including disorganized myocardium and abnormal atrioventricular septation, a picture suggestive of NVM. Pignatelli et al. [11] stress that for several years, patients were diagnosed with dilated cardiomyopathy or hypertrophic cardiomyopathy when in fact they fulfilled the diagnostic criteria for NVM. Indeed, a distinctive feature in children with NVM is the potential for a phenotype with transition between dilative cardiomyopathy and hypertrophic cardiomyopathy. Therefore, when an increase in ventricular mass is detected in ADPKD patients, NVM should be ruled out.

In conclusion, we propose that in patients with ADPKD presenting with LV dysfunction and/or hypertrophy, NVM should be considered, mainly in view of the possibility of cardiovascular accidents, arrhythmias, thromboembolisms and transient or permanent heart failure also prompted by concurrent infections.

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References


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Recipient-derived chronic lymphocytic leukaemia diagnosed shortly after kidney transplantation on protocol biopsy

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Abstract

Here we present the case of a patient with diagnosis of chronic lymphocytic leukaemia (CLL) on routine protocol biopsy 3 months following kidney transplantation. Genetic analysis confirmed the origin of the malignancy, being the recipient. Differential diagnosis with post-transplant lymphoproliferative disorder (PTLD) is extremely important in order to avoid unnecessary devastating treatment. This case is challenging, both in terms of making the correct diagnosis and in terms of optimal treatment. The case underscores that it is extremely important to distinguish between a pre-existing lymphoma diagnosis after transplantation and a true PTLD as the treatment options of both are very divergent.

Keywords: chronic lymphocytic leukaemia; immunosuppression; kidney transplantation; post-transplant lymphoproliferative disorder
Introduction

Secondary malignancy represents a well-recognized complication of immunosuppressive therapy after solid organ transplantation, with non-melanoma skin cancers and post-transplant lymphoproliferative disorders (PTLD) being the most frequent types [1]. Chronic lymphocytic leukaemia (CLL) is a malignant haematological disorder characterized by proliferation and accumulation of small B-lymphocytes. The disease displays a marked clinical heterogeneity, with some patients experiencing a slowly progressive course, whereas others show a more rapid disease progression requiring early treatment [2]. Here we present the case of a patient with diagnosis of CLL on routine protocol biopsy 3 months following kidney transplantation.

Case report

A 68-year-old man, with end-stage renal failure due to chronic glomerulonephritis of unknown origin, underwent a deceased-donor renal transplantation in March 2006. At transplantation, the peripheral blood count showed no abnormalities. Maintenance immunosuppression consisted of steroids, tacrolimus and mycophenolate mofetil.

Three months after transplantation, the patient was admitted to the hospital for a routine protocol biopsy. The patient was asymptomatic and physical examination revealed no palpable lymph nodes nor organomegaly. The results of peripheral blood are shown in Table 1.

Surprisingly, histological examination of the biopsy revealed a pronounced interstitial population of small CD20-positive lymphoid cells, suggesting the diagnosis of a small B-cell non-Hodgkin’s lymphoma (Figure 1). Monoclonality of immunoglobulin heavy chain (IgH) rearrangements was confirmed by polymerase chain reaction (PCR).

Bone-marrow aspiration and trephine biopsy showed the presence of a similar lymphoid population. Immunophenotyping revealed a monoclonal CD5+, CD10−, CD20+, CD23+, FMC7− and CD79b+ population, leading to the diagnosis of CLL. Further prognostic stratification showed a normal karyotype, isolated deletion of chromosome 13q14 by interphase fluorescence in situ hybridization.

Table 1. Clinical and biochemical features at the time of transplantation and during the follow-up

<table>
<thead>
<tr>
<th></th>
<th>Pre-Tx</th>
<th>3 M post-Tx</th>
<th>12 M post-Tx</th>
<th>24 M post-Tx</th>
<th>36 M post-Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>15.4</td>
<td>12.3</td>
<td>13.3</td>
<td>15.0</td>
<td>13.4</td>
</tr>
<tr>
<td>WBC (/µL)</td>
<td>6500</td>
<td>8600</td>
<td>6300</td>
<td>9700</td>
<td>8500</td>
</tr>
<tr>
<td>Neutro</td>
<td>3400 (52.7)</td>
<td>4800 (55.6)</td>
<td>3400 (53.8)</td>
<td>6100 (62.7)</td>
<td>4700 (55.2)</td>
</tr>
<tr>
<td>Eosino</td>
<td>300 (5.1)</td>
<td>200 (2.9)</td>
<td>200 (3.0)</td>
<td>200 (2.2)</td>
<td>200 (2.4)</td>
</tr>
<tr>
<td>Baso</td>
<td>0 (0.3)</td>
<td>0 (0.5)</td>
<td>100 (0.8)</td>
<td>0 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Lympho</td>
<td>2300 (35.7)</td>
<td>3000 (34.7)</td>
<td>2200 (34.3)</td>
<td>3000 (30.7)</td>
<td>3100 (36.5)</td>
</tr>
<tr>
<td>Mono</td>
<td>400 (6.2)</td>
<td>500 (6.3)</td>
<td>500 (8.1)</td>
<td>400 (3.9)</td>
<td>500 (5.9)</td>
</tr>
<tr>
<td>Plat (/µL)</td>
<td>227 000</td>
<td>287 000</td>
<td>264 000</td>
<td>204 000</td>
<td>184 000</td>
</tr>
<tr>
<td>Creat (mg/dL)</td>
<td>9.62</td>
<td>1.52</td>
<td>1.12</td>
<td>1.12</td>
<td>1.26</td>
</tr>
<tr>
<td>Cockroft (mL/min)</td>
<td>7</td>
<td>46</td>
<td>60</td>
<td>59</td>
<td>57</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>424</td>
<td>287</td>
<td>355</td>
<td>313</td>
<td>331</td>
</tr>
<tr>
<td>Immunosuppressive therapy Tacrolimus 5 mg/ day (target 8–10 µg/L) MMF 1g / day MP 4 mg/day Tacrolimus 3 mg/ day (target 8–10 µg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol biopsy Dense population of small CD20-positive lymphoid cells No signs of rejection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tx = transplantation, M = months, Hb = haemoglobin, WBC = white blood cells, Neutro = neutrophils, Eosino = eosinophils, baso = basophils, Lymph = lymphocytes, Mono = monocytes, Plat = platelets, Creat = creatinine, LDH = lactate dehydrogenase, MMF = mycophenolate mofetil, MP = methylprednisolone.

Normal values: Hb 14.0–18.0 g/dL; WBC 4000–8000/µL; Neutro 2500–7800/µL (38–77%); Eosino < = 400/µL (≤ = 6%); Baso < = 100/µL (≤ = 1%); Lympho 1200–3600/µL (20–50%); Mono 200–800/µL (2–10%); Plat 150000–450000/µL; Creat 0.67–1.17 mg/dL; LDH 240–480 U/L.
Fig. 1. Protocol biopsy at 3 months post-transplantation, showing infiltration of the renal allograft by a dense population of small CD20-positive lymphoid cells. (A) Infiltration of the renal cortex by a dense, small cell lymphoid population. The infiltrate was present throughout the whole biopsy, but had a tendency to appear in large nests (silver methenamine stain, original magnification 100×).

(B) The small cell lymphoid population diffusely expressed CD20 (Dako, Glostrup, Denmark; dilution 1/300, original magnification 100×). (C) The tumoural population consisted of a dense population of small lymphocytic elements with a slightly irregular nucleus and a coarse chromatin pattern (silver methenamine stain, original magnification 400×).

The diagnosis of early stage CLL (Rai 0, Binet A) was made. Besides a reduction of the immunosuppression (cessation of mycophenolate mofetil), no other therapeutic measures were taken (‘watch and wait’ approach).

Three years after the diagnosis of CLL, the patient remains in a good condition, without evidence of progressive disease, with a preserved renal function and without clinical or histological signs of rejection of the transplant kidney (Table 1).

Discussion

Median survival of patients with CLL ranges from <2 to >20 years, depending on patient and disease characteristics and response to treatment [2]. Classic prognostic factors such as clinical staging according to Rai and Binet remain simple methods to predict overall survival and guide the start of treatment. New prognostic markers like mutational status of the IgVH genes and cytogenetic abnormalities have repeatedly shown their prognostic value [3]. In the given case, clinical staging (early stage), cytogenetics, FISH, CD38 expression and IgVH mutation analysis all predict a slowly progressive disease and a long overall survival.

Autopsy studies in the 80–90s showed up to 90% of the CLL cases displaying renal infiltration [4]. Despite these findings, kidney involvement does not seem to lead to clinically detectable impaired renal function. This is also illustrated by our case. Post-renal obstruction due to intra-abdominal lymphadenopathy, cryoglobulinaemia and nephrotic syndrome secondary to membranous, membranoproliferative or minimal change glomerulonephritis, though, has occasionally been reported [5]. It should be of note that organ invasion has not been included in the clinical staging systems for CLL.

The use of new and very potent immunosuppressive therapy in solid organ transplantation reduced acute rejection rates, but is counterbalanced by increased occurrence of infection and neoplasms [6]. PTLD encompasses a heterogeneous group of disorders associated with abnormal lymphoid proliferation, occurring as a consequence of immunosuppression in a recipient of a solid organ transplantation.

As the patient had a normal peripheral blood count without any sign of underlying haematological disorder (normal white blood count, lymphocyte, red blood cell, platelet count and normal lactate dehydrogenase), no bone-marrow examination was performed in the pre- or peri-transplant period. However, in order to definitely prove recipient-derived CLL, we explored the status of IgH and IgK (kappa light chain) rearrangements in a diagnostic sample post-transplant and in a stored sample that was taken before transplant. As shown in Figure 2, identical rearrangements were found in both samples. This unequivocally establishes that the lymphoproliferative process diagnosed after transplantation already existed before transplantation.
First line therapy of PTLD almost always consists of reduction of immunosuppression [7]. Indeed, this is not only the first treatment option in PTLD, but should be considered in all conditions in which over-immunosuppression can initiate or worsen potential life-threatening complication, for example serious infections and malignancies. Recently d’Ythurbide et al. reported on the outcome of four cases with recipient-derived CLL engrafted with a deceased-donor kidney. Based on infectious and tumour-related complications, the authors propose a less intensive immunosuppressive regimen in these patients [8]. Another four cases with similar complication rates were reported in the Cincinnati Transplant Tumor Registry [9]. By reducing immunosuppression, our case illustrates the proposed approach.

In the case of no response after reduction of immunosuppression or of very aggressive presentation, PTLD is usually treated with the monoclonal anti-CD20 antibody rituximab either in monotherapy or in combination with chemotherapy [10].

In our patient, however, diagnosed with recipient-derived CLL, these therapeutic modalities would have had devastating consequences:

1. Surgery especially seems to be very effective in the case of isolated allograft localization. Since CLL is as per definition a disseminated disease, removal of the transplant kidney was contra-indicated and would have returned the patient unnecessarily to a state of dialysis dependence. Moreover, re-transplantation would have probably led to recurrence in the re-transplanted kidney.

2. The combination of chemotherapy and immunotherapy is the standard of care in patients with CLL necessitating treatment. However, based on clinical staging and taking into account new prognostic markers, chemotherapy would have subjected our patient to unnecessary complications without proven impact on survival and to worsening of the graft function.

3. Monotherapy with rituximab at conventional dose has proven minimal efficacy in CLL, due to the low density of CD20 antigen on CLL cells. Although treatment with rituximab has a low toxicity profile, this treatment would have not been justified in this case because of the expected low response rates.

In conclusion, our case underscores that it is extremely important to distinguish between a pre-existing lymphoma diagnosis after transplantation and a true PTLD, as the treatment options of both are very divergent.

Conflict of interest statement. None declared.

References


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