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Recurrent Cystitis and Bladder Mass in Two Adults with Chronic Granulomatous Disease

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Two men, aged 23 and 20 years, with recurrent episodes of severe cystitis and X-linked chronic granulomatous disease were studied. Ultrasonography showed large discrete bladder masses that mimicked bladder carcinoma in both patients. Urine and bladder biopsy cultures were negative and histopathologic findings were consistent with chronic inflammation. One patient improved with symptomatic therapy on two occasions; the other patient required prolonged intravenous antibiotic therapy before fever and dysuria resolved. The possible mechanisms by which such inflammatory bladder masses might arise are discussed and eight previously reported cases of chronic granulomatous disease with cystitis are reviewed. From this clinical experience, we recommend prolonged antibiotic therapy. In patients who fail to respond to antibiotic therapy, steroids may be cautiously administered.

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Patients with chronic granulomatous disease have recurrent bacterial and fungal infections. Polymorphonuclear leukocytes from these patients do not produce the bactericidal toxic oxygen by-products needed to kill invading pathogens. The commonest sites of recurrent infection are the lungs, skin, lymph nodes, liver, bone, and gastrointestinal tract (1). Genitourinary tract disease has rarely been reported (2-6). Previous cases have been described only in children. We report the cases of two adults with X-linked chronic granulomatous disease who developed severe cystitis and large bladder masses that mimicked bladder carcinoma.

Patient 1

A 23-year-old Dutch man with X-linked chronic granulomatous disease (7) had had intermittent urinary frequency and burning on urination since age 3. Urine cultures taken at ages 3, 4, 8, and 10 were negative. At age 11 he began cotrimoxazole prophylaxis. At age 15 his urinary symptoms worsened. On rectal examination a mass was palpated in the region of the posterior bladder wall. He was afebrile, and urine culture and urinalysis were normal. Treatment with rifampin and

clindamycin was associated with resolution of symptoms and shrinkage of the bladder mass.

Approximately 6 months later symptoms recurred in association with an increase in size of the palpable mass. Administration of rifampin and clindamycin for 4 weeks was again associated with improvement in symptoms; however, 3 months later dysuria and frequency recurred. Ultrasound examination of the bladder showed a 4-cm tissue density mass in the left posterior lateral bladder wall. Rifampin and clindamycin were administered, and over the next 4 weeks his symptoms slowly improved. Repeat ultrasound examination showed a 2-cm bladder mass. Two weeks after discontinuing antibiotic therapy while continuing cotrimoxazole prophylaxis, his symptoms recurred and the bladder mass had again increased on ultrasonography (4 cm in diameter). A voiding cystogram showed a mass in the bladder wall. Cystoscopy showed polypoid lesions in the left bladder mucosa. Histopathologic examination showed only nonspecific inflammation. Urine and biopsy cultures were negative. He was treated symptomatically with a bladder smooth-muscle relaxant (flavoxate hydrochloride), and cotrimoxazole prophylaxis was continued. Over the next 2 months his symptoms resolved and results of repeat bladder ultrasound examination were normal. He had no further urinary complaints until age 23 when he presented again with urinary frequency (voiding 20 times per day) and dysuria while taking cotrimoxazole. Rectal examination showed a mass in the region of the posterior bladder wall. He was afebrile and urine cultures were negative. He was again treated with flavoxate hydrochloride. Over the next week urinary frequency improved, and his bladder mass markedly decreased.

Patient 2

A 20-year-old white American man with X-linked chronic granulomatous disease (8) was admitted to the hospital with complaints of burning on urination and urgency associated with increased frequency. Two months before admission he had developed an oral temperature of 37.7 °C associated with burning on urination. These symptoms were followed by a sense of urgency and urinary frequency that steadily worsened. The day before admission he was voiding once per hour. Twelve hours before seeing a physician, in addition to his usual prophylactic dicloxacillin (500 mg, twice per day), he began taking cephalixin, 500 mg four times per day. However, low-grade fever and dysuria persisted. Urinalysis showed 10 to 15 erythrocytes and 2 to 8 leukocytes per high-powered field.

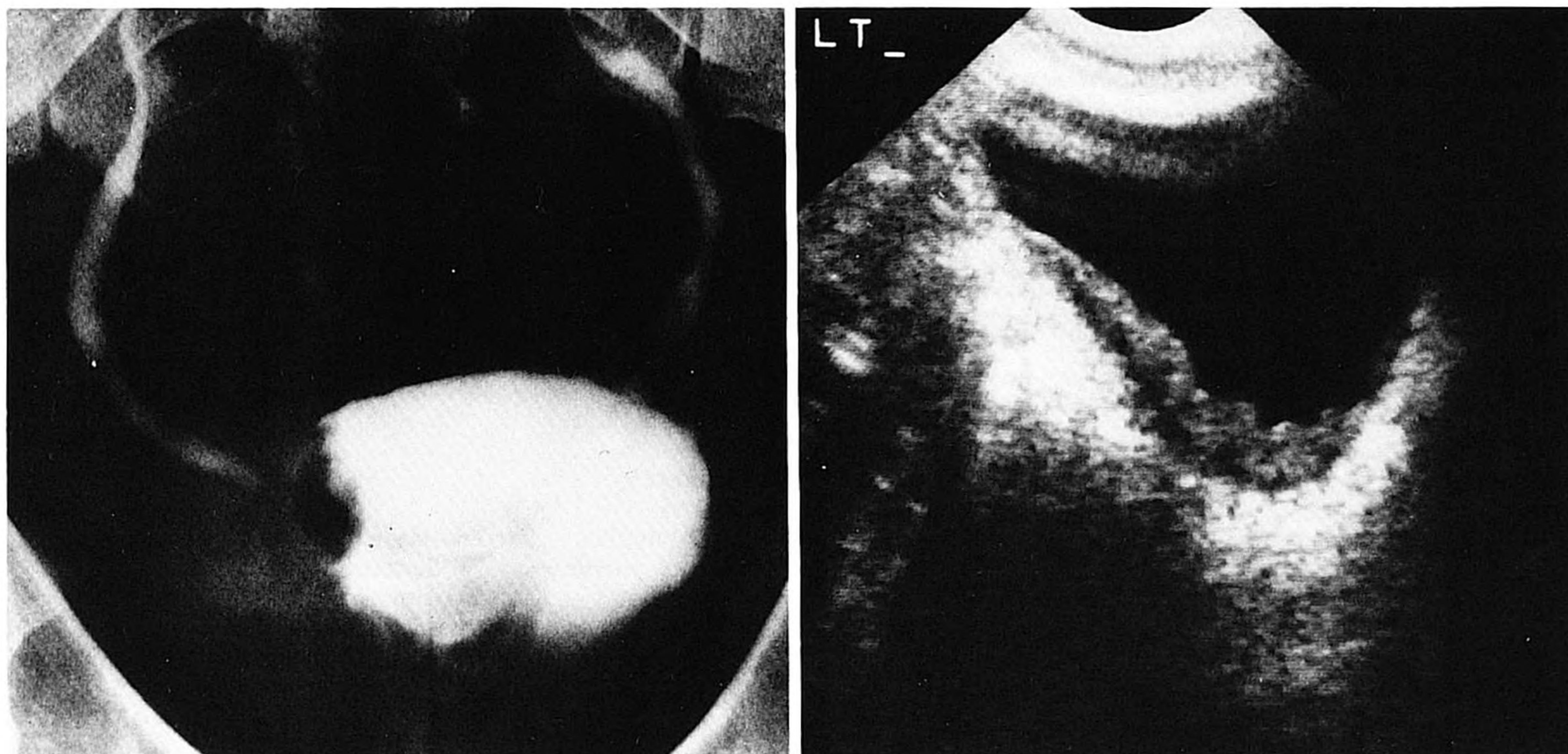


Figure 1 Left. Sagittal view of an intravenous pyelogram, Patient 2, showing a large filling defect in the left side of the bladder. Right. Sagittal view, bladder ultrasound, Patient 2. Marked thickening is seen within the left bladder wall.

Urine culture was negative. Physical examination was normal except for mild suprapubic tenderness. No mass was palpable on rectal examination. Leukocyte count was $7.0 \times 10^9/L$, with 0.12 eosinophils, and erythrocyte sedimentation rate was 11 mm/h. He was switched to tetracycline therapy, 250 mg four times per day and later 500 mg four times per day with resolution of his fever and symptoms. After 5.5 weeks of therapy tetracycline was discontinued. Two weeks later dysuria and frequency recurred. Urinalysis showed no leukocytes or erythrocytes, and urine culture was negative. An intravenous pyelogram showed a large filling defect in the left bladder wall (Figure 1, left). Ultrasound examination showed edema and marked thickening of the same region of the bladder wall (Figure 1, right), and cystoscopy showed an inflamed moderately hemorrhagic bladder mucosa. Histopathologic findings were consistent with chronic inflammation and focal areas of necrosis. No granulomas were seen. Bacterial, mycoplasma, fungal, and acid-fast stains were negative as were cultures of tissue and urine. The mass regressed as assessed by ultrasonography, and symptoms improved during 3.5 weeks of treatment with intravenous oxacillin and gentamicin.

Six months after discharge, he presented to the hospital with a temperature of 39.4 °C. On admission he had no urinary complaints and results of bladder ultrasound examination were normal. During his second week of empiric therapy with intravenous cefotaxime and tobramycin he began having urgency and dysuria. Repeat bladder ultrasound examination showed marked edema of the lower bladder wall, and cystoscopy showed mild inflammation with several polypoid lesions. Histopathologic findings were again consistent with mild chronic inflammation. All bacterial, fungal, and acid-fast stains and cultures were negative. He was treated for 2 weeks with intravenous oxacillin and

gentamicin therapy as well as oral aspirin. His symptoms markedly improved and repeat ultrasound examination showed only mild bladder edema. One week after completion of intravenous antibiotic therapy, dysuria and urinary frequency recurred. Ultrasound examination again showed worsening of bladder edema. Treatment with 4 weeks of intravenous vancomycin and gentamicin was associated with resolution of symptoms and abnormalities on bladder ultrasound examination. Over the last 4 years he has had no urinary complaints.

Discussion

Cystitis is an uncommon complication in patients with chronic granulomatous disease. To our knowledge there have been only eight cases previously reported (2-6) (Table 1). Generally, with the exception of Patient 2, the onset of this complication has occurred during childhood, generally between ages 2 and 3. All patients have been male and had the X-linked form of the disease. The presenting symptoms have been dysuria, urgency, and increased frequency. Findings at cystoscopy have included erythema, necrotic ulcerations, and severe edema. Intravenous pyelograms, when done, showed poor bladder distension and irregular bladder wall margins. Our two patients presented with localized areas of bladder edema that mimicked solid tumors. With the exception of two patients who received chronic steroid therapy (3, 4), inflammation was confined to the bladder. We found ultrasonography to be particularly helpful in defining the extent of bladder edema, allowing an objective assessment of response to therapy.

The cause of cystitis in patients with chronic granulomatous disease is unclear. With the exception of one patient in the literature whose biopsy results showed yeast forms (2), histopathologic examinations have

Table 1. *Clinical Summary of Genitourinary Infections in Patients with Chronic Granulomatous Disease*

| Source (Reference) | Sex, Age <i>yrs</i> | Genitourinary Manifestations | Cultures | Biopsy | Treatment | Resolution |
|--------------------|------------------------|---|----------|---|--|---------------|
| (2) | M, 6 | Cystitis; hydronephrosis | ... * | Yeast in bladder wall | ... | ... |
| (3) | M, 2-18 | Cystitis ureteral obstruction; hydronephrosis | Negative | Granuloma; necrosis; eosinophils | Steroids | No |
| (3) | M, 2-16 | Cystitis | ... | ... | ... | No |
| (4) | M, 3-8 | Cystitis; ureteral reflux; hydronephrosis | Negative | Necrotic polymorphonuclear leukocytes surrounded by histiocytes | Steroids | No |
| (5) | M, 2.5 | Cystitis | Negative | Polymorphonuclear leukocytes; edema | trimethoprim-sulfamethoxazole | Yes, 2 weeks |
| (5) | M, 2.5 | Cystitis | ... | ... | trimethoprim-sulfamethoxazole | Yes, promptly |
| (6) | M, 4 | Cystitis; bladder edema | Negative | ... | Antibiotics; steroids | Yes, promptly |
| (6) | M, 10 | Cystitis; bladder edema; hydroureter | Negative | ... | tobramycin; cefamandole; steroids | Yes, 4 weeks |
| Current Study | M, 3-23 | Cystitis; local bladder mass | Negative | Chronic inflammation; edema | trimethoprim-sulfamethoxazole; flavoxate | Yes, 2 weeks |
| Current Study | M, 20 | Cystitis; local bladder mass | Negative | Chronic inflammation; necrosis; edema | vancomycin; gentamicin | Yes, 4 weeks |

* Not described.

shown only findings consistent with acute and chronic inflammation. All cultures of urine and biopsy material were negative. However, absence of growth on culture does not rule out indolent bacterial, mycobacterial, fungal, or mycoplasma infection. Infecting organisms frequently survive within phagocytic chronic granulomatous disease cells, and cannot be readily grown on conventional culture media. Several patients' symptoms and signs did improve after antibiotic therapy (Table 1). Our second patient improved while receiving antibiotic therapy, and after a prolonged course of treatment had no further episodes of cystitis.

A noninfectious mechanism may also contribute to the prolonged clinical course in some patients. The prompt response to steroid therapy in two patients who had failed to improve on prolonged antibiotic therapy supports this possibility (6). In addition, the spontaneous resolution of symptoms and bladder edema in Patient 1 suggests that the later stages of his illness may have been caused by a self-limited, noninfectious, inflammatory process. The absence of oxidative metabolites has been shown to be associated with an abnormally low pH in phagocytic vacuoles (9). This defect could lead to a delayed breakdown of ingested material in chronic granulomatous disease phagocytes and could explain the slow resolution of the bladder masses in our patients. It has been suggested that amantadine, which raises intralysosomal pH, may correct this abnormality and speed recovery (10). Deficiency of oxidative metabolites may also lead to defective inactivation of chemotactic factors that in turn could cause persistent inflammation (11). Finally con-

tinued inflammation could be caused by indolent infection, and spontaneous recovery could be due to gradual killing of organisms by chronic granulomatous disease phagocytes using a nonoxidative mechanism (12).

Our own experience and a review of the literature indicate that in most instances bacterial infection is probably the initial cause of cystitis in patients with chronic granulomatous disease. Therefore, we recommend a prolonged course of antibiotics as initial therapy. If symptoms and bladder edema fail to respond to antibiotic therapy, steroids may be added. However, steroids should be administered cautiously because they have been associated with spread of the inflammatory process to the upper urinary tract in at least two patients (3, 4).

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