Case Report

Anti-Androgen Treatment of Prostatic Carcinoma May Be a Risk Factor for Development of Rheumatoid Arthritis

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ABSTRACT. There are many rheumatic paraneoplastic syndromes. The association between prostate carcinoma and subsequent development of rheumatoid arthritis (RA) has not been reported. We describe 3 cases of men developing inflammatory arthritis after anti-androgen manipulation for treatment of prostate carcinoma. None had diagnoses supporting other connective tissue disease or crystal arthritis. Only one patient had a weakly positive rheumatoid factor, and another had a positive antinuclear antibody. The cases fulfilled 1987 American College of Rheumatology criteria for RA. The onset of joint symptoms was within weeks to 9 months of starting therapy to suppress testosterone [2 received leuprolide acetate (Lupron) and one cyproterone acetate (Androcur)]. Review of the literature yielded no reports of prostate carcinoma associated with paraneoplastic RA. We review the literature with respect to associations of paraneoplastic RA and prostate carcinoma and discuss published data in the context of the hypothesis of lower testosterone and increased risk of RA. (J Rheumatol 2002;29:2459–62)

Key Indexing Terms:
HORMONE TREATMENT
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Many cancers are associated with rheumatologic paraneoplastic syndromes, especially dermatomyositis, polymyositis, scleroderma, hypertrophic pulmonary osteoarthropathy (HPO), polymyalgia rheumatica (PMR), relapsing seasonal seronegative synovitis with pitting edema (RS_3PE), vasculitis, and rarely rheumatoid arthritis (RA)[1,2]. To date, RA (often seropositive) has been associated with carcinoma of lung (2 cases), breast (one case), pharynx (one case), esophagus (one case), adenocarcinoma of unknown origin (one case), and chronic myelogenous leukemia (one case).

There is a case report of a man with seropositive RA developing HPO with his prostate carcinoma[2]. However, there are no reports of RA as a paraneoplastic syndrome with prostate carcinoma, but dermatomyositis has been observed with prostate carcinoma[2], and we have observed a patient with PMR at onset of his prostate carcinoma that improved as the prostate-specific antigen (PSA) improved. In addition, single case reports of prostate carcinoma with Reiter's syndrome[3] and palmar fasciitis[4] have been described.

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We observed 3 cases of men who had received anti-androgen treatment for prostate cancer, all of whom subsequently developed RA between weeks to 9 months after initiating anti-androgen therapy. We speculate that men who have received anti-androgen treatment for prostate carcinoma theoretically may be at increased risk for developing RA secondary to hormonal manipulation. There seems to be a temporal relationship between the anti-androgen treatment and the development of RA in these men, while the relationship between prostate carcinoma and RA in these cases is not paraneoplastic. The inflammatory arthritis runs a course unrelated to PSA concentrations. The literature supporting the effects of low androgen levels in RA is reviewed.

CASE REPORTS

Case 1. A 66-year-old man presented in October 1995. He had prostatic cancer diagnosed in 1992, and 15 days after starting cyproterone acetate (a drug that blocks binding of dihydrotestosterone in the prostatic carcinoma cell and decreases production of testicular testosterone) in 1995, he developed inflammatory arthritis later diagnosed as RA. At initial assessment he had inflammatory arthritis including bilateral synovitis of his knees and hands. No crystals were seen in the inflammatory synovial fluid. He had a focal erosion at the left ulnar styloid and mild degenerative changes on radiographs. His rheumatoid factor (RF) was weakly positive (37; reference range < 35 is negative). He was treated with a course of prednisone, and then ongoing nonsteroidal antiinflammatory drugs, hydroxychlorquine, and methotrexate, and his RA went into remission in 1997. His prostate cancer continued to be active. He experienced a relapse of RA, where he developed effusions on the suprapatellar bursa and on the medial aspect of the patella of the left knee, and then inflammatory arthritis of the knees and

small hand joints following anti-androgen treatment with bicalutamide (Casodex) (nonsteroidal, competitively inhibiting androgens by binding to androgen receptors in target tissue) in 2000. His PSA remains elevated, and his inflammatory arthritis continues.

Case 2. A 63-year-old man presented in October 1999. He had 3 months of swelling, pain, and stiffness of the second and third metacarpophalangeal (MCP) joints bilaterally, of sudden onset. He was taking leuprolide acetate (gonadotropin releasing hormone analog, suppressing androgens) started one year before, at time of diagnosis for his prostate carcinoma). Other prostate carcinoma treatment included lymph node resection, radiation, and cryosurgery. He denied any joint symptoms prior to his prostate carcinoma diagnosis and treatment. He has persistent synovitis of the first 3 MCP bilaterally, some proximal interphalangeal (PIP) joints, and the wrists. Radiographs revealed no calcium pyrophosphate dihydrate crystals, and the third right MCP had an early erosion. He was given hydroxychloroquine, without improvement, and then switched to sulfasalazine with some benefit. Routine laboratory investigations including complete blood count, erythrocyte sedimentation rate (ESR), albumin, calcium, gammaglobulins, and transferrin saturation have been normal except for a slightly elevated alkaline phosphatase. His PSA tests have all been normal since starting leuprolide acetate. His RF is negative.

Case 3. A 70-year-old man presented in May 2000. He had prostate carcinoma in 1997 with bone metastases treated by prostatectomy, radiation, and ongoing leuprolide acetate (started 8 months before his presentation in May). He presented with a 6 month history of prolonged hand stiffness and pain. He had symmetrical synovitis of MCP and PIP. RF was negative, whereas the antinuclear antibody (ANA) was positive at 1/320 (speckled) and ESR was elevated (42 mm/h), and extractable nuclear antigens and anti-DNA were negative. Radiographs showed no erosions. He was diagnosed with RA and started taking hydroxychloroquine. His PSA remains elevated.

Observations for all 3 patients are summarized in Table 1.

DISCUSSION

The annual incidence of RA, as determined by a report from Olmsted County, Minnesota, USA, is 58 per 10,000[5] in men and women, being less in men, and the annual incidence of prostate carcinoma in men is 85 per 10,000[6]. Thus, the 2 events could rarely occur closely temporally. However, we have 94 men of various ages with RA in our practice, and if we estimated the number expected to have prostate carcinoma, it would be 0.8 (< 1% of this age group), if no other association were present. Thus, this association seems increased, as we have 3 men with carcinoma, but could be coincidental. In a cohort of 3 men with prostate cancer, the expected incidence per year of developing RA would be 0.0174. Since the men in our cohort developed their RA symptoms over one to 3 years, we could expect the incidence of RA among these men to be 0.052. As the observed 3 men all had developed RA, we conclude that although both diseases may be relatively common, the close incidence of the 2 conditions should be rare and is increased in our cohort.

RA is slightly more common in women than in men. Hormonal influences have been speculated to increase the risk of RA in women, but this has not been proven. We observed 3 men with prostate cancer who have developed RA after starting anti-androgen treatment. These men meet the American College of Rheumatology diagnostic criteria for RA[7]. The RA seems to be temporally related to the hormone treatment within 2 to several months after adding hormonal manipulation, and is not associated with onset or worsening of the prostate cancer. In one patient the RA has worsened despite a negative PSA.

It is possible that the men may have been misclassified and have other inflammatory arthritis. They were RF negative (at least 2 of 3). A Canadian study indicated that RA

Table 1. Characteristics of RA found in men who had received anti-androgen treatment for prostate cancer.

Case	Prostate Carcinoma at Age	Anti-androgen Therapy Prior to RA Symptoms	RF	PsA	1st Year Seen by Rheumatology	Diagnosis	Radiograph Results	Therapy
1	63 (1992)	Cyproterone acetate started Fall 1994, then onset after 1 mo	37 (weakly positive); ANA not done	Elevated	1995	RA, 1995	Erosion	Prednisone, NSAID, HCQ, MTX. Remission 1997, and relapse late 2000
2	63 (1999)	Leuprolide acetate started 9 mo prior (PSA negative when diagnosed with RA)	RF negative; ANA not done	Normal	1999	RA, 1999	Periarticular osteopenia and erosion	NSAID, HCQ, sulfasalazine
3	67 (1997)	Leuprolide acetate started Fall 1999; joint pain began < 2 mo later	RF negative, +ANA 1/320 speckled, ENA negative, anti-DNA negative	Elevated	1999	Probable RA, 2000	Negative	NSAID, HCQ

PsA: prostate-specific antigen, RF: reumatoid factor, ANA: antinuclear antibody, ENA: extractable nuclear antigen, NSAID: nonsteroided antiinflammatory drug, MTX: methotrexate, HCQ: hydroxychloroquine.

with onset at older age is less likely to be seropositive[8]. One of our cases was ANA positive, and ANA was not tested on the other 2. As many as 29% of patients with RA are ANA positive[9]. The 3 men clinically did not have systemic lupus erythematosus (SLE). There is a case report of leuprorelin treatment for a uterine leiomyoma exacerbating lupus nephritis[10]. However, there are no reported cases we are aware of where leuprorelin has been thought to cause SLE. We have not done followup radiographs to determine if our cases have had ongoing erosive disease. Their RA seems mild to moderate, as would be expected in some older onset seronegative men with RA[8].

Testosterone levels (free, total, DHEA) may be decreased in men with RA. This is supported by animal and positive human studies, which outweigh the negative studies. Low concentrations of testosterone in RA are not found consistently. In 2 case control studies, men with RA had lower free testosterone than men without RA[11,12]. Another case control study of RA, ankylosing spondylitis, and healthy men revealed that patients with RA had the lowest mean androgen level of the 3 groups[13]. Martens, *et al* reported that men with RA not taking prednisone had increased follicle stimulating hormone (FSH) and luteinizing hormone (LH), while men with RA taking prednisone had decreased testosterone and slightly increased FSH and LH[14]. Even women with RA had lower androgen levels than healthy women[15]. Lower DHEA and testosterone occurred with increased inflammation in both men and women with RA[16]. Animal data have shown that androgens decrease immunoreactivity and cartilage responses to inflammation[17], and with orchidectomies in these animals there was increased cartilage damage that was reversed when androgens were replaced[18]. It has been postulated that RA develops as a consequence of a deficiency of both adrenal and gonadal steroid hormone production[19]. We are unaware, however, of reports in men with RA with orchidectomies (prior to our case series) or men with testosterone receptor problems such as those with testicular feminization syndrome. Reports of normal concentrations of testosterone in RA include a case control study in women and their siblings discordant for RA. It was thought that decreased DHEAS may be an effect of RA, not a cause[20]. In addition, another study of patients with RA and population controls showed no differences, with the same average testosterone and DHEAS levels[21].

There are also data that testosterone treatment may help RA, but the unblinded study was very small. In an uncontrolled case series, 7 men with RA were given oral testosterone, which improved the number of swollen joints and decreased the RF titer[22]. However, in a randomized trial in 35 men with RA, testosterone treatment did not help their signs or symptoms of RA[23]. Both studies are too small to draw any meaningful conclusions.

Immune cells, including synovial macrophages, may be steroid sensitive, responding to sex steroids, which could suggest a plausible mechanism of action when testosterone is suddenly lowered in men with prostate cancer[24]. Kawasaki, *et al* described shorter CAG repeats in the androgen receptor gene, presenting high levels of transactivation activity in men with onset of RA at a younger age[25]. This suggests that androgens may play a role as a modulating factor. Mutations of the androgen receptor can be associated with prostate carcinoma, but also with male infertility and RA[26].

We recognize that there are many limitations to this study, including the small sample size (n = 3), the absence of controls (making it difficult to rule out possible confounding factors), and the controversial previous reports of low androgens in patients with RA; and as both prostate carcinoma and RA are relatively common diseases, the 2 may be spuriously associated. However, the close timing of incident anti-androgen treatment for prostate carcinoma and the onset of new RA can lead to speculating a cause and effect relationship.

We postulate that men who have received anti-androgen treatment for prostate carcinoma may be at increased risk for the subsequent development of RA, although the relationship between the 2 diseases is not paraneoplastic, and may be related to anti-androgen effects on the immune system. Investigations in basic science and epidemiology are necessary to confirm this observation.

REFERENCES

1. Serre H, Simon L, Roques JM. Seropositive rheumatoid polyarthritis associated with a pulmonary hypertrophic osteoarthropathy during metastases of a prostatic cancer. Rev Rhum Mal Osteoartic 1968;35:134-8.
2. Subramonian K, Sundaram SK, MacDonald Hull SP. Carcinoma of the prostate associatated with dermatomyositis. BJU Int 2000;86:401-2.
3. Stevens H, Hickling P, Tyrrell CJ, Hammonds JC. Reiter's syndrome after radiotherapy for prostatic carcinoma. Br J Rheumatol 1986;25:417-8.
4. Van den Bergh L, Vanneste SB, Knockaert DC. Palmar fasciitis and arthritis associated with cancer of the prostate. Acta Clin Belg 1991;46:106-10.
5. Linos A, Worthington JW, O'Fallon WM, Kurland LT. The epidemiology of rheumatoid arthritis in Rochester, Minnesota: a study of incidence, prevalence and mortality. Am J Epidemiol 1980;111:87-98.
6. Cooper GS, Yuan Z, Jethva RN, Rimm AA. Determination of county-level prostate carcinoma incidence and detection rates with medicare claims data. Cancer 2001;92:102-9.
7. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
8. Terkeltaub R, Esdaile J, Decary F, Tannenbaum H. A clinical study of older age rheumatoid arthritis with comparison to a younger onset group. J Rheumatol 1983;10:418-24.
9. Charles PJ, Smeenk RJ, De Jong J, Feldmann M, Maini RN. Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trials. Arthritis Rheum 2000;43:2383-90.

10. Metcalfe W, Boulton-Jones JM. Exacerbation of lupus nephritis in association with leuprorelin injection for uterine leiomyoma. Nephrol Dial Transplant 1997;12:1699-700.
11. Spector TD, Perry LA, Tubb G, Silman AJ, Huskisson EC. Low free testosterone levels in rheumatoid arthritis. Ann Rheum Dis 1988;47:65-8.
12. Cutolo M, Balleari E, Giusti M, Monachesi M, Accardo S. Sex hormone status of male patients with rheumatoid arthritis: evidence of low serum concentrations of testosterone at baseline and after human chorionic gonadotropin stimulation. Arthritis Rheum 1988;31:1314-7.
13. Spector TD, Ollier W, Perry LA, Silman AJ, Thompson PW, Edwards A. Free and serum testosterone levels in 276 males: a comparative study of rheumatoid arthritis, ankylosing spondylitis and healthy controls. Clin Rheumatol 1989;8:37-41.
14. Martens HF, Sheets PK, Tenover JS, Dugowson CE, Bremner WJ, Starkebaum G. Decreased testosterone levels in men with rheumatoid arthritis: effect of low dose prednisone therapy. J Rheumatol 1994;21:1427-31.
15. Cutolo M, Foppiani L, Prete C, et al. Hypothalamic-pituitary-adrenocortical axis function in premenopausal women with rheumatoid arthritis not treated with glucocorticoids. J Rheumatol 1999;26:282-8.
16. Kanik KS, Chrousos GP, Schumacher HR, Crane ML, Yarboro CH, Wilder RL. Adrenocorticotropin, glucocorticoid, and androgen secretion in patients with new onset synovitis/rheumatoid arthritis: relations with indices of inflammation. J Clin Endocrinol Metab 2000;85:1461-6.
17. Masi AT, Da Silva JA, Cutolo M. Perturbations of hypothalamic-pituitary-gonadal axis and adrenal androgen functions in rheumatoid arthritis. Baillieres Clin Rheumatol 1996;10:295-332.
18. Da Silva JA, Larbre JP, Spector TD, Perry LA, Scott DL, Willoughby DA. Protective effect of androgens against inflammation induced cartilage degradation in male rodents. Ann Rheum Dis 1993;52:285-91.
19. Wilder RL. Adrenal and gonadal steroid hormone deficiency in pathogenesis of rheumatoid arthritis. J Rheumatol 1996;23 Suppl 44:10-2.
20. Deighton CM, Watson MJ, Walker DJ. Sex hormones in postmenopausal HLA-identical rheumatoid arthritis discordant sibling pairs. J Rheumatol 1992;19:1663-7.
21. Heikkila R, Aho K, Heliovaara M, et al. Serum androgen-anabolic hormones and the risk of rheumatoid arthritis. Ann Rheum Dis 1998;57:281-5.
22. Cutolo M, Balleari E, Giusti M, Intra E, Accardo S. Androgen replacement therapy in male patients with rheumatoid arthritis. Arthritis Rheum 1991;34:1-5.
23. Hall GM, Larbre JP, Spector TD, Perry LA, Da Silva JA. A randomized trial of testosterone therapy in males with rheumatoid arthritis. Br J Rheumatol 1996;35:568-73.
24. Castagnetta L, Cutolo M, Granata OM, Di Falco M, Bellavia V, Carruba G. Endocrine end-points in rheumatoid arthritis. Ann NY Acad Sci 1999;876:180-92.
25. Kawasaki T, Ushiyama T, Ueyama H, et al. Polymorphic CAG repeats of the androgen receptor gene and rheumatoid arthritis. Ann Rheum Dis 1999;58:500-2.
26. Yong EL, Lim J, Qi W, Ong V, Mifsud A. Molecular basis of androgen receptor diseases. Ann Med 2000;32:15-22.