PRACTICE OBSERVED

Late complications after cardiac transplantation

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Advances in postoperative medical care have contributed significantly to the improved quality of life and long-term survival of cardiac transplant recipients, which is now 72% at 5 years. The major cause of late morbidity and mortality is transplant associated coronary artery disease¹ and this has recently been reviewed.² However, the diagnosis and treatment of opportunistic infection and lymphoproliferative disorders, together with an awareness of common drug interactions with cyclosporin A (CSA) and its long-term side effects, are important aspects of postoperative management.

Opportunistic infection

Cytomegalovirus (CMV) is the commonest opportunistic viral pathogen. In addition to causing morbidity and mortality from infection, the virus may be associated with the subsequent development of coronary artery disease.³ To minimise postoperative infection it is important that CMV antibody negative recipients receive CMV-negative donor organs and blood products whenever possible. It is important to distinguish asymptomatic from symptomatic CMV infection with or without CMV pneumonitis.⁴ Fever, myal-

gias, malaise, abdominal discomfort as well as leucopenia, thrombocytopenia, atypical lymphocytosis, and hepatitis are the usual clinical manifestations of symptomatic CMV infection.⁴ CMV pneumonitis is more common among lung transplant recipients^{5,6}; this may in part reflect the higher levels of immunosuppression these patients receive.⁷ The diagnosis is made by a combination of clinical findings, serological investigations, and detection of early antigen fluorescent foci (deaff test) in blood, saliva, and urine. If there is evidence of pneumonitis, fiberoptic bronchoscopy is performed to obtain bronchoalveolar lavage for deaff testing and transbronchial lung biopsy specimens for histopathological examination. Treatment consists of intravenous ganciclovir (10 mg/kg/day), which may be supplemented by hyperimmune globulin to CMV if necessary.

Routine prophylactic treatment with either co-trimoxazole (960 mg twice daily every third day) or pentamidine isethionate by nebuliser (600 mg fortnightly) has significantly reduced the incidence of *Pneumocystis carinii* pneumonia. However, the organism should always be considered in the differential diagnosis of opportunistic lung infection. The presenting features may be non-specific and though the chest radiograph may show interstitial infiltration, it is often normal. This may be at variance with the clinical presentation of severe respiratory failure and arterial hypoxaemia. Fiberoptic bronchoscopy with analysis of bronchoalveolar lavage fluid and transbronchial lung biopsy specimens (using Grocott's silver methenamine preparation) to identify the organisms confirms the diagnosis. Treatment consists of oral co-trimoxazole (1.92 g four times a day) or if patients are allergic to this, intravenous pentamidine isethionate. Alternatively, combination treatment with primaquine and clindamycin may be used.

Transplant recipients may experience reactivation of latent *Toxoplasma gondii* infection or may acquire primary infection from seropositive donor organs.⁸ An incidence of 2% for toxoplasma recrudescence and 2.4% for primary infection in heart and heart and lung transplant recipients has been reported. Clinical manifestations are mainly neurological, though myocarditis (fig 1), pneumonitis, or disseminated lesions can also occur. Diagnosis rests on serological tests for anti-

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Figure 1 Endomyocardial biopsy specimen from a patient with toxoplasma myocarditis (arrows). Haematoxylin and eosin, medium power. Reproduced courtesy of Dr A Pomerance.

Figure 2 Thoracic computed tomographic scans from a patient with a pulmonary B cell lymphoproliferative disorder (A) showing response to reduction in immunosuppression and acyclovir therapy (B). (Courtesy of Dr R Smith.)

bodies to *Toxoplasma gondii* and the histopathological identification of the organism in biopsy material (fig 1). Treatment consists of a 6 week course of pyrimethamine (0.5 mg/kg/day) and sulphadiazine (50–100 mg/kg/day) with folinic acid (15 mg) twice weekly.

Fungal infections are unusual and are more commonly encountered in patients receiving high dose steroid therapy. The commonest infections are due to *Candida albicans* and *Aspergillus fumigatus*. Cutaneous or oral candidiasis is treated with topical anti-fungal agents. Oesophageal or pulmonary candidiasis is treated with fluconazole. Patients with pulmonary aspergillus colonisation are prescribed oral itraconazole and nebulised amphotericin B. Patients taking itraconazole should not be prescribed H_2 receptor antagonists, as these agents can considerably impair itraconazole absorption. Invasive candidiasis or aspergillosis is treated with intravenous liposomal amphotericin B (a less nephrotoxic preparation) in addition to the above agents. Pulmonary nocardiosis is rare and carries a high mortality. It can be treated with high dose co-trimoxazole or ampicillin. If sulphonamides are prescribed the danger of crystalluria and oliguria necessitate vigorous hydration and urine alkalinisation. Tuberculosis is also rare and is diagnosed in the usual way. Anti-tuberculous drugs are prescribed in accordance with organism sensitivity.

Occasionally infections caused by herpes simplex virus, *Legionella pneumophila*, *Mucormycosis*, or hepatitis C occur. It is important to be aware that many of the agents prescribed for opportunistic infection interact with CSA (see below).

Lymphoproliferative disorders

Lymphoproliferative disorders occur in approximately 1% of adults (4% of children) after cardiac and cardiopulmonary transplantation. They develop in patients whose T cell mediated responses are impaired by CSA, FK506, OKT3, or anti-thymocyte globulin. Both B and T cell types occur but B cell types are more common, are frequently associated with the Epstein Barr virus (EBV), and may be reversible after reduction in immunosuppression.^{9–11} T cell disorders usually occur

independently of diagnosed viral infection. The presentation of both types of abnormality is variable and may include an infectious-mononucleosis-like illness, generalised lymphadenopathy, tonsillar enlargement, or extranodal masses.

No one single investigation is reliable. Therefore the diagnosis is reached by a combination of clinical features, serological investigations (EBV titres, clonal antibody activation to EBV), chest x ray, computed tomography scan of the affected area (fig 2), and biopsy of lesions. Because of the wide variety of histopathological appearances, ranging from changes consistent with viral lymphadenitis to variants of high-grade non-Hodgkin's lymphoma, accurate diagnosis depends on identifying EBV in the biopsy material either by immunohistochemical staining or by in situ hybridisation. Unlike conventional lymphomas, the lesions may be monoclonal or polyclonal for immunoglobulin light chain expression. Classification is based on the degree of cellular pleomorphism and clonality.^{9–12} Initial treatment is conservative, irrespective of the histopathological appearances and clonality, and consists of a reduction in immunosuppression and treatment with high dose acyclovir for B cell disorders. The CSA level is maintained in the region of 80–100 ng/ml (whole blood monoclonal antibody assay). T cell disorders usually respond to reduction in immunosuppression alone.^{6–12} When immunosuppression is reduced, patients must be closely monitored for evidence of allograft rejection. Whereas there is poor correlation between clinical behaviour and histopathological appearances and clonality, up to 60% respond to these conservative measures. These often include those with an infectious-mononucleosis-like illness, which may occur early after transplantation and are associated with a good prognosis. However, conventional lymphoma chemotherapy may be required in clinically aggressive cases that occur late after transplantation and may either progress or recur despite the recommended treatment.

Cyclosporin A: side effects and drug interactions

CSA is prescribed to achieve whole blood

*Drugs that interact with cyclosporin A***Increased risk of nephrotoxicity**
NSAIDsAminoglycosides
Co-trimoxazole
4-Quinolones
Amphotericin
Melphalan**Increased plasma cyclosporin concentration**Erythromycin
Itraconazole
Ketoconazole
Diltiazem
Nifedipine
Verapamil
Omeprazole
Progestogens
Danazol
Colchicine
? Fluconazole
? Amiodarone
? Allopurinol
? Propafenone
? Azithromycin**Reduced plasma cyclosporin concentration**Rifampicin
Carbamazepine
Phenobarbitone
Phenytoin
Primidone
Octreotide
? Griseofulvin

Potassium-sparing diuretics, potassium salts, and angiotensin converting enzyme (ACE) inhibitors increase the risk of hyperkalaemia. There is an increased risk of myopathy with simvastatin and pravastatin, and of neurotoxicity with doxorubicin. NSAIDs, Non-steroidal anti-inflammatory drugs

concentrations of 100–150 ng/ml after the first postoperative year. Long-term treatment can lead to chronic nephropathy with reduced glomerular filtration and renal plasma flow together with tubulointerstitial injury and focal glomerular sclerosis.¹³ Hypertension occurs in up to 50% of patients treated with CSA for one year and usually responds to captopril or nifedipine. Other side effects include hyperkalaemia, hepatotoxicity, gingival hyperplasia, hirsutism, convulsions, and anaemia.^{14,15} Except for anaemia, these often improve when the dose of CSA is reduced. Convulsions, which are more common in patients on intravenous therapy, are usually secondary to metabolic derangements (for example, high CSA concentration with or without hypomagnesaemia); however, intracranial pathology should be excluded. Long-term anticonvulsant treatment is not normally required.⁶ The anaemia resembles that associated with chronic disease, though dysplasia in all cell lines is common (particularly in patients who are also taking azathioprine). Erythropoietin may be of benefit to those with haemoglobin concentrations <10 g/dl (provided serum iron, vitamin B₁₂, and folate are normal) and may obviate the need for repeated blood transfusions. If drugs known to interfere with CSA (table) are prescribed the dose of CSA must be adjusted appropriately and blood concentrations frequently monitored. In this way the risks of toxicity or of rejection caused by subtherapeutic concentrations can be avoided.

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