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Clinical Report

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Symptomatic lymphocele developing soon after acute renal allograft rejection: coincidental or causal connection?

Muhammad Asim[1,2] and Awais Nauman[2]

[1]Weill Cornell Medical College, Doha, Qatar and [2]Department of Medicine, Hamad Medical Corporation, Doha, Qatar

Correspondence and offprint requests to: Muhammad Asim; E-mail: mua2002@qatar-med.cornell.edu; masim13@hotmail.com

Abstract
A renal transplant patient developed a lymphocele soon after an episode of acute rejection (AR). The lymphocele rapidly increased in size causing transplant ureteric and venous obstruction, leading to acute graft dysfunction and swelling of the ipsilateral leg. We appraise the complex relationship that exists between AR, lymphangiogenesis and lymphocele formation to determine whether a case for a causal connection between AR and development of lymphocele can be made in our patient.

Keywords: acute rejection; lymphocele; renal transplantation

Background

When two events overlap or take place in close proximity to each other, then their 'simultaneity' can be attributed to (i) coincidence, which is a conjunction of two independently explicable events, (ii) direct causation, when one event triggers the other and there is a causal relation that links one with the other or (iii) indirect causation, when the two events are each related to a third factor that has triggered each. Acute rejection (AR) and lymphocele formation are well-recognized post-renal transplant complications. Evidence from experimental and observational data points to an association between AR and lymphocele formation, but a causal link has not been established.

Case report

A 50-year-old man who had end-stage renal disease secondary to diabetic nephropathy underwent an uncomplicated right iliac fossa 1-1-2 human leucocyte antigen (HLA) mismatch deceased donor kidney transplantation. The recipient had Class I panel reactive antibodies' (PRAs) titre of 97%, but T- and B-cell IgG flow cytometric crossmatch was negative. Induction therapy with anti-thymocyte globulin (ATG), tacrolimus and mycophenolate mofetil (MMF) was given. The allograft functioned immediately after transplantation and serum creatinine (SCr) decreased to 105 μmol/L (1.18 mg/dL) on the third post-operative day. Ultrasonography (US) of the transplanted kidney performed on the second and ninth post-operative day revealed normal renal blood flow patterns and no hydronephrosis or fluid collection.

An asymptomatic acute rise in the SCr of 147 μmol/L (1.66 mg/dL) was noted 3 weeks after transplantation. Once again US and Doppler studies were unrevealing. Renal allograft biopsy was done; histology revealed severe tubulitis and interstitial inflammation affecting 30% of parenchyma (Banff Type IB, T-cell-mediated rejection) as well as glomerulitis with margination and C4d positivity (Banff Type II, antibody-mediated rejection). Treatment with pulse methylprednisolone (500 mg/day for 5 days), ATG (total of 7.5 mg/kg) along with plasma exchange (PE; eight treatments on an alternate day schedule) and IV immunoglobulin (100 mg/kg after each PE) was given. Frequent infusions of cryoprecipitate were required to correct hypofibrinogenaemia associated with PE therapy. At the end of this treatment, SCr had decreased to 115 μmol/L (1.3 mg/dL). A repeat US showed a peri-transplant fluid collection of 85 mL. Patient was discharged on prednisone, tacrolimus and MMF. Transplant ureteric stent was removed 6 weeks after transplant; a follow-up US did not show any hydronephrosis, but demonstrated that the peri-transplant collection had increased in volume to 226 mL. A renogram showed normal kidney perfusion and excretion. Two weeks later, patient developed acute graft dysfunction [SCr 247 μmol/L (2.79 mg/dL)] and swelling of the right leg. US revealed a large fluid collection (1163 mL; 14.5 × 16.9 × 9.3 cm) medial to the inferior pole of the kidney transplant causing ureteral compression and moderately severe hydronephrosis. Doppler studies of the lower limb did not show any deep vein thrombosis. The collection was drained using a pigtail catheter; biochemical analysis of the aspirated fluid revealed creatinine 91 μmol/L (1.03 mg/dL) and protein 8 g/L (0.8 g/dL) [SCr 93 μmol/L (1.05 mg/dL) and serum protein 58 g/L (5.8 g/dL)]—confirming that it was a lymph. Following removal

of the pigtail catheter, lymphocele re-accumulated and hence, a laparoscopic marsupilization was performed. Patient was discharged with a SCr of 115 μmol/L (1.3 mg/dL). A follow-up ultrasound showed minimal hydronephrosis with no radio-tracer hold-up in the collecting system on renal transplant scintigraphy.

Discussion

Our patient developed a lymphocele in close association with AR, and the question is 'was it a coincidence or was it causally related'? Of course, one may argue that it was a random coincidence; both AR and lymphocele are well-known complications after transplantation and each has its independent set of required conditions. Our patient was at a high-immunological risk of AR in view high PRA and a number of HLA mismatches. On the other hand, lymphoceles are not uncommon after renal transplantation either [1]. Virtually all lymphatic connections of the transplanted kidney and some of the recipient's lymphatic vessels are unavoidably divided during transplantation. It is impractical to ligate/coagulate every transected lymphatic channel, exudation from which can lead to the formation of post-transplant lymphocele [2]. Hence, meticulous lymphostasis and minimization of tissue dissection in the recipient have been shown to reduce the incidence of post-transplant lymphocele [3]. The patient also had diabetes, another recognized risk factor for post-operative wound healing complications, that could have contributed to lymphocele formation [4].

Conversely, we contend that AR and development of lymphocele in our patient represented a cause-effect relationship. Several arguments can be given to support this point of view.

First, the time precedence—serial post-operative ultrasound studies gave us the opportunity to precisely ascertain the onset time of lymphocele. There was no lymph collection at the time of diagnosis of AR; lymphocele accumulated rapidly after the diagnosis and treatment of AR (Figure 1) and achieved sufficient volume to mechanically compress the transplant ureter and iliac veins. Hence, the sequence of events fulfils the 'temporal precedence' criteria for causation, i.e. the cause (AR) preceded the effect (lymphocele). Temporality is considered as a strong causal criterion [5].

Secondly, the biological plausibility—AR as a cause of lymphocele is biologically conceivable. AR causes an intense local vascular and cellular inflammatory response with subsequent dilatation and increased permeability of the small blood vessels. This leads to increased regional lymph production and flow. The experimental mechanistic evidence came from Pedersen and Morris who used a transplant sheep model, where kidneys were implanted in the neck and renal lymphatics were cannulated for monitoring lymph flow [6]. They demonstrated a remarkable 20- to 50-fold increase in renal lymphatic drainage from rejecting allogenic renal grafts compared with unchanged lymph flow in autografts. Experimental evidence is another sound criterion of causality.

Thirdly, the growing evidence from observational studies showing that the majority of the symptomatic/large lymphoceles are associated with prior or concomitant rejection episodes [1, 7–9]. In a prospective study of 118 renal transplants, Khauli *et al.* reported that only AR was associated with a significant risk for lymphoceles by multivariate analysis of risk factors. The occurrence of AR posed a 25- to 75-fold increased likelihood of the development of symptomatic and asymptomatic lymphoceles, respectively. After adjusting for AR, no other risk factor came close to being significant [2].

Finally, there are no plausible explanations for reverse causation–AR can cause development of a lymphocele, but the reverse is not true. In other words, the relationship between AR and lymphocele is unidirectional.

The possibility of indirect causation cannot be ruled out. It is possible that the relationship between AR and

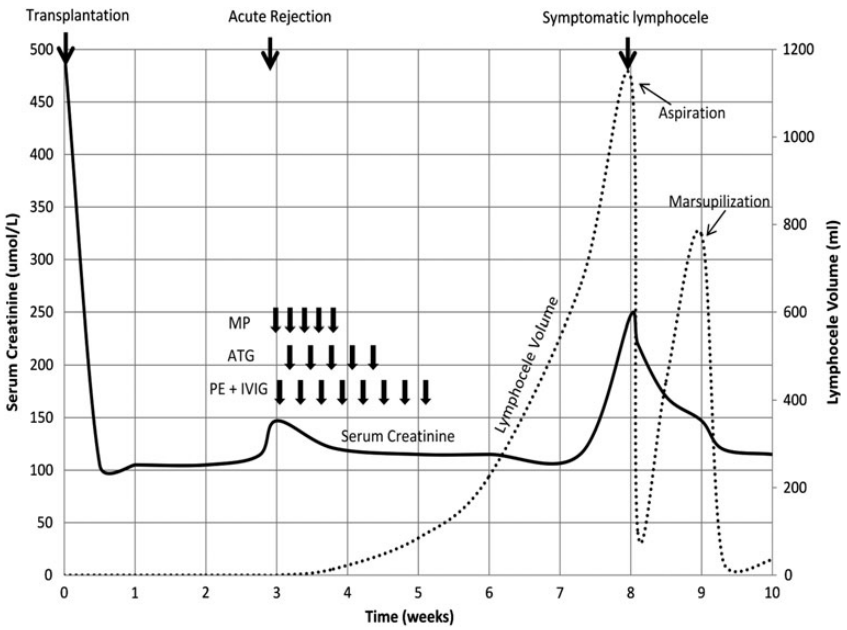

Fig. 1. Timeline of events showing correlation between AR and lymphocele formation. MP, methylprednisolone; ATG, anti-thymocyte globulin; PE, plasma exchange; IVIG, IV immunoglobulin.

lymphocele was spurious and a 'third variable' caused both AR and lymphocele. This missing variable could potentially be lymphangiogenesis. Animal studies have shown that remodelling of the lymphoid system begins as early as 1–2 weeks after solid organ transplantation, so that the graft lymphatics start to establish new connections with the host lymphatic system by means of lymphangiogenesis [10]. Restoration of the lymphatic network can enhance immune cells' traffic to lymphoid tissue thereby initiating the immune response against the donor kidney. A pathological analysis by Yamamoto *et al.* [11] revealed that patients with acute cellular rejection, acute antibody-mediated rejection or peritubular capillaritis exhibited a 4- to 9-fold increase in lymphatic vessel density. Stuht *et al*. [12] also demonstrated in sequential protocol biopsies that cortical lymphangiogenesis can be found in 66% of renal allografts with any cellular infiltrates. These findings, however, might also suggest lymphangiogenesis as a consequence rather than a cause of AR, implying a bidirectional relationship between AR and lymphangiogenesis. Inflammation and increased amount of tissue fluid during AR can stimulate lymphangiogenesis in the allograft in order to provide exit routes for tissue fluid and cellular infiltrates thereby assisting in resolution of inflammation.

The quantitative extent of lymphatic reconnection between the renal allograft and the recipient lymphatic system may eventually determine the size of the lymphocele. If lymph production is overwhelming and remodelling of lymphatic network relatively inadequate, then a relatively large amount of lymph will exude from divided allograft lymph channels into the free space resulting in a bigger lymphocele.

Owing to the close proximity of AR to its treatment, disentangling the causal contribution of each to the development of lymphocele remains a thorny issue. The use of modern immunosuppressive agents has been linked with considerable increased rates of wound healing disorders [13]. Although this appears to be particularly true for sirolimus [14] (not used in our patient), both high-dose steroid therapy and MMF can potentially impair fibroblast-mediated collagen formation and remodelling resulting in impaired healing of disrupted lymphatics and consequently, lymphocele formation [15]. There are, however, controversies in the literature—Tondolo *et al*. [16] demonstrated that incidence of lymphocele was not significantly different among multiple immunosuppressive regimens if careful closure of lymphatics was performed.

In conclusion, we feel that conjunction between AR and lymphocele formation should not be dismissed as a mere coincidence. Although recent multicentre studies do not point to a close relation between AR and lymphocele [17], there is evidence to support a multifaceted relation between AR, lymphangiogenesis and lymphocele formation. AR appeared to be a genuine factor implicated in the pathogenesis of lymphocele in our patient, although the possible additive role of other factors, such as diabetes and immunosuppressive agents, cannot entirely be excluded; temporality, biological plausibility, experimental evidence and observational data—all corroborate causality. An additional well-designed prospective study is required to rigorously evaluate the causal connection between AR and post-transplant lymphocele and to evaluate the relative extent and the role of the other contributing factors.

Conflict of interest statement. None declared.

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