



CKJ REVIEW

Lymphatic disorders after renal transplantation: new insights for an old complication

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Abstract

In renal transplanted patients, lymphoceles and lymphorrhea are well-known lymphatic complications. Surgical damage of the lymphatics of the graft during the procurement and of the lymphatic around the iliac vessels of the recipients has been associated with development of lymphatic complications. However, lymphatic complications may be related to medical factors such as diabetes, obesity, blood coagulation abnormalities, anticoagulation prophylaxis, high dose of diuretics, delay in graft function and immunosuppressive drugs. Consistently, immunosuppression regimens based on the use of mTOR inhibitors, especially in association with steroids and immediately after transplantation, has been associated with a high risk to develop lymphocele or lymphorrhea. In addition, several studies have demonstrated the association between rejection episodes and lymphatic complications. However, before the discovery of reliable markers of lymphatic vessels, the pathogenic mechanisms underlining the development of lymphatic complications during rejection and the influence of mTOR inhibitors remained not fully understood. The recent findings on the lymphatic systems of either native or transplanted kidneys together with the advances achieved on lymphangiogenesis shared some lights on the pathogenesis of lymphatic complications after renal transplantation. In this review, we describe the surgical and medical causes of lymphatic complications focusing on the rejection and immunosuppressive drugs as causes of lymphatic complications.

Key words: kidney transplantation, lymphocele, lymphorrhea, mTOR inhibitors, rejection

Introduction

Since 1970, lymphocele and lymphorrhagia in kidney transplanted patients have been referred to surgical complications as due to the extensive perivascular dissection of the lymphatics associated with iliac vessels of the recipient. Nevertheless, during the past three decades other factors such as certain immunosuppressive drugs, obesity, delayed graft function, alteration in the blood coagulation and rejection episodes have been correlated with the

development of lymphatic complications after renal transplantation. In this review, we describe the surgical and medical causes of lymphatic complications focusing on graft rejection and immunosuppressive drugs as causes of lymphatic complications.

Definitions

Lymphocele has been defined as a lymph-filled collection in the retroperitoneum without an epithelial lining [1]. In kidney

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transplanted patients, lymphocele is a pseudocystic entity with lymph content covered with a hard fibrous capsule frequently localized around the graft [2, 3]. Lymphorrhea or lymphorrhagia is defined as a lymph leak from the surgical drains or from the abdominal wall through the surgical wound.

Incidence

The incidence of lymphatic complications and in particular of lymphocele varies according to the presence or absence of symptoms, size and duration of patient's follow-up after transplantation. In addition, in the past decades the introduction of ultrasound evaluation has contributed to increasing the diagnosis and consequently the incidence of lymphocele especially of the asymptomatic ones. Before ultrasound examination, the incidence ranged from 0.6 to 18.1% [4, 5]. Actually, the incidence of lymphocele varies between 0.6% and 33.9% [2, 6–10]. The reported incidence of symptomatic lymphocele ranges from 0.03 to 26% with a mean of 5.2% [7, 11–13]. A lymphocele may occur from 2 weeks to 6 months after transplantation with a peak incidence at 6 weeks [2, 14]. Nevertheless, in some studies, lymphocele has been reported 3.7 years after transplantation [15].

Surgical risk factors

Surgical causes of lymphatic complications are (i) dissection of the lymphatic around the iliac vessels of the recipient and (ii) dissection of renal lymphatic of the donor either during the time of organ procurement surgery or during 'back table' work. If these fragile lymphatic tissues are not clipped or sutured, they remain open and become an important source of free retroperitoneal lymph, setting up the basis for the development of lymphatic complications. Accordingly, different surgical techniques that implied less lymphatic derangement of the recipients, such as the implantation of the allograft in the omolateral iliac fossa with anastomoses of the renal artery and vein on the common iliac vessels, resulted in a lower rate of lymphocele (2.1 versus 8.5%) [16]. Consistently, with the surgical dissection of the renal lymphatic vessels as cause of lymphatic complications, there are some studies based on laparoscopic procurement of the graft from living donors and data regarding renal transplantation with multiple arteries. Saidi et al. reported a prolonged duration of lymphatic leak in recipients who received kidney grafts procured laparoscopically from living donors compared with recipient transplanted from deceased donors (8.6 ± 2.5 days versus 5.4 ± 2.5 days, respectively, $P < 0.05$). This suggests that a careful ligation of the severed lymphatics of the graft prior to transplantation is strongly recommended, especially in the case of kidneys procured by laparoscopic intervention [17]. Mazzucchi et al. showed that grafts with more than one artery were associated with a lower incidence of lymphoceles (3.1% single artery versus 12.5% multiple arteries, $P = 0.0015$) and speculated that the cause of higher occurrence of lymphocele in transplanted patients with multiple arteries grafts depends to the presence of more abundant lymphatic vessels likely due to insufficient ligation [18]. On the contrary, other studies did not find any significant differences in the rate of lymphatic complication according to different surgical techniques and among patients transplanted by surgeons with a different grade of experience in transplantation [19–21]. Thus, it is reasonable to speculate that lymphatic disorders developing long after surgical intervention in recipients who underwent a careful ligation of the damaged iliac lymphatic vessels, are due to a leakage of lymph from the allograft lymphatics.

Medical risk factors

In addition to acute rejection and mTOR inhibitors that will be discussed separately, many other factors were found to be associated with an increased risk to develop lymphocele after transplantation. Ulrich et al., by using a multivariate analysis, observed a significant association between lymphocele and diabetes in patients treated with calcineurin inhibitors (CNIs), and found a relative risk to develop lymphocele of 2.069, $P < 0.001$. The authors discussed regarding this correlation, indicating that the microangiopathy due to diabetes, a well-known risk for wound healing complications after kidney transplantation, could be responsible also for lymphatic complications [10]. Martinez-Ocana et al. found that a medical risk of developing lymphocele was represented by the presence of adult dominant polycystic kidney disease (ADPKD) as cause of end-stage kidney disease. The authors suggested that in patients affected by ADPKD the enlargement of native kidneys could compress the inferior vena cava reducing the lymphatic flow [22]. Blood coagulation abnormalities such as decreased concentration of thrombin/antithrombin complexes and prothrombin fragments F1 + 2 and LMWH prophylaxis have been correlated with a significant higher incidence of lymphocele formation. The anticoagulation therapy together with the defective coagulation associated with uraemia may impair the sealing of lymph vessels in the wound [23, 24]. Obesity of the recipients with a body mass index $>24 \text{ kg/m}^2$ [8, 25, 26], recipient age [27], acute tubular necrosis-delay graft function [15], warm ischaemia time [27], duration of dialysis treatment [28] and retransplantation [29] have been also associated with a greater risk of lymphocele. It is also known that some immunosuppressive drugs such as rabbit antithymocyte globulin, high dose of mycophenolate mofetil (MMF) ($>2 \text{ g/day}$) and steroids increase the risk of lymphatic complications [15, 27, 30–33]. Finally, the use of diuretics could increase the rate of lymphocele probably through their ability to increase the lymphatic flow [34]. Finally, a case of post-kidney transplantation lymphocele due to lymphatic filariasis has been described [35].

Lymphatic complications and rejection

The association between lymphatic complications and rejection has been described since 1974 by Rashid and coworkers [36]. Here, we review the studies that found this association and the suggested pathogenic mechanisms. Khauli et al. demonstrated a significant risk for the development of lymphoceles in kidney transplants with acute rejection either in a univariate or in a multivariate analysis (all lymphocele—OR: 75.24, $P < 0.0001$; symptomatic lymphocele—OR: 25.08, $P < 0.0003$) [15]. Consistently, a significant correlation with acute rejection ($P < 0.001$) using a multivariate analysis was found also by Goel et al. [8]. Ulrich et al. observed a high risk of lymphocele in patients with rejection (RR: 1.5, $P < 0.01$) using univariate testing. Nevertheless, these data were not confirmed in a multivariate analysis [10]. A significant association between rejection and lymphocele was demonstrated also in other studies performed in transplanted patients treated with CNI [5, 37–42]. In a prospective study planned to discern whether a systematic programme of wound care in transplanted patients treated with *de novo* SRL-MMF and steroids could reduce the incidence of wound healing complications, the authors demonstrated using a multivariate analysis that acute rejection was an independent risk factor for lymphocele formation and lymphocele needing treatment (OR 1.34, $P < 0.03$) [26]. Recently, Veeramani et al. reported an incidence of lymphocele diagnosed as perirenal fluid collection $>5 \text{ cm}$ after the first

postoperative week of 2% (47/1709) in transplanted patients treated with CNI. The incidence of rejection in patients with symptomatic lymphocele was significantly higher compared with the overall rejection rate (51 versus 20%, $P = 0.009$). Among patients with symptomatic lymphocele, 7.2% had at least 1 rejection episode and 40.4% >1. In addition, they reported a lower graft survival at 10 years in patients with lymphocele compared with those that did not develop lymphatic complications (68.14 versus 76.36%) [43].

Renal lymphatic system

The lymphatic system is fundamental in the maintenance of the body-fluid homeostasis by its ability to remove the excess of body fluid from the interstitium both in normal and abnormal physiological conditions [44–46]. It also plays a crucial role in the immune system by conveying immune cells in the site of infection. In addition, the lymphatic vessels allow lymphocytes and antigen-presenting cells to return to the blood [47].

In 1989, Cuttino and colleagues using a microradiography technique described the human renal lymphatics [48]. However, due to the lack of reliable markers that help to distinguish the lymphatic endothelium from the blood capillary endothelium the renal lymphatic system remained not fully documented for several years. In 2006, Ishikawa and coworkers clarified the morphology of the human renal lymphatic system. They performed an immunohistochemistry study on normal and pathological renal tissues using the anti-D2-40 antibody that detect specifically the lymphatic endothelium [49]. This study showed that in normal kidneys the lymphatics are abundant around the interlobar and arcuate arteries and veins. In addition, sporadically some lymphatic capillaries may be seen in the interstitium around the glomeruli and only seldom in the medulla. In humans, as in dogs, there are two lymphatic systems: the capsular and the hilar system. The capsular system is formed by the perforating and communicating lymphatics that drain the lymph from the outer cortex to the subcapsular web and subsequently in the perirenal lymphatic vessels. The hilar system collects the lymph drained from the lymphatic vessels of the cortex and of the medulla in the hilar lymphatic ducts. It is known that there is a communication between the two systems and that in normal conditions, most of the lymph is drained by the hilar system [45]. On the contrary, in pathological conditions such as ureteric obstruction, a diversion of the lymph from the hilar to the capsular system has been demonstrated [50].

Studies conducted by Hall *et al.* in 1965 in sheep demonstrated that there is an active lymph propulsion in lymphatic vessels due to the presence of smooth muscular cells in their wall [51]. These observation were fully confirmed in humans in 1980 [52]. In addition, in the lymphatic vessels there are one-way valves that help the lymph to move away from the tissues preventing the back-flow [53, 54].

It is known that the rejection process leads to an intense local inflammatory process increasing the regional lymph flow. Consistently, Pedersen and Morris demonstrated that the renal lymph flow measured in kidney transplanted sheep increase by 20- to 50-fold during a rejection process [55]. These experiments were performed in sheep because of the peculiar distribution of the lymphatic system. As described by McIntosh *et al.* an important feature of the lymphatic drainage of the sheep's kidney is that there are no capsular lymphatics and lymph drains from the kidney exclusively by vessels leaving the hilum [45]. Thus, Pedersen and Morris recorded the lymph flow produced by the graft using a drain inserted in the hilar lymphatic duct. In renal transplanted

patients, the ligation of the hilar ducts of the graft during the back table work could lead to the escape of the lymph, that is produced in a high amount during rejection from the subcapsular lymphatics.

In addition, a prolonged period of anoxia of the graft before transplantation is associated with an increase of the lymph flow which, however, did not reach the amount found during rejection. This phenomenon is probably due to damage of the endothelium without any immunological reaction and it could explain the association between lymphocele and delayed graft function demonstrated in humans [15].

The low concentration of proteins together with the small amount of red blood cells in the lymph from homografted kidneys suggest that the high amount of lymph flow from the graft was the result of haemodynamic changes within the graft rather than the result of increased capillary permeability [55].

Allograft rejection is an inflammation process and it is known that lymphatic vessels proliferate during inflammation. The formation of new lymphatic vessels from preexisting ones, namely lymphangiogenesis, is an important biological process associated with several pathological conditions, such as chronic inflammation (Crohn's disease, psoriasis), corneal graft rejection, malignancies and metastatic dissemination [56]. Studies over the past 10 years have identified key signalling molecules, such as vascular endothelial growth factors (VEGF)-C and -D and their receptor VEGFR-3, that are involved in the regulation of the lymphatic endothelial cell (LEC) growth, migration and survival. Specifically, VEGF-C and -D are able to bind neuropilin-2, a semaphorin receptor expressed both in the nervous system and in the lymphatic capillaries [57]. During inflammation, the release of inflammatory cytokines may induce the NF- κ B-mediated transcription of VEGF-C resulting in increased growth of lymphatic vessels [58].

The discovery of specific markers for LECs such as LYVE-1, Prox-1 podoplanin permitted the lymphatic vessel distribution and density in the kidney graft during acute rejection episodes to be evaluated [59, 60]. Kerjaschki *et al.* demonstrated that (i) lymphatic vessels are distributed in the normal renal cortex around large and middle size arteries; (ii) the same pattern of lymphatic distribution found in normal kidneys persists in the acute phases of transplant rejection together with mononuclear cell infiltration of the interstitium; (iii) in allograft biopsies containing nodular lymphocyte-rich inflammatory infiltrates, lymphatic density is augmented by 50-fold and their distribution changed reaching the tubular-interstitial space. These data support the hypothesis that the presence of inflammatory infiltrates in the allograft leads to neovessel formation from preexisting ones as indicated by the expression of the nuclear proliferation marker Ki-67. Thus, the authors speculate that lymphangiogenesis might be due to the local release of VEGF-C and VEGF-D by infiltrated CD68⁺CD23⁺ macrophages [60, 61]. In addition, Kerjaschki *et al.* demonstrated that lymphatic progenitor cells of the recipient participated in the neovessels formation in the graft which experienced rejection episodes by the detection of the Y chromosome in gender mismatched transplants. The obtained results indicate that VEGF-3⁺ tissue macrophages, considered lymphatic progenitors, may transdifferentiate into LECs. In addition, macrophages may act indirectly as a major source of VEGF-C and other lymphoangiogenic factors that stimulate the proliferation of resident LECs [62]. Recently, Yamamoto and coworkers found that allografts which experienced acute cellular and antibody-mediated rejection developed an increase in the lymphatic vessel density [63]. On the contrary, Stucht *et al.* did not find a correlation between acute rejection and whole density of lymphatic vessels but they demonstrated a significant higher

density of lymphatics in the areas with cellular infiltrates compared with the noninfiltrated areas (56.9 versus 3.1/mm², $P < 0.001$). They also found that patients with lymphangiogenesis showed a slightly but significantly better graft function at 1 year posttransplantation than patients without lymph vessels. Indeed, a lymphatic vessel density $>6.5/\text{mm}^2$ correlates with a low risk of kidney graft dysfunction within 1 year after transplantation indicating that lymph vessel density can be used as a prognostic marker of kidney graft survival. These authors hypothesized that the increase of lymphatics within the renal cortex might serve to convey the mononuclear cell infiltrates outside of the graft thus preventing the persistence of the inflammatory state [64]. Unfortunately, both Kerjaschki and Stuhl did not describe the immunosuppression regimens of the studied population. Thus, it is not possible to understand whether mTOR inhibitors could affect the neo lymphangiogenesis.

Another important regulator of lymphangiogenesis is sphingosine-1-phosphate (S1P) which by acting through its receptor 1 (S1P-R) is able to induce the development of new lymphatic vessels both *in vitro* and *in vivo* [65, 66]. In addition, it has been demonstrated that an agonist of the S1P-R, namely FTY720, is able to block the egress of lymphocytes from the lymph nodes resulting in a peripheral lymphopenia [67]. Therefore, FTY720 was tested as immunomodulator compound in experimental models of allotransplantation showing a high immunosuppressive effect [68]. On the basis of these results, FTY720 has been studied in kidney transplanted patients in order to reach an optimal immunosuppression, minimizing the drug-related toxicity of CNIs [69, 70]. At present, Phase II and III clinical trials have demonstrated both in adults and in paediatric recipients the safety of the therapeutic regimens based on the combination of FTY720 to CsA [71–74]. Nevertheless, more recent studies failed to demonstrate a beneficial effect of FTY720 compared with the current standard therapy [75, 76]. To date, the incidence of lymphatic complications such as lymphocele in transplanted patients treated with FTY720 remains an open question.

mTOR inhibitors and lymphatic complications

Huber and coworkers demonstrated *in vitro* and *in vivo* the anti-lymphoangiogenic effect of mTOR inhibitors during tissue regeneration. They found that mTOR inhibitors interfere with the intracellular pathway activation of LECs by VEGF-C, the main initiator of lymphangiogenesis and that the anti-lymphoangiogenic activity is a general phenomenon of mTOR inhibition. Thus, this anti-lymphoangiogenic effect could be elicited with both mTOR inhibitors: rapamycin (sirolimus, RapamuneTM) and RAD-001 (everolimus, EVR, CerticanTM) [77].

Consistently, several studies indicated that the use of rapamycin was associated with a significant increase in the incidence of lymphocele compared with other immunosuppressive regimens [8, 25, 42, 78–82].

From systematic reviews and meta-analysis of the randomized control trial on mTOR inhibitors, a higher incidence of lymphocele in mTOR inhibitor-treated patients emerges [83, 84]. In addition, Pengel et al. demonstrated that the immediate use of mTOR inhibitors leads to a higher incidence of wound complications and lymphoceles, suggesting that mTOR inhibitors should be avoided in the first few months after transplantation [83]. Langer and coworkers suggested a more aggressive treatment of perinephric fluid collections and lymphoceles in patients treated with the association SRL-CsA-Pred [42].

Cooper et al. analysed three randomized controlled trials in which 1996 *de novo* kidney transplant recipients were treated

with EVR 1.5 or 3.0 mg or mycophenolic acid (MPA), with CsA and steroids. They found no significant differences in the incidence of lymphoceles between the patients treated with EVR and those treated with MPA but the rates of lymphatic disorders requiring hospitalization were significantly higher in the EVR 1.5 mg group [85].

The incidence of lymphoceles was not affected by the length of the interval between the surgical intervention and the start of the immunosuppression therapy with mTOR inhibitors as demonstrated by Albano et al. and Dantal et al. [86, 87].

Symptoms and diagnosis

Transplanted recipients who developed lymphatic complications are usually asymptomatic. Thus, specifically lymphoceles are detected more sensitively by ultrasound examination, intravenous pyelography, CT and lymphangiography [13, 88]. However, in our experience lymphangiography did not help to diagnose the origin of the lymph either in patients with lymphorrhea or lymphocele. In addition, large lymphoceles may manifest by oedema in the inguinal regions, deterioration of graft function, abdominal discomfort, urgency, vesical tenesmus, compressive syndrome of the vena cava or the portal vein and/or fever.

In the case of a leak from surgical drain of perinephric collection, a biochemical and microbiological analysis of the fluid from the drain or aspirated from the lymphocele using an ultrasound-guided fine-needle percutaneous aspiration must be performed. Biochemical analysis of the creatinine, electrolytes (sodium and potassium), total protein and albumin are needed to differentiate lymphatic complications from leak or accumulation of urine (urinoma) or sera (seroma).

Once established that the fluid from the drain or from lymphocele is lymph we suggested to investigate whether the lymph derived from the renal graft or from the lymphatic of the recipient. Pacovsky et al. demonstrated significant differences in creatine kinase CK enzyme activity depending on the source of the lymph [89]. It is known that CK is an enzyme expressed in various tissues and cell types but predominantly in striated muscles. Thus, CK activity could be a marker of iliac lymph [89–92]. Briefly, according to a graph developed by Pacovsky et al., if CK activity is <35 UI/L, then the proportion of renal lymph over the total will be $>85\%$. Conversely, a CK activity >210 UI/L is associated with a percentage of renal lymph over the total of $<30\%$ [89].

In our centre, we place a surgical drain in the extraperitoneal space close to the ureteroneocystostomy during surgery. The drain will be discontinued after the vesical catheter removal that usually occurs after an average of 10 days from transplantation when the volume of drainage is <50 mL/day for two consecutive days. A routine ultrasound examination of the abdomen is performed after drain removal. In the case of peridrain leakage, we cut the surgical drain in order to allow the application of a colostomy bag that may drain the leakage of fluid. In order to diagnose promptly, the occurrence of lymphorrhea, as well as a lymphocele, we performed the follow diagnostic algorithm. In presence of a leak of fluid >50 mL/24 h from the surgical drain, a biochemical analysis is performed dosing creatinine, sodium, potassium, total protein and albumin concentration in order to distinguish lymph from sera or urine. In addition, a microbiological evaluation is routinely performed to exclude infection. The same analysis is performed on the aspirated fluid in the case of symptomatic lymphocele or asymptomatic but with a diameter >2 cm diagnosed by ultrasound examination. If the biochemical evaluation is suggestive for lymph, a dosage of CK activity in such fluid will be performed in order to calculate the percentage of renal lymph according to Pacovsky et al. [89].

Treatment

Treatment of lymphocele should start with minimally invasive measures [9]. Generally, lymphatic disorders resolve spontaneously and do not require treatment but rather only a close follow-up. The incidence of lymphoceles requiring treatment varies from 0.04 to 14.6% [11, 13]. Placing a surgical drain in the extraperitoneal space during transplantation was shown to decrease the incidence of fluid collection and the need of lymphocele treatment especially in patients with SRL-based immunosuppression [93]. In this study, the drain was left in place until drainage was <50 mL/day for two consecutive days. If the lymphocele is clinically symptomatic or the volume exceeds 140 mL, treatment is often required. In this case, a percutaneous drainage alone or in association with sclerotherapy as been proven to be effective therapy [94]. The effectiveness of aspiration varies between 25 and 41% compared with percutaneous drain placement between 50 and 55% [11, 95].

Sclerosing agents include fibrin glue, 95% ethanol instillation with addition of factor XIII and fibrinogen in cases of failure, sodium tetradecyl sulphate, tetracycline and povidone-iodine. The recurrence rate varies from 31 to 37.5% after the first and 18.7% after the second treatment [11, 42, 96]. However, these procedures may impact the patient's quality of life and increase the risk of infection. Moreover, Krol *et al.* demonstrated that puncture, drainage and sclerotherapy were not effective in patients with a lymphocele volume exceed 500 mL [94].

Since 1992, the treatment of symptomatic lymphocele with laparoscopic fenestration of the lymphocele into the peritoneal cavity has been a safe and efficient method. The rate of recurrence is between 4 and 8%, compared with 16 and 51% for surgical treatment and aspiration, respectively. Laparoscopic surgery represents a valid therapeutic option compared with open surgery and to aspiration on the basis of the low rate of complication. In addition, the laparoscopic surgery is associated with a shorter time of hospitalization compared with open surgery [3, 10, 11, 95, 96]. Capocasale *et al.* reported on the effect of octreotide (0.1 mg three times a day subcutaneously) compared with povidone-iodine instillation on patients with lymphorrhea. They found that with octreotide the mean length of lymphorrhea and the hospital stay were lower with minor patient discomfort than with povidone-iodine. The rationale for the use of octreotide was the expression of somatostatin receptors on the lymphatic vessels [97].

Conclusions

In kidney transplant patients, lymphatic complications and specifically lymphocele still remain a surgical complication due to dissection of the lymphatic of the recipients and the graft. Consistently, transplant surgeons must pay particular attention during both organ retrieval and 'back table' work in order to avoid the dissection of the lymphatic vessels of the kidneys. At the same time, they must preserve as much as possible the lymphatic vessels and lymph nodes of the recipient by clipping the sectioned ones. An optimal surgical procedure represents the best prevention for lymphatic complications.

However, the results of several studies reported in this review, together with the recent advances on lymphoangiogenesis, indicate that lymphatic complications could be associated also with medical causes such as mTOR inhibitors-based immunosuppression and rejection. Consistently, mTOR inhibitors affect neolymphangiogenesis in the graft leading to a failure in new vessel formation and consequently of the reduction of drainage of

lymph from the inflamed allograft. This observation together with the demonstration of the increase of the lymph flow in the kidney graft which underwent rejection could explain the high incidence of lymphatic complications found in several studies both in patients treated with mTOR inhibitors and in patients with acute rejection. In conclusion, these findings suggest that strict monitoring of graft function should be done in patients who develop lymphatic complications in order to diagnose a rejection, especially in recipients with high immunological risk. However, future studies specifically designed to confirm the association between lymphatic complications and rejection in transplanted patients are needed.

Author contributions

A.R. provided substantial contributions to conception and design, revising the literature, drafting the article; G.P.S. contributed to drafting the article and revising it critically for important intellectual content; F.L. contributed by revising the literature and drafting the article; L.B. contributed by revising the article critically for important intellectual content and final approval of the version to be published.

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Conflict of interest statement

None declared.

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