INVITED COMMENTARY

Discordant rejection in simultaneous pancreas and kidney transplantation: true discordance or analysis artefact?

Michela Assalino[1], Karine Hadaya[1,2], Axel Andres[1] & Thierry Berney[1]

1 Division of Transplantation, University of Geneva Hospitals, Geneva, Switzerland
2 Division of Nephrology, University of Geneva Hospitals, Geneva, Switzerland

Correspondence
Thierry Berney MD, MSc, FEBS, Division of Transplantation, Department of Surgery, University of Geneva Hospitals, 4, rue Gabrielle-Perret-Gentil, CH-1211 Geneva 14, Switzerland.
Tel.: +41 22 372 34 04;
fax: +41 22 372 34 33;
e-mail: thierry.berney@hcuge.ch

Transplant International 2018; 31: 17–19

Received: 17 July 2017; Accepted: 20 July 2017

The article by Parajuli *et al.* [1] published in this issue of *Transplant International* is the latest, and perhaps the most convincing in a relatively small body of literature, to suggest that in a situation of simultaneous pancreas–kidney transplantation (SPK), in which both organs are from the same donor, one organ may be undergoing acute rejection independently from the other. The organ hierarchy in immunogenicity and susceptibility to rejection is a long-known biological phenomenon, with the liver at one end of the spectrum and the intestine at the other. It was originally thought that such a hierarchy between kidney and pancreas was in disfavour of the latter [2]. This idea of a more rejection-prone pancreas was challenged by animal studies on porcine and canine models of SPK [3,4] and seminal clinical observations reporting on reasonably concurrent kidney and pancreas graft biopsies [2], suggesting that isolated rejection could occur indifferently in the pancreas or in the kidney.

The fact that acute rejection, either cellular (ACR) or antibody-mediated (AMR), can target one organ specifically while leaving the other – expressing the exact same antigenic determinants – free of immune injury is quite intriguing. In fact, how really discordant is 'discordant kidney and pancreas rejection' in SPK?

Absence of concordance or sampling issue?

Immune rejection involves circulation of donor antigens to secondary lymphoid organs, and immune cell trafficking between lymphoid organs and target grafts. It is therefore by no means a local phenomenon. On the other hand, absolute uniformity is not a fact of nature and intensity of the rejection phenomenon is unlikely to be equally distributed throughout the rejecting organ. In other words, the absence of histological signs of rejection in a core biopsy might simply indicate that the sample was taken in a relatively spared part of the organ. Lack of histological concordance has been described in studies of paired biopsies in kidney grafts, in line with the idea that histological changes in

doi:10.1111/tri.13017

rejecting organs do not occur uniformly [5,6]. There is no reason to think that lack of uniformity does not also occur in the pancreas and that the discordantly negative pancreas biopsies in this study may simply have been the result of sampling issues.

How synchronous is 'concurrent'?

In this study, concurrent biopsies were taken within 30 days of one another. A smaller series also reported a high rate of discordance (8/21; 38%), with 3/8 discordant biopsies taken within a shorter 7-day interval [7]. This is a long interval in the course of a rejection process. Indeed, in an SPK canine study in which simultaneous biopsies of the kidney and pancreas were taken at regular time points between day 0 and day 30 post-transplant, discordant rejection disappeared and became concordant in several cases on the next biopsy taken 2 days later [4]. Additionally, timing and sampling are interconnected inasmuch as the biopsy may have been taken at a time when the rejection infiltrate is still focal rather than diffuse. This suggests that the reported discordance may simply be the result of only a slight asynchronicity and that a shorter time lag may have resulted in concordance, one way or another.

Histology: gold standard or only gilded?

Histology is considered the gold standard in the assessment of graft rejection. Classification schemes and guidelines developed in the Banff meetings, both for the kidney and pancreas, are continuously re-examined and updated and have the huge merit of standardizing definitions and gradings of rejection, thus ensuring that a common language is spoken by transplant pathologists and physicians [8]. However, some diagnostic challenges persist, and histological assessment involves subjective judgement and has limited between-observer reproducibility [9]. The field of molecular pathology is developing in response to these issues and a recent report, based on the comparison of histological and molecular diagnoses in the light of clinical outcome, has shown that molecular diagnosis more frequently agreed with clinical judgement than histology [9]. Diagnostic challenges are especially true in the case of borderline rejection, in which timing, sampling and histological accuracy all come together to contribute to a diagnostic conundrum [10].

Finally, the high level of discordance in rejection type (ACR vs AMR) in the Parajuli study is a confirmation that diagnosing AMR in a pancreas graft remains a challenge [11] and that criteria for pancreatic AMR still have to be refined [8,12].

Does it actually matter and how do we handle this?

Does discordant rejection really exist? Or does it simply reflect the fact that a biopsy is only a snapshot in space and time, analysed with imperfect tools? Is it only a semantic question? At the end of the day, does it matter whether one is facing discordant rejection or a concordant rejection that they are unable to see?

The fundamental issue for the clinician is timely diagnosis of rejection. Because the blood marker for suspecting rejection is more reliable for the kidney (creatinine) than for the pancreas (lipase), and because kidney biopsy is perceived as more straightforward and associated with fewer complications than pancreas biopsy, most transplant physicians have used the kidney as a 'sentinel organ' for diagnosing pancreas rejection. In this context, a discordant rejection in which rejection is seen only in the kidney is of no importance, as it will trigger antirejection treatment anyway. More problematic is the reverse situation, in which rejection is seen only in the pancreas, as it would be missed in a 'sentinel organ' strategy. The good news is that this situation occurred in 'only' 25% of cases in this study, and that an appropriate and useful clinical diagnosis is therefore obtained in 75%.

When rejection of either organ is suspected, we would recommend centres routinely performing pancreas biopsy to biopsy both organs at the same time. There are few studies in the literature reporting on concurrent pancreas and kidney biopsies, but reports on truly simultaneous biopsies are lacking. This approach would provide the clinician in charge with comprehensive information and the pancreas transplant community with valuable data. For those who are reluctant to biopsy the pancreas, taking a biopsy of the kidney only will provide correct information in 75% of cases. If the kidney biopsy comes back with a negative histological result, they always can – and should – proceed to a pancreas biopsy as a second step. But for those who have neither the routine nor the reluctance, this study encourages them to consider including pancreas biopsy as part of their regular diagnostic armamentarium.

Funding

The authors have declared no funding.

Conflicts of interest

The authors have declared no conflicts of interest.

REFERENCES

1. Parajuli S, Arpali E, Astor BC, *et al.* Concurrent biopsies of both grafts in recipients of simultaneous pancreas and kidney demonstrate high rates of discordance for rejection as well as discordance in type of rejection – a retrospective study. *Transpl Int* 2018; **31**: 32.
2. Bartlett ST, Schweitzer EJ, Johnson LB, *et al.* Equivalent success of simultaneous pancreas kidney and solitary pancreas transplantation. A prospective trial of tacrolimus immunosuppression with percutaneous biopsy. *Ann Surg* 1996; **224**: 440.
3. Gruessner R, Nakhleh R, Tzardis P, *et al.* Differences in rejection grading after simultaneous pancreas and kidney transplantation in pigs. *Transplantation* 1994; **57**: 1021.
4. Hawthorne WJ, Allen RDM, Greenberg ML, *et al.* Simultaneous pancreas and kidney rejection: separate or synchronous events ? *Transplantation* 1997; **63**: 352.
5. Solof JM, Vartanian RK, Olson JL, Tomlanovitch SJ, Vincenti FG, Amend WJ. Histopathological concordance of paired renal allograft biopsy cores. Effect on the diagnosis and management of acute rejection. *Transplantation* 1995; **60**: 1215.
6. Piovesan AC, Lucon AM, David DSR, Nahas WC, Antonopoulos IM, Srougi M. Multifocal renal allograft biopsy: impact on therapeutic decisions. *Transplant Proc* 2008; **40**: 3397.
7. Troxell ML, Koslin DB, Norman D, Rayhill S, Mittalhenkle A. Pancreas allograft rejection: analysis of concurrent renal allograft biopsies and posttherapy follow-up biopsies. *Transplantation* 2010; **90**: 75.
8. Loupy A, Haas M, Solez K, *et al.* The Banff kidney meeting report: current challenges in rejection classification and prospects for adopting molecular pathology. *Am J Transplant* 2015; **2017**: 28.
9. Halloran PF, Reeve J, Akalin E, *et al.* Real time central assessment of kidney transplant indication biopsies by microarrays: the INTERCOMEX study. *Am J Transplant* 2017; PMID: 28449409, DOI:10.1111/ajt.14329. Epub ahead of print.
10. Randhawa P. The, "Borderline" renal allograft biopsy in the era of molecular diagnostics: A sampling conundrum? *Am J Transplant* 2012; **12**: 11.
11. Malheiro J, Martins LS, Tafulo S, *et al.* Impact of de novo donor-specific anti-HLA antibodies on grafts outcomes in simultaneous pancreas-kidney transplantation. *Transpl Int* 2016; **29**: 173.
12. de Kort H, Roufosse C, Bajema IM, Drachenberg CB. Pancreas transplantation, antibodies and rejection: where do we stand? *Curr Opin Organ Transplant* 2013; **18**: 337.