Immunosuppressive treatments in Crohn's disease induce myelodysplasia and leukaemia

To the editor: We report on a pediatric and an adult patient suffering from Crohn's disease (CD), treated with mercaptopurine (6-MP) and anti-TNF-α therapy, who respectively subsequently developed MDS with monosomy-7 and acute myeloid leukemia (AML). Although a link between exposure to 6-MP and anti-TNF-α and malignant lymphomas has been documented [1], the risk of developing leukemia or myelodysplasia (MDS) has not been clearly ascertained. Recent studies have shown that a higher risk of malignancies is found when patients on 6-MP, have an associated deficit of its catabolic enzyme thiopurine methyltransferase (TMPT) [2]. Heterozygousity or absence of TPMT gene is associated with myelosuppression, while anti-TNF-α therapy may favor malignancies possibly increasing the risk of developing MDS/leukemia.

Case#1: A 14-years-old male with CD since the age of 8 years (January 2001). Blood count on presentation: Hb 8.8 g/dL, Wcc 21.3 $\times$ 10^9/μL, Platelet 873 $\times$ 10^9/μL. He was commenced on prednisolone (25 mg PO OD). In June 2001 after presenting with new bloody-diarrhea, oral prednisolone was discontinued and 6-MP (50 mg PO OD) was commenced. In April 2003 due to persistent diarrhea weekly anti-TNF-α was started (100 mg IV). In May 2003 he became transfusion-dependent and bone marrow studies showed MDS-erythrodisplasia with monosomy-7. Enzymatic study documented TPMT heterozygousity. In November 2004, a HLA-matched sibling transplant was performed. The patient is currently well 5 years and 8 Months post-HSCT; his last chimerism-study showed 100% donor-chimera.

Case#2: A 21-year-old girl, suffering from CD since November 2006. She was initially treated with prednisone (1 mg/Kg PO OD), then in July 2007 she was started on mesalazine (1200 mg PO BD) and budesonide (Entocort®) (4.5 mg TDS). In September she was commenced on 6-MP (50 mg once a day PO) up until December 2008 when she complained of severe diarrhea. Anti-TNFα was started and continued up to May 2009, when she developed thrombocytopenia and leukocytosis (WBC 15800/μl, Hb 10g/dl, Plts 88000/μl) high fever and laterocervical lymphoadenopaties. A diagnosis of AML M5a was made. She was started on induction chemotherapy with idarubicine 12 mg/m^2 (days 1,3,5), cytarabin (100 mg/m^2 days 1–7), and etoposide (100 mg/m^2 days 1–3), followed by consolidation, with CR. She is currently well, 100% donor-chimera 8 months post allogeneic sibling HSCT.

The presence of heterozygosity for TPMT in case#1 is in keeping with previous studies on intermediate or absent TPMT activity and hematopoietic malignancies. Moreover, CD incidence has shown a constant increase over the past 20–30 years in Western Countries, a pattern mirrored by epidemiological studies of childhood-leukemia [3,4]. Therefore, the existence of a common pathogenic-agent involved in CD and MDS/leukemia, cannot be out ruled. Whorwell et al. identified a virus from CD patients causing cytopathic effects in vitro [6] and similar isolates were demonstrated by Rovigatti et al. from childhood leukemia/lymphoma samples [5]. Additional studies are warranted to clarify the role of immunosuppressive drugs in CD progression toward MDS/leukemia and the hypothesis of a common pathogenic agent between these conditions.

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Effect of oral itraconazole on the pharmacokinetics of tacrolimus in a hematopoietic stem cell transplant recipient with *CYP3A5*3/*3*

To the editor: A 21-year-old woman was diagnosed with Hodgkin lymphoma and went into remission with ABVD combination chemotherapy, but relapsed with multiple nodules in the lung fields. She received an allogenic bone marrow transplant from an one-locus mismatched, unrelated donor in October 2009. She was conditioned using a reduced-intensity regimen of fludarabine 25 mg/m^2 daily for 5 days and melphalan 90 mg/m^2 daily for 2 days. Before starting the conditioning regimen, prospective analysis of the *CYP3A5*3* allele was performed using PCR-RFLP [1]. Tacrolimus 0.03 mg/kg daily (from Day −1) and short-term methotrexate (Day 1, 15 mg; Day 3, 10 mg; Day 6, 10 mg) were also given to prevent graft vs. host disease (GVHD).

On Day 40, we switched from continuous infusion of tacrolimus (0.03 mg/kg/day) to tacrolimus capsules at a dose of 0.06 mg/kg/day, given in equally divided doses every 12 h (at 08:00 and 20:00). On Day 48, we started coadministration of itraconazole. After itraconazole instillation at 200 mg twice daily (10:00 and 22:00) for 2 days (Days 48 and 49), the patient was switched to itraconazole oral solution given at 6:00 each morning, beginning on Day 50. Each day for 2 weeks thereafter, venous blood samples were taken just prior to and 2 h (C_{2h}) after tacrolimus administration (08:00) for determination of the tacrolimus, itraconazole, and hydroxyitraconazole concentrations.

The C_0 of tacrolimus measured before coadministration of itraconazole were controlled in the range of 5.7 to 8.3 ng/mL. On Day 50, the C_0 and C_{2h} for tacrolimus had increased to 16 and 102.4 ng/mL, respectively. From Days 51 to 55, we gradually reduced the tacrolimus dosage from 1 mg/day (0.03 mg/kg/day) administered in two doses to 0.25 mg/day (0.004 mg/kg/day) administered in one dose. Clinically, acute skin GVHD (grade 1) appeared on Day 57, but it was relieved within several days by application of an external steroid. Consequently, the maintenance dosage of 4 mg/day (0.06 mg/kg/day) of tacrolimus alone administered in two doses was reduced to 0.10 mg/day (0.0015 mg/kg/day) with coadministration of itraconazole, which was 1/40 of the dose before combination with itraconazole (Figure 1).

Itraconazole inhibits tacrolimus metabolism via CYP3A, thereby increasing its blood levels [2]. In this case, the C_{2h} for tacrolimus was increased by itraconazole, but the elimination half-life of tacrolimus was always 6.0 ± 0.9 h (range 5.1–7.3 h), which was nearly the same as was obtained with tacrolimus alone. In addition, the drug interaction between tacrolimus and itraconazole was first noted on the day oral administration of itraconazole was begun, which suggests it occurs mainly via intestinal CYP3A.

We were able to predict an approximate next trough concentration for tacrolimus by monitoring the C_0 and C_{2h}, and to quickly adjust the daily tacrolimus dose to one appropriate for achieving the desired blood-trough target level (5 to 15 ng/mL). In addition, to reduce the peak concentration, we administered tacrolimus twice daily, even with itraconazole coadministration, and we avoided trying to control only the trough concentration to less than 20 ng/mL by administering the drug only once daily.

Patients with genetic variants of CYP3A5 can be very sensitive to tacrolimus, and the effect of itraconazole after combined administration can appear more quickly than in patients carrying the *CYP3A5*1* allele [3]. Combining tacrolimus and itraconazole requires that very careful attention be

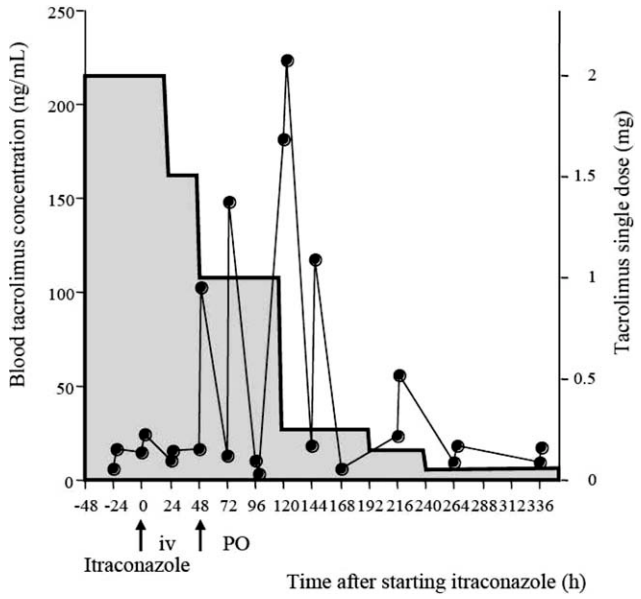

Fig. 1. Blood concentration-time profiles (solid circles) after a single dose (gray box) of tacrolimus before and after coadministration of itraconazole to a patient carrying the *CYP3A5*3/*3* genotype.

paid; however, one may be able simply calculate the next tacrolimus dosage by the monitoring C_{2h}, even in patients with the *CYP3A5*3/*3* genotype. Prospective analysis of *CYP3A5* polymorphism and monitoring of both C_0 and C_{2h} would seem to be extremely important for safe and reliable immunosuppressive therapy with tacrolimus.

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Post-transplant lymphoproliferative disorder presenting as multiple myeloma

To the editor: Post-transplant lymphoproliferative disorders (PTLD) comprise a heterogeneous group of lymphoid proliferations, which have been a recognized complication of solid organ and hematopoietic stem cell transplantation for 40 years. The majority of these disorders are thought to be driven by EBV infection and subsequent proliferation of B cells in a weakened host. Risk factors include lack of previous exposure to EBV [1], or aggressive immunosuppression with agents such as cyclosporine or OKT3 [2]. Post transplant multiple myeloma is a rare entity, with only a few case reports in the literature [3–12]. Here we report a case of aggressive EBV-associated myeloma that occurred in a patient after retransplantation for renal graft failure.

A 57-year-old man with history of renal/pancreas transplant for diabetic nephropathy in 1991 was diagnosed with a plasmacytoma of the lumbar spine in 2001. The EBV status of the plasmacytoma is not known. He was treated with radiation, cyclophosphamide, and thalidomide and went into remission. He gradually developed kidney allograft rejection after treatment for the plasmacytoma and needed to resume dialysis in 2004, however the pancreas transplant remained functional. He underwent another cadaveric kidney transplant in 2007 at which time there was no evidence of systemic myeloma, including on biopsies of the failed kidney. The patient's immunosuppression post transplant was prednisone 5 mg daily, tacrolimus 1 mg bid and mycophenolate mofetil 1 g bid.

The patient developed acute rejection of his pancreas approximately 2 weeks after the transplant and was treated with a course of OKT3. His pancreas function improved, but then a month later, on repeat biopsy showed ongoing acute rejection; therefore he was given another brief course of OKT3. The patient did well until 4 months later; he was noted to have an increase in his creatinine, hypercalcemia, and left sciatic pain. Serum and urine protein electrophoresis were positive for monoclonal kappa light chains and peripheral blood quantitative PCR of Epstein-Barr virus (EBV) EBNA-1 gene revealed 123,800 copies/ml whole blood (normal $<$1000, or 5.1 log copies with normal $<$3.0) [13].

Ten days later, the patient was admitted for fever, anorexia, night sweats, weight loss, productive cough, back and abdominal pain. Exam was significant for the patient appearing uncomfortable, but no respiratory distress. There were a few shotty lymph nodes in the neck, heart exam revealed tachycardia with a 2/6 systolic murmur, and there was diffuse abdominal tenderness with no masses. There were chronic fibrotic changes in the skin on the lower extremities. Laboratory values included Hgb 12.0 mg/dl, WBC 5.6 $\times$ 10^9/L, Plt 170 $\times$ 10^9/L, Cr 1.76 mg/dl, and Ca 12.8 mg/dl. The EBV titer had increased to 2, 693,900 copies/ml whole blood. CT scan of chest/abdomen/pelvis revealed a new 2 cm $\times$ 6 cm $\times$ 3 cm pleural-based mass between the right 5th and 7th ribs, new hepatosplenomegaly, two new $\sim$3 $\times$ 3 cm masses involving the left posterior iliac wing and left L4 spinous process, and soft tissue masses involving left scapula and right femoral neck. CT guided biopsies of the right chest wall and right femoral masses revealed abnormal plasma cells that on immunohistochemistry were positive for CD138, EMA, and dim 56, and lacked PAX5, CD20, CD43, CD45. The neoplastic cells were positive for EBV by in-situ hybridization. This was interpreted as consistent with a plasmacytoma, EBV positive post-transplant lymphoproliferative disorder (PTLD).

The patient's immunosuppression was discontinued, and treatment for the multiple myeloma was initiated with dexamethasone 40 mg IV daily for 4 days. Because of the presence of EBV, the patient was also started on gancyclovir and rituximab 375 mg/m2 weekly to eliminate CD20+ B-cells that may harbor EBV. However, the patient's status gradually declined with respiratory and renal failure. The EBV PCR titer declined, however there was no change in the lung masses based on portable chest X-rays. The patient died because of respiratory failure 10 days after initiating treatment.

This case report illustrates a rare case in which PTLD presented as disseminated EBV-positive multiple myeloma after receiving aggressive immunosuppression for organ transplant rejection. EBV infection produces self-limiting illness in young adults and persists as latent infection in B cells. In vitro, EBV can transform B lymphocytes into immortalized lymphoblastoid cell lines [14]. EBV-specific cytotoxic T-lymphocyte responses are impaired in patients who are treated with immunosuppressants, and this in turn can lead to lymphoproliferative disorders [15]. Early PTLD lesions can present as plasmacytic hyperplasia, which has been shown in some cases to evolve into a plasma cell dyscrasia, [4] however, this is less common than other lymphoid malignancies [3]. In case series, the incidence of PTLD myeloma is reported to be $<$1% [5]. Review of literature showed a number of case reports and series of post transplant multiple myeloma [3–12,16]. Reported cases for which treatment and outcome data are known are listed in Table I. In one study, the incidence of post transplant myeloma was associated with older age, transplant from deceased donor, and ATG treatment [17]. In a large retrospective study, analyzing 7040 patients who received solid organ transplantation, of the 78 patients who developed PTLD, only 7 had plasma-

TABLE 1. Clinical Characteristics of Selected Cases of PLTD Myelomas

Reference Year (Citation)	Type of transplant	Type of M protein	M protein at diagnosis (g/dl)	Age at diagnosis of PTLD (yrs)	Time since transplant	EBV status of tumor	Immunosuppression	Treatment in addition to reduction of immunosuppression	Response
Joseph et al 1994(3)	Liver, Kidney	IgG *k*	3.58	52	15 mos	+	CSA, Azathioprine, Methyl Prednisone	Radiation	CR
Dunphy et al 2002(4)	Heart	NA	NA	57	13 yrs	NA	CSA, Azathioprine, Prednisone	Cytarabine, Bleomycin, Methotrexate, Vincristine	Unknown
Sun et al 2004(7)	Liver	IgG *k*	0.2	67	2 yrs	+	CSA	Radiation/Cytoxan	CR
Sun et al 2004(7)	Kidney	K	0.81	55	3 yrs	+	CSA, MMF	Combination Chemo, Dexamethasone	PR
Sun et al 2004(7)	Kidney	IgG *k*	2.99	61	20 mos	–	Tacrolimus, Dexamethasone	Dexamethasone	PR
Ancin et al 2000(8)	Kidney	IgG *k*	5.5	47	3 yrs	+	CSA, Prednisone	Cyclophosphamide, mitoxantrone, vincristine and prednisone	CR
Au et al 2003(10)	Kidney	None	NA	65	13 yrs	+	CSA, Prednisolone	Combination chemotherapy, ASCT	Died
Papadaki et al 2000(11)	Kidney	IgG *k*	NA	47	12 yrs	+	CSA, Azathioprine, Prednisone	Cyclophosphamide, Dexamethasone	Died in CR
Tcheng et al 2006(12)	Kidney	IgG *k*	1.09	16	11 yrs	+	CSA, MMF, Prednisone	VAD	CR

Abbreviations: CR: complete response; CSA: Cyclosporine; MMF: mycophenolate mofetil; mos: months; NA: Not available; PR: Partial response; VAD: VIncristine, Adriamycin, Dexamethasone; yrs: Years.

cytoma/multiple myeloma [15]. However, this is higher than the incidence in the general population. About 75% of these plasma cell dyscrasias were found to be EBV positive [16]. The reasons for the lower incidence of myeloma compared with lymphoma in the transplant patients are not clear. One observation is that, as myeloma is a disease of elderly and transplant patients in general are younger, overall incidence might be lower in the transplant group [5]. The receptor for EBV on mature B cells, CD21, is not found on plasma cells, which may also account for the lower risk of myeloma [12].

Our patient received aggressive immunosuppression with OKT3 for acute allograft rejection before the diagnosis of his recurrent myeloma. There are a number of retrospective studies examining the role of aggressive immunosuppression and the development of PTLD. In general, the use of OKT3 has been associated with an increased risk of PTLD [2,18,19], although there were a few studies in which there was no association [20,21]. The risk of PTLD may be related to the total degree of immunosuppression, rather than to a single specific agent. Anti-viral prophylaxis has been used to prevent PTLD, [18,22,23] however, its benefit has not been demonstrated in a randomized controlled trial. An important issue is whether it is safe for kidney transplant patients with PTLD who have a failed graft to undergo retransplantation. One small retrospective study has shown that retransplantation can be safely done, after waiting 2 years after complete remission [24]. The minimal waiting time is unknown.

Initial management of patients with PTLD includes reduction of immunosuppresion [25]. Plasmacytic hyperplasia and monoclonal gammopathies have been shown to respond to decrease in the immunosuppression alone [25]. However in patients who develop monomorphic plasma cell dyscrasias, usual practice is to treat systemically with chemotherapeutic agents similar to immunocompetent patients [3].

In summary, plasmacytoma and multiple myeloma need to be recognized as part of the spectrum of PTLD. A reduction in immunosuppression plus standard therapy should be given to those patients who can tolerate it. The role of gancyclovir and rituximab in the management of EBV-positive myeloma PTLD is unclear. Close monitoring for recurrence, and avoidance of extremely high-intensity immunosuppression in patients with a history of PTLD is warranted.

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