

## Use of Ultrasound to Assess the Response to Therapy for Secondary Hyperparathyroidism

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Secondary hyperparathyroidism (SHPT) is a common complication in patients with chronic kidney disease. In SHPT, the biology of parathyroid cells changes significantly toward diffuse nodular hyperplasia. Currently, diagnosis of SHPT is based on intact parathyroid hormone serum levels and parameters of mineral metabolism. The morphologic diagnosis of SHPT relies on high-resolution ultrasonography with color Doppler imaging. This report describes a maintenance hemodialysis patient with severe SHPT treated using conventional therapy (phosphate binders and oral/intravenous vitamin D or analogues) and the subsequent addition of a calcimimetic. The role of color Doppler ultrasonography in the diagnosis, clinical follow-up, and assessment of therapeutic response of SHPT is discussed. This case suggests that the availability of calcimimetics has changed the natural history of clinical SHPT and may change the therapeutic utility of parathyroidectomy. Use of color Doppler ultrasonography further supports these therapeutic advances, allowing evaluation of the morphologic and vascular changes in hyperplastic parathyroid glands and aiding clinical, pharmacologic, and surgical strategies.

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**INDEX WORDS:** Parathyroid sonography; neck high-resolution sonography; secondary hyperparathyroidism; calcimimetic cinacalcet; parathyroid hyperplasia.

### INTRODUCTION

Secondary hyperparathyroidism (SHPT) is a serious complication of chronic kidney disease and maintenance hemodialysis (HD) therapy. Hypocalcemia, phosphate retention, and 1,25 dihydroxyvitamin D<sub>3</sub> deficiency are the stimuli behind the synthesis and release of parathyroid hormone (PTH).<sup>1,2</sup> Loss of renal mass results in persistent overstimulation of the parathyroid glands, resulting in changes to their cell biology, triggering cell hypertrophy-hyperplasia, and leading to the selection of cell clones with decreased calcium receptor and vitamin D receptor density.<sup>1</sup>

Long-term hyperstimulation of the parathyroid glands produces glandular hyperplasia, which is at first polyclonal, then monoclonal and nodular, progressing to a growth disorder (tertiary hyperparathyroidism).<sup>3</sup> Nodular hyperplasia does not involve all glands or affect all patients with chronic kidney disease equally; therefore, it can be assumed that unknown genetic mechanisms may be involved.<sup>4,5</sup>

The identification of healthy parathyroid glands is difficult. However, high-resolution ultrasonography (US) with color Doppler imaging can be used to localize hyperplastic glands. Color Doppler US is the only technique that measures volumetric variations of the hyperplastic glands and provides semiquantitative parameters on glandular perfusion.<sup>6</sup>

In this report, we describe a maintenance HD patient with severe SHPT treated using conventional therapy (phosphate binders and oral/intravenous vitamin D or analogues), then percutaneous ethanol injection,

and finally the calcimimetic cinacalcet. We emphasize the role of color Doppler US to assess the response to therapy for SHPT.

### CASE REPORT

#### Clinical History and Initial Laboratory Data

We present the case of a 51-year-old woman undergoing maintenance HD therapy since 1981 because of bladder exstrophy, urinary obstructive, and reflux uropathy with recurrent urinary tract infections. At 12 years of age, after multiple reconstructive surgeries, serum creatinine was 2.5 mg/dL [221 μmol/L]. Cystography showed bilateral vesicoureteral reflux with grade IV hydronephrosis. A ureteral-sigmoidal-cutaneostomy was performed, but glomerular filtration rate progressively worsened. At the age of 22 years (serum creatinine, 12 mg/dL [1,060.8 μmol/L]), her estimated glomerular filtration rate, calculated using the MDRD (Modification of Diet in Renal Disease) Study equation, was 5 mL/min [0.08 mL/s], so she started maintenance HD treatment. In 1990, after 9 years of maintenance HD therapy and continuous oral therapy with calcium carbonate, 4 g/d, serum calcium level was 11 mg/dL (2.64 mmol/L), serum phosphorus level was 4.9 mg/dL (1.58 mmol/L),

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calcium-phosphorous product was 49 mg<sup>2</sup>/dL<sup>2</sup> (4.17 mmol<sup>2</sup>/L<sup>2</sup>), intact PTH (iPTH) level was 611 pg/mL (611 ng/L), and alkaline phosphatase level was 580 U/L.

### Imaging Studies

In 1990, color Doppler US showed nodular hyperplasia of the right inferior parathyroid gland. The gland measured 13 × 10 × 8 mm with a calculated volume of 543 mm<sup>3</sup>. In 1993, the volume of the right inferior gland was 4,260 mm<sup>3</sup>, and a small left hypoechoic parathyroid with abnormal size (5 × 3 × 4 mm; volume, 31 mm<sup>3</sup>) became evident.

In 1994, color Doppler US showed a further increase in volume of the right inferior parathyroid (23 × 19 × 20 mm; volume, 4,556 mm<sup>3</sup>) and the left gland (81 mm<sup>3</sup>). Subtraction scintigraphy showed only hyperaccumulation of radiotracer near the right inferior pole of the thyroid. From 1997 to 2003, both glands increased in size (5,299 and 210 mm<sup>3</sup>) and an enlarged parathyroid gland (65 mm<sup>3</sup>) was noted at the inferior pole of the left thyroid lobe.

In January 2005, color Doppler US showed 4 hyperplastic parathyroid glands. On the right side, the biggest gland was 22 × 20 × 21 mm with a volume of 4,827 mm<sup>3</sup> and appeared hypervascularized. The second gland was in the superior mediastinum on the right side and measured 9 × 7 × 5 mm with a volume of 164 mm<sup>3</sup>. On the left side, there were 2 parathyroid glands measuring 11 × 8 × 7 mm with a volume of 321 mm<sup>3</sup> (superior) and 9 × 8 × 7 mm with a volume of 263 mm<sup>3</sup> (inferior). Color Doppler showed a hypervascularized pattern.

In 2006, color Doppler US showed a small volume increase in the right inferior parathyroid gland due to cyst-like involutions and widespread hypovascularization. The decrease in volume of the other glands was not significant; however, intraglandular cyst-like areas were noted in the bigger glands.

In 2007, color Doppler US showed wide cystic degeneration of the largest gland, which appeared completely avascularized on color Doppler. A decrease in volume and structural alterations of the smaller gland (cystic areas and loss of color Doppler signal) became more evident. To evaluate the functional significance of the cyst-like involutions, technetium 99m (<sup>99m</sup>Tc) methoxyisobutyl isonitrile scintigraphy was performed. This showed an area of early and late hyperaccumulation of tracer near the inferior pole of the thyroid, but did not identify other glands.

In January 2010, color Doppler US showed that the right inferior gland was 22 × 17 × 20 mm with a volume of 3,979 mm<sup>3</sup>, and its morphologic and vascular patterns were unchanged. The mediastinal gland was hyperechoic and measured 6 × 5 × 3 mm with a volume of 47 mm<sup>3</sup>, the left superior gland was 9.9 × 5.3 × 4.2 mm with a volume of 214 mm<sup>3</sup> and absence of vascularization, and the left inferior gland was no longer distinguishable (Fig 1).

### Diagnosis

SHPT in a maintenance HD patient.

### Clinical Follow-up

Laboratory data, imaging findings, and therapeutic interventions are listed in Table 1.

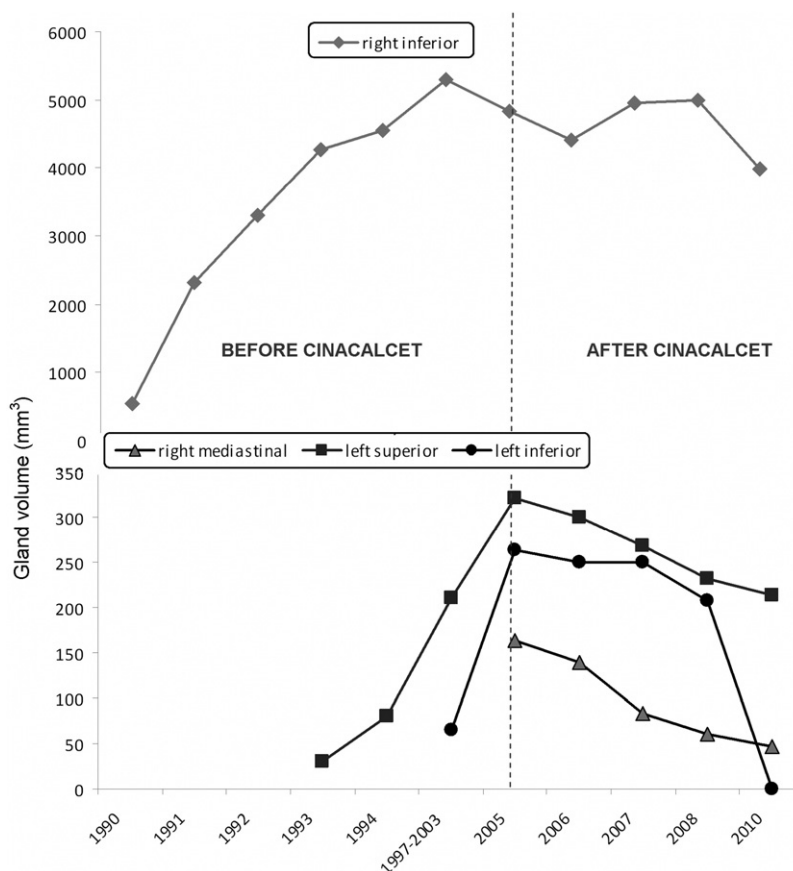


Figure 1. Volumetric variations of the parathyroid glands from 1990 to 2010.

**Table 1.** Clinical History of Patient With SHPT

Year	Clinical and Laboratory Findings	Parathyroid Gland Imaging <sup>a</sup>	Treatment Decision
1990	Ca, 11 mg/dL; P, 4.9 mg/dL; Ca × P, 49 mg <sup>2</sup> /dL <sup>2</sup> ; ALP, 580 U/L; iPTH, 611 pg/mL	RIG, 543 mm <sup>3</sup>	PEI of the only hyperplastic parathyroid gland detectable on US
1990	9 mo after PEI treatment: ALP, 952 U/L; iPTH, 795 pg/mL		
1993	ALP, 500 U/L; iPTH, 700 pg/mL	RIG, 4,260 mm <sup>3</sup> ; LSG, 31 mm <sup>3</sup>	Vitamin D (4 μg 3×/wk); CaCO <sub>3</sub> decreased to 2-3 g/d
1994-1996	ALP, 400-265 U/L; iPTH, 670-450 pg/mL	RIG, 4,556 mm <sup>3</sup> ; LSG, 81 mm <sup>3</sup>	Oral calcitriol replaced by IV calcitriol, 1.5 μg 3×/wk; CaCO <sub>3</sub> stopped; Al(OH) <sub>3</sub> added (3 tablets 2×/wk)
1997-2003	Ca, 12.3 mg/dL; P, 5.6 mg/dL; Ca × P, 68.8 mg <sup>2</sup> /dL <sup>2</sup> ; ALP, 326 U/L; iPTH, 1,350 pg/mL; symptoms: itching, severe osteoarticular/muscle pain, lumbosacral tenderness, walking difficulties	RIG, 5,299 mm <sup>3</sup> ; LSG, 210 mm <sup>3</sup> ; LIG, 65 mm <sup>3</sup>	Calcitriol therapy interrupted due to episodes of hypercalcemia and hyperphosphatemia; parathyroidectomy indicated, but patient refused; calcitriol therapy reintroduced
2005	Ca, 10.1 mg/dL; P, 6 mg/dL; Ca × P, 60.6 mg <sup>2</sup> /dL <sup>2</sup> ; ALP, 740 U/L; iPTH, 1,480 pg/mL	RIG, 4,827 mm <sup>3</sup> ; RMG, 164 mm <sup>3</sup> ; LSG, 321 mm <sup>3</sup> ; LIG, 263 mm <sup>3</sup> ; vascular pattern 3 for all	Calcitriol replaced by IV paricalcitol (5 μg 3×/wk) associated with sevelamer (4,800 mg/d) and CaCO <sub>3</sub> (2 g/d)
2005	Ca, 10.5 mg/dL; P, 5 mg/dL; Ca × P, 52.5 mg <sup>2</sup> /dL <sup>2</sup> ; ALP, 1,243 U/L; iPTH, 1,600 pg/mL		Cinacalcet (maximum dosage, 150 mg/d) added to conventional therapy
2010	Ca, 8.6 mg/dL; P, 5 mg/dL; Ca × P, 43 mg <sup>2</sup> /dL <sup>2</sup> ; ALP, 316 U/L; iPTH, 360-400 pg/mL	RIG, 3,979 mm <sup>3</sup> (cystic degeneration; vascular pattern 0); RM, 47 mm <sup>3</sup> (vascular pattern 0); LSG, 214 mm <sup>3</sup> (vascular pattern 0); LIG <sup>b</sup>	Cinacalcet (120 mg/d), paricalcitol (5 μg 3×/wk) associated with sevelamer (4,800 mg/d) and CaCO <sub>3</sub> (2 g/d)

*Note:* Conversion factors for units: serum Ca in mg/dL to mmol/L, ×0.2495; serum P in mg/dL to mmol/L, ×0.3229; Ca × P in mg<sup>2</sup>/dL<sup>2</sup> to mmol<sup>2</sup>/dL<sup>2</sup>, ×0.077. No conversion necessary for PTH in pg/mL and ng/L.

Abbreviations and definitions: Al(OH)<sub>3</sub>, aluminum hydroxide; ALP, alkaline phosphatase; Ca, calcium; Ca × P, calcium-phosphorus product; CaCO<sub>3</sub>, calcium carbonate; iPTH, intact parathyroid hormone; IV, intravenous; LIG, left inferior parathyroid gland; LSG, left superior parathyroid gland; P, phosphorus; PEI, percutaneous ethanol injection; RIG, right inferior parathyroid gland; RMG, right mediastinic parathyroid gland; SHPT, secondary hyperparathyroidism; US, ultrasonography.

<sup>a</sup>Volume and (when applicable) vascular pattern assessed using color Doppler US.

<sup>b</sup>No longer distinguishable.

**DISCUSSION**

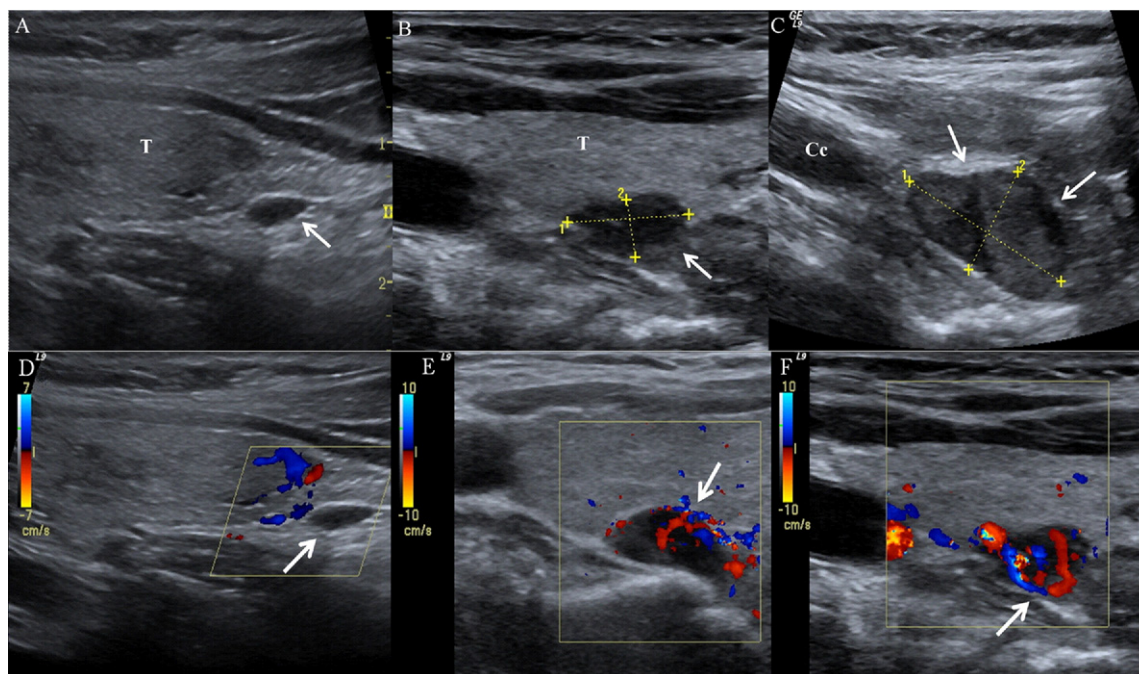
Color Doppler US of the parathyroid glands has a pivotal role in the diagnosis of SHPT, assessing the severity of disease and evaluating response to medical treatment. However, in clinical practice, color Doppler US is not commonly performed and SHPT diagnosis is based on iPTH serum levels and parameters of mineral metabolism.

Because parathyroid glands normally are heavily populated with adipose cells, they can be difficult to distinguish from thyroid parenchyma even with the use of high-resolution probes.<sup>7</sup> However, cellular hyperplasia makes the glands diffusely hypoechoic and easily detectable in the thyroid lodge. There is no set size threshold above which a parathyroid gland is identified as pathologic; however, if each of 2 diameters is >5 mm, a hypoechoic gland is judged hyperplastic<sup>8</sup> (Fig 2). Glandular volume (in cubic millime-

ters) is calculated using the formula of an irregular ellipsoid ( $\frac{4}{3} \pi \times \frac{1}{2}$  anteroposterior diameter ×  $\frac{1}{2}$  laterolateral diameter ×  $\frac{1}{2}$  craniocaudal diameter).

The increase in glandular volume suggests increased PTH secretion and worsening of SHPT.<sup>9</sup> Studies that correlate glandular volume with histologic features of the excised glands at parathyroidectomy show that glands <500 mm<sup>3</sup> are affected mainly by diffuse and polyclonal hyperplasia, whereas glands >500 mm<sup>3</sup> are affected by monoclonal nodular hyperplasia in 80% of cases. Moreover, because there is wide variation in glandular volume, the overall sensitivity of color Doppler US in SHPT diagnosis is 74%-75% (<50% in the localization of parathyroids <500 mm<sup>3</sup> and >90% in glands ≥500 mm<sup>3</sup>).<sup>10</sup>

The ability to assess changes in glandular volume gives color Doppler US a unique advantage over SPECT (single-photon emission computed tomogra-



**Figure 2.** Progression of parathyroid gland hyperplasia. (A) Long-term hyperstimulation of parathyroid glands causes hyperplasia that makes the glands enlarged and diffusely hypoechoic (arrows), easily distinguishable in the thyroid lodge. (B, C) Glandular hyperplasia is at first diffuse and polyclonal, then monoclonal and nodular. The increase in parathyroid gland volume is associated with a widespread increase in vascularity. Color Doppler distinguishes 3 different patterns: (D) glands lacking Doppler signal, (E) hypovascularized glands with only a few color spots in the hilar/endonodular region (weak Doppler signal), and (F) hypervascularized glands fed by an enlarged hilar artery that have a peripheral arc of vascularity and/or ray-like endonodular vessels. Abbreviations: Cc, common carotid; T, thyroid.

phy)–scintigraphy, computed tomography, and magnetic resonance imaging.

The increase in parathyroid gland volume is associated with a widespread increase in vascularity, evident histologically.<sup>11-13</sup> Usually color Doppler distinguishes 3 different patterns,<sup>10</sup> as shown in Fig 2D-F.

According to international guidelines, SHPT diagnosis is based on iPTH serum levels and parameters of mineral metabolism. However, the optimal values for iPTH in maintenance HD patients are still uncertain,<sup>14,15</sup> and hormone levels show great variability.<sup>16</sup> Because levels are influenced by drug therapy, iPTH level does not provide information for grading hyperplasia. Color Doppler US evaluates the degree of hyperplasia and number of glands involved, completing the biochemical diagnosis. We routinely perform color Doppler US of the parathyroid glands when iPTH values are consistently >400 pg/mL (>400 ng/L) and repeat this study annually in maintenance HD patients to evaluate the progression of disease. B-Mode parameters important for the assessment of SHPT progression include: (1) the gland's echogenicity, (2) gland diameter<sup>17</sup> and volume, (3) appearance of anechoic areas with no vascularization suggesting involutive cystic phenomena, and (4) presence of fibrocalcifications.<sup>13</sup>

In our case, nodular hyperplasia of a single gland appeared after a long period of maintenance HD therapy. Color Doppler US was used to perform chemical ablation with percutaneous ethanol injection, but biochemical/morphologic results were poor. Afterward, other hyperplastic glands appeared, showing the slow but continuous progression of SHPT despite oral/intravenous vitamin D treatments. At this stage, the evidence of nodular hyperplasia on color Doppler US, severity of SHPT, and refractoriness to therapy with vitamin D/binders indicated the necessity of parathyroidectomy, which was refused by the patient.

The role of color Doppler US in the presurgical evaluation of SHPT is very different from primary hyperparathyroidism. The sensitivity of color Doppler US in the localization of adenoma/carcinoma is very high (90%-92%) for primary hyperparathyroidism, similar to that of conventional parathyroidectomy (93%-99%).<sup>18</sup> In a patient with SHPT, the role of imaging is less critical because parathyroidectomy is performed using conventional cervicotomy. Moreover, because there is wide variation in glandular volume and the overall sensitivity of color Doppler US for SHPT is lower than for primary hyperparathyroidism, the role of color Doppler US therefore should

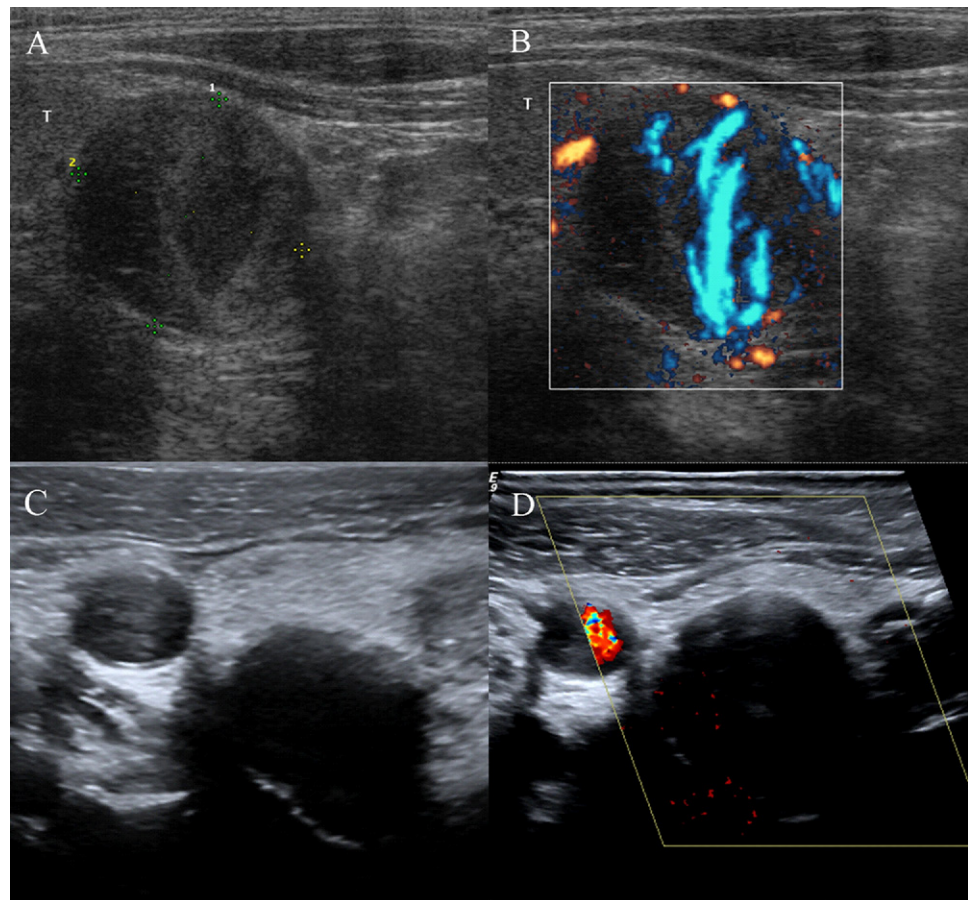
not be to localize the glands, but instead to determine surgical timing. Parathyroidectomy is indicated when color Doppler US evidences one or more hyperplastic glands  $\geq 500 \text{ mm}^3$ , serum iPTH level is  $>700 \text{ pg/mL}$  ( $>700 \text{ ng/L}$ ), and calcium, phosphorus, and calcium-phosphorous product values are no longer controlled using conventional therapy.<sup>19,20</sup>

Glandular volume is related directly to the number of glands detected; it also may be highly variable and not entirely correlated with iPTH level at greater than a certain size/volume threshold. Calculated volume shows a linear correlation with iPTH value only when gland volume is  $<2,000 \text{ mm}^3$  (ie,  $<2 \text{ g}$ ).<sup>8,21</sup> This observation suggests that the biggest glands tend to disengage from receptor control mechanisms (ie, up-regulation of calcium receptor and vitamin D receptor) and grow independently.

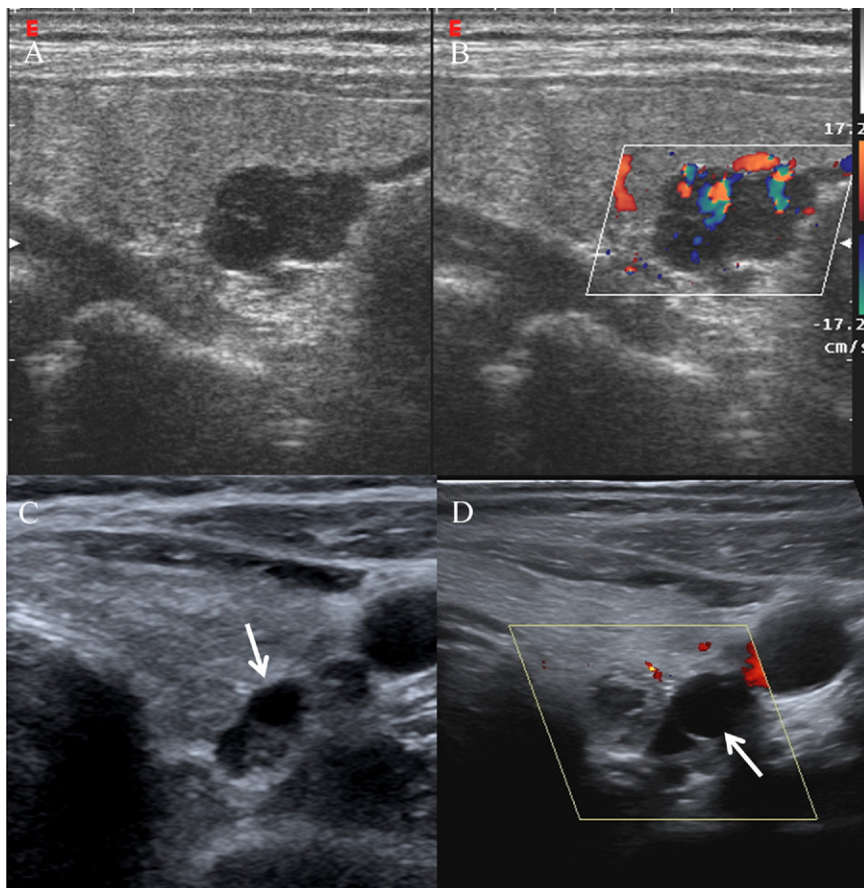
In our patient, the combination of conventional therapy and cinacalcet marked a reversal in the progression of disease: PTH serum levels were decreased, mineral metabolism was stabilized, and color Doppler US showed progressive changes in volume and vascularization. The regression resembled a “chemical parathyroidectomy,” and 5 years after beginning therapy, surgical parathyroidectomy was not necessary.

Color Doppler US showed a volume decrease associated with loss of vascular signal, progressing to complete disappearance of vascularization in the biggest glands ( $\geq 500 \text{ mm}^3$ ; Fig 3). Most glands involute (cystic-like lesions; Fig 4), whereas glands  $<500 \text{ mm}^3$  show a volume decrease accompanied by a structural change toward hyperechogenicity, as if the relationship between cellularity and stromal adipose tissue had been reversed. This suggests that calcimimetic treatment modulates the biological response of cells with uncontrolled proliferation through direct stimulation of calcium receptor and vitamin D receptor expression.<sup>18</sup>

In conclusion, if iPTH serum levels are constantly  $>400 \text{ pg/mL}$  ( $>400 \text{ ng/L}$ ), color Doppler US can be performed to evaluate the presence of hyperplastic glands and complete the clinical diagnosis. This can be repeated once a year to evaluate disease progression. The availability of calcimimetics is changing the natural history of SHPT and may change the therapeutic utility of surgical parathyroidectomy. Use of color Doppler US further supports these therapeutic advances, allowing evaluation of morphologic and vascular changes in hyperplastic glands and aiding clinical, pharmacologic, and surgical strategies.



**Figure 3.** Right inferior parathyroid gland of clinical case before and after cinacalcet therapy. (A) Before cinacalcet therapy, diameters were  $22 \times 20 \times 21 \text{ mm}$  (volume,  $4,827 \text{ mm}^3$ ) and the gland was diffusely hypoechoic. (B) The vascular pattern was rich (type 3) and showed a vascular hilum.  $\tau$ , thyroid. (C) After 2 years of cinacalcet combined therapy, the gland was  $21 \times 21 \times 21 \text{ mm}$  ( $4,838 \text{ mm}^3$ ) and color Doppler ultrasonography showed wide cystic degeneration (D) with disappearance of vascularization. Abbreviation:  $\tau$ , thyroid.



**Figure 4.** (A) Morphologic changes in the left superior parathyroid gland of the clinical case. (B) Before cinacalcet therapy, the gland was hypoechoic with a solid appearance and showed diffused hypervascularization. (C) After 5 years of conventional therapy associated with cinacalcet, the gland shows areas of cystic degeneration (arrows) (D) with no Doppler signal.

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