

Autoimmune Phenomena Following Prostatectomy

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Key words: prostatectomy, autoimmunity, vasculitis

Abstract

Background: Benign prostatic hypertrophy is the most common benign tumor in males, resulting in prostatectomy in 20–30% of men who live to the age of 80. There are no data on the association of prostatectomy with autoimmune phenomena in the English-language medical literature.

Objectives: To report our experience with three patients who developed autoimmune disease following prostatectomy.

Patients: Three patients presented with autoimmune phenomenon soon after a prostatectomy for BPH or prostatic carcinoma: one had clinically diagnosed temporal arteritis, one had leukocytoclastic vasculitis, and the third patient developed sensory Guillian-Barré syndrome following prostatectomy.

Conclusions: In view of the temporal association between the removal of the prostate gland and the autoimmune process, combined with previously known immunohistologic features of BPH, a cause-effect relationship probably exists.

IMAJ 2005;7:575–577

Benign prostatic hypertrophy is a common benign tumor of unknown etiology in men. The pathologic findings consist of epithelial and stromal cell proliferation, and of abundant inflammatory cells with characteristic markers of locally activated immune reaction [1–6]. On the other hand, some data suggest an activation of the immune system in BPH while the prostate tissue itself may play a generally suppressive role [7–13]. In this article we present three patients who developed an autoimmune process shortly after prostatectomy for BPH or prostatic carcinoma, suggesting that prostatectomy can activate a pathologic autoimmune response.

Patient 1

A 71 year old white male was admitted because of fever (38°C) of several days duration. His previous medical history was remarkable only for ischemic heart disease, with mild stable angina pectoris and moderate hypertension, controlled by nifedipine and captopril. A month prior to his admission he had undergone transurethral prostatectomy for BPH, using spinal anesthesia. Postoperatively, he developed bilateral epididymitis that was successfully treated with a 10 day course of ofloxacin. He was well until several days prior to admission, when a temperature of 38°C developed.

BPH = benign prostatic hypertrophy
ESR = erythrocyte sedimentation rate
WBC = white blood cells

Upon admission, the patient was in no apparent distress and in good general condition. Physical examination revealed a temperature of 38.2°C, mild pitting edema of the ankles, and grade I hypertensive retinopathy. The white blood cell count was 13,000/μl, hemoglobin 11 g/dl, with a mean corpuscular volume of 76 and platelet count 370,000/ml. The urine contained only 1–3 red blood cells per high power field. Liver and kidney function tests, muscle enzymes, electrolytes, total proteins, immunoglobulins and serum iron were all normal. Repeated blood, bone marrow and urine cultures were sterile. Serologic tests for infection with cytomegalovirus, hepatitis viruses, Q fever, amoebae and Brucella were normal or negative. There was serologic evidence for previous infection with Epstein-Barr virus. The erythrocyte sedimentation rate was 100 mm/hr. Tuberculin test (PPD, 5 units) and acid fast staining of gastric aspirate were negative. The antinuclear antibodies, rheumatoid factors, antineutrophil cytoplasmic antibodies and complement were negative or within normal limits. Bone marrow biopsy showed minimal plasma cell hypercellularity. Ultrasound examination of the abdomen revealed a right kidney cyst. The chest and skull radiograms, echocardiogram, computerized tomography of the chest, abdomen and pelvis, as well as gallium and technetium scans, were all interpreted as normal.

During the month of his hospitalization, the course of the disease was characterized by complaints of severe bilateral calf pain, with partial relief following administration of diclofenac, spiky fever, elevated ESR and persistent leukocytosis in the range of 15,000–25,000/μl. Knee and ankle radiograms, echodoppler of lower extremities and electromyogram were also performed and found to be normal. A therapeutic trial with prednisone 40 mg/day brought dramatic relief of the leg pain, improvement in his general condition, and normalization of the temperature, ESR and WBC count.

The patient was discharged for ambulatory follow-up with a presumed diagnosis of polymyalgia rheumatica, with slow tapering of the prednisone dose. Several days after lowering the dose of prednisone to 10 mg/day, jaw claudication and right eye visual field scotomata appeared and rapidly developed to total loss of vision in this eye. The ESR increased again. The patient refused temporal artery biopsy. The prednisone dose was raised again with improvement in the patient's general condition, but the right eye blindness remained permanent.

Patient 2

An 80 year white male with no significant medical history was admitted to the hospital because of a 5 day history of fever (39°C), night sweats, weakness and lower extremity pain. Two months prior to his admission he had undergone transurethral prostatectomy for BPH. The operative and postoperative course was uneventful.

Upon admission the patient appeared well and in no apparent distress. Physical examination was remarkable only for fever, a non-tender and firm liver, spanning 18 cm, and 3+ pitting edema to the middle of his calves.

The WBC count was 18,500/ μ l, hemoglobin 10.2 g/dl with low MCV and platelet count 560,000/ μ l. The peripheral blood smear showed mild hypersegmentation and toxic granulation. The ESR was 86 mm/hr. The electrolyte, liver and kidney function tests, muscle enzymes, thyroid function tests, folic acid, vitamin B12 and prostatic-specific antigen were all within the normal ranges. ANA, RF, ANCA, antiglomerular basement membrane antibodies and cryoglobulins were negative. Urinalysis revealed 6–8 WBCs per high power field.

Repeated blood cultures, urine and stool were negative. Studies for mycobacteria, parasites and amoebae as well as serologic tests and Giemsa-stained thick blood smears for plasmodia were negative. The tuberculin test and cerebrospinal fluid examination, chest radiogram, abdominal ultrasound, CT scan of the chest, abdomen and pelvis, and total body gallium scan were negative or normal. Echocardiography revealed mild dilatation of the left ventricle with mild stenotic aortic valve due to calcification. Temporal artery biopsy was negative.

During his stay, the spiky remittent fever persisted, the WBC count increased to 52,000/ μ l and the ESR remained maximally elevated. Paroxysmal atrial fibrillation developed and an episode of pulmonary embolism occurred, which were successfully treated with digoxin and heparin. On day 21 of the hospital stay, non-tender and non-pruritic palpable purpura appeared on both lower extremities. Biopsy specimen of the lesion revealed changes consistent with vasculitis. Prednisone at a dosage of 40 mg daily was started with rapid relief of all the symptoms and normalization of the ESR and other blood parameters.

Patient 3

A 69 year old male was admitted because of pain in his limbs for 2 months. His previous medical history was remarkable for hypertension, controlled by enalapril, trigeminal neuralgia, controlled by carbamazepine, and non-active peptic disease.

The symptoms began 3 days after prostatectomy for carcinoma of prostate. The pain was initially in his left ankle with progress to the left leg and right leg during the first week. One

month later, he complained of pain in his hands. Two weeks prior to his admission he suffered from bilateral temporal headache and from parasthesias in his scalp.

Preoperative evaluation ruled out metastatic disease (CT of abdomen, chest X-ray, and bone scan). Upon admission the patient was in good condition. Physical examination was normal except for the neurologic examination, which revealed small fiber neuropathy. Blood cell count, chemistry, urine test and ESR were interpreted as normal. Lumbar puncture was performed, showing high opening pressure, no cells, glucose 68 mg/dl and protein 106 mg/dl in the CSF. CSF culture was negative. Complement, RF, ANA, ANCA, cryoglobulin, and C-reactive protein, and immunoglobulin G oligoclonal bands in CSF were interpreted as normal or negative. Magnetic resonance imaging of brain with and without gadolinium demonstrated bilateral small foci in the white matter without pathologic enhancement. Nerve conduction velocity test and EMG showed mild proximal sensory polyneuropathy.

The patient's condition was summarized as sensory Guillian-Barré syndrome that might have been due to autoimmune phenomena. He was treated with corticosteroids and his condition improved.

Discussion

We have described three patients who presented with a febrile illness or neuropathic pain shortly after undergoing prostatectomy for BPH or prostatic carcinoma. Extensive workup failed to reveal infectious or malignant etiologies for their acute conditions. In the first patient, temporal arteritis could be diagnosed with a high degree of certainty based on the clinical course, with muscle pain, jaw claudication and acute loss of vision. In the second patient, a diagnosis of idiopathic leukocytoclastic vasculitis was proven by histologic findings. In the third patient, the diagnosis of sensory Guillian-Barré syndrome was based on physical neurologic examination and EMG/NCV tests findings. Based on the temporal association between the inflammatory processes and the removal of prostatic tissue, we assumed a cause-effect relationship but were unable to find similar reports in the English-language literature of an association between prostatectomy and large or small vessel vasculitis. These three autoimmune phenomena are different from one another in their etiopathogenesis and they may have developed secondary to surgical stress, anesthesia, postoperative infection and medications given to patients after surgery. The possibility of their association with prostatectomy is therefore only theoretical. However, these different autoimmune manifestations raise the possibility that autoimmune phenomena following prostatectomy may not be rare; rather, that physicians do not relate them to prostatectomy, an extremely common condition. To prove this hypothesis a large, prospective study is necessary.

BPH is a complex pathologic process of unknown etiology. The epithelial and stromal cell proliferation and hyperplasia found in BPH have been attributed to regulatory signals, mediated by growth factors, hormones and direct cell-to-cell communications. In particular, abundant inflammatory cells

MCV = mean corpuscular volume

ANA = antinuclear factor

RF = rheumatoid factor

ANCA = antineutrophil cytoplasmic antibodies

CSF = cerebrospinal fluid

EMG = electromyograph

NCV = nerve conduction velocity

– consisting principally of T cells (up to 70%), B cells (15%) and macrophages (15%) – are present in the hyperplastic prostate gland. The T cell population consists mainly of CD3+/CD4+ cells that can secrete activation and proliferation factors, which in turn may lead in BPH to the expression of HLA-DR antigens on the normally major histocompatibility complex class II negative prostate epithelial cells [1–6]. These findings imply that in BPH there is a locally activated immune reaction with characteristics of chronic inflammation.

Furthermore, normal prostate and seminal plasma contain substances that suppress proliferation and activation, including transforming growth factor-beta-like substances [7–13]. Striking evidence for the inhibitory impact of BPH on systemic inflammatory cells came from the demonstration of impaired proliferation, CD28 and CD25 expression and interleukin-2 production, by peripheral mononuclear cells from patients with BPH, in response to stimulation with mitogens [14]. Altogether, these data suggest activation of the immune system in prostatic hypertrophy in which the prostate tissue itself may play a generally suppressive role. We postulate that total or partial removal of *hypertrophic* prostatic tissue for BPH or prostatic carcinoma causes removal of antigen, exposure of cryptic antigens and disruption of the equilibrium between pro- and anti-inflammatory forces that may lead in some patients to autoimmune manifestations. Finally, the presence of prostosomes, small, 150 nm, extracellular multi-lamellar organelles secreted by the prostate gland with strong antiproliferative and antiphagocytic activity, suggests an additional anti-inflammatory role [15,16].

We conclude that our patients, who suffered from autoimmune syndromes shortly after prostatectomy, may serve as an example of possible prostatectomy-associated autoimmune response resulting from the immune system activation as a result of prostatectomy for BPH or prostatic carcinoma.

References

1. Steimer G, Gessi A, Kramer G. Phenotype and function of peripheral and prostatic lymphocytes in patients with benign prostatic hyperplasia. *J Urol* 1994;151:480–4.
2. Wanger AD, Goronzy JJ, Weyand M. Functional profile of tissue-infiltrating and circulating CD86+ cells in giant cell arteritis. *J Clin Invest* 1994;94:1134–40.

3. Huston K, Hunder G, Lie J, et al. Temporal arteritis: a 25 year epidemiological, clinical and pathological study. *Ann Intern Med* 1978;88:162–7.
4. McClinton S, Miller ID, Eremin O, et al. An immunohistochemical characterization of the inflammatory cell infiltrate in benign and malignant prostatic disease. *Br J Cancer* 1990;61:400–3.
5. Fowler ER Jr. Secretory immunology of the prostate gland. *Infection* 1991;19:131–7.
6. Theyer G, Kramer G, Assmann I, et al. Phenotypic characterization of infiltrating leukocytes in benign prostatic hyperplasia. *Lab Invest* 1992;66:96–107.
7. Lokeshwar BL, Block NL. Isolation of a prostate carcinoma cell proliferation inhibitory factor from human seminal plasma and its similarity to transforming growth factor β 1. *Cancer Res* 1992;52:5821–5.
8. Ramasharma K, Sairam MA, Seidah NG, et al. Isolation, structure and synthesis of a human seminal plasma peptide with inhibition like activity. *Science* 1992;223:1199–202.
9. Allen RD, Roberts TK. The relationship between the immune suppressive and cytotoxic effects of human seminal plasma. *Am J Reprod Immunol Microbiol* 1986;11:59–64.
10. Sheth AR, Arabatti N, Carlquist M, et al. Characterization of polypeptide from human seminal plasma with inhibition like activity. *FEBS Lett* 1984;165:11–15.
11. Reddy ESP, Bhargava PM. Seminal plasma is a potent inhibitor of *E. coli* RNA polymerase in vitro. *Nature* 1979;279:728–31.
12. Bischoy P, Martin Du Pan R, Lauber K, et al. Human seminal plasma contains a protein that shares physicochemical, immunological and immunosuppressive properties with pregnancy associated plasma protein A. *J Clin Endocrinol Metab* 1983;56:359–62.
13. Valley PJ, Sharrad RM, Rees RC. The identification of factors in seminal plasma responsible for suppression of natural killer cell activity. *Immunology* 1988;63:451–6.
14. Perez-Blas M, Martinez-Martin B, Carballido J, et al. Defective functional response to membrane stimuli in lymphocytes from patients with benign prostatic hyperplasia. *Clin Exp Immunol* 1995;101:521–6.
15. Kelly RW, Holland P, Skibinski G, et al. Extracellular organelles (prostosomes) are immunosuppressive components of human semen. *Clin Exp Immunol* 1991;86:550–6.
16. Skibinski G, Kelly RW, Harkiss D, James K. Immunosuppression by human seminal plasma – extracellular organelles (prostosomes) modulate activity of phagocytic cells. *Am J Reprod Immunol* 1992;28:97–103.

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One of the symptoms of approaching nervous breakdown is the belief that one's work is terribly important. If I were a medical man, I should prescribe a holiday to any patient who considered his work important.

Bertrand Russell (1872-1970), British philosopher, who wrote prolifically on religion, politics and morals, always stimulating interest, often to his own detriment. He was imprisoned and deprived of his Cambridge lectureship for his outspoken pacifism, and in 1940 a U.S. court disqualified him from holding a professorship in New York on account of his moral views. Awarded the Nobel Prize for Literature in 1950).