CONNECTIVE TISSUE DISEASE AND CARCINOMA OF THE PROSTATE TREATED WITH ESTROGENS

A Preliminary Report

ARTHUR L. SCHERBEL, M.D.
Department of Rheumatic Disease

IN reviewing the reports of coexistence of malignancy and a collagen disease, dermatomyositis and a form of arthritis clinically indistinguishable from rheumatoid arthritis are most frequently mentioned.[1] The typical triad of hypertrophic (pulmonary) osteoarthropathy characterized by clubbing of the digits, periostitis, and synovitis occurring in middle life, is well recognized as heralding the onset of a serious visceral disorder, frequently a peripheral bronchogenic carcinoma.[2]

Various neoplasms may coexist with dermatomyositis or arthritis of the rheumatoid type; these include carcinoma arising from the lung, stomach, breast, ovary, colon, and pleura. Other types of neoplastic disorders, such as Hodgkin's disease, multiple myeloma, and reticuloendotheliosis, have been reported[1] to be associated with one of the connective tissue diseases. It is well known that removal of the tumor often results in rapid and permanent improvement of the connective tissue disorder; however, if the primary lesion recurs, there may be reappearance of the connective tissue manifestations.

No report has been found in which carcinoma of the prostate was suspected of being related either to rheumatoid arthritis or to dermatomyositis. In this report, four cases are presented of carcinoma of the prostate gland and rheumatoid arthritis or dermatomyositis. The clinical course of these diseases suggests that a possible relationship exists between the neoplasm and the connective tissue disorders. Moreover, the favorable response to estrogen therapy in these patients is impressive, inasmuch as this form of treatment usually has no significant or lasting effect on rheumatoid arthritis,[3] except possibly on mild nonprogressive arthritis in menopausal women.[4]

Case Reports

Case 1. A 76-year-old man was first examined here because of intermittent swelling, redness, and aching in both wrists and in the dorsum of both hands for two months. He had mild pain in the right shoulder, the ankles, and the knees. During the acute phase, he stated that the pain in the hands was extremely severe and was only partially relieved by narcotics.

Three years before examination here he had acute urinary retention that was treated by a two-stage prostatectomy. One year later a gastric resection was performed after a massive hematemesis; the diagnosis was gastric ulcer. During the past five years, he had lost more than 20 pounds in weight. The only urinary difficulty remaining was a

mild nocturia (one to three times). There was no family history of arthritis or of genitourinary disease. The patient's mother died at age 51 years, of cancer of the stomach. There was no personal or family history of allergy.

At physical examination, the patient appeared gaunt and chronically ill. He weighed 128 pounds and his height was 68½ inches. There was moderate edema of the lower legs and feet. The interphalangeal joints of both hands were enlarged and the wrists were swollen, tender, and limited in motion. Digital examination of the prostate gland, revealed grade 1 enlargement, and a hard, nodular, fixed gland, which was confirmed by Dr. William J. Engel, Department of Urology.

Roentgenograms of the chest revealed slight left ventricular enlargement of the heart and bilateral emphysema. Roentgenograms of the pelvis showed evidence of osteoarthritis of the spine but not of metastatic bone lesions or calcifications in the prostatic area. There was some demineralization of the bones of the left wrist. Examination of the esophagus and stomach revealed good function of the gastric stoma. Results of intravenous urography were normal.

Laboratory studies showed an elevated erythrocyte sedimentation rate (0.95 mm. per minute by the Rourke-Ernstene method), and high concentration of serum acid phosphatase, 1.3 Bodansky units. Urinalysis, blood-urea, blood-sugar, serum-protein values and the albumin-globulin ratio were normal. Serum glycoprotein concentration (Shetlar) was high, 186 mg. per 100 ml. There was no free hydrochloric acid in the gastric fluid after histamine. The serologic test for syphilis was negative.

Stilbestrol, 1 mg. four times daily, was advised, and the patient returned home. Four weeks later it was observed that the joint manifestations had greatly improved. Thereafter he was examined monthly for five months, during which time the prostate became definitely smaller and softer on palpation. The serum gylcoprotein content was reduced to 142 mg. per 100 ml. and subsequently it dropped to 132 mg. His last examination here was six months after the first one, at which time he was asymptomatic; the dosage of stilbestrol was then reduced to 1 mg. three times daily. Two years later the patient's local physician reported that the patient was still receiving estrogen therapy and was asymptomatic. The following year, urinary symptoms recurred, complicated by metastasis to bone from the prostatic neoplasm. Joint manifestations recurred and persisted until the patient's death four months later.

Comment. In this elderly patient, the simultaneous improvement in joint manifestations and decrease in firmness and nodularity of the prostate were thought to be significant after the oral administration of stilbesterol. Two years later a second patient (case 2) was observed and it was decided to try intravenous estrogen therapy to find out whether or not joint manifestations would disappear even more rapidly than they did in the first patient.

Case 2. A 70-year-old man was examined because of migratory polyarthritis involving the knees, hips, shoulders, and metacarpophalangeal joints in both hands, which had been present for about a year. During the past three months, joint symptoms has been more severe, and during the past month, there had been a temperature elevation ranging from 99 to 100 F. He had received treatment with Butazolidin* (100 mg. four times daily) and hydrocortisone injections into the larger joints.

**Butazolidin (brand of phenylbutazone), Geigy Pharmaceuticals.*

At physical examination the patient appeared chronically ill, uncomfortable, and emotionally unstable. Blood pressure was 150/70 mm. of Hg. There was no evidence of disease in the lungs, heart, or peripheral vessels. The liver, spleen, and kidneys were not palpable. There were pain and restriction of motion in both shoulders, hips, and pain in both elbows. Metacarpophalangeal and interphalangeal joints and the knees were swollen and painful. The results of a neurologic examination were negative.

There was grade 2 enlargement of the prostate, which was moderately firm, but not hard or fixed; there were no palpable nodules. At the time of the initial examination the prostatic enlargement was thought not to be due to carcinoma, but a subsequent needle biopsy of the prostate revealed a well-differentiated adenocarcinoma, grade 2.

Urinalysis showed nothing abnormal. The hemoglobin was 10.4 gm. per 100 ml.; cell volume was 38 ml. per 100 ml. of blood. A leukocyte count was 10,000 per cu. mm., with 83 per cent neutrophils, 12 per cent lymphocytes, and 5 per cent monocytes. The serum acid phosphatase concentration was 2.66 Bodansky units. The serum protein value was 6.8 gm. per 100 ml.; serum albumin, 3.3 gm.; and serum globulin, 3.5 gm. per 100 ml. Erythrocyte sedimentation rate was 1.35 mm. per minute (Rourke-Ernstene).

The patient was given 1.0 gm. of Stilphostrol*, diluted in 1 liter of physiologic saline solution, intravenously daily for 10 days. Significant improvement manifested by disappearance of joint swelling and tenderness was noted by the fifth day. He was discharged from the hospital on the fourteenth day, at which time he had only minor aches and pains. Morning stiffness lessened from three hours to less than one-half hour at the time of discharge from the hospital. Continued therapy consisted of stilbestrol, 5 mg. daily, by mouth. A month later, joints were completely asymptomatic and joint stiffness had disappeared. At examination 10 months after discharge, general improvement was reflected in the results of laboratory tests: hemoglobin was increased to 13 gm. per 100 ml., cell volume to 44 ml. per kilogram of body weight, and the leukocyte count was reduced to 7,600 per cu. mm.

Comment. This patient has been re-examined every six months for five years, and the joints have remained entirely asymptomatic. The dosage of stilbestrol has been decreased to 1 mg. daily.

Case 3. A 70-year-old man was examined because of acute diffuse muscular aching and hot painful swelling in the metacarpophalangeal joints, which appeared three days previously. Two years and eight months before onset of joint manifestations a carcinoma of the prostate gland had been diagnosed with confirmation from specimens of a needle biopsy. During the subsequent 32 months, he had been treated with stilbestrol, 5 mg. twice daily, by mouth, and he became asymptomatic. Six months before the onset of the present musculoskeletal symptoms, he had an episode of urinary bleeding. Cystoscopy was performed at that time, and a low-grade cystitis and bleeding from prostatic varices were found. Since the hemorrhagic episode he had nocturia (two or three times). His personal history and his family history were negative for arthritis and for genitourinary disorders.

Physical examination showed swelling and painful limitation of motion in the metacarpophalangeal joints and in the ankles and knees. On digital examination, the prostate was stony hard and had poorly defined, irregular borders. Laboratory tests

**Stilphostrol (diethylstilbestrol diphosphate), Ames Co., Inc.*

disclosed that the hemoglobin was 10.8 gm. per 100 ml.; erythrocyte volume was 35 ml. per 100 ml.; leukocyte count was 4,800 per cu. mm., with 62 per cent lymphocytes (none immature), 33 per cent segmented neutrophils, 4 per cent eosinophils, and 1 per cent monocytes. Results of a latex fixation test were negative. The serum uric acid value was normal, as was the serum acid phosphatase, 0.6 Bodansky unit. The erythrocyte sedimentation rate was normal (Rourke-Ernstene method). Other laboratory findings, including the blood-urea and blood-sugar concentrations, and Wassermann and Kahn reactions, were normal.

Stilphostrol, 0.5 gm. diluted in 1 liter of physiologic saline solution, was administered intravenously daily for 10 days. After seven days there was complete clearing of joint symptoms, but morning stiffness lasting four hours persisted. The dosage of stilbestrol was increased to 5 mg. three times daily, taken orally, for maintenance therapy, and after one month the musculoskeletal symptoms had subsided completely.

Because of the persistence of anemia and of the abnormal leukocyte count, the bone marrow was examined five months later; it revealed evidence suggestive of a chronic monocytic leukemia (leukemic reticuloendotheliosis). Although stilbestrol was continued and the arthritic and prostatic symptoms did not recur, the patient died 18 months after the onset of joint symptoms, as a result of the progression of the leukemic process to an acute myelogenous form.

Comment. This patient is believed to be similar to those already described (cases 1 and 2) except for minor variations. Prostatic carcinoma was known to be present for 32 months (during which time the patient was treated with stilbestrol orally, 5 mg. twice daily). It is believed that the dosage was inadequate prior to the onset of joint manifestations, which disappeared rapidly after intravenous estrogen therapy.

Case 4. A 55-year-old man was first examined because of symptoms of about three months' duration: weakness of the arms and shoulders, and dermatitis of the face and anterior portion of the chest. Dermatomyositis had been previously diagnosed. The patient stated that he had had no cardiovascular, genitourinary, or gastrointestinal symptoms. His personal and family history were negative for rheumatoid arthritis and related disorders.

The patient was overweight: his height was 67½ inches and he weighed 200 pounds. The blood pressure initially was 160/110 mm. of Hg. There was severe weakness, and tenderness of the muscles of both shoulder girdles, winging of the scapulas, and weakness in both upper arms. He was unable to raise his arms above the shoulders. The thigh and gluteal muscles were also weak. Nonpitting edema was present over the forehead, the eyelids, and the zygomatic areas of the face. A deep-red, papular and papulopustular eruption resembling rosacea was on the face, and a deep-red, poikiloderma-like change was over the anterior part of the chest. Dull-red macules, and small, dry, rough plaques were on the dorsa of the hands and fingers. There was deep pitting edema of the lower legs and ankles. A mass of small lymph nodes was palpated in the left supraclavicular area. On digital rectal examination the prostate gland was firm but not fixed or nodular.

Biopsy study of a supraclavicular lymph node revealed adenocarcinoma, grade 3. A specimen of a needle biopsy of the prostate gland showed a similar adenocarcinomatous change. A biopsy specimen of muscle disclosed chronic myositis (compatible with

dermatomyositis) with edema, dense perivascular and interstitial infiltration of lymphocytes and plasma cells, piling up of nuclei of muscle fibers, and perivascular fibrosis. Some of the muscle fibers were pale and swollen, with diminished striation; other fibers were smaller than normal and were vesiculated. A biopsy specimen of skin from the left hand showed: hyperkeratosis and liquefaction degeneration of the basal layer, edema of the upper corium, and infiltration of lymphocytes and eosinophils in the mid-corium. Dermal appendages were surrounded by a similar infiltrate. Roentgenograms of the chest, the entire gastrointestinal tract, and the pelvis, revealed no evidence of neoplasm.

The serum protein determination (Tiselius method) showed: albumin, 1.99 gm.; alpha-1-globulin, 0.40 gm.; alpha-2-globulin, 0.53 gm.; beta-globulin, 0.75 gm.; gamma-globulin, 0.34 gm., and fibrinogen, 0.32 gm. per 100 ml. The serum transaminase (SGOT) values ranged from 20 to 75 units. The serum alkaline and acid phosphatase, blood-sugar and blood-urea values, routine urinalyses and Wassermann and Kahn reactions were normal. Several erythrocyte sedimentation rates were high, as were repeated serum glycoprotein determinations. The hemoglobin was 9.7 gm. per 100 ml. with normal total and differential leukocyte counts. The 24-hour creatine excretion was 0.224 gm., and the creatinine excretion was 1.49 gm.; several times similar results were obtained.

Stilphostrol was administered intravenously, and the initial course of a total dose of 7 gm. given within 10 days brought about dramatic improvement with decreased edema, increased strength, and clearing of the skin lesions. Oral therapy with 10 mg. per day of stilbestrol was started. One month later when the patient returned for evaluation, he appeared to be in relapse. He was readmitted to the hospital for a second course of intravenous estrogen therapy; this time he received a total dose of 5 gm. in 10 days, again with good subjective and objective responses. Because large doses of estrogens only partially controlled the disease, prednisone, 2.5 mg. three times daily, was added to the regimen. During the next three months he gradually regained strength and the skin lesions cleared completely. Chloroquine phosphate* was started; the dosage of prednisone was reduced to 1 mg. three times daily; and estrogen maintenance therapy was continued. Improvement continued, and the patient returned to work about one year after therapy was started, and then was lost to follow-up.

Comment. This is an unusual case because carcinoma of the prostate is associated with dermatomyositis. The response to intravenous estrogen therapy was similar to that of patients with rheumatoid arthritis associated with carcinoma of the prostate.

Treatment and Results

Estrogen therapy was used for all patients. Three of the four patients were followed for from two to five years; one was observed for two years, and then was lost to follow-up. One patient (case 1) received estrogen only by mouth; one (case 3) who was already receiving estrogen when first examined was given additional intravenous estrogen therapy (Stilphostrol); and two patients (cases 2 and 4) received intravenous estrogen therapy (0.5 to 1.0 gm. daily for 10 days), followed by stilbestrol orally, 5 mg. daily. In the one patient who received only oral therapy, significant improvement occurred after four to six weeks. Improve-

**Aralen phosphate (chloroquine phosphate), Winthrop Laboratories.*

ment was more rapid in the two patients who received estrogen intravenously, with significant change occurring between the seventh and twelfth days after beginning the treatment. One patient (case 4) required an additional course of estrogen intravenously before significant improvement persisted.

The erythrocyte sedimentation rate was increased in each patient, and serum protein alterations were manifested by decreased serum albumin and increased serum globulin values. In all patients serum glycoprotein values (Shetlar) were elevated and returned to normal after therapy. Two patients were examined before the latex fixation test was available; in the other two patients the test was negative. In two patients, the acid phosphatase values were high before treatment and returned to normal after estrogen therapy. One patient (case 3) had been receiving stilbestrol orally for more than two years, when first examined here, and his acid phosphatase value was normal. The patient with dermatomyositis (case 4) also had a normal acid phosphatase value, despite distant metastasis to cervical lymph nodes.

In order to evaluate further the effect of Stilphostrol therapy in patients with rheumatoid arthritis, a comparable group of five men and four women with active rheumatoid arthritis (stage I or stage II), whose functional capacity ranged between 1 and 3, were hospitalized to receive intravenously Stilphostrol, 0.5 to 1.0 gm., in 1 liter of 5 per cent dextrose daily for 10 days. During the second week of therapy, mild, temporary improvement manifested by lessening of pain, of swelling, and of inflammation of joints occurred in two men and in one woman, but in no instance was improvement as impressive or as permanent as it was in the patients with neoplasm of the prostate. For this reason, it is believed that intravenously administered estrogen does not exert a significant or selective antirheumatic effect in patients with rheumatoid arthritis.

Discussion

Carcinoma of the prostate is a common disease in men of advanced age. In a reported autopsy series,[5] histologically demonstrable prostatic carcinoma was present in 12.5 per cent in the 50 to 60 year age group, and in 33.1 per cent of those in the 80-year age group. However, clinical diagnosis of prostatic carcinoma was made in only one sixteenth of the cases, and clinical evidence of metastasis was present in only one third of the cases that were correctly diagnosed before death. On the other hand, it is well recognized that rheumatoid arthritis usually appears relatively early in life and in only about 10 per cent of the patients for the first time after the sixth decade.

All four patients had symptoms that suggested urinary obstruction; in addition, one patient previously had a transurethral resection for obstructive symptoms and one had an infection of the urinary tract when he was first examined at the Clinic. On palpation the prostate was typical of neoplasm in only two of the four patients; those glands were firm, fixed to surrounding tissue, and nodular. In one

patient (case 2), the gland was moderately firm only along the left lateral border, and study of a specimen of a needle biopsy was necessary for diagnosis. The prostate gland of the patient with severe dermatomyositis (case 4) was normal to palpation at the time of the initial examination, but enlarged cervical lymph nodes revealed metastatic carcinoma suggestive of prostatic neoplasm, and a subsequent specimen of a needle biopsy of the prostate gland confirmed the diagnosis.

It is possible that these patients with musculoskeletal symptoms had two unrelated diseases that developed simultaneously, but this appears unlikely for several reasons. No patient had a family history of rheumatoid disease. Musculoskeletal manifestations appeared for the first time relatively late in life, usually shortly after the onset of the urinary symptoms; and furthermore, therapy administered primarily to control the prostatic neoplasm resulted in great improvement or in disappearance of muscular and joint symptoms along with shrinking and softening of the neoplasm.

In each patient musculoskeletal manifestations were moderately severe and progressive. Joint disturbances in three patients (cases 1-3) were clinically indistinguishable from those of typical progressive rheumatoid arthritis. However, in one patient (case 3), there was roentgen evidence of periosteal involvement of the long bones; this suggested hypertrophic osteoarthropathy. In no patient was there clubbing of the fingers. The patient with dermatomyositis (case 4) had severely progressive disease that was unresponsive to previous corticosteroid therapy; subsequently intravenous estrogen therapy resulted in significant improvement.

The mechanism of the uniform clinical improvement with respect to the musculoskeletal manifestations in these patients is not understood. In the past, numerous chemical agents have been recommended in the treatment of rheumatoid arthritis, but no agent is consistently effective for long periods, especially when the disease is progressive.[6]

It has been reported[7] that stilbestrol is an effective cytotoxic agent. It is possible that the intravenous administration of Stilphostrol exerts a nonspecific toxic effect on certain mesenchymal cells in patients with connective tissue disorders, which is independent of the estrogenic properties of the hormone.

Carcinoma arising from prostatic epithelium is more or less dependent for its growth on androgenic hormones, but the exact mechanism by which estrogens suppress prostatic carcinoma is not understood. There may be a direct action on prostatic tissue, or the benefits may be derived from the inhibition of pituitary production of gonadotropins in the intact patient. However, evidence has been presented[8] suggesting that the pituitary-testis-adrenal mechanism is not a factor since improvement has occurred in patients who have had both orchiectomy and adrenalectomy.

In those patients who exhibited significant improvement in musculoskeletal manifestations after estrogen therapy, changes also occurred in the prostatic neo-

plasm as manifested by a decrease in size, disappearance of nodules and softening of the prostate gland. Moreover, it was also observed that recurrence or worsening of musculoskeletal symptoms after a prolonged period of improvement of from one to two years was associated with recurrence and spread of the prostatic neoplasm (case 2). One patient (case 3) had had urinary symptoms and known carcinoma of the prostate for 32 months before the onset of acute polyarthritis. He had been taking stilbestrol orally, 5 mg. daily, since identification of the neoplasm, and urinary symptoms were not apparent when musculoskeletal symptoms appeared. Additional intravenous estrogen therapy with Stilphostrol brought about complete regression of joint pain and swelling during the first week of therapy.

The concept of an immunologic mechanism involving circulating antibody which affects pathogenesis, has led to the search for gamma-globulin in various rheumatic lesions.[9] Recently it was reported[10] that patients with disorders of connective tissue often sustain exaggerated reactions to the biogenic amines, serotonin and histamine, both of which are thought to be important agents in allergic, immunologic, and anaphylactoid disorders. These clinical and experimental observations suggest that rheumatoid arthritis and dermatomyositis may occur as a secondary manifestation or host reaction to carcinoma of the prostate. These diseases are closely similar to the connective tissue diseases that have been reported to occur after other forms of neoplastic disease are evident. Apparently almost any malignant neoplasm is capable of inducing this syndrome, and treatment, whether it be by surgical removal, chemotherapy, or irradiation, if it is effective in suppressing the neoplasm, results in alleviation of the connective tissue reaction. At present, we have under observation several women with carcinoma of the breast and rheumatoid arthritis who are receiving testosterone therapy.

Summary

Three patients who sought treatment for rheumatoid arthritis that began after age 60 years, were found to have carcinoma of the prostate gland. A fourth patient, aged 55 years, in whom the typical clinical and pathologic features of dermatomyositis developed, also had carcinoma of the prostate gland. All four patients received estrogen therapy, and those patients with rheumatoid arthritis and prostatic carcinoma responded with complete disappearance of their rheumatic symptoms; the patient with dermatomyositis responded significantly but incompletely.

References

1. Lansbury, J.: Collagen disease complicating malignancy. Ann. Rheumat. Dis. **12**: 301-305, 1953.

2. Vogl, A.; Blumenfeld, S., and Gutner, L. B.: Diagnostic significance of pulmonary hypertrophic osteoarthropathy. Am. J. Med. **18**: 51-65, 1955.

3. Hellbaum, A. A.; Ishmael, W. K.; Duffy, M. L., and Payne, R. W.: Effect of estrogen, androgen, and thyroid in degenerative joint disease. J. Gerontol. **13**: 163-166, 1958.

4. Ishmael, W. K.: Oral stilbestrol therapy in menopause arthritis. Soc. Proc., J. A. M. A. **117**: 1650, 1941.

5. Birke, G.; Franksson, C., and Plantin, L.-O.: Carcinoma of prostate: clinical and steroid metabolic study. Acta chir. scandinav. **109** (Fasc. 2): 129-149, 1955.

6. Scherbel, A. L.: Rational appoach to treatment of rheumatoid arthritis: introduction. Cleveland Clin. Quart. **24**: 69-70, 1957.

7. Taylor, J. R.: Intravenous and oral trial of stilboestrol diphosphate in prostatic carcinoma. Canad. M. A. J. **80**: 880-882, 1959.

8. Flocks, R. H.; Marberger, H.; Begley, B. J., and Prendergast, L. J.: Prostatic carcinoma: treatment of advanced cases with intravenous diethylstilbestrol diphosphate. J. Urol. **74**: 549-551, 1955.

9. Kaplan, M. H.: Fluorescent antibody technic as research tool in study of connective tissue disease. Arth. & Rheumat. **2**: 568-573, 1959.

10. Scherbel, A. L., and Harrison, J. W.: Response to serotonin and its antagonists in patients with rheumatoid arthritis and related diseases. Angiology **10**: 29-33, 1959.