Acute Myelogenous Leukemia Following Treatment with Cyclosporin A in a Nephrotic Patient

Yuji Ikeda, Takanobu Sakemi, Miwako Matsuzaki and Masayuki Sano

Abstract

We report here a very rare case of a nephrotic patient who developed acute myelogenous leukemia (AML, M2) 8 months after receiving cyclosporin A (CsA) therapy. A 30-year-old man with nephrotic syndrome had been taking diphenylhydantoin (DPH, 300 mg/day) for 6 years for treatment of convulsion and then received treatment of prednisolone and CsA (75 mg/day) for a nephrotic syndrome. Approximately 4 months after CsA therapy began, myeloblasts appeared in his peripheral blood at a ratio of 1%. Four months later, bone marrow aspiration and a biopsy confirmed a diagnosis of AML M2, showing hypercellular bone marrow with 60% leukemic cells. He received induction chemotherapy, which led to a complete remission.

Key words: nephrotic syndrome, malignancy, neoplasm, AML, diphenylhydantoin

Introduction

Cyclosporin A (CsA) was first marketed as an immunosuppressive agent in transplantations and recently has been proven to be effective in the treatment of renal diseases. Although CsA does not have carcinogenic or mutagenic potential (1, 2), the use of the drug has been associated with an increased risk of malignancies due to its immunosuppressive properties (3). We report here a very rare case of a nephrotic patient who developed acute myelogenous leukemia (AML) 8 months after receiving CsA therapy.

Case Report

The patient was a 30-year-old man with a history of several relapses of nephrotic syndrome beginning when he was 5 years old. To control the convulsions due to a traffic accident at the age of 24, he had received diphenylhydantoin (DPH, 300 mg/day) for 6 years.

In February 1995, when he was 29 years old, he was transferred to our hospital for the treatment of nephrotic syndrome. His nephrotic syndrome had been well controlled for a while thereafter, but recurred when prednisolone (PSL) was tapered to 10 mg/day. On May 10, 1996, CsA (75 mg/day) was added to the treatment with PSL (20 mg/day). At the time, laboratory tests showed: hemoglobin 16.9 g/dl, hematocrit (Ht) 50.2%, platelets 133,000/μl, and white blood corpuscles (WBC) 5,900/μl with 70% neutrophil with normal morphology and without atypical cells. On hemograms taken monthly on an outpatient basis for one year, no peripheral blood abnormalities, such as anemia, leukocytopenia, thrombocytopenia, or circulating immature cells, were detected. In September 1996, 4 months after the beginning of CsA therapy, 1.0% of myeloblasts appeared in his peripheral blood. The percentage of myeloblasts gradually increased. On December 4, after 7 months of CsA therapy, his blood cell counts revealed Ht of 47.6%, a WBC of 5,100/μl with 10% myeloblasts and 141,000/μl platelets. Bone marrow examination disclosed normocellular bone marrow with 30% myeloid atypical cells. Because an association was suspected between the increased abnormal cells and CsA therapy, on December 4 the CsA therapy was discontinued. On January 29, 1997, his blood cell counts revealed a WBC of 6,400/μl, with 39% myeloid blasts, mean corpuscular volume 102.5 fl, platelets 121,000/μl, and hemoglobin 16.0 g/dl. Serum concentrations of CsA were 174–284 ng/ml 2 hours after taking it and 7 ng/ml at its trough. The second bone marrow aspiration with flow cytometric evaluation and a biopsy confirmed a diagnosis of AML (M2, according to the FAB classification), showing hypercellular bone marrow with 60% leukemic cells. Chromosomal analysis showed no abnormality. The patient declined to be admitted to the hospital. The level of peripheral myeloblasts rose to 72% with time, and Ht and platelets fell gradually to 42.2% and 92,000/μl, respectively, by July 1997, when he was finally admitted to our hospital. He received induction chemotherapy consisting of enocitabine (BH-AC) and daunorubicin hydrochloride (DNR), which led to a complete remission (Fig. 1).
In experimental studies, it was reported that cyclosporin did not cause cancer in the absence of an initiating event (e.g., chemical mutagen) (6). Hojo et al (7) described a tumor growth-promoting effect of CsA in immunodeficient mice. Herman et al (8) suggested that immunosuppressive therapy might interfere with DNA repair and thus contribute to the increased cancer incidence in transplant patients. Although the tumor-promoting effects of CsA seen in this laboratory setting should not be extrapolated to clinical situations, knowledge of an unwarranted effect of CsA in the induction, growth or behavior of neoplasm would be of utmost importance to clinicians and patients.

Indeed, it is rarely reported that therapy with CsA was solely responsible for the development of neoplasm. In the long-term follow-up of patients with aplastic anemia, the development of myelodysplastic syndrome or acute myelogenous leukemia has been observed. In a study by Ohara et al (9), these clonal disorders were found only in children who had received both CsA and recombinant human granulocyte colony-stimulating factor therapy.

The present case had nephrotic syndrome. The association of nephrotic syndrome with neoplastic disease is well known, although carcinomas and lymphomas are common (10). The patient also received DPH, of which immunosuppressive effects and increased risk of malignant lymphomas have been reported (11, 12). We think that the risk of this nephrotic patient developing AML may be facilitated by synergistic or additive immunosuppressive effects of these two agents. A higher frequency of malignancy has been feared for patients with rheumatoid arthritis and psoriasis, and autoimmune diseases intrinsically increase the risk of neoplasm such as lymphoma (13). However, as more experience is gained with cyclosporin in these fields, there is increasing evidence that the development of cancer is not a great concern, at least when cyclosporin is administered at low doses for intermittent periods and without the concomitant use of other immunosuppressive drugs (14, 15).

The hypothesis of cyclosporin promoting neoplasm in nephrotic patients at risk must also be tested with appropriate epidemiological studies such as cohort or case-control studies.

Unfortunately, there have been no data on the best way to administer and monitor CsA to prevent the development of neoplasm. Our experience suggests that we should ask a patient with nephrotic syndrome detailed questions about his or her drug histories before the start of CsA therapy, and avoiding combination therapies with other immunosuppressants may reduce the risk of malignancy.

**References**


**Picture:**

Figure 1. Clinical course. DPH: diphenylhydantoin, PSL: prednisolone, CsA: cyclosporin A, arrows: chemotherapy consisting of enocitabine and daunorubicin hydrochloride, shaded area: myeloblasts.

**Discussion**

Penn has shown, using data from the Cincinnati Transplant Tumor Registry, that leukemia in general represents about 3% of tumors arising after conventional immunosuppressive non-CsA therapy, but less than 1% after CsA therapy (3). Only 2 patients who developed acute myelogenous leukemia following treatment with CsA have been previously reported. One was a renal transplant patient who developed AML 5 years after treatment with CsA and azathioprine (4). The other was a rheumatoid arthritis patient who developed AML 4 months after the beginning of CsA therapy (5). Our patient developed AML a remarkably short time after CsA therapy began, similar to the latter case.

According to Penn, the most common tumors in patients with CsA were non-Hodgkin’s lymphoma, which accounted for 38% of the total in such patients, compared with 12% in patients who had received conventional non-CsA immunosuppressant; furthermore, this type of tumor in CsA-treated patients appeared a remarkably short time after the start of treatment: an average of 10 months, compared with an average of 43 months after conventional therapy (3). In the present case, it is difficult to explain the association between the development of AML and CsA therapy, because the interval between these events was so short.

In experimental studies, it was reported that cyclosporin did not cause cancer in the absence of an initiating event (e.g., chemical mutagen) (6). Hojo et al (7) described a tumor growth-promoting effect of CsA in immunodeficient mice. Herman et al (8) suggested that immunosuppressive therapy might interfere with DNA repair and thus contribute to the increased cancer incidence in transplant patients. Although the tumor-promoting effects of CsA seen in this laboratory setting should not be extrapolated to clinical situations, knowledge of an unwarranted effect of CsA in the induction, growth or behavior of neoplasm would be of utmost importance to clinicians and patients.

Indeed, it is rarely reported that therapy with CsA was solely responsible for the development of neoplasm. In the long-term follow-up of patients with aplastic anemia, the development of myelodysplastic syndrome or acute myelogenous leukemia has been observed. In a study by Ohara et al (9), these clonal disorders were found only in children who had received both CsA and recombinant human granulocyte colony-stimulating factor therapy.

The present case had nephrotic syndrome. The association of nephrotic syndrome with neoplastic disease is well known, although carcinomas and lymphomas are common (10). The patient also received DPH, of which immunosuppressive effects and increased risk of malignant lymphomas have been reported (11, 12). We think that the risk of this nephrotic patient developing AML may be facilitated by synergistic or additive immunosuppressive effects of these two agents. A higher frequency of malignancy has been feared for patients with rheumatoid arthritis and psoriasis, and autoimmune diseases intrinsically increase the risk of neoplasm such as lymphoma (13). However, as more experience is gained with cyclosporin in these fields, there is increasing evidence that the development of cancer is not a great concern, at least when cyclosporin is administered at low doses for intermittent periods and without the concomitant use of other immunosuppressive drugs (14, 15). The hypothesis of cyclosporin promoting neoplasm in nephrotic patients at risk must also be tested with appropriate epidemiological studies such as cohort or case-control studies.

Unfortunately, there have been no data on the best way to administer and monitor CsA to prevent the development of neoplasm. Our experience suggests that we should ask a patient with nephrotic syndrome detailed questions about his or her drug histories before the start of CsA therapy, and avoiding combination therapies with other immunosuppressants may reduce the risk of malignancy.

**References**


