RENAL TUBERCULOSIS IN CHILDREN

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Kidney tuberculosis is a serious complication during childhood, just as in later life.\(^1\) It is serious because the disease tends to invade and to destroy both kidneys. Figure 1 illustrates the progression of untreated renal tuberculosis and the gradual destruction of the only remaining kidney of one patient, over the course of 10 years. This patient died of uremia just prior to the advent of modern chemotherapy.

The diagnosis of renal tuberculosis is not always easy, because symptoms are often mild, the numbers of leukocytes in the urine may be small and the sedimentation rate is not usually elevated, even when advanced cavitation is present.

Whether or not the disease is to become active in only one kidney, or in both kidneys, is completely unpredictable, as is the rate of progression in the destructive lesions. As a consequence, it is our opinion that every patient from whose urine M. tuberculosis is cultured must be treated with chemotherapy just as if progression of the renal lesion was to be expected.

ANALYSIS OF CASE RECORDS

Incidence

On the Pediatric Urological Service of the Babies Hospital, 23 clinical cases of genitourinary tuberculosis have been seen during the past 14 years. We have continued to see one or two new cases each year, despite the advent of modern anti-tuberculosis chemotherapy. Twelve of the twenty-three patients had obvious destructive, cavitary tuberculosis of one or both of the kidneys, while 11 had a positive urine culture for M. tuberculosis but had no obvious cavities in the kidneys by roentgenograms. This study does not include additional cases with tuberculous lesions of the kidney which were discovered only at necropsy.

There were four additional children with suspected genitourinary tuberculosis which was never proven bacteriologically or by histology. Two of these patients had atypical chromogenic bacilli in cultures of

Presented at the Spring Session of the Academy, April 22, 1958.

the urine. The other two patients had an isolated positive smear of the urine sediment which could not be verified subsequently.

Pathogenesis

The pathogenesis of kidney tuberculosis, according to the excellent works of Medlar, is that of hematogenous dissemination from a pulmonary or other primary lesion into glomerular or cortical arterioles, where tiny caseous tubercles form.

Minimal (Noncavitary) Renal Lesions

If tubercles in the glomeruli do not heal quickly, organisms may spill down the tubule and M. tuberculosis will appear in the urine. Medlar believes strongly that tubercle bacilli never appear in the urine by "filtration" through an intact nephron. His studies indicated that patients who have tubercle bacilli in the urine always have a sloughing renal lesion, however tiny, at that moment. He also believes that similar lesions are probably present in both kidneys, because of the hematogenous nature of the dissemination. Such "minimal" tubercles, without pyelographic changes (Fig. 2), may also occur in the kidney without massive miliary disease. They may follow primary pulmonary tuberculosis, and they were seen in 25% of one group of 5,000 patients who died of pulmonary tuberculosis at Bellevue Hospital. It should be noted that not all of the tiny tubercles progress. Indeed, most of them heal spontaneously. Only 4 to 8% of the original patients go on to form progressive cavitary lesions in the kidney.

Minimal renal lesions (no cavities or pyelographic deformities) were present in 11 of the 23 patients in the present series. Six of these children had a positive urine culture during frank miliary disseminations, which caused the death of one of them, before the advent of chemotherapy. The positive urine cultures in all 10 of the children who received chemotherapy have become negative after long-term treatment.

Moderately Advanced Renal Lesions

Moderately advanced lesions (one cavity) were found in three patients; one underwent nephrectomy and two had the disease arrested by a year of therapy with streptomycin, sodium para-aminosalicylic acid and isoniazid.

Cavities in the kidney form because bacilli which pass down the nephron from the tubercle in the glomerulus may stop in the region of the narrow loop of Henle, causing a group of coalescing tubercles in
the medulla. Such an area may caseate and slough into a calyx, either on or beside the papilla of that pyramid. This will cause a small cavity in the medulla which can be demonstrated by pyelography. Once such a cavity starts, it rarely heals spontaneously. It usually grows larger, destroying the entire lobe and pyramid by caseation. Such an “open cavity,” opening into a calyx, is closely analogous to the “open cavity” in a bronchus, which also rarely heals spontaneously.

One of two courses may next occur: First, the caseous contents of the pyramid may be retained and a large white caseous mass will remain in the kidney, bulging against the renal capsule. This may calcify, leaving a large area of mortar-like material replacing the affected pyramid. Or, second, the caseous contents of that pyramid can slough out, leaving a ragged cavity: the margins have a “moth eaten” pattern easily recognized by the roentgenologist as the diagnostic “hallmark” of tuberculosis.

The disease may then spread to involve the entire pelvis and the linings of other calyces with tuberculous granulations. Multiple foci may start up in several pyramids at the same time, because of the hematogenous pathogenesis. If the disease is localized in only one or two pyramids, the walls of the empty cavities may then contract, causing indentations on the outer surfaces of the kidney to mark the site of the destroyed pyramids. These indentations are helpful to the surgeon who may be seeking to resect the involved portion of the kidney. He finds them at the time of operation by stripping the kidney capsule back and looking for the tell-tale indentations (or the bulging caseous areas).

Far-advanced Renal Lesions

When two or more obvious cavities can be seen by roentgenography, it is our practice to describe the kidney lesion as “far-advanced.” Far-advanced cavitary lesions were found in nine patients, six of whom had one kidney removed. Three of these six had severe bilateral renal lesions. One of them was the girl already mentioned, who died of uremia at 19 years of age before the days of chemotherapy. The other two were treated successfully with chemotherapy.

Of the six patients who underwent nephrectomy, four were cured; two went on to develop active tuberculosis in the remaining kidney. By comparison, in the five
patients with cavitary lesions who were treated with a year of therapy with three antibiotics, the urine cultures all became negative. This group has been followed for only 2 years, however, while the post-nephrectomy group has been followed for 16 years.

It must be noted that there was one child with renal tuberculosis, as well as one child with a prostatic lesion, whose urine cultures became negative spontaneously without any treatment.

One patient with a far-advanced lesion was considered a failure after 1 year of streptomycin and para-aminosalicyclic acid, but subsequently the lesion was arrested by 1 year of isoniazid, streptomycin and para-aminosalicyclic acid. Partial bed rest with bathroom privileges was advised during the chemotherapy.

**Symptoms**

The first genitourinary symptom was dysuria in only 8 of the 23 patients. Pyuria was found accidentally, while the patient was being investigated for other reasons, in five more instances. Tubercle bacilli were grown from urine cultures taken routinely in six patients with miliary tuberculosis. Two other patients were found to have positive urine cultures when the urine was routinely examined in the course of examination for bone tuberculosis. Among the eight patients who had dysuria, two had mild, dull pain in the kidney region, and one had gross hematuria. Six patients had no symptoms despite pyuria (3 to 5 or more leukocytes per high power field).

The age at which first symptoms of genitourinary tuberculosis appeared varied, in the majority starting at ages 5 to 11 years, but several being discovered at ages of 2 to 3 years. One child with positive urine cultures was discovered among those who had had 1 year of isoniazid, by means of a positive tuberculin test as part of a Public Health Service study. A year later this patient developed positive gastric and urinary smears and cultures. One girl, who had an isolated positive smear of the urine at age 4 years, became negative spontaneously and then became positive by culture 12 years later, after which she was treated successfully with modern chemotherapy. In one other child it appeared that a spontaneous arrest of a small tuberculous cavity of the kidney occurred, and still another child appeared to have a spontaneous arrest of prostatic tuberculosis after one kidney and both epididymides had been removed. These latter two children have been followed for 12 and 18 years, respectively, since their surgery.

The time interval between the known pulmonary infection and the diagnosis of destructive (cavitary) renal tuberculosis ranged from 2 months to 4 years in this series (it ranges up to 20 years in adults). Only 6 patients with miliary lesions in the lungs had positive urine cultures during the miliary dissemination. It should be noted that many other children with miliary tuberculosis at this hospital (in the series of Alexander and Damrosch) did not have positive urine cultures, nor did they develop kidney tuberculosis later.

Evidence of previous pulmonary tuberculosis was present in 19 of the 23 patients. Six of these were residuals of old miliary lesions and the remainder were calcified primary lesions, often of considerable extent, with large calcified lymph nodes in the hila measuring 1 to 3 cm in diameter.

**Erythrocyte Sedimentation Rate**

The erythrocyte sedimentation rate was normal (< 20 mm/hr) in seven patients, between 20 and 30 mm/hr in two patients, elevated over 30 mm/hr in seven, and elevated in all patients with bone tuberculosis and miliary tuberculosis. The sedimentation rate fluctuated in an unpredictable manner before the treatment was started, but fell toward normal after chemotherapy or nephrectomy. In those patients whose only active lesions were in the kidneys, it was usually not elevated, suggesting that, as in adults, renal tuberculosis does not usually cause an elevation of the erythrocyte sedimentation rate.
If the disease is allowed to continue its natural course, the organisms spilling down the ureter will infect the walls of the ureter, causing strictures and irregularities. The bladder may eventually be infected, with red areas appearing around the ureteral orifices and on the trigone. Isolated ulcers may form in patches on the bladder wall. The ultimate complication may be contraction of the bladder due to fibrosis throughout the wall, causing disabling urinary frequency and dysuria. Fortunately, in children this complication rarely has time to develop before the disease is detected. In males, the bacilli may eventually invade the prostatic ducts and infect the prostate gland and later descend the ductus deferens to infect the epididymis.

Genital tuberculosis was rare in these children. It was detected as a hard mass in the epididymis at the age of 2 years in 2 out of the 12 male patients. One patient underwent epididectomy in the days prior to chemotherapy, and the other regressed after chemotherapy. Bladder involvement was severe in seven patients, mild in three and absent in five. In six the state of the bladder was unknown, since they (the miliary cases) had no cystoscopy. All seven patients with far advanced renal lesions had extensive cystitis which responded satisfactorily to chemotherapy. No child suffered a contracted bladder. A pink-and-white, dotted effect was often noted on the trigones of the patients with renal tuberculosis which persisted even after the disease was quiescent. This made the trigones stand out brightly when viewed through the cystoscope, due to a maze of tiny dilated vessels on a pale background.

**Sex**

The incidence of genitourinary tuberculosis was about equal between the sexes, 12 males and 11 females. The cases of cavitary and noncavitary disease were equally divided between the sexes, as were the cases with miliary tuberculosis. Bone tuberculosis was much more common in the males, with five of the six definite cases of bone tuberculosis occurring in males and only one definite tuberculosis (of the foot) in a female.

**Bone Tuberculosis**

Bone tuberculosis was present in 8 of the 23 patients, and in 4 of the 12 children who had definite (advanced) renal lesions. The hip was the site of the bone lesion in four cases. There were two cases of tuberculosis of the foot and two additional cases of bursitis which were suspected of being tuberculous but were never proven. It should be noted here that there were no cases of vertebral tuberculosis among these children even though vertebral tuberculosis is the most common osseous lesion among adults.

**Miscellaneous Observations**

Tuberculous adenitis was present in two of the children and may have marked the portal of entry of the disease, even though the majority (19) of the 23 children had an obvious old pulmonary lesion demonstrable by roentgenogram, which was the probable site of entry. There were only two children who had no sign of pulmonary or other extra-renal tuberculosis.

The contact from whom these patients had presumably acquired tuberculosis was unknown in 5 and the remainder of the 23 were exposed to persons with open pulmonary tuberculosis in their own households.

The amount of pyuria was slight (1 to 3 leukocytes per high power field) in half the patients, moderate (5 to 10 leukocytes per high power field) in five, and heavy in six. Pyuria decreased sharply or disappeared after treatment in all but two cases of bilateral “advanced” disease.

The time interval between the known primary pulmonary lesion and the development of pyuria and visible destructive lesions of the kidney was of the magnitude of 2 to 4 years in this series. On the other hand, moderate pyuria (4 to 6 leukocytes per high power field) and positive urine cultures for M. tuberculosis did occur simul-
CONVERSION OF URINE CULTURES
24 MONTHS AFTER START OF CHEMOTHERAPY

ADVANCED RENAL LESIONS

Simultaneously with the detection of a miliary dissemination in several cases, presumably due to blood-borne tubercles in the glomeruli, most of which healed spontaneously. When the urine cultures were positive and a cavity was also demonstrable by roentgenogram, the lesions were obviously older and more advanced and were much more difficult to control by chemotherapy alone.

Only two of this group of patients have died, one of miliary tuberculosis, before the advent of modern chemotherapy, and the other in uremia following nephrectomy because of tuberculous destruction of a solitary kidney. Both of these deaths occurred before the advent of modern chemotherapy.

Our as yet unpublished data make us believe that the organisms in the urine of patients with renal tuberculosis are infectious for others. We keep such patients on “dish-and-linen” precautions until treatment is well along.

Results of Treatment

Six children with advanced, destructive lesions of the kidney had been treated by nephrectomy prior to the days of chemotherapy. Four of these were cured, and the other two were failures in that the disease in the remaining kidney continued to progress. This resulted in the death of one of the patients before the days of modern chemotherapy, whereas the other patient was treated successfully with chemotherapy alone. All four of the patients in whom the disease was arrested by nephrectomy have been followed for 16 years.

Chemotherapy alone has been used in treating 15 patients; 5 of these had advanced (cavitary) kidney lesions and 10 had minimal (noncavitary) lesions. Of the cavitary cases treated with chemotherapy, only one out of the five was a failure on the first course of treatment; this child was then treated successfully by a second course using three drugs. The remaining four patients received triple-drug therapy (streptomycin, sodium para-aminosalicylic acid and isoniazid) and have remained negative ever since treatment was completed. This entire group was treated at least 2 years

Fig. 3. The “triple-drug regimen” (right hand column) was always slightly more effective than any other regimen in all of three groups of patients reviewed by these authors.
before the present report.

Noncavitary (minimal) lesions of kidney tuberculosis were present in 10 patients who were treated with chemotherapy, in all of whom urine cultures have become negative. The regimens used for these 10 patients have not been identical, because some were treated for miliary tuberculosis during the early days of chemotherapy, when it was often the practice to start with three drugs and then discontinue one and finally to go to a single drug for the completion of the year of treatment. In spite of this irregular early treatment these patients have all done well. This conforms to our experience with a larger group of adult patients in whom the patients with minimal renal lesions did very well with less-intensive, combined-drug, chemotherapy than that required for those with the cavitary or destructive lesions.

Chemotherapeutic Regimens

Because of the possibility of late relapse in children with kidney tuberculosis, it is now our practice to treat any patient with a positive urine culture with "triple-drug" therapy for 1 year. We are currently employing: streptomycin, 20 mg/kg, given intramuscularly in a single dose twice weekly; isoniazid, 5 mg/kg/day, in three divided doses; and para-aminosalicylic acid, 6 to 12 gm/day in three divided doses. Far-advanced lesions, or lesions in a solitary kidney, are often treated for a total of 2 or even 3 years, if progress is not satisfactory. Genital lesions are treated with the same triple-drug regimen for a period of 1 year.

At the present time we are testing additional chemotherapeutic agents, which can be given by mouth, in the hope that a substitute for streptomycin can be found. This is desirable to avoid the unpleasantness of injections and also to provide an alternative drug for patients who become allergic to one or more of the other medications. The reason for our preference for the triple-drug regimen is shown in Figures 3 and 4 which show comparisons of various regimens at the 2-year point. This superiority of the triple-drug program, while slight, has been consistent in all three of the series of cases we have had opportunity to examine.

Preoperative Chemotherapy

If one kidney is severely destroyed and is nonfunctional, and a secondary infection develops in it, causing the patient to have fever or pain, it may, in rare instances, become desirable to remove that kidney.

In these cases it is our present practice to give isoniazid and sodium para-aminosalicylic acid for 1 to 4 months preoperatively, and to continue postoperatively for a total of 1 year. In this way it is hoped that the chances of dissemination during operation will be reduced and that any tiny tubercules which may be present in the other "good" kidney will be healed.

SUMMARY

Genitourinary tuberculosis in children is not easily detected because symptoms are usually minimal, the erythrocyte sedimentation rate is not elevated and the number of leukocytes in the urine may be very few even when the renal destruction is far advanced. The disease is serious because it tends to invade and destroy both kidneys if untreated.

Nephrectomy alone failed to arrest the disease in two of six children with cavitary tuberculosis. Chemotherapy with three drugs arrested the disease in all of the five patients with cavitary lesions treated to date. The follow-up of the cases treated by chemotherapy is shorter than that of the nephrectomy cases.

Ten patients with noncavitary kidney tuberculosis have all had negative urine cultures since multiple-drug chemotherapy. Tuberculosis showed a tendency to lie dormant in the kidneys for long periods (up to 12 years) and then become active again.

Although this series is small and the follow-up is short, the results to date parallel those found in our larger experience with chemotherapy in adults with genitourinary tuberculosis. In general, as in adults, modern triple-drug chemotherapy appears to be about as effective, if not more effective, then nephrectomy, as treatment for
SM-INH-PAS
FOR 1 YEAR
RENAL TUBERCULOSIS-ADVANCED

CARES

\[ R_x \]

YEARS

\[ 25 \text{ - } 50 \]

\[ -2 \text{ - } 1 \text{ - } 0 \text{ - } 1 \text{ - } 2 \text{ - } 3 \text{ - } 4 \]

- POSITIVE
- 9 NEGATIVES

Fig. 4. Only two patients (black dots in top two rows) have relapsed at the end of 4 years after treatment with triple-drug therapy. Not all patients in this group have completed 4 years of follow-up.

This potentially bilateral disease.

As a consequence, at the authors' clinic, nephrectomies are currently being deferred indefinitely, due to the apparent success of chemotherapy. Whether chemotherapy will entirely replace excisional therapy for genitourinary tuberculosis is still problematical, but it has certainly greatly enhanced the outlook for patients with this once lethal disease.

ACKNOWLEDGMENT

This study has been supported in part by a grant from the National Tuberculosis Association and by the gracious gifts of some of our former patients. This help and the co-operation of the staffs of the Squier Clinic, the Kingsbridge Veterans Hospital Research Unit and the Babies Hospital are gratefully acknowledged.

REFERENCES
