Testicular Sarcoidosis With Elevated Levels of Cancer-Associated Markers

A 31-year-old white man presented in January 2004 with a 1-month history of painful right testicular enlargement. Physical examination revealed a hard testicular mass with no local inflammation or fever. The patient had no significant past medical or surgical history. Scrotal ultrasonography showed a vascularized and heterogeneous mass 4 cm in diameter localized in the center of the right testicle (Fig 1A, echography of testis; Fig 1B, computed tomography). Levels of alpha-fetoprotein (αFP) and β-human chorionic gonadotropin (βHCG) were elevated to 144 Ul/mL and 1.88 mUl/mL (normal levels < 10 and < 0.10), respectively. Tests for erythrocyte sedimentation rate and C-reactive protein were normal. Thoracic, abdominal, and pelvic computed tomography revealed an adenopathy (> 1 cm in diameter) on the right of the vena cava near the hilum of the right kidney (Fig 2, a tuberculoid follicular lesion: some epithelioid cells [yellow arrows] and some giant cells [black arrows]). A right orchiectomy was performed and a testicular prosthesis fitted in February 2004. Following sperm sampling and conservation, surgical examination revealed suspicious lesions on the right testicle. Macroscopical examination of the biopsy revealed an irregular-shaped mass measuring 2.5 $\times$ 2.1 cm along the longest axes with zones of remodelling following hemorrhagic necrosis. The mass was still however localized away from the tunica albuginea. Histological examination revealed on the one hand necrotic lesions and on the other giant cells and epithelioid-specific inflammatory lesions. The necrosis had no caseinlike or tumoral appearance, but evoked a coagulating necrosis resulting in a net hyperplasia of the rete testis. Immunohistochemistry showed a weak antibody labeling against carcinoembryonic (Gold's) antigen at the level of these structures, but none with anti-βHCG and anti-αFP. A second pathological anatomic opinion was sought from Dr A. Vieillefond (Hôpital Cochin, Paris, France). The diagnosis of tuberculoid granulomatous orchitis with reactive hyperplasia of the rete testis was made (Figs 2A and 2B). No testicular malignant tumor was found following complete pathological anatomic analysis of the specimen. All differential diagnoses for noncaseating epithelioid cell granulomas were eliminated, including tuberculosis (*Mycobacterium tuberculosis* sputum and urine, tuberculin skin test), syphilis (*Treponema pallidum* hemaglutination assay, Venereal Disease Research Laboratory test), brucellosis, toxoplasmosis, and schistosomiasis by serodiagnosis.[1,2] No inflammatory syndrome existed, and erythrocyte sedimentation rate and C-reactive protein were normal. In all, following negative results to numerous assessments into a possible of a pathogenic agent, the diagnosis of sarcoidosis was concluded. This unusual case consisted more of an isolated genital involvement with no sarcoidosis found elsewhere and no preoperative or postoperative evidence of intrathoracic lesions. Postoperative levels of tumor markers normalized 3 weeks following intervention. The patient showed good general health 24 months postoperatively with no inflammatory symptoms; normal thoracic, abdominal, and pelvic scan; and spontaneous disappearance of the retroperitoneal adenopathy.

This observation of a uniquely genital localization of sarcoidosis is clinically and biologically exceptional. Symptomatic genital involvements are rare, estimated at 0.2% of clinically diagnosed cases and 5% of those diagnosed at autopsy. In January 200,6 less than 70 published cases existed of histologically proven sarcoidosis involving the male reproductive tract. In addition, it is mostly found in African American patients with a previous history of months or years before the appearance of the genital involvement,[1] generally associated with a pulmonary sarcoidosis.[2-3] The genital involvement is unilateral in most cases, with epididymal localization the most frequent (67% to 73%); though the testis, spermatic cord, and prostate are also affected in 47% to 58%, 8% to 12% and 3% to 5% of cases, respectively.[2-3] The occurrence of a genitourinary involvement as the first disease symptom is thus exceptional. To the best of our knowledge, this is the first case of a patient with testicular sarcoidosis with elevated levels of αFP and βHCG and yet no signs of testicular cancer. Given the conflicting biologic anatomic findings, the assays were later verified to ensure no error was made. Following orchiectomy, the tumor markers normalized in the expected period following their respective half lives. The only observation of sarcoidosis with elevated levels of tumor marker published to date concerns mediastinal localization with increased levels of αFP.[5] αFP is a glycoprotein with elevated levels in the fetus and gradually decreasing levels during the first year after birth. We eliminated all other causes of increased levels of αFP (benign hepatic affections; lung cancer; cancers of the pancreas, liver and stomach) and of βHCG (cancers of the lung and bladder). An associated testicular tumor, which could have accounted for such an increased level of tumor-associated marker, was also eliminated. The different pathological proofreading showed no associated tumor even though the complete biopsy was included, and patient follow-up showed no progression or

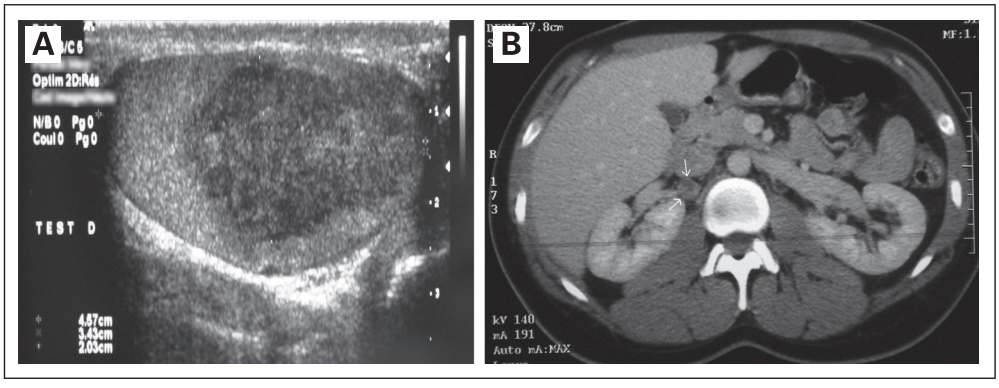

Fig 1.

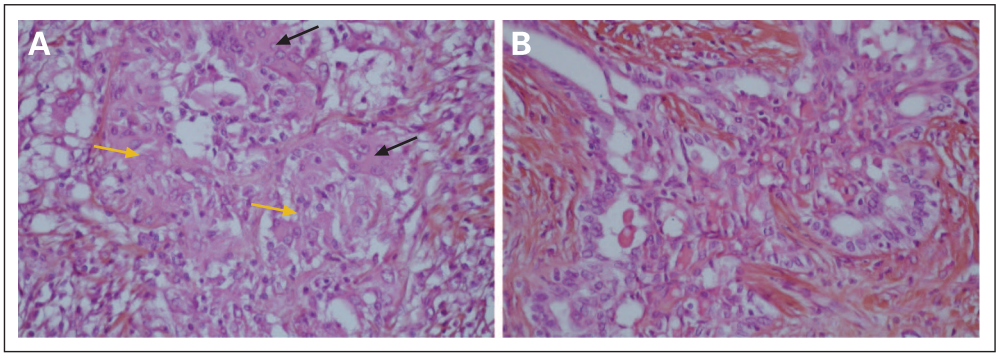

Fig 2.

tumor recurrence after two years. One hypothesis that we could therefore conceive would be the presence of a germinal testicular tumor bordering the testicular sarcoidosis, which would have regressed and left behind only scar tissue (burn out tumor). The adenopathy, which was probably of reactive origin, had spontaneously regressed. Coexistence of pathological sarcoidosis and malignant disease has previously been reported, with the largest series being that of the Mayo Clinic[4] with 14 cases in 46 years (1950-1996). In this series, they estimated that the cumulative incidence of testicular carcinoma in patients with sarcoidosis is 652.5 per 100,000, and that the incidence of sarcoidosis in patients with testicular carcinoma is 617.3 per 100,000. In the majority of cases, the testicular carcinoma appears before the sarcoidosis with an average interval of 5 years. It is interesting to note that the rate and age at onset of these two pathologies is approximately the same. In addition, ultrasonography cannot distinguish between the two pathologies as not one has sufficiently specific anatomic characteristics. It is therefore necessary to assay the tumor-associated markers and proceed by an inguinal approach to surgical testicular exploration. If sarcoidosis is not preoperatively considered, there is a risk of performing an orchidectomy for a benign pathology. However, we would not recommend applying a wait-and-see tactic when faced with a case of testicular masses found in a young male patient. In cases where contralateral orchiectomy has already been performed, it is recommended to carry out biopsy on the remaining testicle to prevent anorchism for a benign pathology. Concerning treatment, there is no specific therapy for urogenital cases.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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