Chimerism in women with end stage renal diseases

Who's who?

Laetitia Albano,¹ Justyna M. Rak,² Doua F. Azzouz,² Elisabeth Cassuto-Viguier,¹ Jean Gugenheim^{3,4} and Nathalie C. Lambert^{2,*}

¹UMC Transplantation Rénale; Hôpital Pasteur; Centre Hospitalo-Universitaire de Nice; Nice France; ²INSERM UMRs1097; Parc Scientifique de Luminy; Marseille, France; ³Service de Chirurgie et Transplantation Hépatique; Hôpital l'Archet 2; Université de Nice Sophia Antipolis; Nice, France; ⁴INSERM U526, IFR 50; Faculté de Médecine; Université de Nice Sophia Antipolis; Nice, France

Many sources of foreign or semi-foreign cells, known as microchimerism (Mc), can be found in healthy individuals. We have recently shown in women with end stage renal disease (ESRD) that Mc frequencies and levels are exacerbated prior to kidney transplantation. Is Mc arising from pregnancy a protective factor for renal diseases explaining lower incidence in women? Is Mc helpful in slowing down disease progression? However, natural Mc is not the only actor as post blood transfusion Mc is also found at high levels in women with ESRD. The difficulty is therefore to distinguish the different types of Mc and this is made even more complicated when the recipient receives a potentially chimeric organ. What part does each source of chimerism play in disease and transplant fate, and can one decipher each role knowing that one chimerism may hide another?

cells is still being debated. They may be beneficial, leading to better tolerance of grafts, participate in tissue repair or be deleterious if involved in chronic lesions.⁴

Many studies have tried to correlate the persistence of circulating donor cells with clinical outcome of recipients,⁵⁻⁷ but very few have considered the presence of foreign DNA/cells either in the recipient blood or allograft prior to transplantation.⁸ For the first time, in a recent study we provided evidence that women with end stage renal disease (ESRD) carry male microchimerism (Mc) in peripheral blood mononuclear cells before kidney transplantation.⁹ When compared with healthy women, the presence of male Mc was more frequent (62% vs. 16%) and at higher levels [98 vs. 0.3 genome equivalent of Mc cells per million host cells (gEq)] in women with ESRD.

This male Mc could be fetal in origin for women who had never had a blood transfusion (BT) and had at least one son. This has previously been demonstrated in healthy women and women with autoimmune diseases, as the result of transplacental traffic of cells during pregnancy,¹⁰ whether complete or incomplete.^{11,12} It could also be iatrogenic for women who had a BT from a male donor, as previously described in immune competent transfusion recipients.¹³ Or it could be from both origins, which are not distinguishable with the quantification method we used based on sex mismatch by PCR of a Y chromosome sequence.¹⁴ Other sources of Mc could come from older siblings through maternal circulation, or from a

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*Correspondence to: Nathalie Lambert;
Email: nathalie.lambert@inserm.fr

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In the field of kidney diseases, chimerism has been studied essentially after kidney transplantation as a possible biomarker for tolerance or rejection. Two types of chimerism can be acquired through kidney transplantation: an induced chimerism in combined kidney and bone marrow transplantation to generate immune tolerance in the recipient¹ and spontaneous chimerism corresponding to recipient-derived cells colonizing the renal allograft^{2,3} and/or donor-derived hematopoietic cells persisting in the recipient blood. The biological significance of these chimeric cells infiltrating the graft and replacing donor's

Figure 1. Diagram representing the possibilities for kidney transplantations and their associated chimerism sources. To make Mc transfer easier to understand, we have arbitrarily represented a gravid woman when the donor or the recipient is a woman, although the woman may be nulli-gravid and would then be identical to a man in terms of chimerism sources. Furthermore, to avoid complicating the diagram, we have not represented fraternal/twin and/or post transfusion Mc. In cases (A and B) the recipient is a woman, in cases (C and D) the recipient is a man. In cases (A and C) the donor is a woman, in cases (B and D) the donor is a man.

recognized or unrecognized (vanished) twin. The phenomenon of the vanished twin, not so uncommon in healthy pregnancies, has been recently demonstrated by our group in a 40-y-old man diagnosed with a scleroderma-like disease.¹⁵ In this case report, we were able, with detailed family history, to assert the origin of Mc by PCR based on human leukocyte antigen (HLA) polymorphism.¹⁶

A gravid woman has more opportunities to harbor Mc than a man if only through the feto-maternal exchange she experiences during pregnancy. From this

observation was born the hypothesis that being a privileged recipient for Mc could contribute to a higher predisposition to autoimmunity and would explain the higher incidence of autoimmune diseases in women.¹⁷

However, for many renal diseases, the incidence seems higher in men than in women (for a review see ref. 18). Similarly, the progression rate is affected by gender and a strong meta-analysis comprising a total of 11,345 patients from 68 studies, reported that renal disease in women with polycystic kidney disease, IgA

nephropathy, membranous glomerulopathy and “chronic renal disease of unknown etiology” progresses at a slower rate than it does in blood pressure- and lipid level-matched men with these diseases.¹⁹ The most common factors invoked to explain this gender disparity are sex hormones, diet, kidney and glomerular size and differences in glomerular hemodynamics.¹⁸ Mc has not previously been postulated as a possible explanation for gender disparity in ESRD but if it was, it could be considered as protective, as suggested in breast cancer.²⁰ We could hypothesize that with the loss of renal function, Mc of stem cell origin would try to replace the damaged organ, as suggested in type I diabetes with maternal cells.²¹ Although the course of the disease is not stopped, it could slow down the rate of dysfunction.

However, Mc arising from pregnancy is not always responsible for the difference observed between Mc levels/frequencies in healthy women and in women with ESRD. Moreover, women with ESRD often had a history of leuko-reduced BT which could leave iatrogenic Mc.¹³ We demonstrated, however, that the difference observed in women with ESRD was not dependent on transfusion history, as results remained significant in women who never had a BT;⁹ intriguingly, the difference did not correlate either with pregnancy history, since having given birth to a son or not had no influence on the results. In other words, women with ESRD who had never had a male pregnancy and for whom male Mc was most probably due to BT, maintained high levels of male Mc in their blood with a range of 0 to 1382 gEq. High post-transfusion levels may be due to diminished response to donor cells from highly microchimeric women as previously shown.²² Another explanation could be that any source of chimerism, because of its stem origin, is used as a repair cell when needed, recruited from its niche, and is therefore visible in peripheral blood at that time.

The origin of male Mc in women with ESRD prior to transplantation is already difficult to determine, but the addition of post transplantation Mc when the donor is male makes it even more difficult. Even if the donor is female, male chimerism from prior BT and/or pregnancies can be found

in her organs as described by Koopmans et al.²³ Therefore many sources of Mc can theoretically be found in a kidney recipient and coexist at a given time (Fig. 1). If we take the case of a gravid woman transplanted with a kidney from another gravid woman, five different sources of chimerism could be then present in the recipient: her maternal cells, her fetal cells, maternal and fetal cells from her donor as well as donor cells, and if additionally both donor and recipient have been transfused and/or had twins, this would increase to 9 genetically different cells in the same recipient!

Again, a caveat of our study is that the presence of male Mc, detected by Y

chromosome sequence PCR, only provides presumptive evidence that it derived from the expected source. When the donor was male, we could not distinguish male Mc as a post BT consequence from natural Mc originating from a previously born son. Of course, the reason we used Y chromosome PCR assays is that we had no other possibility since DNA from patient's family members was not available for HLA investigations.

On the basis of our results, studying donor-induced chimerism after kidney transplantation requires very cautious planning: having the recipient and allograft donor's blood samples as well

as those of their family members before transplantation in order to identify preexisting chimerism in each of them by HLA specific Q-PCR, analyzing specific donor HLA antigens in the recipients.

Our study has been a first step, revealing that Mc in women with ESRD prior to their first kidney transplantation is at high levels. Many other studies need to be done to determine the origin of the different kinds of chimerism and their various roles in the disease itself, its prevalence, its progression, but also their impact on transplant outcome. The most important is first to distinguish who is who, to know who does what.

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