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Donor Monoclonal Gammopathy May Cause Lymphoproliferative Disorders in Solid Organ Transplant Recipients

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Prior research on donor monoclonal gammopathy of undetermined significance (MGUS) has been inadequate regarding the risk for lymphoproliferative disease in solid organ transplantation recipients. Seven organ recipients from two different donors developed lymphoproliferative disease. The origin of the malignancy was determined by use of microsatellite analysis, and the plasma of the two donors was analyzed with the use of electrophoresis. The clinical courses of the seven recipients were followed for 36–60 months. One donor transmitted lymphoplasmacytic lymphoma to two kidney recipients and MGUS to a liver recipient, all IgMκ. A second donor caused IgGλ myeloma in two kidney and one liver recipient, and IgGλ gammopathy in a heart recipient. Transplant nephrectomy was performed in three kidney recipients and remission was achieved. The fourth kidney recipient has kept the graft and the disease has progressed. The liver recipient died from myeloma. There were no clinical signs of lymphoproliferative disease in the donors, but retrospective serum analyses showed M-components, IgMκ (37 g/L) and IgGλ (8 g/L). Donors with MGUS may cause donor-transmitted malignancies via passenger lymphocytes/plasma cells in solid organ recipients. The results call for a large register study of the incidence of donor MGUS and lymphoproliferative disease in their recipients.

Abbreviations: CMV, cytomegalovirus; EBV, Epstein–Barr virus; LPL, Lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia); M, monoclonal; MGUS, monoclonal gammopathy of undetermined significance; MSA, micro satellite analysis; PCR, polymerase chain reaction; PEL, primary effusion lymphoma; PTLD, posttransplant lymphoproliferative disorder; SOT, solid organ transplantation

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Introduction

The immediate risk of transmitting malignant disease along with the graft in solid organ transplantation (SOT) is estimated to be as low as 0.05% (1,2). In cases when the malignancy of the donor is known, however, a risk of transmission has been shown (3). This contraindicates transplantation from donors with most malignancies (4).

Posttransplant lymphoproliferative disorders (PTLDs) are well-recognized complications that occur after SOT (5). PTLDs represent a spectrum of disorders from Epstein–Barr virus (EBV)-driven reactive changes in lymphoid organs via polymorphic PTLDs to full-blown lymphomas, of which diffuse large B-cell lymphoma is the most common form. The incidence of PTLDs in SOT studied in 193 905 recipients followed from 1999 to 2008 was 1.58% (6). PTLDs are regarded as deriving from recipient cells as *de novo* tumors in the immunosuppressed patient after transplantation. In many cases, a defective immune surveillance of the EBV is known to be important (7).

Monoclonal gammopathy of undetermined significance (MGUS) is a common condition that is defined by a serum monoclonal (M) protein of κ or λ type, but it does not fulfill other criteria for malignant disease (8). The prevalence in the general population increases with age and is 4% in whites older than age 50 (9). Usually, the condition is benign and asymptomatic, but it may progress to multiple myeloma, lymphoplasmacytic lymphoma (LPL [Waldenstrom macroglobulinemia]), or other kinds of lymphoproliferative disease accompanied by an M component. The risk of progression into a lymphoproliferative disorder is approximately 1% per year (10). The risk increases with non-IgG M protein, M protein concentration >15 g/L, altered serum ratio of κ/λ free light chains, and light chain proteinuria. In SOT recipients, MGUS has been found in 0.7% before transplantation and develops in an additional 0.5% during the posttransplantation period (11). For a known MGUS patient, immunosuppression has not been shown to increase the risk of progression (12).

It is so far not known how MGUS in SOT donors will affect the recipients. A premalignant condition could be potentially transmitted from the donor and develop into one of a spectrum of lymphoproliferative diseases. Among blood donors, MGUS has a prevalence of 1.3%, but its transmission to a recipient has never been described (13). In Scandinavia, organ donors are older than blood donors; in our center, about 10% are 70 years or older.

Multiple myeloma in general is defined according to International Myeloma Working Group 2014 criteria: >10% bone marrow plasma cells, > 30 g/L M component in serum, and/or end organ damage (CRAB criteria, as specified by hypercalcemia, renal failure, anemia, and bone lesions) (14). LPL Waldenström's macroglobulinemia is defined based on the World Health Organization criteria as the presence of lymphoplasmacytoid cell infiltration in bone marrow or other tissue and the presence of an IgM component (15). Most cells express surface and cytoplasmic Ig and, in the majority of cases, IgM with κ light chain restriction.

Plasmacytoid PTLD presents as a monoclonal plasma cell proliferation (16) and is uncommon in transplanted patients, although in a recent register study, a 1.8 increased risk of plasma cell neoplasms was seen after SOT (17).

The subject origin of the lymphoproliferative cells may be determined by the microsatellite allelotyping (MSA) used in forensic investigations and paternity identification. MSA can also be used to discriminate between donor and recipient origin in tumors that arise in organ transplants (18–20).

This study reports the transmission of lymphoproliferative disorders to seven solid organ recipients from two donors. At the time of organ retrieval, there were no records or clinical signs of hematologic disease in the donors, but retrospectively, both showed a monoclonal gammopathy. Paraproteins corresponding to those in the donors developed in all the organ recipients. We hypothesize that testing or saving a pretransplantation sample of donor plasma for later analysis for the presence of M components may help to predict the risk of donor transmission and alert the physician to the possible risk of serious disease in organ recipients.

Methods

Study design and patients

This study is a clinical follow-up of seven recipients of transplants from two donors in 2010–2011. Donors fulfilled brain death criteria while being ventilated in an intensive care unit. The study was performed according to the Helsinki Declaration and followed the recommendations of the local ethical board.

Organ donors

Donor A was a 60-year-old man with chronic obstructive lung disease who arrived at the emergency department with sudden cardiac arrest. The coronary vessels were without calcifications, and ultrasonography of the heart revealed enlargement of the right atrium, indicating the possibility of pulmonary embolism. There was no indication of any current disease other than chronic obstructive lung disease either at physical examination or in the patient's history. Standard laboratory blood tests showed low hemoglobin (106 g/L) but no other indications of disease. Kidneys and liver were donated to three recipients. There were no enlarged lymph nodes noted during the donor operation. The donor was EBV IgG positive.

Donor B was a 65-year-old woman with history of gastritis but no other significant disease who fell unconscious and was diagnosed with a large subarachnoid bleed. There was no indication of current disease either at physical examination or in the patient history. Standard laboratory blood tests and physical examination did not show any indications of current disease other than the subarachnoid bleed. There were no enlarged lymph nodes noted at the donor operation. She became the donor of kidneys, liver, and heart to four different recipients. The donor was EBV IgG positive.

Histopathologic evaluation

All the biopsy samples were stained with hematoxylin–eosin and, in addition, with special stains when needed. Immunostaining was performed on paraffin sections after antigen retrieval by using an automated procedure (EnVision™ Flex High pH (Link) detection kit Dako K8000, Copenhagen, Denmark). The following monoclonal antibodies were used to type the lymphoid cell tumors: CD3 (IR503, Dako), CD20 (IR604, Dako), CD38 (NCL-CD38-290, Novacastra, Leica, Newcastle, UK), CD79a (IR621, Dako), CD138 (IR642, Dako), κ light chains (A0191, Dako) and λ light chains (A0193, Dako).

Microsatellite analysis

MSA was used to ascertain whether the different tissues originated from the donor or the recipient. A commercially available MSA system was used (Power Plex 16 HS System, Promega, WI). Areas containing tumors were obtained from paraffin sections and compared with both pretransplantation recipient tissue and donor tissue from the implant biopsy samples. DNA was extracted and analyzed at 16 different polymorphic microsatellite loci, including *x/y*. Loci were considered separate if the donor and recipient produced two bands that were clearly different from each other. Analyses were considered to be concordant when identical or practically identical bands were detected.

M component detection

Serum M protein (monoclonal Igs) was analyzed using capillary zone electrophoresis (Capillarys HR, Sebia Capillarys 2, Cedex Evry, France). The M protein concentration (g/L) was calculated from the relative size of the M spike area in the electropherogram in relation to the total protein measured using colorimetric assay (Cobas, Roche Diagnostics, Mannheim, Germany). The identification of M proteins (immunotyping) was made with immunofixation (Hydragel IF, Sebia Hydrasys 2). Because the serum sample volume from the deceased donors was limited (200 μL), an immunochemical quantification of free light chains could not be performed.

Results

The solid organ recipients are grouped into those who received organs from donor A and those who received

organs from donor B. The demographics of the recipients, including immunologic data and immunosuppression, are presented in Table 1.

Recipients from donor A with IgMκ

Kidney recipient A1: A plasmacytic PTLD was diagnosed by renal biopsy in a male subject 14 months after kidney transplantation (KTx) (Table 1) due to increasing serum creatinine. This patient had an earlier liver transplantation. There was no focal mass in the transplanted kidney at ultrasound, but dense plasma cell infiltration with strong κ chain dominance was found in a biopsy (Figure 1). Serum electrophoresis showed a monoclonal Ig type IgMκ, 1–2 g/L. Serum and blood polymerase chain reactions (PCRs) were negative for EBV and cytomegalovirus (CMV). About 24 months after KTx, the IgMκ level increased to 12 g/L and creatinine increased to 160 μmol/L. Repeated staging was performed without showing signs of extrarenal tumor. Because morphologic and immunohistochemical examinations revealed positivity to CD20, CD38, and CD138, as well as the type of the M component, the tumor was defined as an LPL. MSA confirmed the donor origin of the lymphoplasmacytic cells. Mycophenolate mofetil was withdrawn and treatment with rituximab was initiated but had no effect on the M component. Transplantectomy was performed 33 months after KTx and pathology confirmed LPL (Figure 1). Although the transplant recipient still received immunosuppression (tacrolimus and prednisolone) due to his liver graft, the IgMκ level then decreased from 5–6 g/L to 2.2 g/L at month 51 after KTx (Figure 3).

Kidney recipient A2: Serum electrophoresis was performed 2 years after KTx on this male subject due to the findings in the paired kidney recipient. This showed a paraprotein-type IgMκ, of 10 g/L (Table 1). A kidney biopsy sample revealed lymphoplasmacytic cell infiltration identical to that seen in recipient 1, and MSA confirmed the donor origin of the infiltrating clonal cells. Clinical findings, progression, and treatment were similar to those of recipient 1 (Figure 3). This patient did not agree to transplant nephrectomy. At 48 months, IgMκ rose to 31 g/L and a computed tomography scan showed small lytic changes of unknown significance in the skeleton of the pelvis and lower spine. A bone marrow specimen showed infiltration of lymphoplasmacytic cells positive for CD138, CD20, and CD79a.

Liver recipient A: A small M component was detected by screening 3 years after liver transplantation. Serum electrophoresis showed a weak band of IgMκ estimated to 0.25 g/L and a minimal trace of Bence Jones protein, type κ. Some 48 months after liver transplantation, an M component of 5 g/L (i.e. MGUS) was found. The patient has not yet developed any clinical signs of hematologic disease (Figure 3).

Table 1: Demographics, immunology, and immunosuppression of the solid organ transplant recipients before PTLD diagnosis

	Donor A (IgM)			Donor B (IgG)			
	Kidney 1	Kidney 2	Liver	Kidney 1	Kidney 2	Liver B	Heart B
Age at Tx (years)	57	44	53	59	58	59	69
Sex	Male	Male	Male	Male	Male	Male	Female
Primary disease	Secondary to liver Tx (PSC) + CGN	DM1	Alcohol cirrhosis	Lithium +CGN	PCK	HCV HCC	Congestive cardiomyopathy
EBV IgG at Tx	Pos	Pos	Pos	Pos	Pos	Pos	Pos
Induction IS	IL2-R, MP	IL2-R, MP	N.D.	IL2-R, MP	IL2-R, MP	IL2-R, MP	N.D.
Primary IS	Tac, MMF, CS	Tac, MMF, CS	N.D.	CyA, MMF, CS	Tac, MMF, CS	Tac, MMF	CyA, MMF, CS
HLA-Ab at Tx	No	No	N.D.	No	No	No	Pos. I, pos. II
HLA-A, -B, -DR mismatch	2/1	2/2	N.D.	3/2	4/0	1/1	3/2
Rejection (months post Tx)	No	No	No	Banff 1A (3)	No	No	No
IS at PTLD diagnose	Tac, MMF	Tac MMF CS	Tac, MMF	Tac, MMF	Tac MMF CS	Tac, MMF	Tac, MMF, everolimus CS,

All kidney recipients underwent transplantation at our center and received low-dose Tac (5–8 μg/L) or CyA (100–150 μg/L), MMF 1 g twice daily, and steroids. In case of rejection, the aim is a Tac level of 10 μg/L. Liver recipient B received low-dose Tac and MMF according to the same principles. One liver–heart recipient was transplanted at another center.

PSC, primary sclerosing cholangitis; CGN, chronic glomerulonephritis; DM1, diabetes mellitus type 1; PCK, polycystic kidney disease; Pos, positive; HCV, hepatitis C virus ; HCC, hepatocellular carcinoma; IS, immunosuppression; IL-2-R, anti–interleukin-2 receptor induction; MP, methylprednisolone; Tx, transplantation; Tac, tacrolimus; CyA, cyclosporine A; MMF, mycophenolate mofetil; CS, corticosteroids; N.D., no data; HLA-Ab, HLA antibodies; I, II, Luminex class I and II antibodies.

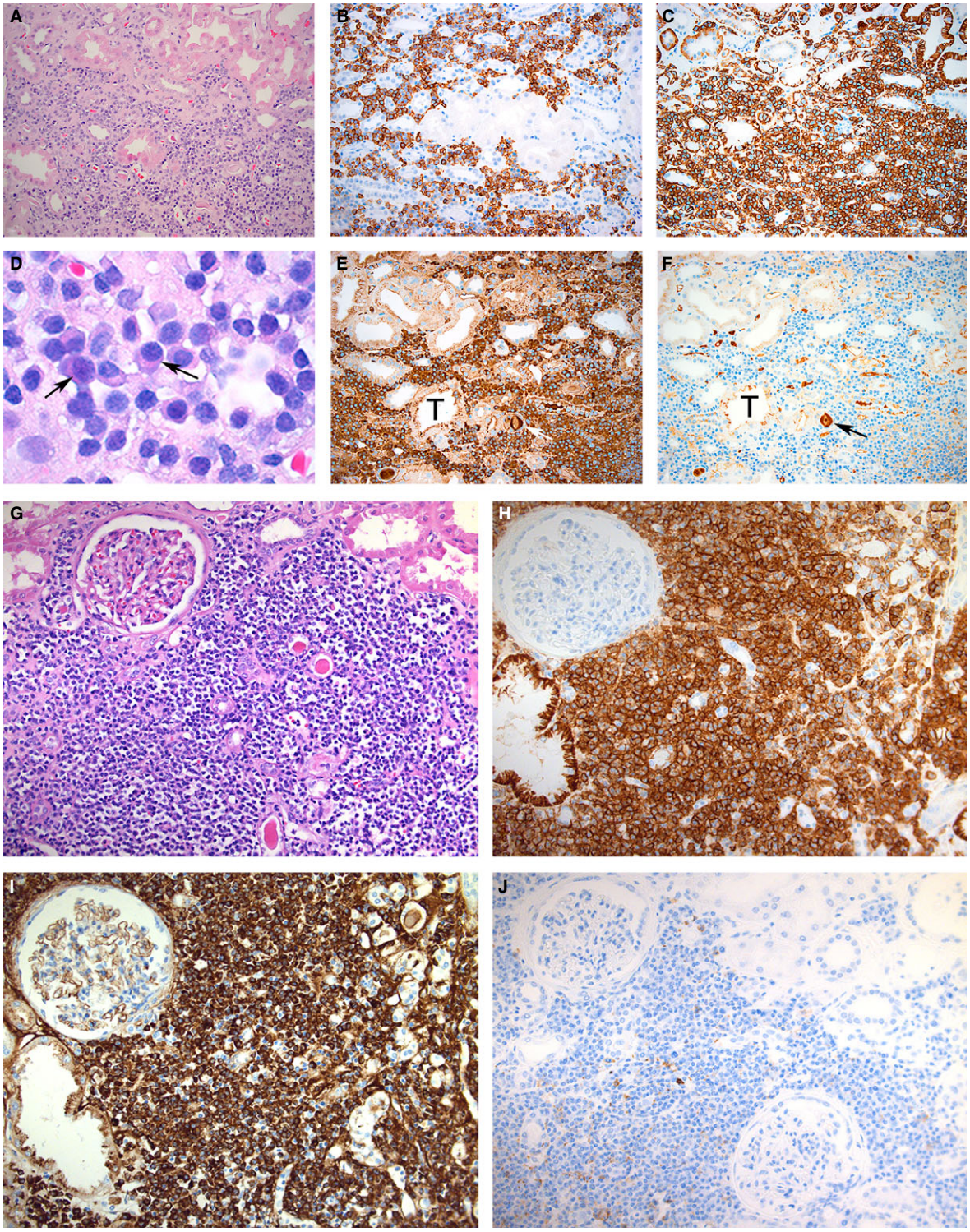

Figure 1: Light microscopy and immunohistochemical staining of kidney transplant biopsy (A–F) and transplantectomy specimen (G–J) from patient A1. (A) Infiltrate of lymphoplasmacytic cells. Hematoxylin & eosin staining, enlarged in (D), shows plasma cell phenotype in some cells (arrows). The majority of infiltrating leukocytes stained for CD20 (B) and almost all cells stained for CD138 (C). The tumor cells were κ monoclonal (E) and negative for λ chains (F), except in a few normal plasma cells and occasional tubular casts (arrow). Infiltrate of lymphoplasmacytic cells; hematoxylin and eosin staining (G). The infiltrate was CD138 positive (H), κ chain restricted (I) but negative for CD20 (J) (rituximab treated). T, tubule.

Recipients from donor B with IgGλ

Kidney recipient B1: An extramedullary plasmacytoma was detected in the transplanted kidney, 32 months after KTx, due to increasing creatinine levels (Table 1). At staging, multifocal graft tumors and lytic areas in the tibia and humerus were found. Dense infiltrates of cells, positive for CD38 and CD138 and expressing λ chain clonality, were found in the graft tumor biopsy (Figure 2). Serum electrophoresis showed monoclonal IgGλ, 22 g/L, but serum PCR for EBV/CMV was negative. MSA confirmed that the tumor cells were of donor origin. Some 33 months after KTx transplantectomy was performed, immunosuppression was withdrawn and bortezomib and radiotherapy were given. The M component was undetectable 5 months posttransplant nephrectomy (Figure 3).

Kidney recipient B2: Due to findings in the paired kidney recipient, serum electrophoresis was performed on a male subject 34 months after KTx and an M component of IgGλ, 5 g/L, was found (Table 1). Bone marrow aspiration and ultrasonography of the graft were both normal. Six months later, a multiple myeloma was diagnosed with solid tumors in the graft and lytic areas in both the femur and humerus. A transplant nephrectomy was performed 41 months after KTx, but local, radical resection was not achieved. Immunosuppression was withdrawn, chemotherapy was given, and today there is no detectable M component (Figure 3).

Liver recipient from donor B: Due to complaints about severe skeletal pain in the lower spine, a multiple myeloma was detected in a male subject 33 months after liver transplantation (Table 1). Serum electro phoresis showed IgGλ-type M component of 33 g/L, and magnetic resonance tomography (MRT) and bone marrow evaluation showed multiple myeloma. MSA confirmed donor origin. No test for EBV viremia was performed. Immunosuppression was reduced to tacrolimus monotherapy, and chemotherapy was initiated. Despite treatment, the patient died due to myeloma at 48 months after liver transplantation (Figure 3).

Heart recipient from donor B: A female, HIV-negative recipient was detected with a primary effusion lymphoma (PEL), hydrothorax, and skeletal pain 4 years after heart transplantation. She also had a history of a successfully treated Kaposi sarcoma (Table 1). One year earlier, routine serum electrophoresis had shown an IgGλ monoclonal Ig of 1 g/L. The PEL cells were strongly positive for herpes virus 8 but EBV negative, and flow cytometry from the pleural effusion showed positivity for the non–lineage-associated antigens CD38 and CD138, which are usually positive in PEL. The MSA of pleural cells revealed the recipient origin of the PEL. There was no sign of malignant plasma cells, but an M component in serum was present (7 g/L). The recipient died shortly after the PEL diagnosis without any bone marrow or heart biopsy being performed.

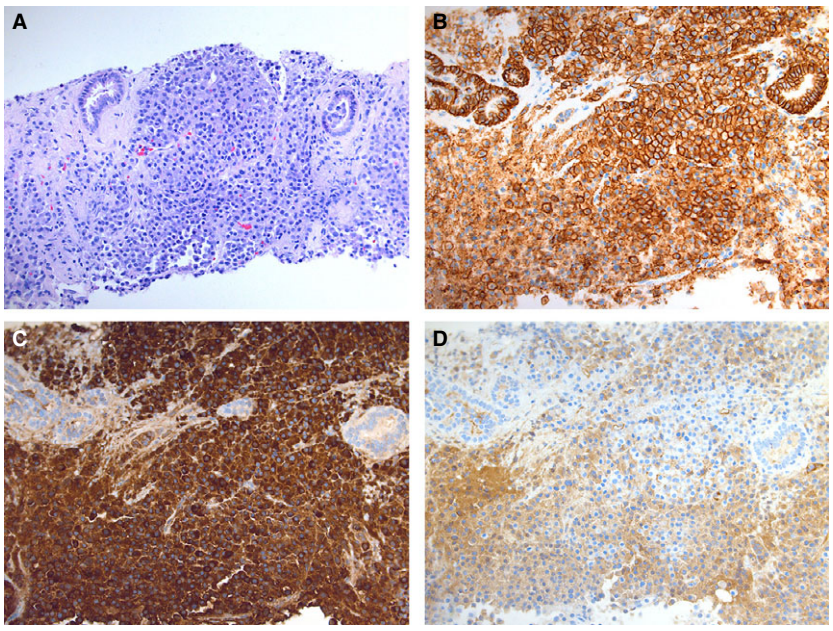

Figure 2: Light microscopy and immunohistochemical staining of kidney transplant biopsy sample from patient B1 at 32 months. (A) Infiltrate of plasma cells; hematoxylin and eosin staining. The cells were positive for CD138 (B) and λ chains (C), while κ chain staining was negative (D).

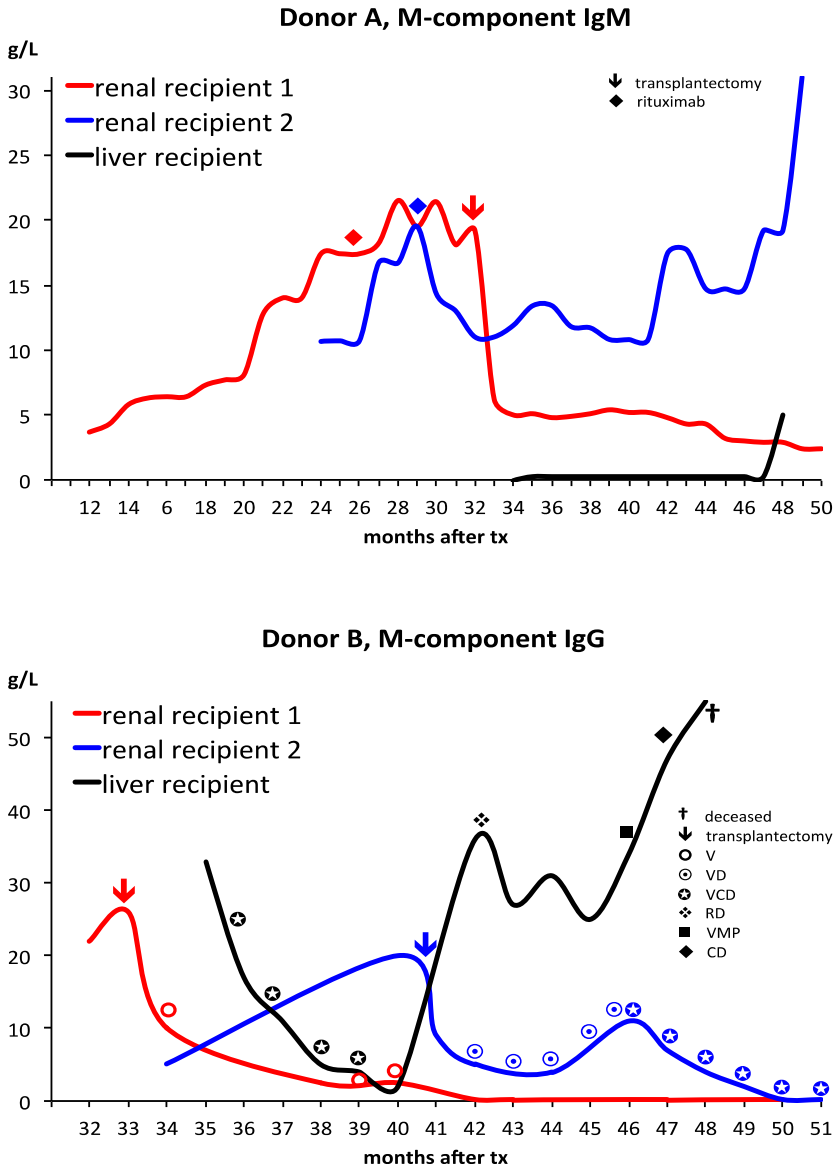

Figure 3: Serum M component in solid organ recipients. V, bortezomib; VD, bortezomib, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; RD, lenalidomid, dexamethasone; VMP, bortezomib, melphalan, prednisolone; CD, cyclophosphamide, dexamethasone.

Analyses of donor plasma

Capillary electrophoresis in stored samples plasma from donor A demonstrated IgMκ 37 g/L and from donor B demonstrated IgGλ 8 g/L. No bone marrow biopsies or other hematologic investigations had been performed on either of the donors. The level of IgM in donor A is suggestive of the presence of LPL at the time of donation.

Discussion

Seven organ recipients from two donors all developed lymphoproliferative disorders after SOT. Subsequent analyses showed that both donors had MGUS, a fact that was unknown at the time of organ donation.

The three recipients of organs from the donor with high IgMκ all had proved paraprotein of type IgMκ. The two renal recipients developed LPL in the kidney grafts with a slow progression rate in both cases. The third patient developed MGUS. The findings in the IgMκ recipients may be explained by an asymptomatic LPL in the donor that was transmitted to the recipients with passenger cells at transplantation. Another explanation is that transformed donor-derived B cells, which are antigen experienced (mature, germinal-center experienced B cells), will

be exposed to antigen-driven stimulation and acquire genetic lesions during expansion in the recipient environment as a donor-derived malignancy (21). In the present case, however, this latter theory is not supported by the findings of a high level of an M component in the donor serum, which suggests that the donor had an established malignancy.

The four recipients from the donor with IgGλ all had paraprotein of type IgGλ and three recipients developed multiple myeloma. These three had osteolytic bone lesions at the time of diagnosis. In a German Registry Study, eight patients with plasmacytoma-like PTLD after SOT were recently described (16). Extranodal manifestations were common, while osteolytic lesions were seen in only two, and in no patient was bone marrow involved. The fourth, a heart recipient, developed MGUS. The same patient also developed the rare condition of PEL, a postgerminal center, "null" lymphocyte phenotype lymphoma entity, expressing plasma cell markers that occurs in the setting of immunodeficiency (22,23). MSA from malignant effusion in the pleura showed recipient origin. This patient was thus harboring a dual-lineage lymphoproliferative disease of both donor and recipient origin.

Despite an M component level of IgGλ 8 g/L, transmission of disease occurred. In the general population, this level is associated with only a moderate risk of progression to multiple myeloma. One interpretation is that donor B had an MGUS disorder and that premalignant cells were transmitted to the recipients where they developed and expanded in the immunosuppressed environment.

In contrast to what has been reported earlier for donor origin PTLDs (7,24), the presence of lymphoproliferative disorder in this series was rather late occurring. The median time from transplantation to paraprotein detection was 32 months. None of the patients tested (three of seven) had either EBV proliferation in serum or latent EBV protein in the tumor sample (five of seven).

The donor origin was suspected because of the similarities in the clinical and morphologic pictures within the donor–recipient groups. In five recipients, the donor origin of the malignant cells was verified with MSA. After bone marrow transplantation, lymphomas in recipients are generally derived from the transplanted pool of lymphoid cells (25), while in SOT, PTLDs are usually of host origin (26,27). However, in a recent series of 43 PTLDs, 37% were found to be of donor origin (7). Earlier reports show that the majority of PTLDs are diffuse large B cell lymphomas (5,21,28). In contrast, the patients in this series showed only mature, postgerminal center neoplasms, again underlining the probability of donor-transmitted disease.

There are no published data on donor transmitted MGUS in either SOT or bone marrow transplantation. According to the European Bone Marrow Group and American Society for Blood and Marrow Transplantation, most laboratory abnormalities, including MGUS contraindicate bone marrow donation. There are, however, a few case reports of donor-derived LPL and malignant myeloma occurring after kidney transplantation (29–31). In contrast to the present findings, a report of two cases of living donor kidney transplantation from donors with known MGUS at donation did not show evidence of progression to multiple myeloma in the recipients 36 and 42 months posttransplantation, respectively (32).

To validate the impact of the findings in this report, it seems important to study the incidence of MGUS in donors. Undiagnosed MGUS and/or lymphoproliferative disease in donors may be a risk factor for malignancy in SOT recipients. This might be even more important in the future, when we face an even older donor population.

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Disclosure

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