Presentation of Case

Dr. Michael S. Abers (Medicine): An 84-year-old man was evaluated at this hospital because of painless right testicular swelling.

The patient had been in his usual state of health until 6 weeks before this evaluation, when he noted while showering that the right testicle was approximately 3 times larger than the left testicle. The testicle was soft and nontender on palpation, and the enlargement had not been present the previous day.

The next day, the patient was evaluated at a local urgent care clinic. He reported no trauma, heavy lifting, recent sexual intercourse, testicular or scrotal pain, abdominal or back pain, skin changes or rash, obstructive urinary symptoms, hematuria or dysuria, or discharge. He had no constitutional symptoms, such as fever, night sweats, or weight loss. On examination, the right testicle had a large, soft, mobile posterior mass; the left testicle was normal. A presumptive diagnosis of a hydrocele was made, and the patient was advised to use scrotal support and, if pain occurred, to take nonsteroidal antiinflammatory drugs. Testicular ultrasonography was scheduled for the following day.

Dr. HeiShun Yu: The next day, ultrasonography (Fig. 1) revealed marked asymmetric enlargement and hypervascularity of the right testicle. A hypoechoic region in the mediastinum testis was most likely related to edema due to infection or inflammation. The epididymis was also enlarged and hypervascular. An associated complex hydrocele, with septations and internal debris, was present on the right side. These findings were compatible with right epididymo-orchitis. The left testicle had normal echotexture and no focal lesion. There was an incidental left varicocele.

Dr. Abers: A 10-day course of oral levofloxacin was prescribed. Six weeks later, at a follow-up visit with his primary care physician, the patient reported persistent testicular swelling. He noted that there had been a mild decrease in the swelling after he had completed the levofloxacin course but that the testicle continued to...
enlarge thereafter, causing inconvenience owing to its bulk and the pressure in the right groin, which made it difficult for him to sit and to flex his upper leg. There were no additional symptoms, such as pain or fever.

The patient had long-standing benign prostatic hypertrophy with associated nocturia, as well as Raynaud’s phenomenon, mild normocytic anemia, peptic ulcer disease, colonic diverticulosis, hypercholesterolemia, hearing loss, and cataracts. An episode of syncope had occurred after exercise on a hot and humid day 3 years earlier, and he had undergone left inguinal herniorrhaphy with mesh placement 13 years earlier. Medications were aspirin, omeprazole, tamsulosin, finasteride, nifedipine as needed for symptoms of Raynaud’s phenomenon, and pravastatin. The patient had no known allergies. He performed aerobic exercise daily. He was married, had no children, and had immigrated to the United States from Turkey when he was 20 years of age. He was a retired health care professional; he reported that he had had at least one negative tuberculin skin test in the past. More than 40 years earlier, he had smoked cigarettes for 5 years; he did not consume alcohol or use illicit drugs. He had traveled to Canada, Western Europe, and the Caribbean in the past. His mother had died in her 70s after a stroke, his father had lived beyond 90 years of age, a brother had prostatic hypertrophy, and a sister had multiple sclerosis. There was no family history of cancer.

On examination, the patient appeared well. The temperature was 36.3°C, the heart rate 54 beats per minute, the blood pressure 119/64 mm Hg, and the oxygen saturation 98% while he was breathing ambient air. The weight was 72.3 kg, and the body-mass index (the weight in kilograms divided by the square of the height in meters) 28.3. A firm, nontender right scrotal mass (7 cm in diameter) was located in the posterior region, protruding superiorly to the external inguinal

Figure 1. Initial Ultrasound Images.
A transverse ultrasound image of the scrotum shows asymmetric enlargement and edema of the right testicle (Panel A, arrow), and a corresponding color Doppler image shows asymmetric hypervascularity of the right testicle (Panel B, arrow). A sagittal ultrasound image of the right hemiscrotum shows enlargement of the right epididymis (Panel C, arrow), and a corresponding color Doppler image shows diffuse hypervascularity of the right testicle and epididymis (Panel D).
The mass transmitted light on transillumination. The scrotal skin was normal, with no erythema or peau d’orange (orange peel) changes. The left testicle had changes consistent with a varicocele. The prostate was small and benign on palpation. There was no inguinal lymphadenopathy. The remainder of the examination was normal. Urinalysis showed yellow, clear urine, with a specific gravity of 1.011 (reference range, 1.001 to 1.035), a pH of 6.0 (reference range, 5.0 to 9.0), and no evidence of leukocyte esterase or occult blood. A culture of the urine was sterile.

**Dr. Yu:** Repeat testicular ultrasonography (Fig. 2) revealed further enlargement of the right testicle. The right testicular volume was approximately 33 ml; it had been approximately 19 ml on an image obtained 6 weeks earlier. The hypoechoic region in the right mediastinum testis had increased in size. The right testicular parenchyma and epididymis remained hypervascular. Multiple new nonspecific hypoechoic areas were scattered throughout the remaining testicular parenchyma. The left testicle was normal.

**Dr. Abers:** A diagnostic procedure was performed.

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**DIFFERENTIAL DIAGNOSIS**

*Dr. Ryan W. Thompson:* This 84-year-old man presented with a 6-week history of painless swelling of the right testicle. In formulating a differential diagnosis, the two key considerations are establishing the most worrisome or “can’t miss” diagnoses and establishing the most likely diagnostic possibilities according to age and epidemiologic and other features of the patient’s presentation. In an 84-year-old man with unilateral testicular swelling, with a solid testicular mass in the absence of systemic inflammatory symptoms that would be suggestive of acute infection, my initial impression is cancer. In fact, such a clinical presentation in an older man would be considered cancer until proven otherwise.

Two additional considerations in narrowing the differential diagnosis are the degree of pain and the pace of onset. Causes of testicular enlargement that develop suddenly and often involve considerable pain include testicular torsion and acute testicular infections, such as epididymitis and orchitis. Although these diagnoses fall into the “can’t miss” category because of the risk of testicular loss due to torsion or systemic spread of infection, they are unlikely diagnoses in this case, given the patient’s gradual onset of symptoms and the absence of pain on presentation.

**HERNIA AND HYDROCELE**

Common causes of painless testicular enlargement in elderly men include hydrocele, varicocele, and inguinoscrotal hernia. Assessment for a hernia can easily be performed on physical examination. Although this patient had previously undergone a left inguinal hernia repair, a hernia on the right side was a consideration. However, the transmission of light on transillumination rendered a diagnosis of inguinoscrotal hernia unlikely and confirmed the presence of fluid inside the scrotum, a finding consistent with a hydrocele. Therefore, hydrocele was the leading consideration on the patient’s initial ex-
amination at the urgent care clinic. Although a hydrocele was indeed seen on subsequent testicular ultrasonography, the fluid contained separations and internal debris, which were indicative of a more complex process that probably involved inflammation.

INFLAMMATION
The patient’s ultrasound images also showed hypervascularity of the right testicle and epididymis, a finding suggestive of an inflammatory process. Infection was initially thought to be present and levofloxacin was prescribed, but the absence of tenderness and of other symptoms of infection raises concerns about a more subacute and invasive process that perhaps caused obstruction of drainage or of flow through the mediastinum testis. Although the patient had a mild decrease in testicular swelling after the course of levofloxacin, he did not have complete improvement while he was receiving the drug, which argues against an acute bacterial infection as the cause of his condition.

CANCER
Could this patient have testicular cancer? The most common cause of testicular tumors in patients older than 60 years of age is primary testicular lymphoma. Overall, primary testicular lymphoma is rare, accounting for only 1 to 2% of non-Hodgkin’s lymphomas and only 1 to 9% of all primary testicular tumors. The most common presenting feature of primary testicular lymphoma is painless enlargement of the testicle, similar to that seen in this patient. At the time of diagnosis, constitutional symptoms are uncommon and an accompanying hydrocele is present in approximately 40% of patients. Common findings on imaging include hypervascularity and hypoechochogenicity or hyperechochogenicity of involved tissue. Other testicular tumors — including germ-cell tumors (e.g., seminoma), rhabdomyosarcoma, and stromal tumors (e.g., Leydig-cell, granulosa-cell, and Sertoli-cell tumors) — are even more rare. In this patient, it would be reasonable to check serum tumor markers, since germ-cell tumors can produce increases in levels of alpha-fetoprotein and beta subunit of human chorionic gonadotropin. In addition, pseudolymphoma is a rare, benign condition that mimics lymphoma and can be manifested by scrotal or testicular enlargement. In this case, pseudolymphoma should be considered as a diagnosis of exclusion, only when all other plausible diagnoses have been ruled out.

GENITOURINARY SARCOIDOSIS
Genitourinary sarcoidosis can have a gradual onset and can involve the testes, epididymis, and any other scrotal structure. In most case reports of genitourinary sarcoidosis, the affected patients were 20-to-40-year-old men of African descent. Because of these epidemiologic factors, sarcoidosis is low on the list of possible diagnoses for this patient.

GENITOURINARY TUBERCULOSIS
Could this patient have genitourinary tuberculosis? He was originally from Turkey, a region in which tuberculosis is endemic, but he had not lived there for more than 60 years. It is possible that he had been exposed to tuberculosis in the United States, but as a health care worker, he had presumably undergone a tuberculin skin test more than once. Although genitourinary tuberculosis is rare, some reports suggest that it accounts for a small percentage of cases of extrapulmonary tuberculosis; middle-aged men are most commonly affected. In most patients with genitourinary tuberculosis, symptoms typically develop gradually and a scrotal lump is usually present for more than 3 months. A testicular mass due to tuberculosis may be either painful or painless on examination. Urine cultures and acid-fast staining for mycobacteria can be positive, but the sensitivity of staining is low and cultures can take several weeks to show a positive result. Nucleic acid testing has become a useful clinical diagnostic test for genitourinary tuberculosis because of its more favorable test characteristics and fast turnaround time. Genitourinary tuberculosis typically develops after disseminated disease. Patients often (but not always) present with systemic inflammatory symptoms, such as fever, night sweats, anorexia, and weight loss. In this case, it is notable that the patient had some improvement after taking levofloxacin, an antibacterial agent with possible antituberculous activity.

NARROWING THE DIFFERENTIAL DIAGNOSIS
The differential diagnosis in this case can be reasonably narrowed to tuberculosis and cancer. In elderly men presenting with a relatively pain-
less, firm testicular mass and no systemic symptoms that would suggest infection, cancer would be the most common diagnosis. However, in this case, the absence of a discrete mass on imaging makes the diagnosis of cancer unlikely.

Given that the imaging studies do not support a diagnosis of cancer, the most likely diagnosis in this patient is genitourinary tuberculosis. The small, scattered hypoechoic lesions that were noted on imaging could be consistent with tuberculosis. The fact that the testicular symptoms improved with levofloxacin is also suggestive of tuberculosis. Patients with renal tuberculosis classically have “sterile pyuria”; in this case, the absence of white cells in the urine makes renal tuberculosis unlikely, but the negative urine culture does not rule out the possibility of testicular tuberculosis.

Several features of this patient’s presentation do not fit perfectly with a diagnosis of tuberculosis. First, the painless testicular enlargement is somewhat unusual, since most patients with genitourinary tuberculosis present with at least some pain. Second, he had no urinary or systemic inflammatory symptoms. Finally, he had been a health care worker and reported having had at least one negative tuberculin skin test. Although the presence of pain, systemic symptoms, and a positive tuberculin skin test would support the diagnosis of tuberculosis, their absence does not rule out this diagnosis. I suspect that this patient had genitourinary tuberculosis and that the diagnostic procedure was a right orchiectomy.

Dr. David M. Dudzinski (Medicine): Dr. Dahl, what was your clinical impression when you evaluated this patient?

Dr. Douglas M. Dahl: Because the abrupt onset of right testicular enlargement would be most consistent with bacterial epididymitis and reactive hydrocele, I thought it was unusual that the patient did not have fever, pain, or a clinically significant response to a fluoroquinolone antibiotic agent. Thus, his presentation raised concerns about testicular lymphoma, which is the cancer that is most likely to cause a testicular mass in an elderly man. I obtained a pelvic magnetic resonance imaging study, which did not show any findings in the genitalia or pelvis that were consistent with lymphoma or other cancers. The hydrocele persisted unabated. The patient had no systemic inflammatory symptoms, leukocytosis, or other evidence of an infectious process. Thus, testicular lymphoma could not be ruled out, and the patient consented to and subsequently underwent right orchiectomy.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

CLINICAL DIAGNOSIS

Testicular lymphoma.

DR. RYAN W. THOMPSON’S DIAGNOSIS

Genitourinary tuberculosis.

PATHOLOGICAL DISCUSSION

Dr. Dipti P. Sajed: Evaluation of the right orchiectomy specimen revealed an ill-defined tannish-yellow mass (3.6 cm in greatest dimension) punctuated by small yellow nodules that involved both the testicle and the epididymis (Fig. 3A). Results of histologic examination mirrored the gross appearance, with well-formed granulomas in a nodular pattern that were confluent in some areas and discrete in others (Fig. 3B). The nodules were apparent in both the testicular parenchyma, in a predominantly interstitial pattern, and the epididymis. The granulomas contained numerous epithelioid histiocytes with a rim of lymphocytes surrounding a central area of necrosis (Fig. 3C). In formulating the differential diagnosis of a granulomatous process of the testicle, there are two important considerations. First, the presence of necrotizing granulomatous inflammation most commonly suggests an infectious cause, such as tuberculous or nontuberculous mycobacteria, brucella species, Treponema pallidum, blastomyces species, or other bacteria or fungi. Second, a granulomatous process in a primarily interstitial location is most likely due to infection; on rare occasions, it is due to sarcoidosis of the testicle, which very rarely causes necrosis and is generally a diagnosis of exclusion. In contrast, nonspecific (idiopathic) granulomatous orchitis, which is one of the most common forms of non-neoplastic testicular enlargement, has a predominantly intratubular pattern; in addition, it does not cause necrosis or well-formed granulomas. Taken together, the features of this case indicated that infection was a likely cause of the granulomatous inflammation and warranted further investigation. A his-
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A chemical stain for acid-fast organisms was performed and revealed a few acid-fast bacilli in areas of necrosis (Fig. 3D). The final anatomical diagnosis is therefore mycobacterial epididymoorchitis, with further classification contingent on microbiologic studies.

**Figure 3. Right Orchiectomy Specimen.**
A photograph of the orchiectomy specimen (Panel A) shows an ill-defined, tannish-yellow nodular mass in the testicle (arrows) and epididymis (arrowheads). A hematoxylin and eosin stain of the mass (Panel B) shows well-formed granulomas in a nodular pattern that are confluent in some areas (arrows) and discrete in others (arrowhead). At high magnification (Panel C), the granulomas contain palisading epithelioid histiocytes (arrows) with a rim of lymphocytes (arrowheads) surrounding a central area of amorphous necrotic debris. A Ziehl–Neelsen stain (Panel D) shows a few acid-fast bacilli (arrows) in the necrotic areas of the granulomas.

**DISCUSSION OF MANAGEMENT**

Dr. Rocio M. Hurtado: Our clinical approach to this patient’s treatment was first focused on making a definitive microbiologic diagnosis. Although the differential diagnosis of mycobacterial epididymoorchitis is small, the diagnosis has management-related implications. *Mycobacterium tuberculosis* infection was our top consideration, but there are other nontuberculous mycobacterial infections, including some that grow rapidly and some that grow slowly. There were no overt clues or risk factors for *M. leprae* or *M. bovis* infection; *M. bovis* infection causes an orchitis that is classically associated with the administration of bacille Calmette–Guérin in the context of therapy for transitional-cell bladder cancer.

It was critically important to obtain microbiologic confirmation of *M. tuberculosis* in order to choose an effective drug regimen and to rule out the presence of drug resistance, given the rising rates of drug resistance throughout the world. However, the strain in this patient had most
likely been acquired several decades earlier. The patient’s older age increased the likelihood of hepatotoxicity from standard antituberculosis therapy. Therefore, the performance of antimicrobial susceptibility testing was key in selecting the most appropriate alternative regimens in the event that drug toxicity were to develop. Because fluoroquinolones are often included in regimens for patients with hepatotoxicity, it was also important to rule out fluoroquinolone resistance in this patient, who had previous exposure to this class of drugs.

Unfortunately, the determination of a microbiologic diagnosis in this patient was hampered by the fact that mycobacterial infection had not been previously suspected and therefore no tissue specimen was available for culture. Since tuberculosis is a systemic disease and more than 50% of patients with genitourinary tuberculosis have renal involvement (suggesting local spread in addition to the postulated hematogenous spread in other forms of tuberculosis), we performed mycobacterial cultures of the urine, including three 50-ml urine samples obtained during the first morning void and one sample obtained after prostatic massage. We pursued this line of investigation even in the absence of clinically significant abnormal urinary sediment, since up to 15% of patients with genitourinary tuberculosis have bland urinary sediment. This patient was also evaluated for other sites of potential concomitant pulmonary or extrapulmonary involvement. Ultimately, all four mycobacterial cultures of the urine grew *M. tuberculosis*.

The patient began first-line therapy for drug-susceptible tuberculosis with isoniazid, rifampin, ethambutol, and pyrazinamide with pyridoxine. Clinically significant hepatotoxicity developed after 2 weeks of therapy, which prompted discontinuation of all medications for 2 weeks, followed by reintroduction of isoniazid and ethambutol first and then rifampin. The drugs were administered without further toxic effects. Follow-up cultures of urine obtained at 2 months of treatment and at the end of treatment were sterile. Results of drug susceptibility testing confirmed a fully drug-susceptible organism. Ethambutol was discontinued, and the patient completed 9 months of therapy with isoniazid plus rifampin and pyridoxine.

Of note, the recommended length of treatment for genitourinary tuberculosis has not been definitively established, although the standard course for tuberculosis is 6 months. Given this patient’s clinical presentation, the surgical debulking of the primary reservoir by means of orchiectomy, his ability to receive first-line drugs (isoniazid and rifampin, with documented therapeutic levels during treatment), and the objective evidence of culture conversion during treatment, we elected to treat him for 9 months. He had no evidence of relapse at 1 year after treatment.

The patient recovered during the weeks after surgery and the initiation of treatment. He had complete resolution of his symptoms.

**A Physician:** If the urine cultures had been performed before surgery, confirming the microbiologic diagnosis, would orchiectomy have been necessary?

**Dr. Dahl:** Even though the active infectious process could be controlled in this case, the hydrocele would still have needed to be surgically corrected, since it was causing the most discomfort — making swimming and exercise difficult — and may or may not have resolved. If it was going to resolve, it would have taken a very long time. From a practical point of view, there was no reason not to perform an orchiectomy.

**Dr. Hasan Bazari (Medicine):** Why were you able to reinitiate antimycobacterial therapy without further toxicity?

**Dr. Hurtado:** Many drug reactions are idiosyncratic, and a proportion of patients who have toxic effects from medications can do well when the drugs are reintroduced. Given this patient’s age, we chose not to rechallenge him with pyrazinamide because we wanted to decrease the overall burden of hepatotoxicity, especially since we already knew that the organism was drug-susceptible. Instead, we elected to treat him without pyrazinamide for longer than the standard treatment period.

**Dr. Dudzinski:** Did the fact that he had some improvement with the levofloxacin have an effect on therapeutic decision making?

**Dr. Hurtado:** Unfortunately, up to one third of patients with urinary tuberculosis may have concomitant bacterial pathogens, so this feature alone cannot be used in decision making. It is true, however, that widespread fluoroquinolone use, especially in Asia, remains a concern, since a growing body of literature documents rising rates of primary resistance to fluoroquinolones among patients with tuberculosis.
Mycobacterial epididymo-orchitis due to *Mycobacterium tuberculosis*.

**REFERENCES**


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**LANTERN SLIDES UPDATE**

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