CYCLOSPORINE-ASSOCIATED LYMPHOPROLIFERATION, DESPITE CONTROLLED CYCLOSPORINE BLOOD CONCENTRATIONS, IN A RENAL ALLOGRAFT RECIPIENT

J B Dossetor, T Kovithavongs, M Salkie, J Preiksaitis

University of Alberta, Edmonton, Canada

Summary

In a patient receiving sulfinpyrazone (Anturan, Geigy) an unusually high dose of cyclosporine (Cys) was required to maintain serum values in the range of 50–200 ng/ml. After eight months of 1300–1500 mg/day, the patient complained of increasing malaise and symptoms of cyclosporine side-effects. This clinical state was accompanied by splenomegaly and two monoclonal peaks in the gamma region on serum electrophoresis. Concomitantly, rising cytomegalovirus IgM titres, following by rising IgG titres, indicated a primary cytomegalovirus infection. This ominous biclonal proliferation markedly diminished during the subsequent six months, during which time the cyclosporine dose was minimised. He returned to good health, splenomegaly and monoclonal gamma globulin virtually disappearing. He remains well at 16 months post-transplantation.

Clinical events

This case presentation, as summarised above, concerns the post-transplant course of a 55-year old man, J.S., with renal failure due to membrano-proliferative glomerulonephritis, who received an HLA-identical sibling’s kidney on May 11th, 1983. During the operation, atheromatous plaques were removed from the hypogastric artery; this prompted the use of the platelet inhibitor, sulfinpyrazone, from the sixth post-operative day when serum creatinine rose from 145 to 200 µmol/L. He was also given three daily doses of 1.0 g intravenous methylprednisolone at this time and serum creatinine fell to 124 µmol/L by day 11. The immediate post-operative course was otherwise uneventful and he went home at 14 days.

He was then maintained on (a) cyclosporine, in doses determined by regular estimation of serum cyclosporine concentrations; (b) prednisone dose which rapidly decreased to 15 mg on alternate days; and (c) sulfinpyrazone (100 mg, four times daily).
Figure 1. Parameters of cyclosporine dosage and serum concentration, period of sulfinpyrazone administration, and cytomegalovirus titres, for patient J.S. during the first 15 months after transplantation.

Some parameters of J.S.'s post-operative course are illustrated in Figure 1. During the early follow-up months, he complained of listlessness, mild but persistent conjunctivitis, oily blistering in the scalp, gynaecomastia with slight white secretion, increased hair on chest, scalp and eyebrows and a bitter taste in the mouth which was occasionally associated with excessive flow of saliva. During this time, June 1983 to January 1984, mean serum creatinine was 173μmol/L (n=27) despite the high dose of cyclosporine (1300–1500mg/d) which was needed to keep the serum Cys value in the therapeutic rage of 40–200ng/ml.
On admission on January 12th, 1984 (8 months post-transplant), it was found that he had developed splenomegaly and two monoclonal proteins in the gamma globulins (on serum electrophoresis), one IgG (\(\lambda\)), the other IgM (\(\kappa\)), measured at 5.3 and 6.8g/L, respectively, as seen in Figures 2 and 3.

**Figure 2.** Sequential serum electrophoresis patterns, showing monoclonal gamma globulin peaks; IgG and IgM titres of antibody to cytomegalovirus.
There were no other abnormal physical signs on physical examination or extensive tomography. No other abnormalities were found on skeletal X-ray or radionuclide bone scan, or on liver and spleen scan. Haemoglobin was 14g/dl, white blood count $7.8 \times 10^5$/cu.mm without an unusual differential white blood cell count. Platelet count was $168 \times 10^5$/cu.mm. Bone marrow aspiration was refused and biopsy of the enlarged spleen was not contemplated.

Urine and throat secretions were sent for viral culture and blood for viral titres. It was later reported that IgM titres to cytomegalovirus were high. Prior values had been negative. Subsequent titres for IgM and IgG antibody to cytomegalovirus are listed in Figures 1 and 2.

At the time of this admission, sulfinpyrazone was discontinued but cyclosporine administration continued unchanged. Unexpectedly, a threefold increase in serum concentrations of cyclosporine was immediately noted, as shown in Figure 1.

Thereafter, the dose of cyclosporine was reduced to a low total intake and he quickly noted a sense of increased wellbeing. Although the two monoclonal gamma globulins indicated an oligoclonal B-cell lymphoproliferation, it was decided not to give further treatment apart from minimising the degree of immunosuppression.

During subsequent months, the monoclonal abnormalities in serum immunoglobulins have largely disappeared (see Figure 2) and the spleen is no longer
palpable. Renal function is good with a mean serum creatinine (for months 9–15, post-transplant of 161μmol/L (n=21).

Discussion

Cleary et al [1] found evidence for monoclonal or oligoclonal lymphoproliferation in the abnormal lymphoid tissue in all of 10 cardiac transplant recipients, when analysed for immunoglobulin gene rearrangement using the Southern blot DNA hybridisation technique. This characteristic of B-cell lymphomas was found even when there was no immunoglobulin being synthesised in the cells or detectable on lymphoid cell membranes. Nine of these patients died of their lymphoproliferative disease. Others have noted that lymphoma is common in such patients [2,3], who differ from renal transplant patients in that marked reduction or discontinuation of immunosuppression is usually not possible. Starzl et al [4] has recently reviewed post-transplant lymphomas and lymphoproliferative disorders in patients receiving cyclosporine and steroids and have shown that regression of the lymphoproliferation often occurs if immunosuppression is drastically reduced. Thus seven of eight renal transplant recipients are alive, tumour-free, up to several years after marked reduction or cessation of immunosuppression, even though three of them lost the kidney graft from rejection. Thus the line of distinction between lymphoma and reversible lymphoproliferation, in immunosuppressed patients, is quite blurred.

Although there is no tissue diagnosis of lymphoproliferation in this case, the occurrence of splenomegaly and monoclonal lymphoproliferation, and their resolution when cyclosporine dosage was minimised, provides evidence that J.S. had a similar disorder.

Many have noted the association of Epstein-Barr virus infection in such patients [4,5] and have speculated on its role in lymphoma causation. The association in this patient is with a primary cytomegalovirus infection. The relationship between monoclonal lymphoproliferation and primary cytomegalovirus infection, in this instance, is purely speculative, but of considerable interest. The low ratio of T.h to T.cyt/sup in the peripheral T lymphocytes provides further evidence of significant viral infection at the time of maximal ill-health (data not shown).

In an effort to find out if this patient’s cells showed evidence of malignant change, one of our colleagues, Dr Chris Bleakley, Department of Biochemistry, studied the DNA of peripheral blood lymphocytes of J.S. for evidence of gene rearrangement, using DNA hybridisation; these studies have not been completed, but thus far have shown no deviation from normal. Immuno-phenotyping of J.S.’s peripheral blood leucocytes has also been studied by a pathologist, Dr Gordon Bain, looking for an abnormality in the ratio of kappa to lambda light chains on B-lymphocyte membranes, but no such abnormality was found.

Additionally, this case-history shows the interaction of sulfipyrazone and cyclosporine which resulted in administration of an unusually high dose of cyclosporine over an eight month period. This is presumed to be the cause of a lymphoproliferative disease in which cytomegalovirus primary infection may have played a central role.
The case illustrates the state of ignorance of interactions of other drugs with cyclosporine, even though those with phenytoin [6], intravenous sulphadimidine and trimethoprim [7] and ketoconazole [8] have been described. Presumably sulfinpyrazone might complete with Cys for binding sites and thus lead to aberrant metabolism or tissue distribution. Because of clinical evidence of cyclosporine side effects in this case, it is unlikely that the action of sulfinpyrazone was to induce increased metabolism of cyclosporine, such as is the case with phenytoin [5]. Studies of the interaction of these two drugs in vivo are in progress.

Conclusion

1. It is concluded that sulfinpyrazone interfered with either the assay or tissue distribution or metabolism of cyclosporine, making serum cyclosporine-RIA assays invalid as a basis for dosage.

2. Excessive dosage of cyclosporine, caused cyclosporine side-effects (but not nephrotoxicity) and led to lymphoproliferation which had some properties (monoclonality) which are often associated with lymphoid cell ‘malignancy’ in the non-immunosuppressed subject.

3. Primary cytomegalovirus infection played a special role in this lymphoid proliferation.

4. Marked reduction of immunosuppression was associated with disappearance of splenomegaly and the monoclonal peaks in serum electrophoresis, and patient wellbeing was restored. The latter continues at 16 months, post-transplant.

References

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