabetic retinopathy requiring surgery. At the age of 23 he developed rapidly progressive renal failure without the usual diabetic prodrome of nephrotic syndrome, which culminated in a renal biopsy. Interestingly the biopsy revealed endocapillary and mesangial proliferation, subendothelial electron-dense deposits positive for IgG and complement in the same localization, on a background of mild diabetic glomerulopathy. There was reduplication of the basement membrane with tram-tracking. There was no evidence for systemic vasculitis by history, serologies, or other laboratory data. A diagnosis of membranoproliferative glomerulonephritis type III was made and a course of steroids was attempted.

After a brief period of haemodialysis, renal function recovered either consequent to or in spite of steroid therapy. During the next 4 years the diabetic diathesis marched briskly along with increasing retinopathy, sensorimotor polyneuropathy, and the onset of probable diabetic nephropathy seen on the original biopsy and now the probable cause of renal deterioration with the first the nephrotic syndrome, fixed hypertension, and then renal failure. Just prior to the need for renal replacement by dialysis he received a 1B, 1DR matched cadaver renal allograft which functioned immediately, lowering the serum creatinine to 1.4 mg/dl managed by anti T-cell antibody induction, and sequential quadruple immunosuppression. He was discharged to the clinic on cyclosporin, prednisone, and azathioprine.

Over the next 15 months renal transplant excretory function remained superb, but gross haematuria, proteinuria, with 2.3 g for 24-h excreted despite a glomerular filtration rate by isotopic clearance methods of 74 ml/min per 1.73 m² necessitated a renal biopsy that looked virtually identical to the original biopsy. This patient could have been presented and discussed, therefore, as a case of recurrence of the original glomerulonephritis in the allograft, if it were not for other interesting events that transpired several months after the renal biopsy.

On the day prior to his admission for his extraordinarily interesting disease, routine teeth extraction was performed under antibiotic prophylaxis. Despite such prophylaxis, the patient presented with fever, chills, swelling and pain of the right jaw, and an inability to eat or drink. Background immunosuppression included prednisone 10 mg, azathioprine 50 mg, and cyclosporin A 300 mg.

On admission the patient's temperature was 103°F, blood pressure was 184/106 mmHg supine, with a sinus tachycardia at the rate of 137 b.p.m. and tachypnoea of 22 per min. He had a right-eye prosthesis, and a cataract and diabetic retinopathy on the left. There was a large, tender, non-fluctuant, non-movable swelling to the right side of the jaw. The oral cavity revealed the recent dental surgery. The neck was supple without nuchal rigidity and with no adenopathy. Examination of the heart, lungs, and abdomen were unremarkable. A kidney transplant in the right iliac fossa, was small and non-tender. There was no bruise at or around the allograft. The examination of the central nervous system was unremarkable. There were no rashes, arthritis, nailbed changes, or oedema.

The laboratory data on admission included Na of 123 mEq/l, K 6 mEq/l, Cl 82 mEq/l, CO₂ 19 mEq/l, glucose 612 mg/dl, creatinine 2.6 mg/dl, BUN 68 mg/dl, Ca 7.8 mg/dl, P 4.7 mg/dl, albumin 2.8 g/dl, bilirubin 1.5 mg/dl, SGOT 65 U/l, and LDH 1924 U/l. The cyclosporin level was therapeutic. The urinalysis revealed 4+ sugar, 2+ albumin, blood, specific gravity of 1.024, 8-14 RBCs, a hyaline cast. Radiological studies revealed a chest X-ray with old granulomatous disease, a KUB with mild distension of the stomach, and the large and small bowel in an ileus pattern, a CT of the maxillofacial region with opacification of the right maxillary sinus.

After extensive cultures were obtained, broad-
spectrum antibiotics were begun without improving the clinical picture. By the second hospital day the temperature was 104°F, and the patient’s complete blood count changed radically. The hematocrit fell to 35, the platelet count dropped to 57,000/mm³. The fibrinogen was 500 mg/dl, fibrin split products became positive. The abdominal distension worsened with generalized abdominal pain. Pertinent negative examinations included a cardiac echo for bacterial endocarditis, lung scan for pulmonary embolism, cultures, and chest X-rays. An ultrasound of the abdomen ultimately revealed a 3-cm mass lesion in the posterior segment of the right lobe of the liver and masses or nodes in the porta hepatitis leading to obstruction with gallbladder distension. CT scan confirmed these mass lesions and demonstrated additional ones in the liver (Figure 1). Ultrasound-guided liver biopsy was performed and led to additional biopsies especially of the bone marrow (Figures 2 and 3).

The ultrasound-guided fine-needle aspirate of the liver mass showed mononuclear, lymphoid tumor cells with multiple nucleoli, basophilic cytoplasm, and mitotic figures which by flow cytometry revealed a population of monotypic B lymphocytes (markers CD19, CD20, CD10, IgM kappa) (Figure 2). The bone-marrow biopsy confirmed the liver mass diagnosis, malignant lymphoma of the small, non-cleaved highly aggressive type (Figure 3). Cytogenetic studies revealed a 46 XY karyotype with a small 14q11 deletion.

This case represents an aggressive form of post-transplant lymphoproliferative disorder (PTLD) of the monoclonal and rapidly progressive type. Despite the withdrawal of immunosuppression, treatment with acyclovir, gammaglobulin and interferon alfa, the patient began to deteriorate. CT scan of the abdomen revealed progression in size and number of the hepatic metastases. Chemotherapy was offered and declined by the family. The patient died a few days later with a total course from fever to death of less than 2 weeks. Incidentally, the Epstein–Barr virus (EBV) serology was negative 2 months prior to the febrile illness and was very positive at the time of death, with positive markers for this virus on the tumour cells as well.

Discussion

This patient represents one of the more aggressive forms of a dreaded complication of immunosuppression used for renal transplantation, the post-transplant lymphoproliferative disorder (PTLD). This disorder runs the gamut from mere activation or transformation of B lymphocytes by EB virus on the benign side to this very aggressive neoplastic transformation of the same cells on the malignant side. The virus can effect either a poly-, or more commonly a monoclonal, transformation of the lymphocytes [1].

First reported in 1968, PTLD is associated with EB virus and also with progressive immunosuppression. Seroconversion followed by PTLD has helped to prove the pathogenetic role for EB virus, but more often the syndrome occurs in reactivation of seropositive individuals often in the face of anti-T-cell antibody therapy on the background of basal immunosuppression. The B lymphocyte has a special predilection for this virus, since it bears the surface receptor, C3d, necessary for
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the engagement and internalization of virus genome into the cell. In normal individuals infected by EBV, infection is limited by MHC class I restricted, virus specific cytotoxic T-cells but not completely eliminated, so that clinical symptoms disappear, but the virus is harboured in a latent state. When T-cell surveillance  
has been reduced by agents such as cyclosporin, steroids, or more importantly anti-T-cell antibodies, the B-cell pool that has been EB virus infected can expand and lead to the lymphoproliferative disorder described in this case [2,3].

PTLD occurs in between 1 and 5% of solid-organ transplant recipients with those receiving the kidney having the smallest incidence (1%) while receiving the least stringent immunsuppressive regime, and those with a heart/lung transplant the most, associated with the most strict regime. Four unique clinical syndromes have been recognized; (1) a fever of unknown origin resembling mononucleosis with polyclonal expansion of lymphoid tissue responding to a reduction in immunosuppression; (2) a polyclonal, rapidly progressive and fulminant form resembling the infectious mononucleosis seen in patients with X-linked lymphoproliferative syndrome; (3) single or multiple mass lesions with poly- or monoclonal markers typical of the lymphoma in the non-transplant patient almost always responding to reduction in immunosuppression; (4) a monoclonal, highly aggressive, fulminant form, unresponsive to immunomodulation with response to chemotherapy controversial [4].

The management of patients with PTLD varies according to which of the four clinical syndromes the patient falls into. For almost all patients a reduction or cessation of immunomodulatory drugs or therapies is essential [5]. Overall response rate to this therapeutic approach has been quoted as 40% with the solid-mass tumours and the mononucleosis-like syndrome most responsive [5]. Antiviral agents such as acyclovir or ganclovir have been shown in single case reports to be of some help, while interferon alpha, despite its success in a small series, should be used as a last resort because it has the capacity to initiate acute rejection [5]. Anecdotes aside, chemotherapy has a poor tract record if immunosuppression cessation has failed. Experimental approaches using donor-derived MHC restricted and viral specific cytotoxic T-cells are under investigation [6].

References