

CASE REPORT

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Disseminated Polyomavirus Infection in Chronic Lymphocytic Leukemia (CLL) Following Salvage Chemo-Immunotherapy

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Abstract: Chemo-immunotherapy treatment for chronic lymphocytic leukemia (CLL) induces high response rates and improves progression free (PFS) and overall survival (OS) as compared to chemotherapy alone. The fludarabine, cyclophosphamide, and rituximab (FCR) regimen is a standard first line and salvage treatment for CLL. However, FCR is associated with significant immunosuppression and an increased risk of opportunistic infections (OIs). Here, we report a case of disseminated polyomavirus infection despite standard anti-infective prophylaxis in a relapsed CLL patient in a sustained clinical complete remission (CR) after FCR therapy.

Keywords: CLL, FCR, BK virus, polyomavirus, opportunistic infections

Lymphoma and Chronic Lymphocytic Leukemias 2010:2 7–10

doi: [10.4137/LCLL.S5877](https://doi.org/10.4137/LCLL.S5877)

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Introduction

CLL is the most common leukemia in the Western world. Although generally slowly progressive, CLL with poor prognostic features has a median survival of only a few years. Chemo-immunotherapy has significantly prolonged survival in poor prognosis CLL and more indolent CLL that has progressed to a point that merits treatment. Unfortunately, chemo-immunotherapy induces substantial immunosuppression, which predisposes to life threatening OIs. This case report describes a patient who succumbed to disseminated polyoma (BK) virus despite achieving a sustained clinical CR with FCR.

Case

CT, a 66 year old male, presented in 1/2003 with asymptomatic lymphocytosis and palpable peripheral lymphadenopathy (LNs). He had a history of essential hypertension (HTN), mild chronic obstructive pulmonary disease (COPD) and 8 years without relapse after radical prostatectomy for early stage prostate cancer. On physical exam, he had bilateral cervical and axillary LNs less than 2.5 cm in maximum dimension. Computerized tomography (CT) of chest, abdomen and pelvis revealed mediastinal and retroperitoneal LNs, separately less than 3 cm with a 10 cm cluster of intra-abdominal LNs. His complete blood count (CBC) had a white blood count (WBC) of $24.5 \times 10^3/\text{cc}$ with 32% neutrophils and 63% lymphocytes, and a normal hemoglobin and platelet count. His B2 microglobulin was elevated (2.1) but his lactate dehydrogenase (LDH) and quantitative IgG, IgA and IgM were normal. His bone marrow (BM biopsy) showed 90% involvement with a nodular pattern CLL, which was CD38- by fluorescence associated cell sorting (FACS). Cytogenetics revealed that 2 of 20 metaphases had a +12 chromosomal abnormality.

The patient received fludarabine and rituximab (FR) for 4 cycles from 4–7/03 and experienced a partial response (PR). A rising WBC and enlarging LNs prompted 6 cycles of FR, from 11/04 to 4/05, and he again had a PR. By 2/07, his rising WBC and now palpable LNs up to 5 cm triggered treatment with fludarabine, cyclophosphamide and rituximab (FCR). He received neutropenia prophylaxis with pegfilgrastim (N), 6 mg subcutaneously (SC) the day following FCR, and OI prophylaxis

with trimethoprim-sulfamethoxazole (TMP-SMX), one DS tablet 3 times per week, and valacyclovir (Val), 500 mg twice daily. After 4 cycles of FCR, he developed shortness of breath and diffuse pulmonary infiltrates. He was admitted and treated with 3 weeks of high dose (20 mg/kg TMP each day) TMP-SMX intravenously for bronchoscopy proven pneumocystis pneumonia (PCP). There was no evidence of a viral pneumonia, and he recovered fully. At that point, he was in a clinical CR.

After recovering from Herpes zoster of the T10–12 dermatomes of the right chest, the patient agreed to repeat treatment of his then progressive CLL in 10/08. He was started on a 2nd course of FCR with pegfilgrastim, TMP-SMX, and VAL infection prophylaxis. He completed 6 cycles by 2/09 with a clinical complete response and recovery of his CBC to normal. His anti-infection prophylaxis was continued for 4 months after finishing FCR.

His routine blood tests first showed renal insufficiency in 6/09 with a BUN of 19, Creatinine (Cr) of 1.5 and an estimated glomerular filtration rate (GFR) of 56 cc/min. When his GFR worsened to 36 in 7/09, he underwent a workup and medication adjustment by Nephrology. By 9/09, after recovering from a COPD exacerbation treated with a prednisone taper, his renal function had declined dramatically (GFR = 12). He was hospitalized, given supportive care and underwent a kidney biopsy. Pathology at Cedars Sinai (Los Angeles, CA) diagnosed extensive polyomavirus infection by electron microscopy and immuno-fluorescence microscopy with immuno-staining for polyomavirus. His urine contained high levels of both BK and JC virus DNA, and was negative for CMV DNA by quantitative polymerase chain reaction (PCR). An Infectious Disease (ID) consultant initiated cidofovir 1 mg/kg ideal body weight (IBW) intravenously every 2 weeks from 9 through 12/09.^{1–3} Unfortunately, the patient became hemodialysis dependent.

In 4/10, the patient became progressively short of breath and was hospitalized with a multi-lobe pneumonia and altered mental status. Bronchoscopy and lung biopsy revealed disseminated polyomavirus confirmed by both immuno-histochemistry and in situ hybridization positive for both BK and JC viruses. Lumbar puncture revealed 8 million copies of BK virus DNA/micro liter in CSF and blood contained 1 million copies BK DNA/micro liter by



quantitative PCR. JC and CMV tests were negative. During this time the patient was treated for polyomavirus with ciprofloxacin, leflunomide, steroids and IVIG,⁴⁻⁷ without benefit. At that point, the patient and family decided to stop antibiotics and hemodialysis, and the patient was discharged home on hospice. His CLL remained in a clinical CR.

Discussion

CLL is associated with both increased auto-immunity and immunosuppression, particularly hypogammaglobulinemia and neutropenia.⁸ Most effective treatments for CLL cause additional immunosuppression. Purine analogue chemotherapy, like fludarabine, causes lymphopenia, which is often profound and persists for months up to several years after therapy.⁹ The lymphopenia involves both B and T lymphocytes, particularly CD4+ helper cells.⁹ Fludarabine also induces neutropenia, especially in repeat treatments. In the FR and FCR regimens, rituximab (R) substantially improves response rates and progression free survival but exacerbates the B cell lymphopenia and neutropenia with fludarabine.¹⁰ There is an increased risk of opportunistic infections, including pneumocystis carinii pneumonia (PCP) and disseminated herpesvirus infections, particularly involving cytomegalovirus (CMV).¹¹ TMP-SMX, in any of several different dosing regimens, is used to prevent PCP and decrease bacterial infections. Acyclovir—type anti-viral drugs, like valacyclovir, are used to suppress reactivation or dissemination of CMV and other herpesviruses.¹² The optimal duration of prophylactic anti-microbials once chemo-immunotherapy is stopped is unclear. While lymphopenia and immunosuppression can persist after treatment is stopped, there may be less need for infection prophylaxis if the therapy has induced a major clinical response.¹²

Polyomaviruses comprise a family of DNA viruses, including JC, BK, SV40 and a novel Merkel cell polyomavirus.¹³ JC and BK viruses commonly cause sub-clinical infections in children. By adulthood, there is a 60%–85% sero-prevalence.¹⁴ Clinically, significant infection can occur in the setting of immunosuppression, but there is no clear link to human malignancy from the most common polyomaviruses, BK and JC.¹⁵ Likely because BK viruses have tropism for genitourinary epithelium, BK viruses can cause nephritis and interstitial cystitis in renal transplant patients.¹⁶

There have been two well documented cases of BK virus nephropathy in a patient with CLL.^{17,18} As in our patient's case, treatment with IV cidofovir failed both to control the kidney damage and to suppress viral replication, as documented by rising BK DNA levels.^{17,18} Several cases of progressive multi-focal leukoencephalopathy (PML) caused by JC virus have been reported in CLL patients treated with fludarabine,^{19,20} including one case with JC virus documented in cerebrospinal fluid (CSF) and which progressed despite treatment with cidofovir.¹⁹ As with our patient, a fatal case of polyomavirus pneumonia was documented in a patient with CLL undergoing chemotherapy treatments.²¹ In addition to PCP and non-neutropenic infections,^{22,23} rituximab has been associated with Hepatitis B virus reactivation and JC virus-induced PML.^{22,23}

Our patient illustrates the challenge of opportunistic infections, particularly reactivation of latent viruses that can occur in CLL patients despite receiving effective chemo-immunotherapy. Even standard anti-microbial prophylaxis with TMP-SMX and VAL and amelioration of chemotherapy-induced neutropenia with pegfilgrastim failed to prevent either PCP or progressive polyomavirus infection. The BK virus did not respond to cidofovir and other anti-polyoma virus therapy, as described in several other CLL patients.¹⁷⁻²¹ In addition, our patient's CLL was not treatment refractory but rather had been in a sustained clinical complete response over 1 year after completing FCR.

There is no established prophylaxis for polyomavirus reactivation and limited efficacy of treatment for established infection. With CLL patients undergoing repeated courses of chemo-immunotherapy, clinicians need to be vigilant for less common opportunistic infections, particularly reactivation of latent, non-herpes family viruses. Perhaps earlier detection and more aggressive treatment than single agent cidofovir or leflunomide could yield better outcomes with polyomavirus infections in CLL.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest.



The authors confirm that they have permission to reproduce any copyrighted material. Written consent was obtained from the patient or relative for publication of this study.

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