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## Ureteral obstruction may activate kidney latent tuberculosis. A qualitative study

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### ABSTRACT

**Objectives:** To analyze the hypothesis that ureteral obstruction may activate kidney latent tuberculosis through a qualitative study of Urogenital Tuberculosis patients.

**Methods:** A qualitative study was conducted using semistructured interviews in eight patients with Urogenital Tuberculosis. The progression of the disease from the initial symptoms was characterized through the analysis of the clinical and radiological data. The presence of ureteral obstruction prior to the onset of renal tuberculosis was observed in three patients.

**Results:** Patient 1: A 58-year-old female had five episodes of acute left ureteral lithiasis in two years prior to left kidney tuberculosis. Patient 2: A 55-year-old male patient had a 1.2 cm proximal left ureteral stone and in the following six months, the diagnosis of tuberculosis was made in a nonfunctioning left kidney with ureteral thickening and stenosis. Patient 3: A 47-year-old male patient had a 1.2 cm stone in the proximal right ureter and developed urinary tuberculosis with a nonfunctioning right kidney and a contracted bladder.

**Conclusion:** Kidney tuberculosis may appear in the same kidney that had previously suffered stone ureteral obstruction, which may have created local conditions for the activation of latent foci of renal tuberculosis.

### 1. Introduction

Urogenital tuberculosis (UTB) is one of the most common forms of extrapulmonary tuberculosis and occurs after hematogenous spread of the bacilli from the lung to the bilateral renal parenchyma, prostate and epididymis. For patients who enter the latent phase, the time interval between pulmonary tuberculosis and active clinical UTB can vary from one to more than 40 years [1]. In latent UTB, there are bilateral microscopic granulomas without caseous necrosis in the renal cortex. Reactivation of renal tuberculosis occurs from one of these latent foci and, in almost all cases, in only one kidney. Classically, the reactivation of the renal focus and the onset of the disease occur due to a systemic factor associated with a decrease in immunity, for example, diabetes mellitus, malnutrition, alcoholism or HIV infection [1]. However, the unilateral nature of renal tuberculosis suggests that local factors may also play a role in this activation.

The immune response to infection by *Mycobacterium tuberculosis*

involves the formation of a granuloma that controls the bacilli, spatially limiting the infection, but the bacilli are not eradicated, leading to latent tuberculosis. The reactivation of these foci may be caused by an imbalance between the bacilli and patients' immune response. In addition to the known systemic factors, local factors such as ischemia, surgical manipulation, urinary tract obstruction or local trauma could contribute to the activation of a latent renal focus. In fact, pulmonary miliary tuberculosis can occur after extracorporeal lithotripsy for the treatment of kidney stones [2] or after endoscopic manipulation (passage of a ureteral catheter) [3], showing that local aggression to the renal parenchyma can precipitate the activation and dissemination of bacilli from latent renal foci. There has also been a description of a patient with a nonfunctioning kidney due to obstruction by a stone in the renal pelvis with associated active renal tuberculosis [4]. In this case, we do not know whether the two findings coincided or whether the obstruction precipitated the activation of tuberculosis.

Quantitative studies do not allow the individual observation of the

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evolution of urogenital tuberculosis since symptom onset. In contrast, qualitative studies, based on interviews or document analysis, allow determining the sequence of events and offer the possibility of new discoveries about the pathophysiology of UTB [5]. Our hypothesis is that the presence of urinary tract obstruction leads to the activation of renal tuberculosis. This hypothesis can be initially tested through the evaluation of clinical cases in which these diagnoses occur.

The objective of this study was to conduct a qualitative analysis of patients with UTB and to describe the evolution of the disease by identifying patients in whom there was urinary obstruction prior to ipsilateral renal tuberculosis onset, with the aim of determining whether there is a chronological correspondence between urinary obstruction and UTB.

## 2. Patients and methods

This study was conducted in accordance with the Consolidated Criteria for Reporting Qualitative Research (COREQ) guidelines [5].

The qualitative content analysis study was conducted using semi-structured interviews. The interviews, data collection and analyses were performed by two researchers: 1) urologist (AAB), graduated in 1996, with 20 years of experience in the public and private sectors in the care of patients with urological complaints; and 2) urologist since 2002, PhD in Urology from the University of São Paulo in 2006 and currently Associate Professor at the School of Medicine of the Federal University of Juiz de Fora with experience in clinical care and research of patients with UTB. The interviews were conducted at University Hospital of the Federal University of Juiz de Fora, Brazil, in the urology sector in 2020 and 2021. The sample consisted of all patients diagnosed with UTB and contracted bladder treated in the last 10 years.

The study sample consisted of eight patients, i.e., six men and two women between the ages of 30 and 72 years. For two patients, a definitive diagnosis of UTB was confirmed by a positive urine culture, and for six patients, the diagnosis was confirmed through histology. All subjects had a contracted bladder, characterized by a thickened bladder with a capacity of less than 100 mL, associated with a diagnosis of UTB. This study was approved by the Research Ethics Committee of University Hospital of the Federal University of Juiz de Fora (number 4,418,369). Informed consent was signed by all participants.

The semistructured interviews were conducted between December 2020 and December 2021. The beginning of the interview consisted of the following question: "Describe in detail how the diagnosis of tuberculosis occurred beginning from the day you were well and without symptoms." Subsequently, the interviews were conducted so that the patient and family members could report in detail the clinical evolution of and experiences that occurred between the onset of symptoms and diagnosis of UTB. The interviews were audio-recorded and transcribed in the subsequent weeks, allowing the collected data to be analyzed.

After transcribing the interviews into text, two authors (AAB and AAF) read the transcripts separately. For each patient, the progression of the disease from the initial symptoms was characterized through the analysis of the clinical and radiological evolution of the disease.

In three patients, there was the presence of ureteral stones with ipsilateral urinary obstruction prior to the onset of symptoms and radiological changes associated with UTB. The clinical history of the three patients was assessed by analyzing the available data, characterizing the chronological evolution of symptoms and the laboratory and radiological findings of the urinary tract. When available, the radiological characteristics of the upper urinary tract were compared at two consecutive time points: 1) time of ureteral obstruction due to lithiasis; and 2) time after resolution of the lithiasis and at the time of diagnosis of UTB.

## 3. Results

### 3.1. Patient 1

A 58-year-old female patient sought care from a urologist in February 2010 complaining of persistent left low back pain associated with hematuria for eight months. She had a history of episodes of left renal colic with visible passing of stones, with five episodes in the last two years. Computed tomography of the abdomen revealed ureterohydronephrosis with ureteral dilation up to where the iliac vessels cross, where there was ureteral thinning and a nonfunctioning left kidney (Fig. 1a). At this time, in view of this radiological finding and the history of ureteral stones on the left, the suspected diagnosis was ureteral stricture, and the patient underwent nephrectomy. The histological diagnosis was chronic inflammatory process with extensive necrosis but with negative acid-fast bacilli (AFB) histochemistry. No diagnosis or specific treatment for urinary tuberculosis was initiated at this time. Over the years, the patient developed a contracted bladder (voiding interval of 10 min) and reflux into the remaining right kidney. The definitive diagnosis of UTB was only made in November 2015, based on the presence of granulomatous cystitis on bladder biopsy in addition to the radiological diagnosis of contracted bladder, unilateral nonfunctioning kidney (left nephrectomy) and contralateral reflux (Fig. 1b). We observed that the presence of ureteral stones preceded the onset of ipsilateral unilateral renal tuberculosis.

### 3.2. Patient 2

A 55-year-old male patient who sought urological care had a history of lumbar pain, initially on the left, but then bilaterally associated with macroscopic hematuria for some months. The diagnosis of bilateral ureteral stones was made in May 2017 and a two-step bilateral endoscopic ureterolithotripsy was performed, initially on the right and a few days later on the left. On the right, there was a stone measuring 0.8 cm in the distal ureter, while on the left, there was a stone measuring 1.2 cm in the proximal ureter (Fig. 2a). After the second surgery, for six months, the patient reported persistent left low back pain associated with the



**Fig. 1a.** Abdominal tomography with normal right kidney, normal bladder but diffuse calicial dilatation with parenchyma atrophy in a nonfunctioning left kidney. There was previous history of five episodes of spontaneous elimination of left urinary lithiasis.



**Fig. 1b.** Cystography showing contracted bladder with right ureteral reflux, five years after left nephrectomy.



**Fig. 2b.** Time 2 - abdominal tomography showing left urinary tract dilatation with ureteral thickening and areas of stenosis with parenchyma atrophy of the left kidney and a bladder with diffuse thickening and decreased capacity.



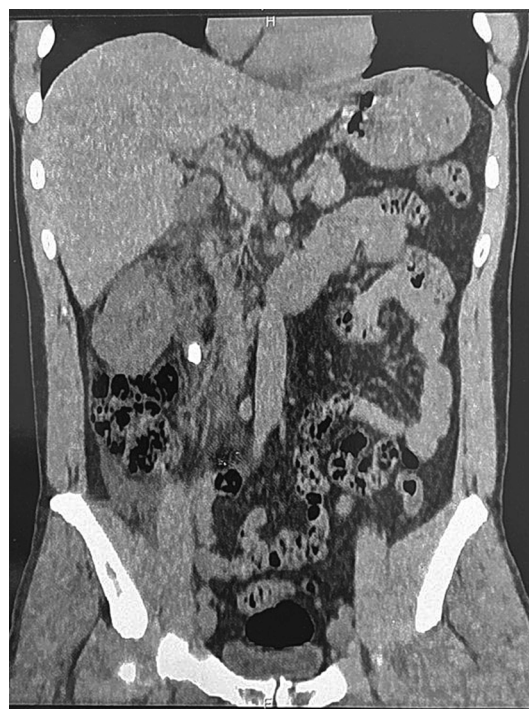
**Fig. 2a.** Time 1 – abdominal tomography showing a 1.2 cm ureteral stone in proximal ureter with urinary tract obstruction and a normal bladder.

onset of pollakiuria with progressive worsening. A new radiological investigation revealed left ureterohydronephrosis with ureteral thickening and areas of stenosis and a bladder with diffuse thickening and decreased capacity (Fig. 2b). A cystourethrogram revealed a contracted bladder with bilateral vesicoureteral reflux, grade I on the left and grade III on the right. In view of these findings, in January 2019, the patient was diagnosed with UTB due to a urine culture positive for *Mycobacterium* sp. Comparing the urinary tract at the time of left kidney obstruction by a ureteral stone and at the time of diagnosis of tuberculosis, we observed that ureteral obstruction temporally preceded the subsequent changes with the onset of ureteral thickening and stenosis and contracted bladder. Activation of renal tuberculosis occurred in the left kidney with the previous presence of ureteral obstruction due to lithiasis and subsequent endoscopic ureterolithotripsy.

### 3.3. Patient 3

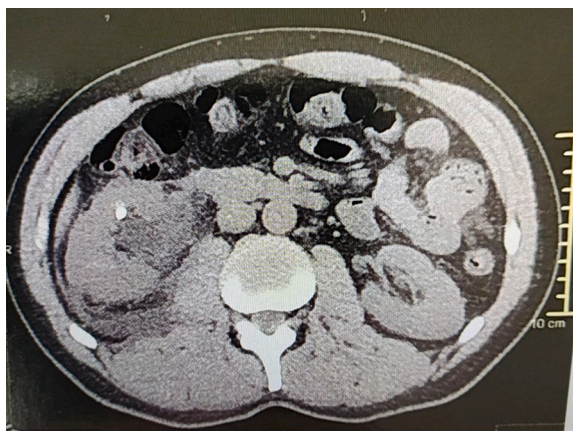
A 47-year-old male patient sought urological care in February 2016

due to right low back pain for more than 30 days. A CT scan revealed a 1.2 cm stone in the proximal right ureter (Figs. 3a–3c). He underwent successful surgical treatment with endoscopic ureterolithotripsy. In the following six months postoperatively, the patient, with a double J catheter, presented two episodes of acute pyelonephritis with fever and low back pain, which improved with the use of conventional antibiotic therapy. After this period, the patient developed lower urinary tract symptoms with a predominance of storage symptoms in the form of pollakiuria. In the period from 2016 to 2018, there was a gradual and

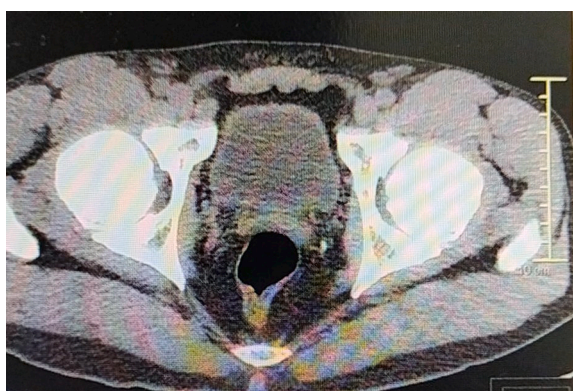


**Fig. 3a.** Time 1- abdominal tomography showing a 1.2 cm ureteral stone in proximal right ureter.



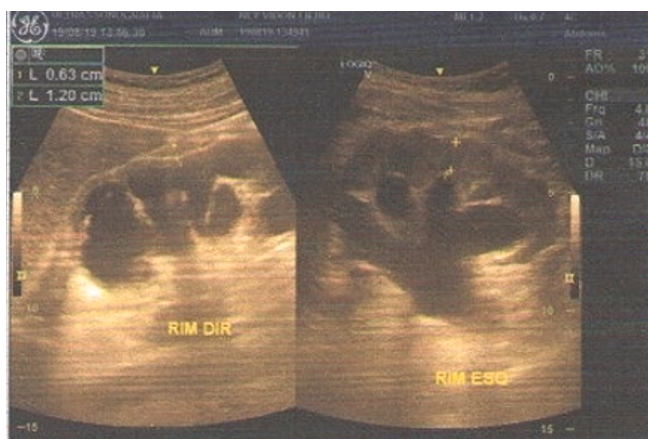


**Fig. 3b.** Time 1 - abdominal tomography showing right kidney dilatation with normal kidney parenchyma.



**Fig. 3c.** Time 1 - abdominal tomography showing normal bladder.

clear worsening of symptoms, culminating in severe pollakiuria, with a daytime voiding interval of less than 30 min. During this period, the patient was wrongly diagnosed and pharmacologically treated with prostatic obstruction and overactive bladder, progressing to end-stage renal failure. In May 2018, ultrasonography, tomography and cystourethrography showed features typical of UTB with hydronephrosis and a nonfunctioning kidney on the right and a contracted bladder and



**Fig. 3d.** Time 2 - ultrasonography showing bilateral urinary tract dilatation but two different patterns. The right kidney (left in the image) presents diffuse calicinal dilatation, parenchyma atrophy and nondilated renal pelvis (typical of renal tuberculosis). The left kidney presents pyelocaliceal dilatation with normal parenchyma (due to ureteral reflux).

vesicoureteral reflux on the left (Figs. 3d–3g). Urine culture for AFB was negative, but histopathology of the right kidney after nephrectomy confirmed the diagnosis of urinary tuberculosis. Interestingly, there was small nonactive granulomas in the renal cortex but active medullary granuloma with caseous necrosis, ulceration and erosion of the renal papillae (Figs. 4a, 4b). The patient underwent bladder augmentation with a detubulized sigmoid and is awaiting kidney transplantation. In this patient, ureteral obstruction due to a stone with subsequent surgical manipulation preceded the activation of tuberculosis in the same obstructed kidney with the subsequent onset of symptoms of urogenital tuberculosis, excretory stenosis with a nonfunctioning kidney and subsequent bladder tuberculosis with contracted bladder and contralateral reflux.

**4. Discussion**

UTB is always secondary to the hematogenous spread of pulmonary tuberculosis. These initial kidney lesions are bilateral, with granulomas without caseous necrosis or nodule formation and, therefore, without radiological alterations [6]. Medlar [7] studied the kidneys of 30 patients who died of advanced pulmonary tuberculosis who did not have symptoms or renal changes in imaging tests to characterize subclinical latent renal lesions. Renal granulomas were found in 22 patients (73.3%), always bilateral, with 75% located in the cortical region, 11% in the medulla and 14% in the corticomedullary region. In fact, in a study of histological changes in surgical specimens of renal tuberculosis, initial granulomas were identified in the juxtaglomerular cortical region, favored by good flow in the afferent arteriole and viscosity in the efferent arteriole. Subsequently, the bacilli reach the proximal convoluted tubule and loop of Henle, with granuloma formation in the medullary region [8]. Granulomas that become active in the presence of disease reactivation are medullary granulomas, with the appearance of caseous necrosis, ulceration and erosion of the renal papillae to the excretory system with bacilluria and descending spread of the disease. In our study, It was observed in the kidney histology of patient 3. Changes in the renal papilla characterize the initial radiological signs of renal tuberculosis [9]. The disease spreads to the ipsilateral urinary tract (renal pelvis and ureter) with intramural inflammation and granulomas formation, causing thickening and eventually obstruction [8].

Despite the initial bilateral colonization of the renal cortex, the



**Fig. 3e.** Time 2 - abdominal tomography showing right kidney with diffuse calicinal dilatation and parenchyma atrophy and left kidney with pyelocaliceal dilatation with normal parenchyma (due to ureteral reflux).





Fig. 3f. Time 2- abdominal tomography showing contracted bladder with diffuse thickening and continuity with left ureter due to reflux.



Fig. 3g. Time 2- cystography showing contracted bladder with left ureteral reflux.

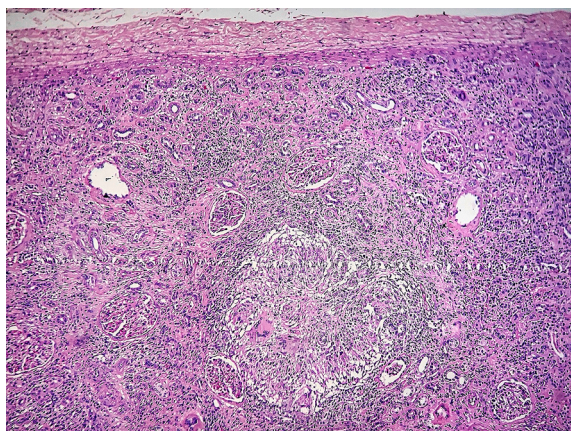


Fig. 4a. HE 40x. Nonactive granuloma in the renal cortex.

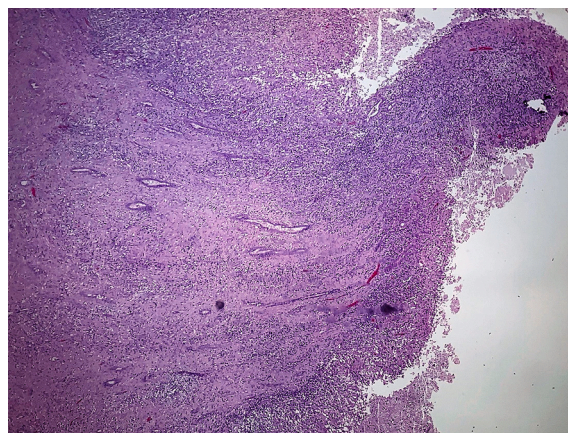


Fig. 4b. HE 40x. Medullary granuloma with caseous necrosis, ulceration, and erosion of the renal papillae to the excretory system.

primary event of this evolution is the reactivation of tuberculosis in only one kidney and, in particular, in one of its lobes. In fact, Barrie [10] conducted a relevant study of 61 patients with UTB who underwent nephrectomy. In almost all cases, it was possible to identify in which renal lobe the onset of infection occurred, showing that reactivation of tuberculosis occurs in one kidney and more specifically in a single renal lobe, predominantly in the upper pole.

Therefore, renal tuberculosis always occurs after the reactivation of a latent renal parenchymal focus, and this occurs almost always in only one kidney. Hence, unilateral renal tuberculosis is predominant. The latency period of renal tuberculosis is highly variable, but reactivation has always been credited to a decrease in patient immunity. Thus, malnutrition, AIDS, alcoholism and diabetes mellitus may occur with renal tuberculosis reactivation. However, the role of local factors on this reactivation has been neglected. Why does tuberculosis reactivation occur in only one kidney and at a certain point in life?

Shabad et al. [11] describes the clinical characteristics of patients with UTB in Russia, emphasizing the paramount importance of local factors for the reactivation of renal tuberculosis. Changes in renal urinary flow, i.e., obstruction and decreased renal perfusion, were responsible for this reactivation. In the evaluation of clinical cases, the author describes that most lesions are located in the upper pole, a site with less renal vascularization, as observed by Barrie [10]. Among men, there is an equal distribution (1:1) of the side affected, whereas among women, the affected side is predominantly the right kidney (1.2:1), a finding that may be associated with the predominance of right renal changes due to pregnancy. In addition, individuals with abnormal kidneys are more prone to tuberculosis, as are those with chronic nonspecific pyelonephritis. A nonspecific inflammatory process may precede a specific process. A final clinical feature is the well-known association between renal lithiasis and tuberculosis.

In fact, in a later publication that was more detailed and had a larger sample size [12], Shabad evaluated 1464 cases of renal tuberculosis in the two largest hospitals in Moscow between 1946 and 1971. In this study, the following were observed over the years:

- Higher incidence of renal tuberculosis in female patients, with a predominance of cases in women (63.4 %) in the last decade;
- In 71 % of the cases, there was a lesion in the upper pole, and in 61 %, there was an intrarenal pelvis, which was associated with a greater chance of obstruction;
- In 15 % of the cases, there was a history of previous kidney disease, such as malformation, nonspecific chronic pyelonephritis, kidney stones and kidney trauma;

- In patients with unilateral renal malformation, tuberculosis occurred in the malformed kidney at a frequency five times higher than in the normal contralateral kidney;
- Women with previous pregnancies had a higher frequency of tuberculosis in the right kidney than the left kidney (ratio 1.5:1); and
- In 30 % of women, the onset of renal tuberculosis occurred in connection with pathological pregnancies and deliveries and gynecological diseases or surgeries;

Shabad also conducted a study with 63 rabbits infected with intravenous or intravesical culture of *Mycobacterium tuberculosis* (bovine type) with obstruction (ligation or resection) of the left ureter [11]. The kidneys of the rabbits were studied microscopically. The right kidney (without obstruction) had few tuberculosis foci (mostly only one focus), which were small and located in the renal cortex, along small vessels with some healing. However, in the hydronephrotic left kidney, there were multiple large foci in the renal cortex and medulla, with caseous necrosis and destruction. In the dilated renal pelvis, there was thick pus with the bacilli and, in some cases, necrotic changes in the wall of the urinary tract. The authors concluded that obstruction of the ureter do not influence the emergence of subclinical miliary foci of tuberculosis, but they are very important for the development and activation of destructive and necrotic tuberculosis.

In conclusion, UTB appeared in the same kidney that had previously suffered ureteral obstruction by a stone. This observation, as well as the data reviewed in the literature, strengthens the hypothesis that urinary obstruction with a consequent increase in intrarenal pressure and ischemia may create local conditions that favor the activation of latent foci of renal tuberculosis. The renal papilla region is the classic site of renal tuberculosis onset and, in fact, is the site affected earliest by increased intrarenal pressure resulting from obstruction.

## 5. Author contributions section

André Avarese Figueiredo: Conceptualization, Methodology, Investigation, Writing - Original Draft.

Augusto de Azevedo Barreto: Methodology, Investigation, Data Curation, Writing - Original Draft.

Humberto Elias Lopes: Conceptualization, Writing - Review & Editing.

José Murillo Bastos Netto: Conceptualization, Writing - Review & Editing.

## 6. Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of University Hospital of the Federal University of Juiz de Fora (number 4,418,369). All subjects signed an informed consent to participate in the present research. The study was performed in accordance with the

Declaration of Helsinki.

## Conflict of interest

There is no conflict of interest to disclosure.

## Funding

There is no funding to disclosure.

## CRediT authorship contribution statement

**André Avarese Figueiredo:** Conceptualization, Methodology, Investigation, Writing – original draft. **Augusto de Azevedo Barreto:** Methodology, Investigation, Data curation, Writing – original draft. **Humberto Elias Lopes:** Conceptualization, Writing – review & editing. **José Murillo Bastos Netto:** Conceptualization, Writing – review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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