Plasma cell neoplasia after kidney transplantation: French cohort series and review of the literature

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Abstract

Although post-transplant lymphoproliferative disorder (PTLD) is the second most common type of cancer in kidney transplantation (KT), plasma cell neoplasia (PCN) occurs only rarely after KT, and little is known about its characteristics and evolution. We included twenty-two cases of post-transplant PCN occurring between 1991 and 2013. These included 12 symptomatic multiple myeloma, eight indolent myeloma and two plasmacytomas. The median age at diagnosis was 56.5 years and the median onset after transplantation was 66.7 months (2–252). Four of the eight indolent myelomas evolved into symptomatic myeloma after a median time of 33 months (6–72). PCN-related kidney graft dysfunction was observed in nine patients, including six cast nephropathies, two light chain deposition disease and one amyloidosis. Serum creatinine was higher at the time of PCN diagnosis than before, increasing from 135.7 (±71.6) to 195.9 (±123.7) μmol/l (p = 0.008). Following transplantation, the annual rate of bacterial infections was significantly higher after the diagnosis of PCN, increasing from 0.16 (±0.37) to 1.09 (±1.30) (p = 0.0005). No difference was found regarding viral infections before and after PCN. Acute rejection risk was decreased after the diagnosis of PCN (36% before versus 0% after, p = 0.004), suggesting a decreased allogeneic response. Thirteen patients (59%) died, including twelve directly related to the hematologic disease. Median graft and patient survival was 31.7 and 49.4 months, respectively.
PCN after KT occurs in younger patients compared to the general population, shares the same clinical characteristics, but is associated with frequent bacterial infections and relapses of the hematologic disease that severely impact the survival of grafts and patients.

**Introduction**

Risk of neoplasia is increased in solid organ transplantation [1], and post-transplant lymphoproliferative disorder (PTLD) is the second most common type of cancer, after skin cancer [2]. According to the International Society of Hematology, plasma cell neoplasia (PCN), including multiple myeloma (MM) and plasmacytoma occurring in solid organ transplantation, forms part of monoclonal PTLD.

MM is a disorder of post-germinative B-cell malignant proliferation, in which a monoclonal immunoglobulin (M-protein) is secreted. MM is consistently preceded by a pre-tumoral stage known as monoclonal gammopathy of undetermined significance (MGUS) [3,4]. After several chromosomal and genetic events, MGUS can move towards smoldering multiple myeloma (SMM), MM and eventually plasma cell leukemia [5,6].

Actual knowledge about PCN in kidney transplantation (KT) is scarce. PCN arising after KT represents only 4% of PTLD in KT in France [7]. An epidemiologic study in the United States performed in 202,600 solid organ transplant recipients between 1987 and 2009 estimated a prevalence of 0.7/1000 [8]. Although PCN occurs very rarely in KT, relative risk compared with the general population is increased two-fold in KT, and is significantly higher for plasmacytoma than for MM [8]. Relative risk is also higher in patients younger than 35 years, and Epstein-Barr virus (EBV) seronegative patients [8].

Until recently, only case reports of PCN arising after KT have been reported in the literature. Kidney graft plasmacytomas have been reported in five patients [9–13]. The tumor originated from the donor in three cases [9,10,12]. Four multiple plasmacytomas [14–16] and nine isolated plasmacytomas [16–24] located outside the graft have been described. Among 11 patients tested, EBV in situ hybridization was positive in seven cases [14–16,18,19, 21,24], suggesting the virus played a role in disease development. Thirteen patients developing MM after KT have been reported in case reports from 1983 to 2011, but no conclusion could be made about their particularities and prognosis [25–28]. Recently, Safadi et al. [29] reported seven cases of MM occurring after KT between 2001 and 2012. Most of these patients had MGUS before KT, and MM could occur at any time after transplantation. Graft failure was often related to the evolution of the hematologic disease. Median survival was 80 months [29], and comparable to the general population [30].

In the present study, we report 22 cases of PCN emerging after KT over a period of 22 years (1991 to 2013) in France.

**Materials and methods**

**Patients**

This was a multicenter, retrospective, cohort study conducted at 14 French renal transplantation centers. A questionnaire was sent to the 33 French centers involved in renal transplantation in order to recruit renal transplanted patients with PCN. Fourteen centers responded favorably and 22 patients were included after identification through the computerized records. Medical records of patients were accessed and data were analyzed anonymously. Inclusion
criterion was PCN (SMM, MM or solitary plasmacytoma) occurring after renal transplantation. MGUS non-evolving to MM was not included. The diagnosis of SMM, MM and plasma cytoma was based on the criteria of the International Myeloma Working Group [31]. Responses to treatments were classified according to the International Myeloma Working Group criteria [32].

Related-organ or tissue impairments (ROTI) were as follows: hypercalcemia defined by serum calcium > 0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL), renal insufficiency defined by creatinine clearance < 40 ml/min or serum creatinine > 177 μmol/L (>2 mg/dL), anemia defined by hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L, presence of one or more osteolytic bone lesions [31].

Demographic, clinical and laboratory data were assessed for each patient before kidney transplantation (sex, previous history of non-hematologic or hematologic neoplasia, age at End Stage Renal Disease (ESRD), native kidney disease, dialysis duration, number of previous KT); at the time of renal transplantation (age at KT, type of induction therapy, initial maintenance immunosuppression); and after KT, before and after the diagnosis of PCN (serum creatinine evolution, acute or chronic graft rejection, infections (bacterial, viral and fungal), evolution of immunosuppressive treatments, transplant status, dialysis post-transplant, and graft loss and patient outcome (death)). Data about PCNs were also precisely recorded (age at diagnosis, time of diagnosis, time after KT, known monoclonal peak before KT, known monoclonal peak after KT, paraprotein at MM diagnosis, medullary plasmacytosis at diagnosis, M Spike level at diagnosis, progression of SMM to MM, Bence Jones proteinuria, type of ROTI, new types of ROTI during follow up, related plasma-cell related disorders (plasmacytomas, hyperviscosity, amyloidosis), treatments, and relapses). Progression free survival was defined as the time from the first dose of the first treatment for PCN to disease progression or death, whichever came first.

Statistical analysis

Quantitative data are presented as mean (1 standard deviation) or median (range).

The prevalence rate was calculated from the number of cases of PCN occurring between 2002 and 2013 (19 cases), and the number of patients aged over 18 receiving KT in the 14 transplantation centers during the same period. The French Biomedical Agency (ABM) provided the exact number of KTs during this period in these centers (14 551 KTs). As data before 2002 was not accurately recorded, three older cases of PCN were excluded from the calculation.

The annual rate of bacterial and viral infection was compared before and after the diagnosis of PCN, and each patient was his own control.

Serum creatinine was compared before and at the time of diagnosis of PCN. Creatinine before diagnosis was either nadir creatinine for patients with early onset of PCN <1 year after KT, or creatinine measured 1 year ± 2 months before diagnosis of PCN for patients with later PCN, > 1 year after KT.

The Wilcoxon matched-pairs signed rank test was used to compare the annual bacterial or viral infection rate before and after the diagnosis of PCN, and serum creatinine before and at the time of diagnosis of PCN.

The Mann Whitney test was used to compare the onset of PCN of patients with or without a known MGUS before KT.

The number of acute rejections before and after the diagnosis of PCN for each patient was compared using Fisher’s exact test.
Analysis of patient and graft survival uses Kaplan-Meier curves. All comparisons are two sided and a value of $p<0.05$ is considered significant.

Results

Characteristics of patients and renal transplantation

Twenty-two patients (15 men and seven women, odds ratio = 2.1), who developed PCN after KT were included. The patients were transplanted between 1986 and 2012 and PCN was diagnosed after KT between 1991 and 2013. Characteristics of patients and KT are presented in Table 1.

The calculated prevalence rate was 1.3/1000. The median age at end stage renal disease was 46.2 years (19.2–63.5; 18/22 patients). Three patients had a previous history of non-hematologic neoplasia, and one had a previous history of benign B-cell proliferation. The median age at renal transplantation was 47.5 years (27.2–71.5). Two patients were transplanted from a living donor. One patient had a dual kidney transplant, and one a combined kidney-pancreas transplant.

Characteristics of PCN after renal transplantation

General characteristics. The median age at diagnosis of PCN was 56.5 years (41.8–72.3). At diagnosis, 12 patients had MM, eight with SMM and two with solitary plasmacytoma. The occurrence of PCN appeared to be constant over time. It could be diagnosed at any time after KT, from 2 to 252 month(s), with a median time of 66.7 months (Fig 1). Only eight patients had known MGUS before renal transplantation (36%), but they did not develop PCN significantly earlier after KT compared to patients without known monoclonal peak (respectively $53.5 \pm 67.9$ versus $103.4 \pm 83.4$ months, $p = 0.18$). Moreover, one patient had IgA lambda MGUS progressing as a lambda light chain myeloma, and another patient had IgA kappa MGUS and developed IgG kappa MM, suggesting either immunoglobulin class switch recombination, or the development of a new clonal plasma cell. Among the fourteen patients with no MGUS detected before KT (64%), five had light chain monoclonal proteins.

Of the 12 MM patients, six had kidney graft failure: five had cast nephropathy, three of which were confirmed by biopsy, and one had biopsy-confirmed light chain deposition disease (LCDD). The two remaining patients were considered as having cast nephropathy because of the association of acute kidney failure and massive proteinuria, composed of large amounts of monoclonal free light chains.

Four out of the eight SMMs progressed to MM during follow-up. One patient had cast nephropathy-related kidney graft failure and one evolved to plasma cell leukemia. Progression from SMM to MM was a median of 33 months (6–72). In the four non-progressing patients, one had amyloid light chain (AL) amyloidosis related to a kappa light chain, with cardiac and kidney graft failure. One had biopsy-confirmed graft failure due to LCDD, which was related to a kappa light chain. One had hyperviscosity syndrome, with an IgA lambda protein, but no end-organ damage. SMM persisted in the last patient at the end of follow-up.

Of the two patients with plasmacytoma at diagnosis, one patient had two solitary plasmacytomas in the sternum and the sacrum, which relapsed with multiple localizations (bone, gut and brain) after treatment. The other had a solitary plasmacytoma in the thoracic spine, which relapsed as multiple plasmacytomas. There was no bone marrow involvement in either patient.

The general characteristics of patients are summarized in Table 2.

Infections. There was a particular risk of infection in the first year following the diagnosis of PCN with 19 bacterial infections in 12/22 patients, four viral infections, and two
Table 1. Characteristics of patients and kidney transplantation.

| Patient | Initial diagnosis of the PCN | Sex | Native kidney disease | Dialysis (year) | Number of previous KT | Age at KT | Induction therapy | Initial Maintenance immunosuppression | Acute rejection episodes | chronic grafted dysfunction and chronic rejection | Transplant status | Dialysis post transplant | Outcome |
|---------|-----------------------------|-----|-----------------------|-----------------|------------------------|----------|------------------|----------------------------------------|------------------------|-----------------------------------------|-------------------|--------------------------|---------|
| 1       | Male | diabetic nephropathy | 3.6 | 1 | 50.4 | ATG | Ciclosporine | Imurel Prednisone | 0 | Failed allograft to cast nephropathy | yes | Dead (disseminated Aspergillosis) |
| 2       | Female | toxic chronic tubulo-interstitial nephropathy | ? | 58.6 | ATG | Ciclosporine | Imurel | 0 | Dead with a functional graft | no | Dead (hemorrhagic stroke) |
| 3       | Male | unknown | 13.7 | 46.8 | ATG | Ciclosporine | Cellcept | Prednisone | 1 | chronic graft dysfunction | yes | Alive in hemodialysis |
| 4       | Female | Congenital dysplasia | 0.9 | 35.9 | ATG | Ciclosporine | Imurel | 1 | chronic rejection | Failed allograft to chronic graft dysfuncion | yes | Dead (disease progression) |
| 5       | Male | Autosomal Dominant Poly cystic Kidney Disease | 1 | 48.5 | ? | ? | 1 | Dead with a functional graft | no | Dead (disease progression) |
| 6       | Male | Chronic glomerulopathy | 1.5 | 61.8 | Basiliximab | Tacrolimus | Cellcept | Prednisone | 0 | Failed allograft to cast nephropathy | yes | Dead (pneumoniae) |
| 7       | Female | chronic tubulo-interstitial nephropathy | 3 | 65.5 | Basiliximab | Tacrolimus | Cellcept | Prednisone | 0 | Dead with a functional graft | no | Dead (disease progression) |
| 8       | Male | unknown | 5.4 | 68.9 | ATG | Ciclosporine | Cellcept | Prednisone | 0 | Dead with a functional graft | no | Dead (disease progression) |
| 9       | Male | Autosomal Dominant Poly cystic Kidney Disease | 9.1 | 65.1 | Basiliximab | Tacrolimus | Cellcept | Prednisone | 0 | cast nephropathy | no | DEAD |
| 10      | Male | hypertensive nephropathy | 0.7 | 56.5 | Basiliximab | Tacrolimus | Cellcept | Prednisone | 0 | cast nephropathy | no | Alive |
| 11      | Male | unknown | ? | 27.2 | ? | Ciclosporine | Cellcept | Prednisone | 0 | functional graft | no | Alive |
| 12      | Female | unknown | 7.2 | 65.2 | Basiliximab | Sirolimus | Cellcept | Prednisone | 0 | cast nephropathy | no | Alive |
| 13      | Male | Alport syndrome | 23.6 | 43.2 | ATG | Ciclosporine | Cellcept | Prednisone | 0 | cast nephropathy, Dead with a functional graft | no | Dead (pneumoniae) |
| 14      | Female | Membranous glomerulopathy | 7.8 | 43.3 | ATG | Ciclosporine | Cellcept | Prednisone | 1 | Dead with a functional graft | no | Dead (disease progression) |
| 15      | Male | Chronic glomerulopathy | 6 | 28.6 | ATG | Ciclosporine | Imurel | Prednisone | 1 | Dead with a functional graft | no | Dead (disease progression) |
| 16      | Male | unknown | 0.9 | 43.9 | ATG | Ciclosporine | Cellcept | Prednisone | 0 | Failed allograft to LCDD | yes | Dead (sepsis) |

(Continued)
| Patient | Initial diagnosis of the PCN | Sex  | Native kidney disease | Dialysis duration (year) | Number of previous KT | Age at KT | Induction therapy | Initial Maintenance immunosuppression | Acute rejection episodes | Chronic graft dysfunction and chronic rejection | Transplant status | Dialysis post transplant | Outcome |
|---------|-----------------------------|------|-----------------------|--------------------------|-----------------------|----------|-------------------|---------------------------------------|------------------------|-------------------------------------------|-------------------|------------------------|----------|
| 17      | SMM                         | Male | AA Amyloidosis        | 15                       | 71.5                  | Basiliximab Tacrolimus Cellcept Prednisone | 1                   | functionnal graft | no                           | Alive                         |
| 18      | SMM                         | Male | Kimura's disease      | 13.3                     | 1                     | 41       | ATG               | Tacrolimus Cellcept Prednisone | 1                     | chronic rejection            | Failed allograft to chronic rejection | yes                  | Alive                |
| 19      | SMM                         | Male | membranoproliferative glomerulopathy | 1.5                     | 1                     | 46.7     | ATG               | Tacrolimus Cellcept Prednisone | 0                     | chronic rejection            | functionnal graft | no                           | Alive                         |
| 20      | SMM + Amyloidosis           | Female | chronic tubulo-interstitial nephropathy | ?                       | 2                     | 47       | ATG               | Tacrolimus Cellcept Prednisone | 0                     | Renal Amyloidosis. Dead with a functionnal graft | no                  | Dead (cardiac failure) |
| 21      | Plasmacytoma                | Male | Chronic glomerulopathy | 2.3                      | 48                    | ATG      | Ciclosporine Cellcept Prednisone | 1                     | functionnal graft | no                           | Alive                         |
| 22      | Plasmacytoma                | Female | vesicoureteral reflux | ?                        | 35.2                  | ?        | ?                 | Dead with a functionnal graft | 0                     | Dead (Disease progression) | no                  | Dead (Disease progression) |

MM: Multiple myeloma. SMM: Smoldering myeloma. KT: kidney transplantation. ATG: anti-thymocyte globulin.

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opportunistic infections (one pulmonary aspergillosis and one candidemia). During the fol-
low-up, the most frequent bacterial infections were pneumonia and graft pyelonephritis. The
annual bacterial infection rate was significantly higher after the diagnosis of PCN, rising from
0.16 (±0.37) to 1.09 (±1.30) (p = 0.0005). Most of the bacterial and fungal infections occurred
during treatments of PCNs (36/46, 78%), including 4 of them directly related to autologous
stem cell transplant (ASCT). Data regarding bacterial infections are presented in Fig 2.
Conversely, the annual viral infection rate was not significantly different before and after
the occurrence of PCN (0.09 versus 0.11, p = 0.83). No BK virus associated-nephropathy was
observed. EBV receiver serology was positive in 16/16 patients and donor serology was positive
in 10/13 patients. Only three patients had EBV replication in blood during the follow-up,
including the two patients with plasmacytomas. In situ hybridization using EBV-encoded
RNA (EBER) was tested on the tumoral proliferation (two plasmacytomas and one bone mar-
row biopsy) in these three patients, and was only positive in the patient with multiple plasma-
cytomas localized to the gut, sternum and brain.

Impact on allograft rejections. Eight patients had an acute rejection before the diagnosis
of PCN versus none after (36% versus 0%, p = 0.004). Chronic graft dysfunction occurred in
four patients, including three biopsy-proven chronic allograft rejections, and was responsible
for graft loss in two patients.

Immunosuppressive treatment after PCN diagnosis. Except in one patient who returned
to hemodialysis, maintenance therapy was reduced in 11 patients (50%) because of severe infec-
tions (7/11) or chemotherapy (4/11). The choice to reduce the maintenance therapy in case of severe infections was always taken during or after severe bacterial, viral or fungal infections, and not preventively. The reduction of maintenance therapy alone was never chosen as an option to treat PCNs. The therapeutic adaptations were highly variable. During the first year after diagnosis, three patients had an overall decrease in their immunosuppressive doses, calcineurin inhibitors were replaced by sirolimus in four patients, and mycophenolate mofetil was stopped in one patient. During follow-up, calcineurin inhibitors were stopped in one patient, and two patients had all immunosuppressive treatments discontinued because of severe infections.

Treatment(s) for PCN. The 16 patients with symptomatic MM (12 initial MM and four
SMM evolving to MM) were treated. One patient received only dexamethasone, and severe
| Patient | Initial diagnosis of the PCN | Age at PCN diagnosis | Time of diagnosis (in year) | Time after KT (in month) | Paraprotein prior to KT | Paraprotein after KT | Paraprotein at MM diagnosis | Medullary plasmacytosis at diagnosis | M Spike (g/L) | Free light chain (mg/L) | Bence Jones proteinuria | Related Organ or Tissue Impairment (ROTI) at diagnosis | New type of ROTI during follow up | Related plasma-cell related disorders |
|---------|----------------------------|----------------------|-----------------------------|--------------------------|------------------------|----------------------|---------------------------|-----------------------------|----------------|-----------------------|---------------------------|-----------------------------------|-----------------------------|-----------------------------------|
| 1       | MM                         | 51.6                 | 1991                        | 15                       | no                     | no                   | IgG kappa                 | 13%                        | 33             | yes                   | Hypercalcemia, Bone, renal insufficiency | Bone, anemia                      |                              |                                  |
| 2       | MM                         | 67.6                 | 1997                        | 107                      | no                     | IgG lambda            | IgG lambda              | *                          | 35             | *                    | Bone with medullar compression       | Bone, renal insufficiency              |                              |                                  |
| 3       | MM                         | 53                   | 2005                        | 74                       | no                     | no                   | IgG kappa                | 13%                        | 20.6           | *                    | Bone, anemia                        |                                  |                              |                                  |
| 4       | MM                         | 55                   | 2006                        | 229                      | no                     | IgG kappa             | IgG kappa               | 51%                        | 59             | yes                   | Bone, anemia, renal insufficiency   |                                  |                              |                                  |
| 5       | MM                         | 56.8                 | 2006                        | 98                       | no                     | no                   | kappa                    | *                          | *              | *                    | Bone                                    |                                  |                              |                                  |
| 6       | MM                         | 62.2                 | 2006                        | 5                        | IgA kappa              | IgG kappa             | IgG kappa               | 70%                        | 54             | yes                   | Hypercalcemia, Bone, renal insufficiency | Bone, anemia                      |                              |                                  |
| 7       | MM                         | 66.6                 | 2010                        | 23                       | IgG kappa              | IgG kappa             | IgG kappa               | 20%                        | 10             | no                    | Bone                                    |                                  |                              |                                  |
| 8       | MM                         | 72.3                 | 2010                        | 16                       | IgG lambda             | IgG lambda            | 14%                      | 9.7                        | no             | Bone, anemia            | Bone, renal insufficiency           |                                  |                              |                                  |
| 9       | MM                         | 68.5                 | 2012                        | 40                       | no                     | no                   | lambda                   | 32%                        | 1090           | yes                   | Anemia, renal insufficiency          |                                  |                              |                                  |
| 10      | MM                         | 57.4                 | 2013                        | 41                       | IgA lambda             | lambda                | 53%                      | 5200                       | yes            | Hypercalcemia, Bone, renal insufficiency |                                  |                              |                                  |
| 11      | MM                         | 41.8                 | 2013                        | 10                       | no                     | IgG lambda            | IgG lambda              | Bone marrow and plasmacytoma biopsies | 59.6       | no                    | Bone                                    | Huge iliac plasmacytoma             |                              |                                  |
| 12      | MM                         | 66.9                 | 2013                        | 174                      | IgG lambda             | IgG lambda            | 20%                      | 14                         | yes            | Renal insufficiency      | Bone, anemia, renal insufficiency   |                                  |                              |                                  |
| 13      | SMM                        | 43.3                 | 1996                        | 20                       | IgG lambda             | IgG lambda            | 13%                      | 30                         | no             | Bone, anemia, renal insufficiency | Bone, renal insufficiency          |                                  |                              |                                  |
| 14      | SMM                        | 48.2                 | 2004                        | 2                        | IgG kappa              | IgG kappa             | 15%                      | 14.7                       | no             | Plasma cell leukemia and anemia | Bone, renal insufficiency          |                                  |                              |                                  |
| 15      | SMM                        | 47                   | 2009                        | 59                       | no                     | no                   | IgG kappa                | 10%                        | *              | no                    | Bone, anemia, Frontal plasmacytoma  |                                  |                              |                                  |
| 16      | SMM +LCDD                  | 45.9                 | 2010                        | 222                      | no                     | no                   | kappa                    | 16%                        | 964            | yes                   | Renal insufficiency                | Bone, anemia                      |                              |                                  |
| 17      | SMM                        | 71.5                 | 2010                        | 2                        | no                     | no                   | kappa                    | 11%                        | 1000           | yes                   | Bone                                    |                                  |                              |                                  |
| 18      | SMM                        | 49                   | 2011                        | 97                       | no                     | IgA lambda            | IgG lambda              | *                          | 34             | yes                   | hyperviscosity                        |                                  |                              |                                  |
| 19      | SMM + Amyloidosis          | 59                   | 2011                        | 148                      | IgG lambda             | IgG lambda            | 15%                      | 13                         | no             | no                    | Cardiac, liver and renal amyloidosis |                                  |                              |                                  |
| 20      | SMM + Amyloidosis          | 53.4                 | 2012                        | 76                       | no                     | no                   | kappa                    | 11%                        | 62             | yes                   | Cardiac, liver and renal amyloidosis |                                  |                              |                                  |
| 21      | Plasmacytoma               | 61.7                 | 2004                        | 164                      | IgG lambda             | 0%                    | 4                        | no                         | no             | no                    | recurrent costal and vertebral plasmacytomas |                                  |                              |                                  |
| 22      | Plasmacytoma               | 56.2                 | 2013                        | 253                      | no                     | IgG lambda            | IgG lambda              | 0%                         | 13             | no                    | recurrent biliary, digestive and cerebral plasmacytomas |                                  |                              |                                  |

PCN: plasma-cell neoplasia. MM: Multiple Myeloma. SMM: Smoldering Myeloma. LCDD: Light-Chain Deposition Disease. M-Spike: Monoclonal Spike. * = unknown.

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infection led rapidly to death before further treatment could be applied. Three patients diagnosed before 1998 were treated with melphalan-prednisone; two of the patients died shortly thereafter. Bortezomib regimen treatments were used as first-line in 10 patients. Five had no relapse at the end of follow-up, and were all alive at the end of the study, with a median follow-up of 15 months (range 11–41). Relapsing patients all died after other second-, third- or fourth-line chemotherapies, with a median survival of 32 months (range 14–98).

Among 13 patients under the age of 65 eligible for ASCT, four received this treatment after first-line chemotherapy, and one after two lines of chemotherapy. Four patients died before they received a transplant. ASCT was probably contraindicated in one patient because of graft failure. Three patients did not receive ASCT for unknown reasons. Treatments, responses and outcomes are presented in Table 3.

Outcome of patients and kidney grafts. Thirteen patients (59%) died during follow-up. Seven patients died because of severe bacterial or fungal infection, occurring during treatments for multiple myeloma in six of them, and before initiation of treatment in one patient. Four patients died because of disease progression after two or more regimen treatments. The patient with AL amyloidosis died from cardiac failure. The last death (from a stroke) was not related to PCN.

Serum creatinine was higher at the time of diagnosis of PCN than before, increasing from 135.7 (±71.6) to 195.9 (±123.7) μmol/l (p = 0.008). This impact on graft function was explained by the specific PCN-related kidney graft failure already described. Of the 15 grafts lost (68% patients), 12 (80%) were caused by PCN. Nine graft losses were linked to the patient’s death, including eight deaths directly attributable to PCN. Four graft losses were associated with specific kidney graft failure: two because of LCDD, respectively 4.4 and 1.0 years after diagnosis, and two because of cast nephropathy immediately after diagnosis. Only three graft losses were unrelated to PCN, two because of chronic graft dysfunction, respectively 9.6 and 13.7 years after renal transplantation, and one from death due to a stroke. Median progression free survival after the first treatment for PCN (20/22 patients) was 14 months [2–91]. Median graft and patient survival after KT were equal at 156.9 months. Median graft survival after the diagnosis of PCN was 31.7 months and median patient survival after the diagnosis of PCN was 49.5 months (Fig 3). Removing the three patients diagnosed before 2002 treated with Melphalan regimens gave similar results: median graft and patient survival after KT were equal at 157.3 months, median graft survival after the diagnosis of PCN was 21.1 months, and median patient survival after the diagnosis of PCN was 47.4 months (S1 Fig).

Fig 4 shows the evolution of serum creatinine after KT, combined with the occurrence of asymptomatic or symptomatic PCN, hemodialysis and death for each patient.
| Patient | Date of diagnosis | Initial/Final diagnosis | 1st treatment | Response to the 1st treatment | Progression free survival after the first treatment (in months) | 2nd treatment | Response to the 2nd treatment | Progression free survival after the second treatment (in months) | 3rd treatment | Response to the 3rd treatment | Progression free survival after the third treatment (in months) | 4th treatment | Response to the 4th treatment | Progression free survival after the fourth treatment (in months) | Outcome | Cause of death | Follow up from diagnosis, in months | Follow up when symptomatic MM (if different) |
|---------|------------------|-------------------------|---------------|-------------------------------|-------------------------------------------------------------|---------------|-------------------------------|-------------------------------------------------------------|---------------|-------------------------------|-------------------------------------------------------------|---------------|-------------------------------|-------------------------------------------------------------|---------|-----------------|-----------------------------|-----------------------------|
| 1       | 1991             | MM                      | MP            | PR                            | 2                                                           | Dead          | Progressive disease           | 26                                                         | RD            | SVPR                          | Alive                                      |                | PR                            | Alive                                      | Died       | Aspergillosis during treatment | 3                                     | 49                          |
| 2       | 1997             | MM                      | MP + Radiotherapy | PR                            | 49                                                          | Dead          | Progressive disease           | 26                                                         | RD            | SD                            | Alive                                      |                | PR                            | Alive                                      | Died       | Stroke                                      | 49                        | 49                          |
| 3       | 2005             | MM                      | TD            | PR                            | 91                                                          | Dead          | Progressive disease           | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Progressive disease                                      | 14                        | 48                          |
| 4       | 2006             | MM                      | BD + plasmacytoma | BMT + ASCT                   | VGPR                                                        | Dead          | Progressive disease           | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | 96                                          | 26                        | 48                          |
| 5       | 2006             | MM                      | CD + plasmacytoma | PR                            | 14                                                          | BD            | progressive disease           | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Progressive disease                                      | 14                        | 48                          |
| 6       | 2006             | MM                      | Dexamethasone | unrated                       | 20                                                          | RD            | Progressive disease           | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Progressive disease                                      | 14                        | 48                          |
| 7       | 2006             | MM                      | VMP           | PR                            | 12                                                          | RD            | Progression free Survival    | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Progressive disease                                      | 12                        | 48                          |
| 8       | 2006             | MM                      | VCD           | PR                            | 12                                                          | RD            | Progression free Survival    | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | 12                                          | 26                        | 26                          |
| 9       | 2006             | MM                      | VTD           | PR                            | 14                                                          | RD            | Progression free Survival    | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Progressive disease                                      | 14                        | 48                          |
| 10      | 2006             | MM                      | VMP           | PR                            | 12                                                          | RD            | Progression free Survival    | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Progressive disease                                      | 14                        | 48                          |
| 11      | 2006             | MM                      | VCD           | PR                            | 12                                                          | RD            | Progression free Survival    | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Progressive disease                                      | 14                        | 48                          |
| 12      | 2006             | MM                      | VTD           | PR                            | 12                                                          | RD            | Progression free Survival    | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Progressive disease                                      | 14                        | 48                          |
| 13      | 2006             | MM                      | VCD           | PR                            | 12                                                          | RD            | Progression free Survival    | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Progressive disease                                      | 14                        | 48                          |
| 14      | 2006             | MM                      | VTD           | PR                            | 12                                                          | RD            | Progression free Survival    | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Progressive disease                                      | 14                        | 48                          |
| 15      | 2006             | MM                      | VCD           | PR                            | 12                                                          | RD            | Progression free Survival    | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Sepsis during treatment and progressive disease | 32                        | 48                          |
| 16      | 2006             | MM                      | VCD           | PR                            | 12                                                          | RD            | Progression free Survival    | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Sepsis during treatment and progressive disease | 48                        | 48                          |
| 17      | 2006             | MM                      | VCD           | PR                            | 12                                                          | RD            | Progression free Survival    | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Sepsis during treatment and progressive disease | 48                        | 48                          |
| 18      | 2006             | MM                      | VCD           | PR                            | 12                                                          | RD            | Progression free Survival    | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Sepsis during treatment and progressive disease | 48                        | 48                          |
| 19      | 2006             | MM                      | VCD           | PR                            | 12                                                          | RD            | Progression free Survival    | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Sepsis during treatment and progressive disease | 48                        | 48                          |
| 20      | 2006             | MM                      | VCD           | PR                            | 12                                                          | RD            | Progression free Survival    | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Sepsis during treatment and progressive disease | 48                        | 48                          |
| 21      | 2006             | MM                      | VCD           | PR                            | 12                                                          | RD            | Progression free Survival    | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Sepsis during treatment and progressive disease | 48                        | 48                          |
| 22      | 2006             | MM                      | VCD           | PR                            | 12                                                          | RD            | Progression free Survival    | Alive                                      |                | Alive                          | Alive                                      |                | PR                            | Alive                                      | Died       | Sepsis during treatment and progressive disease | 48                        | 48                          |

PCN: plasma-cell neoplasia. MM: multiple myeloma. SMM: smoldering myeloma. MP: melphalan prednisone. TD: thalidomide dexamethasone. VD: velcade dexamethasone. ASCT: autologous stem cell transplantation. VMP: melphalan prednisone, VCD: velcade cyclophosphamide dexamethasone. VTD: velcade thalidomide dexamethasone. RD: revlimid dexamethasone. VCD: melphalan prednisone, VTD: melphalan dexamethasone, VMC: melphalan cytarabine. ICE: ifosfamide cytarabine etoposide. PR: partial response. SD: stable disease. VGPR: very good partial response. CR: complete response.

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Discussion

PCNs in KT are rare. The prevalence calculated in our study was analogous to the one reported in the United States [8], around 1/1000. In the present study, MM occurred at any time after KT, and the incidence seems to be steady over time post-transplantation. Plasmacytoma

![Fig 3. Graft and patient survival. A: Progression free survival (in months) after the first treatment for PCN. Median progression free survival (20/22 patients) was 14 months. B: Survival (in months) from kidney transplantation (KT) of patients (solid) and grafts (dotted). Median graft survival after KT was 156.9 and median patient survival after KT was 156.9 months. C: Survival (in months) from the time of diagnosis of PCN of patients (solid) and grafts (dotted). Median graft and patient survival after diagnosis of PCN was 31.7 months and 49.4 months, respectively. PCN: plasma cell neoplasia.](https://doi.org/10.1371/journal.pone.0179406.g003)

Fig 3. Graft and patient survival. A: Progression free survival (in months) after the first treatment for PCN. Median progression free survival (20/22 patients) was 14 months. B: Survival (in months) from kidney transplantation (KT) of patients (solid) and grafts (dotted). Median graft survival after KT was 156.9 and median patient survival after KT was 156.9 months. C: Survival (in months) from the time of diagnosis of PCN of patients (solid) and grafts (dotted). Median graft and patient survival after diagnosis of PCN was 31.7 months and 49.4 months, respectively. PCN: plasma cell neoplasia.

![Fig 4. Evolution of serum creatinine after kidney transplantation, combined with the occurrence of asymptomatic or symptomatic PCN, hemodialysis and death for each patient.](https://doi.org/10.1371/journal.pone.0179406.g004)

Fig 4. Evolution of serum creatinine after kidney transplantation, combined with the occurrence of asymptomatic or symptomatic PCN, hemodialysis and death for each patient. Evolution of serum creatinine (μmol/l) over time (in years) after kidney transplantation, for each patient. Patients were classified in six groups, and approximate time of diagnosis of SMM (smoldering multiple myeloma), symptomatic PCN (plasma-cell neoplasia), hemodialysis and death were added. MM: Multiple Myeloma. MGRS: Monoclonal Gammapathy of Renal Significance. LCDD: Light Chain Deposition Disease.
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develops later in the post-transplantation period. Although rare, PCN after KT occurs in younger patients compared to the general population, in which the median age of PCN at diagnosis is over 70 [5]. This may be mostly due to the fact that KT patients belong to a selected population, i.e., in France the median age is 55 years. Older patients, who are at risk of developing PCN, are less often transplanted. Engels et al.[8] made the same observation in their epidemiologic study in the United States regarding PCN after solid organ transplantation.

In the general population, MGUS is a premalignant plasma cell proliferative disorder with a constant risk of progression to MM. In KT, monoclonal gammopathy is 10 times more frequent than in the general population, but is not associated with a high occurrence of PCN [33–36]. Most of these MGUS are transient, and probably reflect the temporary loss of control of the B-cell lymphoid population secondary to immunosuppressive therapy [33,34,37]. There is probably no risk of these particular transient MGUS, which differ from classic MGUS, evolving to MM.

The fact that classical MGUS was often present before KT in our study does not argue in favor of PCN being classified as PTLD, but raises the question of a pre-transplant lymphoproliferative disorder for some of the cases. Onset kinetics of PCN was not influenced by presence of MGUS before KT; however, presence of light chain was not systematically screened before KT. Although it is not given in the KDIGO recommendations, such screening could be more systematic, before and after KT. At the moment, development of a clonal plasma cell may occur either before or after KT, and it is not clear that KT influences the onset of MM.

It should be noted that two patients with plasmacytomas had no MGUS before KT, developed their disease more than 10 years after KT, and thus had definitive PTLD.

A virus or immunosuppression may favor the onset of PCN after KT. The two patients with plasmacytomas had EBV replication in blood, with evidence of EBV replication in situ in one of them, and published data strongly suggest a link between plasmacytoma and EBV infection [8,14–16,18,19,21,24,38,39]. The role of EBV in onset of myeloma is less clear, and this also suggests that plasmacytoma and myeloma may have different courses of pathophysiological development.

Immunosuppressive therapy could also accelerate the development of the hematologic disease. In post-transplant lymphomas, immunosuppressive depletive treatments lead to the loss of control of the B-cell population and clearly favor the onset of hemopathy [40]. Conversely, immunosuppressive therapy may have a beneficial effect. For example, the inhibition of the mammalian target of rapaymycin/Akt pathway has been associated with an anti-tumor effect in MM cells treated with pomalidomide [41]. Mycophenolate mofetil has an anti-proliferative effect on MM in vitro [42], and cyclosporine may sensitize MMs tumoral cells to chemotherapy in vitro [43]. Nevertheless, these results are not sufficient to form a conclusion about the effects of immunosuppressive therapy on PCN in vivo in KT. Furthermore, cyclosporine had no additional effect when it was combined with vincristine doxorubicin and dexamethasone in a phase II/III clinical trial in patients with advanced refractory MM [44].

MM occurring after KT shares the same clinical characteristics as MM in the general population. SMMs often become symptomatic MMs. Bone lesions, anemia, hypercalcemia and kidney failure are the common manifestations in renal transplant patients. Progression to plasma cell leukemia was even diagnosed in one patient. The kidney graft was a potential target of the hematologic disease as it would be for native kidneys, and presented the same histological lesions, such as cast nephropathy, LCDD or AL amyloidosis.

The patients in the present study showed a substantial increase in the number of bacterial infections after the diagnosis of PCN, especially during treatments. This suggests that patients were highly immunocompromised. On the other hand, acute rejections prior to diagnosis of PCN were frequent. This suggests that immune stimulation plays a role in the development of
disease, or enhances the potentially harmful nature of the immunosuppressive therapy which was probably increased after the rejection episode. Conversely, no acute rejection occurred after the diagnosis of PCN, despite a decrease of immunosuppressive therapy in half of patients. The immunosuppressive effects of PCN certainly decrease the allogeneic response of the transplanted kidney as it reduces the response to bacterial attacks. All these facts suggest that immunosuppressive treatments should be drastically and preventively reduced in KT patients with symptomatic PCN, and even be discontinued in the case of severe infectious complications. The risk of rejection is indeed much lower than the risk of infection and most of these patients are treated with high doses of corticosteroids and bortezomib, also used in the treatment of transplant rejection.

Contrary to the recent study of seven patients by Safadi et al. [29], the present findings suggest that KT patients die early from PCN. Median progression free survival was low at 14 months, compared to 21 months in the classical association of bortezomib plus dexamethasone for the frontline treatment of multiple myeloma [45]. Median survival is almost twice as low as the current median survival in the general population [30]. This increased mortality is not explained by the long period of inclusions, because it remains when the three patients treated with melphalan are removed from the analysis. Severe bacterial or fungal infections occurring during treatments for PCNs were the principal cause of death. The conjunction of maintenance therapy for kidney graft and treatments for PCN may favor the risk of lethal infections in these patients. The control of PCN by auto-immunity may also have been compromised by the immunosuppressive therapy. In our study, PCN also had a huge impact on graft outcomes, at the time of diagnosis because of specific kidney failure, and later as a cause of the majority of graft losses. Survival of graft and patients was indeed very similar, closely dependent on the hematologic disease.

The treatments were heterogeneous, and reflected the rapid evolution of chemotherapies during the last twenty years. From 2004, the principal first-line treatment was a combination of chemotherapy using bortezomib and dexamethasone, with or without another agent (primarily, cyclophosphamide or thalidomide). MM occurring after KT should be treated with the same rigor as in the general population, according to the most recent guidelines. In particular, ASCT was not systematically proposed for all eligible patients; this treatment should be more widely applied.

There are several limitations to this study. It was retrospective in nature, and because of the rarity of the disease patients were included over a long period of time. Because hematological disease differed depending on whether it was MM, SMM or plasmacytoma, patients were heterogeneous. Immunosuppressive treatments and chemotherapy were equally diverse, and it was not possible to precisely analyze their potential multiple effects on the evolution of PCN. Further prospective studies are needed to refine the epidemiology and outcome of these patients, and to explore ways of improving the prognosis. Despite these limitations, the present study is to our knowledge the largest case series of descriptive PCN after KT, and already provides useful findings.

Supporting information

S1 Fig. Graft and patient survival after 2002. The three patients diagnosed before 2002 treated with Melphalan regimen were removed from the analysis. A: Survival (in months) from kidney transplantation (KT) of patients (solid) and grafts (dotted). Median graft survival after KT was 157.3 and median patient survival after KT was 157.3 months. B: Survival (in months) from the time of diagnosis of PCN of patients (solid) and grafts (dotted). Median graft and patient survival after diagnosis of PCN was 21.1 months and 47.4 months, respectively. PCN: plasma cell neoplasia.
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