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## **Correction of both immunodeficiency and hypoparathyroidism by thymus transplantation in complete DiGeorge Syndrome**

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### **Abbreviations**

cDGS complete DiGeorge Syndrome, HPT hypoparathyroidism, RSV respiratory syncytial virus, HHV6 human herpes virus 6, PTH parathormone,

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## ABSTRACT

Combined immune deficiency due to athymia in patients with complete DiGeorge Syndrome can be corrected by allogeneic thymus transplantation. Hypoparathyroidism is a frequent concomitant clinical problem in these patients, which persists after thymus transplantation. Co-transplantation of allogeneic thymus and parental parathyroid tissue has been attempted, but does not achieve durable correction of the patients' hypoparathyroidism due to parathyroid graft rejection. Surprisingly, we observed correction of hypoparathyroidism in one patient after thymus transplantation. Immunohistochemical analysis and Fluorescence in Situ Hybridisation confirmed presence of allogeneic parathyroid tissue in the patient's thymus transplant biopsy. Despite a lack of HLA-matching between thymus donor and recipient, the reconstituted immune system displays tolerance towards the thymus donor. Therefore we expect this patient's hypoparathyroidism to be permanently cured. It is recognised that ectopic parathyroid tissue is not infrequently found in the thymus. If such thymuses could be identified, we propose that their use would offer a compelling approach to achieving lasting correction of both immunodeficiency and hypoparathyroidism.

## INTRODUCTION

Complete DiGeorge Syndrome (cDGS) is characterized by athymia and results in primary immunodeficiency due to severe T cell deficiency, which can be corrected by thymus transplantation<sup>1,2</sup>. However, most cDGS patients also have hypoparathyroidism (HPT) and this remains a clinical issue after thymus transplantation. Co-transplantation of parental parathyroid grafts at the time of allogeneic thymus transplantation in cDGS only temporarily corrects HPT, as patients develop alloreactivity and parathyroid graft rejection over time<sup>3</sup>. We report a case in which inadvertent co-transplantation of parathyroid tissue from the thymus donor durably corrected HPT.

## CASE REPORT

A female child with cDGS caused by poorly controlled maternal diabetes during gestation, presented at birth with absent T cells, neonatal hypocalcaemia, skeletal abnormalities and mild supravalvular pulmonary stenosis. She was referred for allogeneic thymus transplantation. Prior to transplantation she was infected with respiratory syncytial virus (RSV), rotavirus and human herpes virus 6 (HHV6). She received a thymus graft without immunosuppression from a male infant donor. Four weeks after transplantation she developed proteinuria, associated with low C3 and complement function. Renal biopsy showed mesangioproliferative IgA glomerulonephritis. Treatment with Prednisolone and Eculizumab resulted in rapid and permanent resolution of the problem and immunosuppression was tailed off over 4 weeks. Biopsies from the site of transplantation at three months post-transplantation displayed viable thymic epithelium, though with few associated CD3+ cells, possibly because of the earlier corticosteroid treatment. A nodule of endocrine tissue, estimated to be 1mm in diameter, was also observed. This tissue expressed parathormone (PTH) and was shown to be of male origin by XY-FISH (Figure 1 A-C). Circulating PTH levels were undetectable prior to transplantation, but rose from four months after transplantation to normal levels at seven months (Figure 1 D). Treatment with calcium and calcitriol was discontinued, though she continued on standard cholecalciferol nutritional supplementation. At 48 months post-transplantation, PTH and plasma calcium levels remain within the normal range. In terms of immune reconstitution, T cells were first detected in the periphery at six months after transplantation and continued to rise with the appearance of naïve cells after 12 months (Figure 2). Normal levels were not achieved, as typically seen after thymus transplantation<sup>1,2</sup>. However, a normal proliferative response was restored after stimulation with PHA and CD3, as well as in a pooled mixed lymphocyte culture experiment against third party targets. Additionally, the patient produced class-switched memory B cells and normal antibody responses to tetanus, diphtheria and pneumococcal vaccines (data not shown). Importantly, pre-

transplantation infections were cleared, as was a later-acquired CMV infection, and a subsequent EBV infection remains controlled. All prophylactic measures, including immunoglobulin replacement therapy, have been stopped. The patient remains well at 48 months after transplantation with persistent correction of hypoparathyroidism and immunodeficiency.

## DISCUSSION

HPT was found in 94% of cDGS patients treated at our centre and was present in the majority of patients in the other reported series<sup>2</sup>. This usually requires ongoing treatment with calcium and active vitamin D metabolites to prevent hypocalcaemia and its consequences, in particular an increased risk of seizures. Such treatment may lead to the development of complications including nephrocalcinosis, renal impairment, cataract and cerebral calcifications<sup>4</sup>. Moreover, despite supplementation, cDGS patients remain susceptible to hypocalcaemia, especially in the context of infections. After thymus transplantation, these patients continue to display HPT and its management remains a challenging component of their care. Replacement therapy with recently approved recombinant human PTH preparations is not recommended, given the increased risk of osteosarcoma in paediatric patients with open epiphyses<sup>5</sup>. Potentially curative parathyroid transplantation would be valuable, but is complicated due to graft rejection. In fact, persistent parathyroid graft function after parathyroid transplantation has mainly been observed in the context of long-term immunosuppression in adult patients who previously received a renal allograft<sup>6</sup>. In cDGS patients, parental parathyroid transplantation in combination with allogeneic thymus transplantation resulted in parathyroid graft rejection, except for one patient in whom induction of tolerance was reported<sup>3</sup>. This was likely due to matching of the parental donor's HLA class II alleles with either the thymus donor or the recipient.

In our patient parathyroid tissue was co-transplanted with thymus by chance and has resulted in correction of the HPT. As far as we are aware this has not previously been observed in any other patient post-thymus transplantation<sup>1,2</sup> (and personal communication ML. Markert, Duke University Medical Center, Durham, North Carolina; April 2019). The thymus is the most common site of ectopic or supernumerary parathyroid glands and must have been the source of parathyroid tissue in this case. In fact, in some cohorts, intrathymic parathyroid tissue has been found in nearly half the patients undergoing parathyroidectomy with bilateral cervical thymectomy for renal hyperparathyroidism<sup>7</sup>. In the context of thymus transplantation for cDGS we use HLA-mismatched thymic tissue from infants undergoing open heart surgery via median sternotomy<sup>1,2</sup>. Thymus transplant patients exhibit immunological tolerance towards the thymus donor<sup>8</sup>, which most likely explains the durable correction of the HPT without the need for immunosuppression after co-transplantation of intrathymic parathyroid tissue in this patient. In the future, we aim to

develop strategies to identify thymuses containing parathyroid tissue prior to transplantation, which might allow their preferential use for correction of HPT in other patients.

In conclusion, co-transplantation of thymus and parathyroid tissue from the same donor, as occurred in the patient reported here, is a promising treatment strategy to pursue for successful parathyroid allotransplantation and enduring correction of primary hypoparathyroidism in cDGS.

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## **Disclosure**

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Adrian J. Thrasher is an equity/stock holder for Orchard Therapeutics, and is a member of the scientific advisory board. He also receives remuneration from Rocket Pharmaceuticals, Generation Bio and 4Bio Capital in return for scientific advice. The other authors have no conflicts of interest to disclose.

## **Data Availability Statement**

Data Citation: Kreins AY et al. Correction of both immunodeficiency and hypoparathyroidism by thymus transplantation in complete DiGeorge syndrome. Data stored within the firewall of UK National Health Service. The data that support the findings of this study are available on request from the corresponding author.

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## FIGURE LEGENDS

Figure 1: Co-transplanted parathyroid tissue leads to enduring correction of hypoparathyroidism.

A-C: Immuno-histochemistry. A. H&E staining showing endocrine nodule, surrounded by muscle (X40). B. Immunostaining of this nodule with parathormone (X40). C. Fluorescent in situ hybridisation using centromeric probes. Red = X centromere. Green = Y centromere. D. Calcium levels (left axis) and parathormone levels (right axis) over time (in months) post transplantation.

Normal ranges: Calcium 2.2-2.5mmol/L and PTH 14.9- 56.9pg/mL.

Figure 2: T cell immune reconstitution after thymus transplantation. T cell and T cell subset numbers ( $\times 10^6/L$ , left axis) and TRECS/ $10^6$  T cells (right axis). Naïve T cells (CD4 and CD8) were those expressing CD45RA+CD27+.

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Figure 1

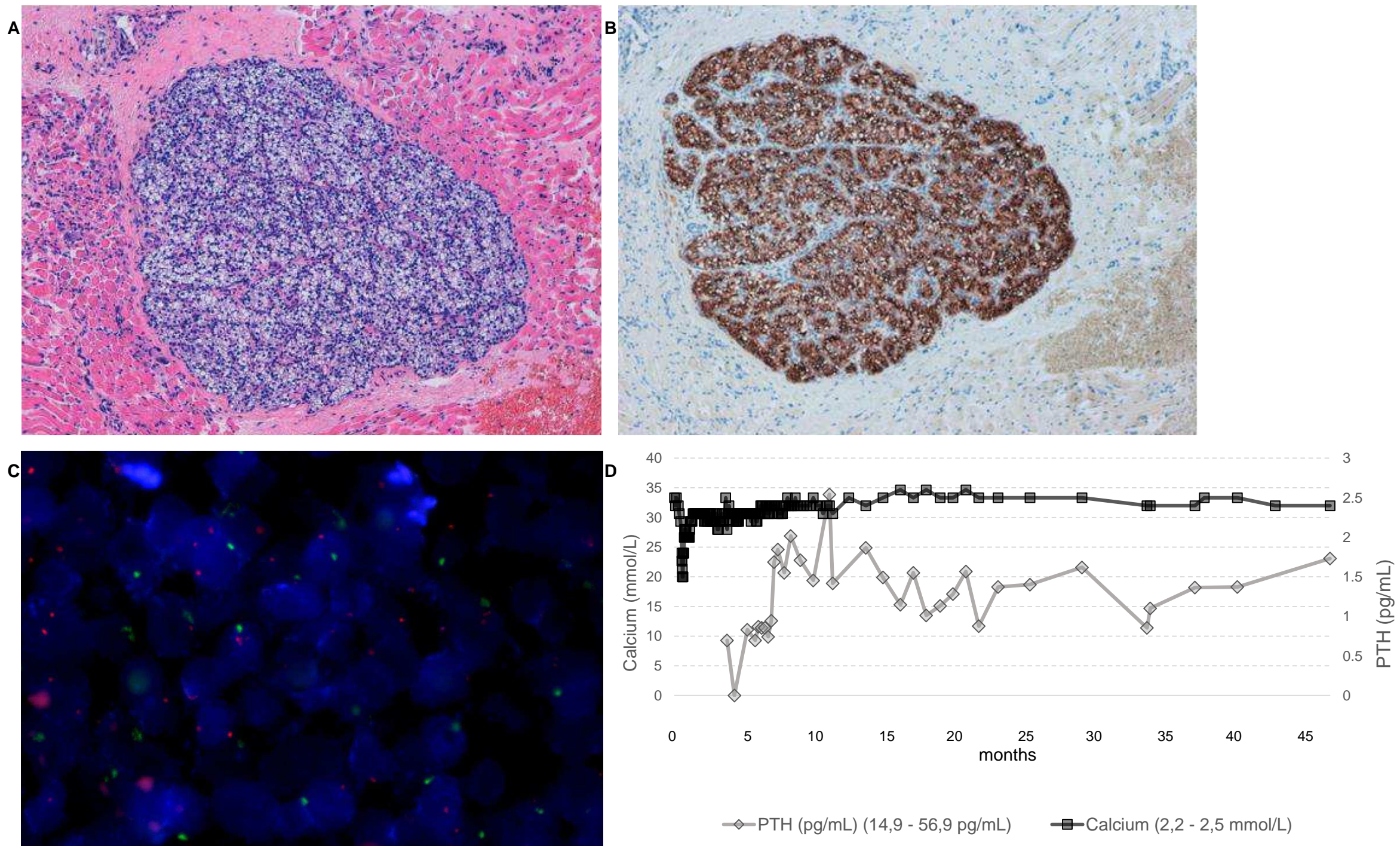


Figure 2

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