Pigmented villonodular synovitis responsive to imatinib therapy

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In 2002 when he was 27 years old, our patient sought care for a 2-year history of right hip pain that he first noted after jogging. The pain progressed to where he could not run. He saw his family practitioner, who thought it might be a hernia. Later, the pain progressed, and he was referred to an orthopaedic surgeon. He was referred to Baylor University Medical Center at Dallas for further evaluation in April 2004.

At the time of this evaluation, he had no significant past medical history other than a penetrating eye injury in 1983, followed by retinal surgery in 1989. He still has difficulty with vision. He was not taking any regular medications, other than occasional nonsteroidal antiinflammatory drugs for pain. On physical examination, he had a very mild coxalgic hip gait and slight limitation in the internal rotation of the right hip compared with the left. He said he occasionally felt a grating or popping sensation when hyperflexing his hip. Magnetic resonance imaging (MRI) and x-ray studies in 2004 were interpreted as pigmented villonodular synovitis (PVNS) involving the right hip with extraarticular extension into the pelvis (Figure 1).

An open synovectomy was performed in May 2004 through a lateral approach to both the anterior and posterior aspects of the hip. A large mass arising beneath the vastus lateralis muscle was excised (Figure 2). The short external rotators were deformed, and the lesion had extruded posteriorly surrounding these tendons. A capsular window was created posteriorly to leave enough attachment for circulation of the femoral head, and the PVNS material within the joint was cleaned out posteriorly and superiorly. A cyst located in the femoral neck at the subarticular surface was curetted and grafted with Norian, a bone graft substitute.

The surgical specimen showed a tumor that demonstrated expansion of the synovium and subsynovium by sheets of mononuclear ovoid cells with moderate amounts of variably hemosiderin-laden cytoplasm (Figure 3). Scattered multinucleate giant cells were present, as were numerous mitotic figures. The tumor infiltrated beyond the synovium to erode and penetrate adjacent bone. Stains confirming the diagnosis of diffuse PVNS, synonymously known as diffuse giant cell tumor of tendon sheath, included a positive CD68, an elevated MIB-1, and a positive Prussian blue stain for iron. Tumor was present at multiple margins of resection.

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The high likelihood of recurrence and adjuvant treatment modalities were discussed with the patient, and it was agreed that his progress would be monitored with a follow-up MRI in 6 months.

The patient did not complete the 6-month MRI, citing finances and other reasons, but returned for an office visit in April 2006, complaining of swelling and frequent discomfort in the hip. He had a Trendelenburg gait, fullness in the anterior aspect of the hip, and pain with range of motion. Radiographs of the pelvis showed more radiolucency in the medial wall of the acetabulum (Figure 4a). The Norian fill in the superior femoral neck had been resorbed to some extent. An MRI scan showed extensive recurrent intraarticular and extraarticular disease with erosions (Figure 4b).

Reexcision with total hip arthroplasty was contemplated. The patient completed “hip school” and understood that a revision would be likely in the future and there would be some limitation of activity. Total hip arthroplasty was done in June 2006 (Figure 5). Surgical findings included extensive involvement of periarticular structures, including bone in the medial wall of the acetabulum. The tumor also extended down the iliopsoas muscle medially into the true pelvis, which prevented complete surgical excision. (Martin et al indicated that radical resection with negative margins was not necessary in most cases [1]). Pathologic examination confirmed the presence of recurrent PVNS.

The patient recovered well from the surgery, and x-rays taken 3 weeks postoperatively showed good position of both components. After consultation with other physicians in the Baylor Sammons Cancer Center bone site tumor conference, it was decided to reserve radiation but stress to the patient the importance of long-term follow-up. An MRI scan in December 2006, 6 months postoperatively, showed that the size and erosions of the medial PVNS into the pelvis and anterior to the hip joint in the iliopsoas bursa were

Figure 3. Pigmented villonodular synovitis (diffuse giant cell tumor of tendon sheath) following the May 2004 open synovectomy. (a) Tumor in the pelvic bone. (b) An admixture of mononuclear cells with and without hemosiderin, multinucleate giant cells, foamy histiocytes, and small numbers of lymphocytes.

Figure 4. Radiological studies for the recurrence in 2006. (a) Radiograph. (b) MRI image.

Figure 5. Total hip arthroplasty in June 2006. Modular metal-on-metal hip components with Norian fill at medial wall.
unchanged (Figure 6). He continued to use a cane for another year and had essentially a normal gait when the cane was used.

In March 2009, nearly 3 years after his hip replacement, the patient returned. At this point, he walked well and had full range of motion but was concerned that the lump on the anterior aspect of his leg might be larger. Physical examination showed an area of fullness in the proximal thigh above and below the inguinal ligament on the right side. X-rays showed no bony problem. However, an MRI showed that the residual PVNS in the anterior aspect of the hip and thigh had enlarged since the scan 2 years earlier (Figure 7). The anterior deposit surrounded the neurovascular bundle in the pelvis and groin.

We reviewed treatment options for our patient, which included reexcision and radiation therapy, as well as recently reported adjuvant imatinib treatment based upon a single case report. Treatment with this drug is expensive, at about $4600 a month, and considerable effort was expended to see if this treatment option could be arranged. The insurance company agreed to cover the drug, and the patient was started on imatinib at a dose of 400 mg daily. A follow-up MRI after 3 months of imatinib therapy showed reduction of tumor volume (Figure 8). Unfortunately, a change in insurance coverage occurred in January 2010, and the new carrier would not furnish the drug. The patient’s symptoms of anterior thigh tightness slowly recurred. His treatment with imatinib was restarted in May 2010 after much effort was expended to influence the insurance carrier. To date, the largest reduction in tumor volume has been 38% in the anteromedial component (from 5.3 × 4.2 × 3.8 cm initially to 4.3 × 3.0 × 4.1 cm) and 6% in the anterior component (from 14.3 × 8.2 × 5.9 cm to 13.8 × 8.1 × 5.8 cm).

DISCUSSION

PVNS is an uncommon disease, with an incidence of one case per 1.8 million people per year (2). It has been considered to be both an inflammatory or reactive lesion and a benign neoplasm. Recently, both ideas were shown to be correct: it is a neoplastic process with a reactive component stimulated through the self-stimulatory effect of colony-stimulating factor 1 (CSF1) (3). This opens the possibility of treatment with imatinib, sunitinib, or another CSF1 receptor inhibitor.

A review of 64 PVNS cases involving the hip showed an average age of occurrence of 35 years (4). Patients with this condition often report slow, progressive symptoms. PVNS has a variable course and leads to local destruction and more severe symptoms such as joint pain, limitation of range of motion, swelling, erythema, and hemorrhagic effusion. Lesions involving the hip are more likely than lesions elsewhere to cause

Figure 6. MRI scan of December 2006.

Figure 7. MRI in September 2009, showing enlargement of the anterior and medial mass.

Figure 8. MRI in December 2009 after imatinib therapy, showing slight reduction of tumor volume.
bony erosions, and some researchers have hypothesized that the smaller intraarticular space in the hip may prevent the tumor from expanding without increasing pressure on femoral and acetabular cartilage (5). Although PVNS is uncommon, it should be considered in the differential diagnosis of younger patients with symptoms at one site, especially when bony erosions or a soft-tissue component is present.

When PVNS is suspected, MRI is the most sensitive and specific diagnostic test. The “pigmented” part of PVNS’s name comes from the brownish hemosiderin deposits within the joint that characterize the disease. Both T1- and T2-weighted images show low signal intensity due to hemosiderin deposition. With the blooming phenomenon, the lesion may be artifactualy enlarged on long echo time images because of hemosiderin’s magnetic susceptibility effect (6). In addition, the superior tissue contrast of MRI allows visualization of lobulated or nodular synovial proliferation, bony erosions, and joint effusion (7).

Synovectomy has been the principal treatment modality. However, a significant percentage of patients with diffuse PVNS experience recurrences. As Horoschak et al (8) summarized, relapse rates with surgery alone have ranged from 8% to 56%, depending on resection status (9–15). Based on results from 99 patients, Schwartz et al reported a mean time for recurrence of about 5 years, with a risk of 7% at 1 year, 15% at 5 years, and nearly 35% at 25 years (9). Vastel et al (16) noted that many past studies did not differentiate between recurrence and secondary osteoarthritis, which is another complication of PVNS. Either problem, however, may lead to the need for total hip arthroplasty. Among Vastel et al’s patients, two of four required revision arthroplasty after 11 or 14 years—not because of recurrence but because of aseptic loosening of the acetabular component. These issues arise because of the young age of the PVNS patients. These young patients, at whatever stage, are often also supported with conservative treatments such as physical therapy to preserve range of motion, assistive devices for ambulation, and analgesics and nonsteroidal antiinflammatory medications (17).

In 2008, Blay et al (18) reported a complete response to imatinib in PVNS. Their 34-year-old patient experienced a relapse of PVNS of the right elbow and was treated with 400 mg a day of imatinib. She had a partial response by month 2, a complete response by month 5, a relapse at month 9 (after the drug was discontinued at month 7), and a second complete remission at month 12, which was confirmed at month 14. Thus, it appears that the drug targets an essential mechanism of tumor growth. The recent description of a characteristic gene translocation, (1;2) (p13;q37) of the collagen 6A3 gene and the macrophage colony-stimulating (M-CSF) gene (col6A3/CSF1) (19), suggests that imatinib activity is related to M-CSF receptor blockade (18).

Another option is radiation therapy. Radiation therapy has been effective among patients with diffuse PVNS after recurrences (8, 20, 21). A recent study showed that among 41 patients with PVNS from 14 different radiotherapy departments receiving doses of 30 to 50 Gy, 95% of patients achieved local control, and 93% had little or no functional impairment (21). However, most agree that it is best to reserve radiation for recurrent lesions and to consider the potential for local complications such as swelling, fibrosis, wound healing problems, and risks to bone graft incorporation (22).

Adjuvant treatment with intraarticular injection yttrium 90 has also been studied (23, 24), with reports of stabilization of disease and no major complications. However, this approach has largely fallen out of favor (25).

Our plan is to continue the imatinib and make a change in treatment based on clinical findings. It will be necessary to continue to collect appropriate data elements in a patient-centric, longitudinal fashion until the outcome is known. In time, the aggregation of multiple similar cases could provide useful clinical knowledge about the disease process and treatments.

Acknowledgments

We thank Cynthia Orticio, MA, ELS, for editorial contributions.


April 2011

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**Images in medicine**

### Heart and sole

A 70-year-old woman presented for an annual exam a few days after Valentine’s Day. She belatedly mentioned that the bottom of her right foot was sore and recalled that she had first noticed this after a walk in the gym. On Valentine’s Day she took a closer look at the bottom of her foot and noticed a heart-shaped area of irritation. On exam the sole finding on the sole of the foot was a heart-shaped red blister/hematoma located overlying the metatarsal ridge. Applying some tender loving care, I reassured her of the benign nature of this, and she recovered uneventfully.

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