

WHAT IS PTH-RP AND SHOULD SURGEONS KNOW ANYTHING ABOUT IT?

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QUESTIONS:

1. Are parathyroid hormone (PTH) and parathyroid hormone-related protein (PTH-rP) one and the same?
2. What are the biochemical effects of excessive PTH-rP secretion?
3. Which tissues/organs may secrete PTH-rP?

CLINICAL ASPECTS:

Surgical consultation was sought for a young, pregnant (24 weeks) woman with severe hypercalcemia. Urgent parathyroidectomy was requested by the referring medical service.

Physical examination documented this 27-year-old woman's pregnant state and marked bilateral mammary hypertrophy (Figures 1A and B). The patient had gained 60 pounds during her 24 weeks of pregnancy, and the weight of her breasts made walking impossible. The breasts were engorged but not painful.

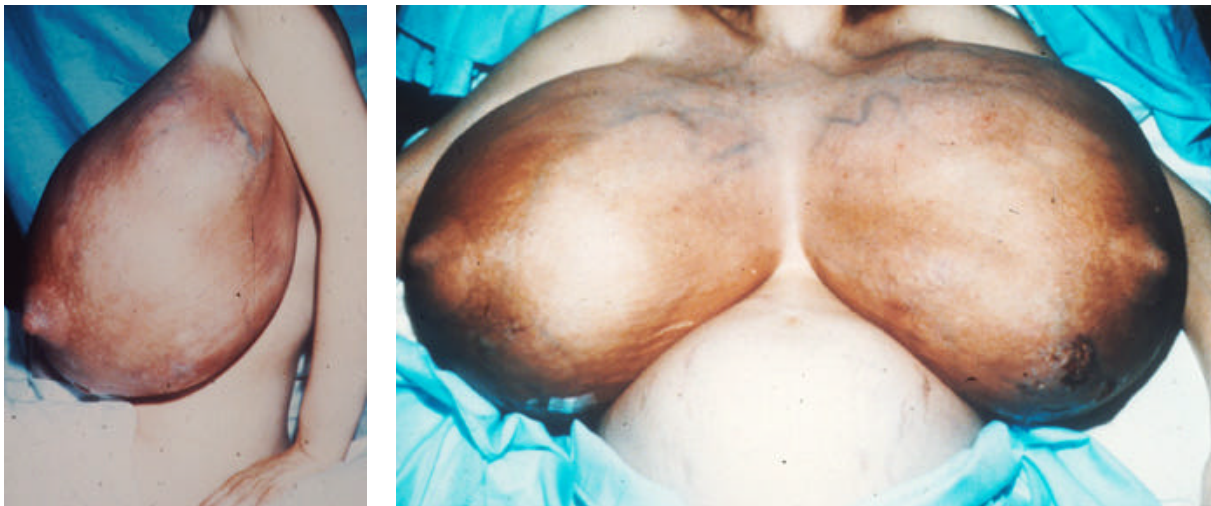


Figure 1A and B: Photographs showing marked bilateral mammary hypertrophy.

Available biochemistry was as follows:

Normal

Serum calcium	13.7 mg/dL (9.0 – 10.1)
Ionized serum calcium	8.7 mg/dL (4.75 – 5.3)
Serum phosphorus	1.4 mg/dL (2.5 – 4.5)
Serum creatinine	0.5 mg/dL (0.6 to 0.9)

By the time of surgical consultation, an ultrasound of the neck had been done and was normal. However, the serum PTH result was not yet available. Overnight observation with fluid replacement and diuresis was instituted. The following morning, an undetectable PTH level (<0.1 pmol/L) was reported.

In view of her breast size, impending skin ulceration, her immobility, and the severe hypercalcemia, urgent bilateral “simple” mastectomies were advised and performed. The patient required 16 units of blood during the operation with the combined weight of the breasts being 53 pounds. Present histology identified “virginal” mammary hypertrophy (Figure 2).

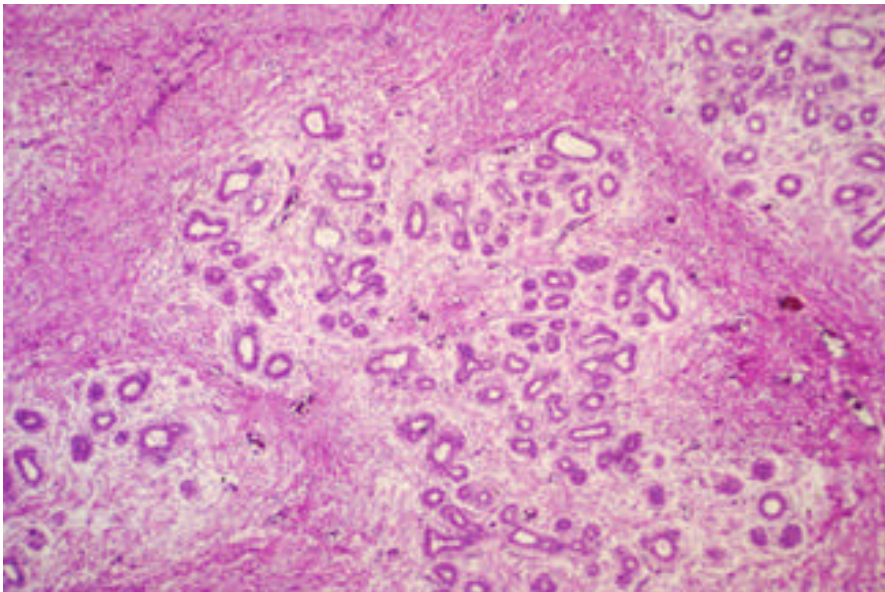


Figure 2: Histology of the breast parenchyma showing “virginal” hypertrophy.

The patient's serum calcium dropped precipitously within 24 hours to a level of 7.2 mg/dL – this required the institution of aggressive (oral and intravenous) calcium and vitamin D replacement. She remained in the hospital for 12 days, during which time her serum calcium stabilized. She was slowly weaned off all calcium and vitamin D supplementation over a three-month period. The remainder of her pregnancy was uneventful – at term she delivered a healthy male infant. PTH-rP levels in her serum were found to be markedly elevated.

The patient has been carefully followed for 15 years. Both she and her teenage son are healthy. There has been no recurrence of her hypercalcemia. Bilateral breast reconstruction was performed with an excellent cosmetic result.

DATA SUMMARY:

PTH-rP is a paracrine/autocrine factor produced in almost every cell type in the body at some point, whether in childhood development or normal adult life. The peptide is critical for normal life. It is the agent responsible for humeral hypercalcemia of malignancy.

PTH-rP is a distinct gene product that varies from 139 to 173 amino acids long and may mimic PTH (84 amino acids) in that 8 of the initial 13 amino acids in each protein are identical. This area of similarity (called the amino-terminal domain) is important since this is the area responsible for the activation of the shared receptor of these two unique proteins – the PTH – PTH-rP receptor.

This structural similarity results in similar biologic actions. Both produce humeral hypercalcemia by increasing bone resorption as well as increasing the renal absorption of calcium and hypophosphatemia via a phosphaturic effect on the kidney.

Overall, 80% of hypercalcemic cancer patients will have increased levels of PTH-rP. The tumors include most solid tumors and a few patients with multiple myeloma, lymphoma, or

leukemia (adult T-cell leukemia syndrome in particular). Some rare benign conditions may produce hypercalcemia by increased PTH-rP secretion: these include pheochromocytoma, vasoactive intestinal polypeptide secreting tumors, lactation, and massive mammary hypertrophy, as in our index patient.

PTH-rP was identified in 1983. Cloned and purified in 1987, PTH-rP has effects beyond hypercalcemia:

- stimulates the proliferation of chondrocytes in the growth plate and retards the mineralization of hypertrophic cartilage,
- regulates the differentiation of skin and skin appendages,
- regulates the mammary gland (it is secreted into milk at levels of 10,000-fold higher than serum levels), and
- functions as a smooth muscle relaxant being produced in smooth muscle (vascular, uterine, bladder, and gastrointestinal) in response to stretch.

ANSWERS:

1. Although there is some similarity in the structure of PTH and PTH-rP, they are two different proteins.
2. The principal biochemical effect of excessive PTH-rP secretion is hypercalcemia. PTH-rP is the principal cause of the humeral hypercalcemia of malignancy.
3. All organs/cells in the body may secrete PTH-rP. In addition, many diverse solid tumors and some benign conditions, e.g., lactation, may secrete excessive amounts of PTH-rP.

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“Growing old is mandatory

Growing up is optional.”

-- Unknown