TUMOUR-LIKE GROWTH OF PARATHYROID AUTOGRRAFTS IN URAEMIC PATIENTS

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Summary

Total parathyroidectomy with autotransplantation of parathyroid tissue into the forearm musculature has been recommended as surgical treatment for renal hyperparathyroidism. Five of 41 patients, in whom this procedure was performed, developed hyperparathyroidism 7 to 33 months after surgery due to graft hyperplasia. Grafts had to be removed. Whereas about 20–25mg were implanted, the removed grafts weighed 0.9–3.1g. Morphological examination showed signs of accelerated growth, infiltration of adjacent structures and invasion of blood vessels. For total removal, repeated and extensive surgery was necessary. Conservative treatment failed to prevent tumour-like growth of autografts. We no longer recommend parathyroidectomy with autotransplantation of parathyroid tissue as the method of choice for the surgical treatment of renal hyperparathyroidism.

Introduction

In recent years several authors have suggested total parathyroidectomy with autotransplantation of parathyroid tissue into the forearm as a useful technique for the surgical treatment of renal hyperparathyroidism [1–4]. Initial shortcomings of the method were graft failure or insufficient graft function resulting in hypoparathyroidism [5]. This problem could be overcome by cryopreserving removed parathyroid tissue for a second transplantation in case of failure of the first transplant [6,7]. As in subtotal parathyroidectomy relapse of hyperparathyroidism due to hyperplasia of the graft has been reported [8].

We performed total parathyroidectomy with autotransplantation of parathyroid tissue (PTX + Auto-TX) in 41 uraemic patients. Whereas four grafts failed, in 37 patients transplantation was successful and serum PTH became normal. In five of these patients however, after a short period of time, recurrent hyperparathyroidism due to tumour-like growth of autografts was observed.
Methods

The surgical technique of PTX + Auto-TX has been described extensively elsewhere [2,3]. Briefly, following total parathyroidectomy, removed parathyroid tissue was preserved in cooled Ringer's solution while a frozen section was examined.

After the material had been identified as parathyroid tissue, 20–25mg, as little slivers, were implanted in the forearm musculature.

Function of grafted tissue was examined at 3 to 6 month intervals by measurement of PTH in the cubital vein blood of both the grafted and non-grafted arm. PTH was determined by use of an amino-terminal radioimmunoassay.

Parathyroid tissue removed from the neck as well as removed autografts were studied histologically following haematoxylin, eosin and trichromic acid staining. One micron sections stained with toluidine-blue were examined for the diameter of the nuclei. A Feulgen stain was performed for estimation of the DNA content of the nuclei. The extinction of the stained nuclei was measured using the universal microspectrophotometer (UMPS I Zeiss) and DNA histograms were plotted by the technique described by Böhm [9].

Patients and clinical course

Clinical data of the five patients with recurrent hyperparathyroidism and tumour-like growth of the autografts are summarised in Table I. Four of the patients were on regular haemodialysis treatment for 27 to 80 months. The remaining patient had been maintained in preterminal renal failure for four years. In all cases PTX was indicated because of severe symptoms such as bone pain, pruritus and fractures in the presence of very high serum PTH levels and elevated serum calcium and phosphorus concentrations. Conservative treatment with phosphate binders and vitamin D metabolites had failed.

Because of recurrent hyperparathyroidism grafts had to be removed between 7 and 33 months following PTX + Auto-TX. Whereas only 20 to 25mg had been implanted, the weights of excised autografts ranged from 0.9 to 3.1 grams. In four cases, because of obviously incomplete removal, as indicated by persistently higher PTH levels in the grafted than in the non-grafted arm, a second or even third excision was necessary. In two of these patients despite extensive surgery, hyperparathyroidism due to persistent graft function is still present. In a third patient, nine months after the last surgical intervention, PTH levels are still normal, whereas the fourth patient, without proven graft function, is suffering from hyperparathyroidism of unknown origin.

Case report

From March 1974, a 40-year old male patient, suffering from terminal renal failure due to glomerulonephritis underwent regular haemodialysis treatment. After 18 months of RDT he developed hypercalcaemia with serum calcium concentrations up to 3.0mmol/L. Serum phosphate levels also rose in spite of a daily intake of 4g aluminium hydroxide. Serum levels of PTH were significantly elevated at the
TABLE I. Clinical data of patients with relapsing hyperparathyroidism

<table>
<thead>
<tr>
<th>Patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 1st PTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of RDT (months)</td>
<td>27</td>
<td>Preterminal</td>
<td>80</td>
<td>71</td>
<td>79</td>
</tr>
<tr>
<td>Maximum PTH (Norm. &lt;675 pg/ml)</td>
<td>4812</td>
<td>3975</td>
<td>2681</td>
<td>2408</td>
<td>4550</td>
</tr>
<tr>
<td>Maximum serum Ca (mmol/L)</td>
<td>3.0</td>
<td>2.5</td>
<td>2.75</td>
<td>2.75</td>
<td>2.6</td>
</tr>
<tr>
<td>PTH 3–6 months after 1st PTX</td>
<td>TX-arm</td>
<td>Non-TX-arm</td>
<td>TX-arm</td>
<td>Non-TX-arm</td>
<td>TX-arm</td>
</tr>
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<td>874</td>
<td>150</td>
<td>344</td>
<td>105</td>
<td>266</td>
<td>167</td>
</tr>
<tr>
<td>Interval between 1st PTX and Auto-TX-relapse (months)</td>
<td>10</td>
<td>14</td>
<td>33</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>PTH before 2nd PTX</td>
<td>5056</td>
<td>1323</td>
<td>6060</td>
<td>1000</td>
<td>2400</td>
</tr>
<tr>
<td>Weight of removed graft (g)</td>
<td>3.1</td>
<td>0.9</td>
<td>1.3</td>
<td>2.9</td>
<td>2.8</td>
</tr>
<tr>
<td>PTH before 3rd PTX</td>
<td>2659</td>
<td>1100</td>
<td>1400</td>
<td>700</td>
<td>1370</td>
</tr>
<tr>
<td>PTH before 4th PTX</td>
<td>1100</td>
<td>800</td>
<td>12</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Interval since last PTX (months)</td>
<td>40</td>
<td>12</td>
<td>13</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Present PTH</td>
<td>2600</td>
<td>1400</td>
<td>2700</td>
<td>1900</td>
<td>700</td>
</tr>
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</table>
same time. Conservative treatment failed. In 1976 total PTX + Auto-TX were performed. After a transient return of PTH to normal levels the parathyroid autograft started a period of rapid growth, resulting in a tumour of 2.5cm diameter 9 months after surgery. This took place despite treatment with vitamin D₃ (0.25mg/day) and a high dialysate calcium. Serum calcium concentrations rose and venous PTH levels were markedly elevated; more pronouncedly in the grafted than in the non-grafted arm. In July 1977, a tumour consisting of about 3.1g of parathyroid tissue was removed from the site of the previous autograft. Two further surgical interventions with extensive removal of fat, fascia and muscle, were necessary to restore PTH to normal. Thereafter calcium and PTH levels dropped to normal, the latter remaining higher in the grafted arm. Today, 40 months after the last excision hyperparathyroidism - obviously again due to growth of parathyroid tissue in the grafted arm - has recurred.

**Morphological findings**

Light microscopy of tissue from the parathyroid glands used for transplantation showed nodular or diffuse chief cell hyperplasia. Water clear cells with intracytoplasmatic vacuoles typical of parathyroid adenoma could not be detected.

Light microscopy of the autografts removed from all five patients showed

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**Figure 1.** HE-stain of autografted tissue: Parathyroid tissue in the lumen of a blood vessel. In the lower part parathyroid tissue infiltrating musculature (Magnification 400 x)
larger and smaller cords and sheets of regular shaped cells with light cytoplasm enclosed in connective tissue, fat and muscle. The stroma was well vascularised. The cells had infiltrated into the adjacent structures, especially in the neighbourhood of blood vessels. Sometimes vascular invasion could be observed (Figure 1).

Figure 2. HE-stain of autografted tissue: In the right and lower part parathyroid tissue, in the left and upper part highly vascularised parathyroid tissue (Magnification 400 x)

The nuclei showed slight polymorphism and enlarged nucleoli. Mitotic figures were a rare finding. In one patient, enclosed in the hypertrophic parathyroid tissue, a small highly vascularised tumour was found. The cytoplasm of its large irregularly shaped cells was glycogen rich and the nuclei hyperchromatic (Figure 2).

Morphometry showed that the diameters of the nuclei of autografted cells were larger than those of the cells of the original hyperplastic glands or normal parathyroid glands. In four of the patients DNA histograms were made of the original tissue and of the excised grafts. In two cases, prior to transplantation there were only nuclei with a diploid chromosomal content, whereas after grafting an increased number of nuclei with a DNA content corresponding to a tetraploid set of chromosomes was observed. Two cases before transplantation had diploid as well as tetraploid nuclei. After grafting a shift to more tetraploid nuclei occurred.
Discussion

Recurrence of hyperparathyroidism following total PTX + Auto-TX has been reported before [4,7,10–12]. However no data about the time interval between grafting and relapse nor about morphology were given. Only one case of primary hyperparathyroidism with total PTX + Auto-TX has been extensively analysed [8]. There was a short interval between grafting and relapse and repeated surgery was necessary to remove the graft.

The most striking feature of the cases observed by us was the rapid growth of grafted tissue. In spite of comparable conservative treatment hypertrophy and hyperparathyroidism developed much faster in autografts than in the original glands. Accordingly the results of the morphological studies showed more signs of accelerated growth — such as increased diameter and DNA content of nuclei — in autografted than in the original tissue.

The question arises whether there exist local factors stimulating the growth of grafted parathyroid tissue. Locally operative stimulators might be hypoxia, acidosis and hypocalcaemia. The histological investigations in all cases showed good vascularisation of the grafts. Therefore local hypoxia, acidosis and hypocalcaemia appear not to be responsible for continuous growth, but might be active during the initial phase following grafting.

Another explanation for the tumourlike growth of the autografts could be that autonomous material was transplanted. From the histological findings it can be concluded that no parathyroid carcinoma or adenoma of the water-clear cell type was transplanted. There are no certain histological criteria to distinguish between primary and secondary chief cell hyperplasia, but it is very unlikely that primary chief cell hyperplasia was transplanted, because it is highly improbable that in a population of only 41 uraemic patients five cases of primary hyperparathyroidism would occur.

For the phenomenon of persisting renal hypercalcaemic hyperparathyroidism despite adequate therapy or even after successful renal transplantation the term tertiary hyperparathyroidism has been introduced [13].

The features of this so-called tertiary hyperparathyroidism correspond to our observations in autografted patients. Two explanations for the phenomenon of tertiary hyperparathyroidism have been discussed [13]. Firstly, basal, calcium-independent PTH secretion from an extremely enlarged parathyroid cell mass can result in hypercalcaemic hyperparathyroidism. Secondly, after a long period of 'uraemic' stimulation a set point defect in the calcium dependence of parathyroid secretion takes place. Whereas the first explanation is not comparable with our observations in autografts, the second may be applicable. The occurrence of the set point defect may be a pre- or post-transplant event. Our data do not permit a final answer regarding the causative mechanisms. From our clinical and morphological observations we draw the following conclusions:

1 Surgical treatment of renal hyperparathyroidism by PTX + Auto-TX may result in unexpected and very accelerated growth of grafted tissue.

2 Because of invasive growth there exists the risk of uncontrolled spreading of parathyroid tissue.
3 Graft removal may turn out to be difficult and may require repeated and extensive surgery.
4 Until the observed phenomena are totally understood we no longer recommend PTX + Auto-TX as an alternative to subtotal PTX in the surgical treatment of renal hyperparathyroidism.

References
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Open Discussion

RITZ (Heidelberg) The occurrence of graft hyperplasia is the more intriguing since Pavlovich here in Paris demonstrated in experimental vitamin D deficiency that parathyroid autografting prevented parathyroid hyperplasia. You excluded the possibility of primary hyperparathyroidism because tumour-like growth was observed in 5 out of 40 grafted patients; however, according to Christensen’s data from Stockholm, the prevalence of primary hyperparathyroidism in the general population may well be around 1 per 100, so it may well be true that you are dealing with patients with latent primary hyperparathyroidism. Could you give an estimate of the sample from which these patients were drawn? Do you have any information on Epstein-Barr virus infection or cytomegalovirus infection and potential virus markers on the cells?

FREI To your second question: We have no information about viral disease in these patients. To your first question: These five patients derive from a population of about 400 patients. With this incidence the possibility of primary hyperparathyroidism cannot be excluded.

DRÜEKE (Paris) In our experience we have not seen any recidivating tumour in autografted patients now numbering 30 patients from Necker Hospital. Our surgeon has done re-interventions in 2 patients who had recurrent hyperparathyroidism. This was due to a supernumerary fifth or sixth gland and in these cases there was atrophy of autografted fragments in the forearm. I want to know whether you have also found, at least in some patients with recurrent
hyperparathyroidism due to a supernumerary gland in the neck, the opposite phenomenon of atrophy?

FREI In our population of 41 operated patients there is one patient with a fifth gland in the neck. His autograft did not undergo atrophy. After the removal of the gland from the neck, the autograft is functioning.

DRÜEKE I suppose that all these autografted patients had immediate parathyroid autografting. Have you also done deferred autografting, with cryo preservation in the meantime, and in that case have you seen recidivating tumours?

FREI No, we have not transplanted cryo preserved tissue.

WINNEY (Edinburgh) Did you maintain your patients on vitamin D metabolites after the subtotal parathyroidectomy auto transplantation?

FREI Our line of therapy after autotransplantation was a high dialysate calcium combined with vitamin D₃. In the beginning, 80 to 100,000 units per day were given; later on, up to 20,000 units per day. We did not give other vitamin D metabolites.

WINNEY I wonder if Dr Drüeke maintains his patients on vitamin D metabolites? We have done over 10 subtotal parathyroidectomies with autotransplantation in the last year and I find this figure very disturbing, obviously, for the future. Could Dr Drüeke tell us if he maintains his patients on vitamin D metabolites?

DRÜEKE Yes, of course. I think it is very important to control hypoparathyroidism, after autografting, with vitamin D metabolites in order to avoid recidivating hyperparathyroidism at a new set point, as the primary stimulus to hyperparathyroidism is maintained in these patients.