Benign Tumors That Cause Big Problems

By Bryan Tutt

About 100,000 people in the United States, most of them women, are diagnosed with primary hyperparathyroidism each year. About 90% of these cases are caused by a single benign tumor, or adenoma, in one of the parathyroid glands, while a small number involve multiple glands. About 5% of parathyroid tumors are caused by familial syndromes.

In some of these syndromes, notably multiple endocrine neoplasia type 1, benign tumors of the parathyroid are the first manifestation of disease, followed by potentially malignant tumors in other parts of the body, such as the pancreas. Identifying this form of parathyroid disease can help doctors screen, monitor, and provide earlier intervention for the prevention or treatment of malignant disease.

The symptoms of hyperparathyroidism result from the excess production of parathyroid hormone (PTH). High levels of PTH in the body signal for calcium increases in the blood. Because much calci-

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...um is stored in the bones, high PTH levels can lead to osteopenia or osteopenia. According to Nancy Perrier, M.D., a professor in The University of Texas M. D. Anderson Cancer Center’s Department of Surgical Oncology, Section of Surgical Endocrinology, patients with hyperparathyroidism are often diagnosed because of these skeletal manifestations, which cause cortical bone reduction. “If on routine screening a primary care physician identifies osteopenia or osteopenia, consideration should be given to a high level of PTH workup and discussion to understand whether the patient has hyperparathyroidism,” she said, adding that some patients with parathyroid tumors present with nonspecific symptoms like fatigue, depression, aches and pains, or even kidney stones.

An elevated or high normal blood calcium level can be an indicator of hyperparathyroidism. Because high blood calcium can have other causes—such as metastatic tumors, myeloma, breast cancer, or some medicines—the patient’s serum PTH level should be tested to make the diagnosis of hyperparathyroidism. In healthy patients, when serum calcium is high, the PTH level should be low, and vice versa. People with hyperparathyroidism have high levels of both calcium and PTH.

While some asymptomatic patients have the option of medical observation, patients with symptoms need to undergo a parathyroidectomy. “If they have osteoporosis, kidney stones, broken bones, or a hypercalcemic crisis, then they need an operation to remove the parathyroid adenoma,” Dr. Perrier said.

Minimally invasive procedure

Fortunately, most parathyroid tumors can be removed by minimally invasive parathyroidectomy in an outpatient setting. Dr. Perrier said that about 200 of these procedures are done each year at M. D. Anderson.

Although the surgery is in a high-risk region, parathyroidectomy is a fairly quick procedure for experienced surgeons. With the patient sedated, the neck is hyperextended, and the surgeon makes an incision about 2 cm long. “The precise incision location is based on preoperative imaging studies. The goal is to minimize the dissection, allowing for a very focused procedure,” Dr. Perrier said. Once the surgeon has removed the gland with the suspected tumor, an immuno-chemiluminescent assay is used to determine whether the patient’s serum PTH level has decreased. Because the half-life of PTH is 3 minutes, a decreased PTH level at 5 minutes, confirmed by a second test at 10 minutes, verifies that the surgeon has removed the gland that is causing the problem. “We close the incision, the patient goes to the recovery room, and then the patient goes home 4–6 hours later,” Dr. Perrier said. Because only 3% of patients experience a recurrence of parathyroid tumors, doctors at M. D. Anderson typically see patients for immediate and 6-month follow-up visits and send them back to their referring physicians.

Roadmap for surgery

Imaging studies are crucial to the success of minimally invasive parathyroidectomies. Dr. Perrier described these imaging studies as a roadmap for surgery. “If we know exactly where the adenoma is, we can target our incision and minimize the dissection,” she said. Although a parathyroidectomy could be done without preoperative imaging, the surgeon would have to make a larger incision and then explore the cervical region to locate the tumor-containing gland. “With the imaging, we know where the gland is before we make the incision,” Dr. Perrier said. Although some institutions use a radio-guided probe to locate the adenoma, Dr. Perrier said that the imaging studies done before the operation make the probe unnecessary.

Beth S. Edeiken-Monroe, M.D., a professor in M. D. Anderson’s Department of Diagnostic Radiology, said at least two imaging studies—usually ultrasonography plus four-dimensional com-
Computed tomography, a nuclear medicine study, or both—are done on most patients before surgery. The combination depends mainly on the patient's body habitus and whether or not the patient has had prior surgery. Dr. Edeiken-Monroe does the ultrasonography studies for many of Dr. Perrier's patients and said the test is done to locate the parathyroid tumors at the time of the surgical procedure.

To facilitate communication between radiologists, surgeons, and other specialists, a classification system was developed at M. D. Anderson in which the possible locations of the parathyroid glands are labeled alphabetically, A–G. "The radiologist can read the report and say that the tumor is in a left-side, type B gland, and we'll know exactly what that means in relation to important structures like the thyroid, the recurrent laryngeal nerve, and the carotid," Dr. Perrier said.

**Benefits of treatment**

Research shows up to 15% improvement in bone density 2–5 years after parathyroidectomy. "That's very significant for individuals, particularly postmenopausal women or women with bone loss," Dr. Perrier said. "No drug will increase bone density like curing this disease will."

Improved bone density is not the only benefit of parathyroid surgery. The high calcium and PTH levels, which are alleviated by the surgery, could put untreated patients at a higher risk for cardiovascular disease and carotid artery distensibility. High levels can also affect cognitive function. "We completed a randomized controlled trial here at M. D. Anderson that demonstrated that patients had improved functional performance and sleep following parathyroidectomy," Dr. Perrier said. These results suggest that high PTH levels affect circadian rhythms and disrupt stage 4 sleep in patients, impairing verbal memory, learning, and attention. "This can be very critical in elderly patients who already are declining in these areas. If we can restore their independence by curing a metabolic problem, we might prevent downstream disability." Dr. Perrier and her colleagues also observed that, in the patients who underwent surgery, decreased PTH levels correlated with the ability to walk farther. "Parathyroidectomy really does improve functional capacity," she said, "even in patients with a parathyroid adenoma who appear to be asymptomatic."

**The future of surgery**

Although a minimally invasive parathyroidectomy leaves a scar of only 1–2 cm on the neck, Dr. Perrier is excited about a new robotic procedure in which the incision is virtually invisible. Surgeons at M. D. Anderson were the first in the United States to perform a parathyroidectomy using the robot. "We make an incision under the arm," Dr. Perrier said. "Then we deploy small instruments that have excellent precision when guided from a console. Additionally, a high-definition videoscope offers improved visualization of the anatomy. We use our feet to manipulate the scope, and we use our hands to manipulate the instruments." Dr. Perrier said she and other surgeons have done about a dozen thyroid resections and a few parathyroidectomies with the robot thus far.

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**Further Reading**


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By Joe Munch

Cancer patients experience many sequelae during and after treatment for their disease. With many patients now surviving decades after treatment has ceased, late-stage sequelae and their effects on overall health and quality of life have become important concerns. High among these concerns is bone loss.

Mimi Hu, M.D., an assistant professor in the Department of Endocrine Neoplasia and Hormonal Disorders, is working with her colleagues at M.D. Anderson Cancer Center to identify patients at risk of developing low bone density (osteopenia) and osteoporosis, which may lead to debilitating fractures that cause severe pain, complicate care, or decrease quality of life.

"Ultimately, what is clinically relevant to these patients is whether they will develop fractures," Dr. Hu said. "And when we talk about fractures, we're not talking about high-impact fractures such as those that can occur in a motor vehicle accident. We're concerned about fractures caused by very low or minimal trauma. In these patients, even a sneeze or cough could cause a spinal fracture.”

Causes of bone loss in cancer patients

Several factors contribute to bone loss in cancer patients. Patients may have underlying conditions such as vitamin D deficiency or abnormal calcium metabolism due to hyperparathyroidism, or they may have malignancies such as multiple myeloma and leukemia that actually cause bone loss. In some patients, poor diet owing to treatment intolerance can cause diarrhea, leading to poor calcium and vitamin D absorption.

More often, loss of bone mass is due to cancer treatments themselves. Radiation therapy can break down bone-building cells, making bones susceptible to insufficiency fractures—a major concern in patients with gynecologic cancers who receive radiation to the pelvis. Steroid therapy, commonly given to patients with nonsolid cancers such as leukemia and lymphoma, stimulates osteoclasts, cells that destroy bone tissue. Various chemotherapies can also cause bone loss. Cyclophosphamide (a component of Re-vimmune, Cytoxan, Neosar, and other drugs) suppresses bone marrow growth, and taxane-based chemotherapies such as paclitaxel and docetaxel can induce early menopause in addition to stimulating osteoclasts.

"Early induction of menopause is a risk factor for bone loss, especially in breast cancer patients," Dr. Hu said. "Within 5–10 years after natural menopause, women can lose approximately 2% of their bone mass every year. But with chemotherapy-induced early menopause, patients can lose 3%–8% per year, and that’s a significant amount.”

Breast cancer patients and prostate cancer patients, who comprise the majority of cancer patients, are most affected by bone loss and its repercussions.

In prostate cancer patients, efforts are often made to shrink the cancer or cause it to grow more slowly by reducing testosterone levels through orchitectomy—the surgical removal of one or
both testicles—or hormonal ablative therapy with chemicals such as leuprolide (Leupron) or bicalutamide (Casodex). However, Dr. Hu said, “We’re finding that estrogen levels, as well as testosterone levels, are important for bone health in men. There are more and more data to support that estrogen reduction is actually the more important aspect in osteoporosis in men.”

In breast cancer patients, selective aromatase inhibitors such as anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin), which inhibit the enzyme that synthesizes estrogen, are used to lower patients’ estrogen levels and thus slow tumor growth. But while lower estrogen levels may impede tumor growth, they also impede bone growth.

“Aromatase inhibitors are very important in further reducing estrogen levels, especially in patients who are already postmenopausal, and that further reduction of estrogen will significantly inhibit bone formation and increase bone resorption,” Dr. Hu said.

Preventive treatment
In addition to basic preventive treatment—getting plenty of calcium and vitamin D and adhering to a regimen of weight-bearing exercise—several drugs have emerged in the past decade that can be used to curb bone loss in cancer patients. Ten years ago, salmon synthetic calcitonin (Calcimar, Micacalcin, others), a hormone that suppresses osteoclast activity, was standard therapy for bone loss. Although calcitonin is effective in reducing bone loss, the drug is not as effective as other medicines available today. Among these newer drugs are bisphosphonates such as alendronate (Fosamax), risedronate (Actonel), ibandronate (Boniva), and zoledronic acid (Zometa), which are considered initial therapy for bone loss.

“Bisphosphonates get taken up by osteoclasts and cause cell death,” Dr. Hu said. “By causing osteoclasts to die, bone degradation is reduced, which can then decrease fracture risk.”

In contrast to bisphosphonates, teriparatide (Forteo), a synthetic form of parathyroid hormone, can stimulate bone growth. The drug is approved for up to 2 years of use. However, because teriparatide has been observed to cause osteosarcoma in rat models, the drug is contraindicated in patients who have an increased baseline risk for osteosarcoma, including patients with Paget’s disease of the bone or previous external beam or implant radiation involving the skeleton. “We must be cautious in the use of this drug in our cancer survivors given the extent of radiation therapy in this population and also the possibility of occult malignant cells.”

Raloxifene (Evista), which is in the same drug class as tamoxifen, has been found to increase bone mass in postmenopausal women. As an added benefit, raloxifene has also been found to be at least as effective as tamoxifen in reducing breast cancer recurrence in high-risk patients.

However, even as medications become more effective in preventing or curbing bone loss, the guidelines for their use must be constantly reconsidered and revised.

“Today, we must weigh the risks and benefits of therapy for bone loss for each individual patient,” Dr. Hu said. “(Continued on page 8)
Leukemia Cells Observed Burning Fat to Evade Death

Recent studies showing that leukemia cells can prolong their survival by metabolizing fatty acids suggest a previously unexplored approach to controlling hematologic cancers.

It was previously established that leukemia cells, like all cancer cells, derive energy from the metabolism of glucose. However, as demonstrated by scientists at The University of Texas M. D. Anderson Cancer Center and The University of Texas Medical School at Houston, leukemia cells also readily consume fat.

Burning fat blocks the action of proteins that help control the programmed death of abnormal cells (apoptosis). In this way, leukemia cells are apparently able to avoid one of the body’s main defenses against cancer proliferation.

However, drugs already used to treat noncancerous conditions may be able to switch off leukemia cells’ appetite for fat, allowing apoptosis to proceed. Thus, therapeutically targeting leukemia cells via their metabolism may be possible, said Michael Andreeff, M.D., Ph.D., a professor in M. D. Anderson’s Department of Stem Cell Transplantation and Cellular Therapy and co–senior author of the research. “If these initial results hold up, inhibitors of fat oxidation may become a new way to treat leukemia patients,” he said.

One of those inhibitors is etomoxir, a drug used to treat heart failure. In laboratory experiments, the researchers demonstrated that etomoxir inhibited the growth of leukemia cells in culture in a dose-dependent manner. They also found that etomoxir sensitized leukemia cells to drugs that cause apoptosis. The fatty acid synthase/lipase inhibitor orlistat also sensitized leukemia cells to programmed cell death.

Experiments in mice showed that combining etomoxir with the apoptosis-inducing drug ABT-737 or with cytarabine, a frontline drug for acute myelogenous leukemia, reduced the number of leukemic cells and increased median survival duration. Etomoxir was also found to decrease the number of quiescent leukemia progenitor cells in half of blood samples taken from human patients with acute myeloid leukemia.

The research was published in the January issue of the Journal of Clinical Investigation.

Assessment Tool Takes Aim at Graft-versus-Host Disease

A new assessment tool developed by M. D. Anderson researchers measures the severity of chronic graft-versus-host disease (cGVHD), a debilitating side effect of allogeneic hematopoietic stem cell transplantation.

cGVHD occurs when transplanted donor cells recognize the recipient as foreign and attack the patient’s organs and tissue. Symptoms of the disease, which occurs in 40%-80% of transplant patients, can be treated, but inadequate diagnosis and assessment is a major barrier to successful treatment.

“There was a real need to develop an assessment tool because chronic graft-versus-host disease is a vexing side effect that can become a serious condition in a very short period of time,” said Loretta Williams, Ph.D., R.N., an instructor in the Department of Symptom Research at M. D. Anderson and lead author of a study used to develop the assessment tool.

Researchers began with the existing M. D. Anderson Symptom Inventory, or core MDASI, a patient-reported outcome measure. In the study, patients used the core MDASI to rate the severity of 13 symptoms common in cancer patients and to what extent those symptoms affected six interference items, or general aspects and activities of daily life. Patients also rated 14 additional cGVHD-specific symptom items.

Statistical analysis determined that 5 of the 14 cGVHD-related symptoms were clinically significant and unique to cGVHD patients: muscle weakness, skin problems, eye problems, joint stiffness or soreness, and changes in sexual function. The resulting comprehensive MDASI, which combined the 13 core symptoms with the 5 cGVHD symptoms, was sensitive to the presence of the disease. Results from the survey also correlated significantly with a patient’s report of overall quality of life.

On a scale of 0–10, the new tool rates the severity of symptoms common to patients with cGVHD and to what extent those symptoms interfere with their daily life. The MDASI-cGVHD joins 10 other MDASI tools for symptom management used by clinicians at M. D. Anderson.

“For the first time ever, we have a reliable tool to provide better support to patients following their transplant,” Dr. Williams said. “The survey will help open the conversation about cGVHD between doctors and patients and identify complications more quickly. This may lead to better outcomes following stem cell transplantation.”

The team’s research was presented at the 2010 Bone and Marrow Transplant Tandem Meeting.
The body’s immune system has defenses that are designed to stop cancer at its earliest stages. Unfortunately, those defenses don’t always work, and when they don’t, cancer is able to progress beyond what the immune system can suppress.

Immunotherapy for cancer attempts to jumpstart the body’s ability to seek out and destroy malignant cells. Important advances in immunotherapy have been made in recent years, giving some patients and their physicians more options for treating cancer.

**How immunotherapy works**

Cancer begins when cells lose control over their growth and reproduction. These abnormal cells sometimes give off signals that prompt the immune system to destroy the cells.

But the immune system may not be able to recognize or destroy cancer cells, which can act a lot like normal cells or might even employ their own defenses against an immune system attack. Immunotherapy works by helping the body recognize and kill cancer cells or by introducing immune system compounds that attack cancer cells directly.

**Monoclonal antibodies**

One common form of immunotherapy uses particles called monoclonal antibodies, which are created in the lab using animal tissue, human tissue, or both. Monoclonal antibodies work against cancer in various ways—some mark cancer cells for destruction by the immune system, while others stop cancer cells from functioning. Just as viral antibodies can find specific viruses in the body, monoclonal antibodies seek out cancer cells by detecting antigens (proteins that serve as markers) expressed by the specific type of cancer.

The monoclonal antibodies currently used for cancer immunotherapy include:

- **Bevacizumab (Avastin)**
  Approved to treat certain cancers of the breast, colon, lung, brain, and kidney

- **Ofatumumab (Arzerra)**
  Approved to treat chronic lymphocytic leukemia

- **Rituximab (Rituxan)**
  Approved to treat non-Hodgkin lymphoma

- **Trastuzumab (Herceptin)**
  Approved to treat breast cancer

- **Cetuximab (Erbitux)**
  Approved to treat colorectal and head and neck cancers

- **Panitumumab (Vectibix)**
  Approved to treat colorectal cancer

Since monoclonal antibodies can detect cancer cells specifically, radioactive substances or chemotherapy agents are sometimes attached to monoclonal antibodies. These “loaded” or “labeled” monoclonal antibodies then deliver their cancer-killing payload directly to tumor cells, which may increase the therapy’s effectiveness.

**Vaccines**

A second, less common form of immunotherapy is the use of vaccines to prompt an immune response. The concept is very similar to the use of vaccines for infectious disease: essentially, parts of cancerous cells are injected into the body, which will hopefully recognize the material as foreign and remove it—along with any other cancer cells of the same type.

Cancer vaccines are being studied to fight many types of cancer, including melanoma, leukemia, lymphoma, and cancers of the breast and ovary. So far, however, all cancer vaccines are available only through clinical trials (that is, none has been approved for use outside a study).

**Other applications**

In the future, immunotherapy may rely more on our understanding of genetics and cancer biology. Compounds now in early development include immune system cells that are genetically altered in the laboratory to more efficiently seek out and kill cancer cells. Other approaches rely on using immunotherapy as just one part of a cancer-fighting arsenal, given in combination with chemotherapy or other treatments. The long-term hope is that immunotherapy can be used to restore the body’s natural defenses against cancer whenever those defenses break down.

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J. LeBas
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questions I constantly face are: when is the right time to prescribe these drugs for bone loss, will I improve my patient’s overall health, will therapy decrease long-term fracture risk, and how long should I treat my patient with these therapies? The first thing a physician needs to do is to recognize that patients with cancer are at risk for bone loss and then to consider personalized therapy in the context of their overall cancer care.”

For more information, please contact Dr. Hu at 713-792-2841.

In addition to making lifestyle changes—increasing vitamin D and calcium intake, for example, or performing weight-bearing exercises regularly—cancer patients may be able to take any of a number of drugs to curb or prevent bone loss.

• **Salmon synthetic calcitonin** (Calcimar, Miacalcin, others), a hormone that suppresses osteoclast activity, was the first drug approved for osteoporosis and was standard therapy for bone loss 10 years ago. Calcitonin is given as a nasal spray, and a typical side effect is mucous membrane irritation from constant use. Calcitonin may also decrease bone-related pain from arthritis or fractures.

• **Bisphosphonates** such as alendronate (Fosamax), risedronate (Actonel), ibandronate (Boniva), and zoledronic acid (Zometa), which cause osteoclast death, are considered initial therapy for bone loss and can be given as pills, injections, or infusions. Side effects include reflux disease, esophageal erosion, increased kidney dysfunction in patients with kidney disease, and muscle aches, especially in patients with an underlying vitamin D deficiency.

• **Teriparatide** (Forteo), a synthetic form of parathyroid hormone that is self-injected once daily, stimulates bone growth. Currently, teriparatide is approved for only 2 years of use. It is contraindicated in patients with underlying, ongoing skeletal malignancy, patients who have received external or implant radiation therapy, and patients with Paget’s disease of the bone.

• **Raloxifene** (Evista), a selective estrogen receptor inhibitor, has been found to increase bone mass in postmenopausal women and be at least as effective as tamoxifen in reducing breast cancer recurrence in patients at high risk of recurrence. However, raloxifene can increase the risk of a cerebrovascular event in patients with a history of stroke and in patients who smoke.