Original Article

Xanthogranulomatous pyelonephritis: Case series – Clinical, radiologic, therapeutic, and histological aspects

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Abstract

Purpose: Xanthogranulomatous pyelonephritis (XGP) is a chronic and severe infection of the kidney. We aimed to review the main clinical, imaging, and histological findings and to assess predictors of surgical complications or hospitalization >10 days (no deaths reported).

Materials and Methods: We retrospectively searched all patients with XGP treated at our institution from 2005 to 2019, with 57 patients enrolled. Clinical data were retrieved by a single reader, computed tomographic (CT) examinations by two radiologists, and histopathological specimens by an experienced pathologist.

Results: The patients' mean age was 44.3 ± 16.2 years and 41 (71.9%) were female. The most common symptoms were flank/lumbar pain (89.5%), fever (43.9%), and recurrent urinary tract infection (43.9%). The mean time until the presumptive diagnosis was 365.1 days and the median hospitalization period was 11 days. Blood tests showed anemia (78.9%), leukocytosis (43.6%) with left shift (21.6%). Urinalysis showed hematuria (75.6%), bacteriuria (40.9%), and leukocytes (93.2%). Urine cultures showed *Escherichia coli* in 14.8%, *Proteus mirabilis* in 7.4%, while 59.3% were negative. Of 40 patients with CT examinations, 38 (95%) presented with hydronephrosis and perinephric inflammatory changes (PIC) and 22 (55%) with Bear Paw sign. PIC was the only independent predictor at multivariate analysis for surgical complications. For prolonged hospitalization, fever and PIC were independent predictors at univariate, but only fever at multivariate analysis.

Conclusions: XGP is a worrisome condition, with unclear pathophysiological mechanisms. Fever and PIC at CT examinations were predictors of poor outcomes.

Keywords: Calculi, pathology, pyelonephritis, radiology, xanthogranulomatous pyelonephritis

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Received: 05.11.2021, **Revised:** 31.05.2022, **Accepted:** 10.05.2022, **Published:** 07.09.2022

INTRODUCTION

Described in 1916 by Schlagenhaufer,[1,2] xanthogranulomatous pyelonephritis is an uncommon type of chronic infectious pyelonephritis that evolves with a suppurative process and severe impairment of the renal function. Adult women and the elderly are most affected and are commonly associated with urinary tract obstruction and/or infection. Children are rarely affected,[3] as well as bilateral impairment.[4]

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/ua.ua_180_21

How to cite this article: Pais JS, Rocha MB, Muglia VF, Chahud F, Molina CA, Ruellas HR, *et al*. Xanthogranulomatous pyelonephritis: Case series – Clinical, radiologic, therapeutic, and histological aspects. Urol Ann 2022;14:383-8.

Histologically, there is progressive destruction of the renal parenchyma, replaced by a diffuse granulomatous inflammatory infiltrate with macrophages containing lipids in their cytoplasms called xanthomatous cells,[5-7] amid the purulent secretion. The exact pathogenesis is still unknown.[8]

XGP may present as focal, segmental, or diffuse forms, and the latter is the most common. The segmental and focal forms are challenging diagnoses and can be confused with neoplasia. The perirenal fat tissue is equally compromised by the inflammatory infiltrate, associated with intense fibrosis and strong adhesion to the parenchyma, interfering in the identification of the anatomic layers.[9]

Due to its life-threatening potential, radical surgical treatment[6] is often indicated, while conservative therapy with antibiotics is generally ineffective. Progression of inflammatory processes can compromise adjacent organs such as the duodenum,[10] liver, spleen, psoas muscle, colon,[11] and large vessels. Some patients can present cutaneous fistula draining purulent secretion[12] or pleural effusion.[13,14] Such situations require careful clinical and radiologic evaluation to program adequate treatment and guarantee satisfactory postoperative evolution.

The delay in recognizing the main characteristics of the disease and confirming the diagnosis may lead to serious complications. As its major clinical signs and symptoms are related to kidney stones and/or urinary tract infection, commonly patients are only referred when there is severe abdominal pain, weight loss, or recurrent urinary tract infections and sepsis. Blood in urine and abdominal palpable mass can also be present. We hypothesized that XGP is still often unrecognized by a non-specialist, demanding a better understanding of its clinical and radiologic features, especially those that can be associated with a worse prognosis. Accordingly, we conducted this retrospective, observational study to assess clinical, imaging, and pathological parameters associated with poor outcomes in XGP.

MATERIALS AND METHODS

Patient selection

This was a retrospective, observational, single-center, nonconsecutive case series of XGP diagnosed and treated in a 15 years' period (2005–2019). The study was conducted by the urology (surgery), imaging, and pathology departments of a tertiary care university hospital. The study was approved by the institutional review board.

All patients with nephrectomy specimens and histopathological diagnosis of xanthogranulomatous pyelonephritis from 2005 to 2019 were included in this study. Specimens were re-evaluated by a pathologist and cases without criteria for XGP after thorough revision were excluded. Of the 58 cases initially selected, 1 was excluded due to the absence of all criteria, with the diagnosis of endodermal sinus tumor.

Clinical and laboratory data

Clinical and laboratory data were obtained from the patient's file records. Data retrieved were sex, age at diagnosis, clinical presentation (flank or lumbar pain, recurrent urinary tract infection, weight loss, palpable abdominal mass, nausea or vomiting), time from the beginning of symptoms until diagnostic hypothesis of XGP, time of hospitalization, other diagnostic hypothesis assumed, kidney affected, laboratory examinations (blood count, urinalysis, cultures of urine, and secretion from the nephrectomy specimens), use of antibiotics prior to nephrectomy, type of surgery and complications. Poor outcome was defined as intra- or post-operative complications and time of hospitalizations longer than 10 days. When data were not available, information was categorized as "not available" in the Excel tables and was not taken into account in calculations.

Imaging analysis

A dedicated radiological review of pertinent computed tomographic (CT) images (Brilliant-16 detectors-Philips, Best, The Netherlands, and Aquillion One-Toshiba, Japan) and ultrasonography (US) studies (Logic P6 and E9, GE Healthcare-Milwaukee-USA) was performed by two dedicated radiologists. All patients had, at least, an abdomen and pelvis CT sequence without intravenous administration of contrast media at hospital admission. If available, sequences after intravenous contrast media were analyzed together. In some cases, CT examinations were performed after the US, and these images were also assessed. The parameters observed were degree of renal dilation (hydronephrosis), presence or absence of urolithiasis, urothelial enhancement, perirenal inflammatory changes (heterogeneous attenuation, fat strandings, and enhancement), and presence of the bear paw sign.

Pathological analysis

Histopathological data were obtained by revision of the nephrectomy specimens by a dedicated uropathologist, with more than 20 years of experience. Parameters observed were the presence of xanthomatous macrophages, granulomatous reaction, necrosis, calcification, cavitation, fibrosis, and involvement of the perinephric fat. The

material was fixed in 10% formalin and appropriately grossed as per the standard protocol for tissue processing and paraffin embedding. Sections were at 3-μm thickness and stained with hematoxylin and eosin stain.

Statistical analysis

All data were stored in Excel files (Microsoft Word). The statistical analysis was carried out in Stata Software, (Stata Co. Texas-USA), version 15.

The categorical variables were registered in proportions and comparisons between groups with good and poor outcomes were performed using Fisher's Exact Test. The continuous variables were assessed for normality using the Shapiro–Wilk test. For comparison between groups, the Student's *t*-test was used for parametric variables and Mann–Whitney for nonparametric variables. The continuous variables were presented as mean ± standard deviation when shown a normal distribution, otherwise as median + interquartile range.

For assessing potential variables associated with poor outcomes, a univariate and multivariate regression analysis was used. The level of significance was set at 0.05.

RESULTS

The age of patients ranged from 6 to 83 years, with mean age of 44.3 ± 16.2. The distribution according to decades was 0 to 10 years: 1 (1.8%); 11 to 20 years: 3 (5.3%); 21 to 30 years: 8 (14%); 31 to 40 years: 7 (12.3%); 41 to 50 years: 18 (31.6%); 51 to 60 years: 12 (21.1%); 61 to 70 years 5 (8.8%); 71 to 80 years: 2 (3.5%); and 81 to 90 years: 1 (1.8%).

Of 57 cases, 16 (28.1%) were male and 41 (71.9%) were female with male-to-female rate of 1:2.56. The mean time from the beginning of the symptoms to the first documented diagnostic suspicion of chronic pyelonephritis was 365.1 days, the median was 120, 25th percentile 30, and 75th percentile 365 days. The median hospitalization period was 11 days.

The right kidney was involved in 32 cases (56.1%), the left one in 23 (40.4%) and there was bilateral involvement in 2 (3.5%) cases.

The main symptoms present at the time of diagnosis are shown in Table 1 and the main laboratory results are in Table 2. Urinalysis showed that red cells were present in 75.6% (34/45) of the patients, bacteria in 40.9% (18/44), and leukocytes in 93.2% (41/44) of the patients.

Table 1: Clinical presentation (signs and symptoms)

	n (%)
Flank or lumbar pain	51 (89.5)
Fever	25 (43.9)
Recurrent urinary tract infection*	25 (43.9)
Weight loss#	17 (29.8)
Palpable abdominal mass	14 (24.6)
Nauseas and vomiting	14 (24.6)

*Recurrent urinary tract infection: ≥3 episodes in 1 year or ≥2 episodes in 6 months, #Weight loss: ≥10% in 1 year or ≥5% in 6 months

Table 2: Laboratory test results in hospital admission and hospital discharge

	n (%)
Hospital admission	
Anemia	45/57 (78.9)
Leukocytosis#	24/55 (43.6)
Neutrophilia*	19/53 (41.50)
Lymphocytosis*	7/53 (13.20)
Left shift	11/51 (21.6)
Hospital discharge	
Anemia	45/53 (84.9)
Leukocytosis**	23/52 (44.2)
Neutrophilia	18/50 (36)
Lymphocytosis	3/50 (6)
Left shift	6/44 (13.6)

*3/53 (5.66%) patients had both neutrophilia and lymphocytosis, **1 patient presented eosinophilia, #1 patient presented monocytosis

The uroculture analysis was available in 54 cases. *Escherichia coli* was present in 8 (14.8%) cases, *Proteus mirabili*s in 4 (7.4%), *Klebsiella pneumoniae* in 3 (5.6%), *Pseudomonas aeruginosa* in 2 (3.7%), *Enterococcus faecalis* in 2 (3.7%), yeast fungi in 2 (3.7%), *Staphylococcus aureus* in 1 (1.9%), and *Streptococcus agalactiae* in 1 (1.9%). In 32 (59.3%) cases, there was no bacterial growth.

Culture of the fluids from the nephrectomy specimens was available in 22 cases, with growth of *P. mirabilis* in 4 (18.2%) samples, *E. coli* in 3 (13.6%), *E. faecalis* in 2 (9.1%), *Staphylococcus aureus* in 1 (4.5%), yeast fungi in 1 (4.5%), and *S. agalactiae* in 1 (4.5%) sample. In 11 (50%) samples, there was no bacterial growth.

At hospital admission, previously to the confirmation of XGP diagnosis, the hypothesis of kidney abscess were assumed in 13 cases, pyonephrosis in 10 cases, obstructive uropathy in 8 cases, nonspecific renal neoplasia in 5 cases, and psoas muscle abscess in 1 case. After histopathological analysis, 3 cases were confirmed of mixed diagnosis, XGP associated with pyonephrosis.

All patients underwent surgery [Figure 1], total nephrectomy in 56 (98.2%) and partial in 1 (1.8%). The surgical procedure was open laparotomy in 46 (80.7%) patients and video laparoscopic in 11 (19.3%) patients. Antibiotics were used

prior to surgery in 30 (52.6%) patients and the median time of use was 2, 25th percentile 0, and 75th percentile 7 days.

Surgical or postoperative complications were present in 13 (22.8%) patients, which counted as 3 infections of the surgical wound, 3 cutaneous fistulas, 3 retroperitoneal collections, 2 septic shocks, 2 splenic lesions that required splenectomy, 1 incisional hernia, 1 duodenal perforation (primária rafia), and 1 necrotizing pancreatitis.

Computerized tomography (CT) scans were available in 40 patients and these exams were preceded by ultrasonography in 14 cases. Only two patients had no dilation of the renal collecting system at CT scans [Table 3]. Of patients with CT scans, 90% had moderate-to-severe hydronephrosis. Signs of perirenal inflammation were present in 90% of patients, and 42.5% had abscesses.

At CT examinations [Figure 2], when hydronephrosis was present, the presence of urolithiasis was the preponderant cause. The causes of obstruction are described in Table 4.

The results of the re-analysis of the 59 surgical specimens (55 unilateral and 2 bilateral) are presented in Table 5 and Figure 3.

Poor outcome was defined as intra- and post-operative complications and time of hospitalization longer than 10 days, as no deaths were reported. Perinephric inflammatory findings (odds ratio 3.725 ± 1.967, $P = 0.01$) were the only predictor of surgical complications at univariate regression analysis [Table 6]. Fever and perinephric inflammatory findings were predictors of prolonged time of hospitalization at univariate analysis, but only fever (odds ratio 9.362 ± 7.356, $P = 0.004$) at multivariate analysis regression [Table 7].

Table 3: Computerized tomography results (40)

	n (%)
Hydronephrosis	
Absent	2 (5)
Mild	1 (2.5)
Moderate	4 (10)
Severe	32 (80)
Urothelial enhancement	
Present	11 (27.5)
Perinephric inflammatory enhancement	
Absent	2 (5)
Perirenal fat stranding	12 (30)
Elongated collections	9 (22.5)
Abscess	17 (42.5)
Bear paw sign	
Present	22 (55)

Table 4: Causes of obstruction

	n° (%)
Staghorn calculi	30 (52.6)
Nonstaghorn calculi	16 (28.1)
Ureteral calculi	5 (8.8)
UPJ stenosis; renal neoplasia; bladder neoplasia	2 (3.5)
Neurogenic bladder; persistence of urogenital sinus	1 (1.8)

UPJ: Ureteropelvic junction

DISCUSSION

As previously described,[6,8] a female predilection was seen of 71.9%, and more than half of cases involved patients in their fifth or sixth decade of life. The right kidney was more often involved and generally unilateral.

Long periods of diagnostic investigation before referral to our hospital were observed (median, 25th, and 75th percentiles, respectively, of 120, 30, 365), suggesting the lack of knowledge about PXG and reinforcing the necessity of improving dissemination of diagnostic

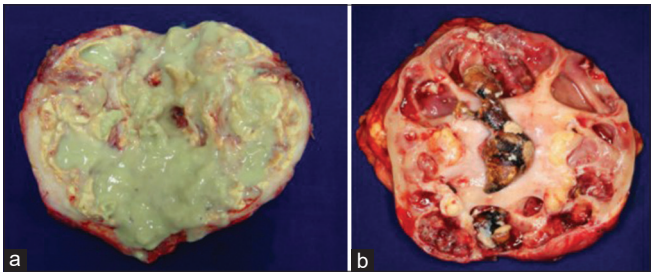

Figure 1: Gross photograph: (a) Enlarged kidney with suppurative secretion and loss of parenchymal architecture. (b) Enlarged kidney with the presence of staghorn calculus occupying the renal pelvis and calyces

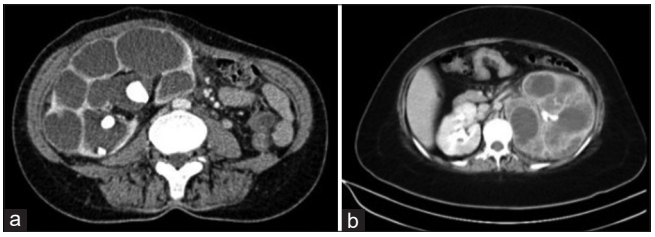

Figure 2: (a and b) Contrast-enhanced computerized tomographies showing impacted coralliform calculus in the renal pelvis, determining upstream pyelocaliceal dilatation and thinning of the parenchyma (hydronephrosis), compatible with xanthogranulomatous pyelonephritis

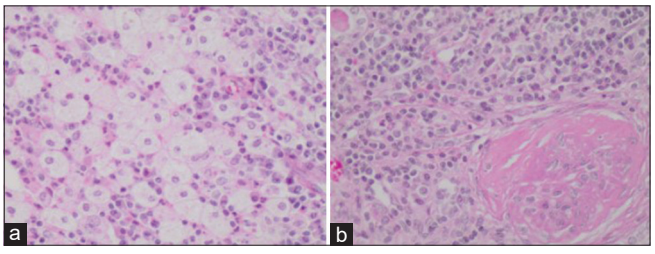

Figure 3: (a) Mixed inflammatory infiltrate composed of histiocytes with large, pale, microvacuolated cytoplasms (foamy histiocytes), lymphocytes, plasma cells, and neutrophils (H&E, ×400). (b) Dense interstitial inflammatory infiltrate associated with glomerulosclerosis (H&E, ×400)

Table 5: Histological analysis results

	n° (%)
Xanthomatous macrophages	59 (100)
Granulomatous reaction	58 (98.30)
Fibrosis	58 (98.30)
Necrosis	39 (66.10)
Calcification	19 (32.20)
Cavitation	2 (3.38)
Involvement of perinephric fat	59 (100)

Table 6: Outcome: Surgical complication

Predictor	Odds ratio	*P*
Univariate analysis		
Age	1.006±0.019	0.75
Lumbar pain	1.538±1.76	0.38
Palpable mass	1.511±1.05	0.59
Fever	2.541±1.648	0.15
Leukocytosis	0.30±0.218	0.09
Hematuria	0.375±0.289	0.20
Pyuria	2.115±1.6	0.99
Staghorn calculi	1.6±1.031	0.73
Perinephric inflammation	3.725±1.967	0.01
Hydronephrosis	0.924±0.362	0.84

Table 7: Outcome: Time of hospitalization longer than 10 days

Predictor	Odds ratio	*P*
Univariate analysis		
Age	0.967±0.017	0.07
Lumbar pain	0.50±0.455	0.44
Palpable mass	1.98±1.28	0.28
Fever#	6.64±4.42	0.002
Leukocytosis	0.764±0.42	0.62
Hematuria	0.607±0.435	0.48
Pyuria	3.27±2.17	0.07
Staghorn calculi	1.146±0.613	0.80
Perinephric inflammation#	2.142±0.789	0.03
Hydronephrosis	0.789±0.301	0.54
Multivariate analysis		
Fever	9.362±7.356	0.004
Perinephric inflammation	1.187±0.773	0.16

criteria. Moreover, PXG was challenging also because some differential diagnoses were assumed as the main hypothesis before histopathological analysis. These results indicate the need for better diagnostic criteria.

Clinical presentation can be nonspecific,[15] with symptoms suggestive of nephrolithiasis or common pyelonephritis, but what is noticeable is the long-term duration. In agreement with Kundu *et al*.,[6] in the present study, the most common clinical presentation was abdominal pain (89.5%), followed by fever (43.9%) and urinary tract infection (43.9%). The fact that less than half of the patients presented fever even though the evident and advanced kidney infection suggests that, for yet unknown reasons, the pathological agent can develop a symbiosis with the host, restraining the inflammation process within the kidney parenchyma for long periods.

Laboratory data are also nonspecific.[16] Hematology alterations were common, such as anemia, leukocytosis, and left shift. Urine analysis showed red cells, leukocytes, and bacteria. Cultures, as expected,[17] showed a predominance of *E. coli* and *P. mirabilis*.

Recurrent urinary tract infections and chronic obstruction are physiopathological hallmarks of the XGP.[8,18,19] Urolithiasis was present in 89.5% of patients of our series as the cause of obstruction, with staghorn calculi in more than half of patients.

Xie *et al*.[20] demonstrated the benefits of long-term antibiotic treatment before video laparoscopic approach. In our study, only 11 (19.29%) patients were submitted to laparoscopic procedure and most patients used little time of antibiotics prior to surgical resolution (median 2 days, 25th percentile 0 days, and 75th percentile 7 days). All patients were submitted to total nephrectomies, except for 1 case in which XGP was associated with clear cell renal cell carcinoma. Although no deaths were reported, the disease was associated with relevant morbidity. Patients frequently seek medical care for diagnosis and, after temporary symptoms relief, long periods were observed (months to years) until recurrence. Besides, all patients lost renal function due to nephrectomies. In addition, there was a huge impact on the healthcare system, since there was prolonged hospitalization time, as previously shown.

The histopathological findings revealed an intense polymorphic, granulomatous inflammatory infiltrate composed of neutrophils, plasma cells, lymphocytes, frequent foamy macrophages with clear, microvacuolated cytoplasm, and occasional multinucleated macrophages. Foci of necrosis with neutrophilic infiltration were common. There was significant destruction of the renal parenchyma. The inflammatory infiltrates extended to the perirenal adipose tissue. Fibrosis was a common finding and, in some cases, small foci of calcification were also found.

Regarding the radiological analysis, some of the main findings reported in the literature, such as the "bear's paw sign," often considered pathognomonic,[16] were not frequent as expected. It was also observed that the ultrasound had a minor role in the patient's assessment. In view of these findings, it is necessary to determine more accurate radiological criteria, which could shorten the search for the correct final diagnosis.

Fever and perinephric inflammatory findings in CT scans were predictors of poor outcome. Fever was related

to longer periods of hospitalization and perinephric inflammation to both time of hospitalization and surgical complications. These aspects were corroborated by the extension of the inflammatory process to perirenal fat on pathological analysis. In our experience, perinephric inflammation in CT images correlates to fibrosis and adhesions around the kidney, which may lead to complex surgical procedures as dissection gets more difficult, and, consequently, more surgical complications. Even though the obvious renal inflammatory process, unexpectedly, only 43.9% of the patients presented with fever. In comparison to the perinephric inflammation in CT images, fever can also be interpreted as an indicator of more severe inflammation, which may extrapolate the organ, leading to systemic involvement and a longer period of recovery.

There are a few relevant limitations in our study. First, it is retrospective nature, prone to bias, especially selection one. Second, it is an observational study. However, considering the low prevalence of disease, prospective studies are difficult. In addition, as a tertiary care center, we have a referral bias: only patients with more severe clinical conditions were sent to our hospital, of course, they frequently have more comorbidities. Another bias is related to the variable forms to retrieve medical information in the past 20 years, besides not all patients had the same laboratory examinations proposed to be analyzed. A similar situation is seen with imaging studies, the CT and US protocols and scanners have changed several times in this period. Nonetheless, the main findings described here have been regularly depicted on both methods for more than three decades.

CONCLUSIONS

XGP is a worrisome infectious condition of the kidney. Our data indicated long periods of symptoms without a definitive diagnosis, associated with long periods of hospitalization, intra- and post-operative complications.

Fever and perinephric inflammatory changes were predictors of poor outcome, suggesting that while the infection is restricted to the organ, there is a milder presentation. However, it is still unknown the determinants of the infection's behavior.

Our findings might help develop more accurate diagnostic criteria and may contribute to a better comprehension of the parameters associated with poor outcomes in XPG.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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