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Xanthogranulomatous Pyelonephritis: A pooled quantitative analysis of published cases

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Abstract: Xanthogranulomatous Pyelonephritis (XGP) is a serious and rare inflammatory disease of unknown etiology. This systematic review analyzes XGP cases. We performed a literature search for "Pyelonephritis, Xanthogranulomatous." The primary composite outcome was recovery with post-surgery complications, partial recovery, death, or chronic kidney disease. The secondary outcome was any presentation or treatment complication. Predictor variables consisted of demographics, history, symptoms, and diagnosis/management. Among the 251 patients, the mean age was 36.1 years, and 57.4% were female. The most common symptom and finding were fever (55.0%) and renal stones (53.8%), respectively. There were 15.5% with the composite outcome. There were 51.0% with any presentation or treatment complication. Multivariate logistic regression analysis for the composite outcome showed that kidney of both/horseshoe (OR:3.86, 95% CI:1.01, 14.73, p = 0.048), dialysis required (OR:8.64, 95% CI:2.27, 32.94, p = 0.002), and operative treatment of nephrostomy or nephrostomy followed by nephrectomy (OR:4.57, 95% CI:1.58, 13.17, p = 0.01) were each significantly associated with increased odds. Fever (OR:3.04, 95% CI:1.63, 5.67, p <0.001) and renal stones (OR:2.55, 95% CI:1.35, 4.81, p = 0.004) were each significantly associated with increased odds for any presentation/treatment complication. In conclusion, XGP patients with involvement of both or horseshoe kidneys, dialysis requirements, or treatment of nephrostomy or nephrostomy followed by nephrectomy may require aggressive treatment to mitigate poor patient outcomes.

Keywords: Pyelonephritis, Xanthogranulomatous, urology, nephrology, nephrolithiasis.

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Introduction

Xanthogranulomatous Pyelonephritis (XGP) is a rare chronic inflammatory form of pyelonephritis that destroys the renal parenchyma and replaces it with lipid-laden foamy macrophages [1]. Renal destruction most commonly results from chronic inflammation associated with urinary tract infection, scarring, stones, and obstruction. Incidence of XGP ranges from 0.6% to 1.0% across all cases of renal infections in either diffuse, segmental, or focal form [1]. XGP predominantly occurs in females with prevalence ranging from 64.0%–85.4% [2–4]. The symptoms associated with XGP include fever, flank or abdominal pain, weight loss, lower urinary tract symptoms, gross hematuria, pallor, and malaise [2–5].

Preoperative evaluation includes computed tomography (CT) with contrast, and/or magnetic resonance imaging (MRI). Such imaging may identify multiloculated renal architecture that is pathognomonically referred to as the "bear paw" sign, which may lead to a pre-operative diagnosis of XGP [2, 3]. Histological post-operative diagnostic confirmation is often performed to rule out possible renal malignancy [1].

The treatment of choice is partial or radical nephrectomy after failed conservative management with antibiotics and nephrostomy placement [1]. Complications of open nephrectomy include postoperative surgical site infection and prolonged hospitalization, abscess, fistulae, and sepsis [6, 7]. Diffuse forms of XGP may lead to complications such as psoas abscess, nephrocutaneous fistula, renocolic fistula, or perinephric abscess [2, 3].

Studies regarding XGP are small with retrospective studies and case analyses ranging from 16 to 87 patients [2, 4, 5, 8, 9]. To our knowledge, we are not aware of any non-case series study that analyzed the association with outcomes of recovery or complications. We obtained data from case studies to perform multivariate analyses for the primary outcome of a composite outcome of recovery with post-surgery complications, partial recovery, death, or chronic kidney disease, and the secondary outcomes of presentation or treatment complications. Predictor variables consisted of demographics, history, symptoms, findings, and diagnosis/management variables.

Materials and Methods

Literature Search

We conducted a search from January 1st, 1990 through December 31st, 2020 of PubMed, Web of Science, and Scopus for case reports and series discussing patients diagnosed with XGP with the MeSH term of "Pyelonephritis, Xanthogranulomatous." Eligible case reports and case series were in English language and contained extractable data of patients diagnosed with XGP. Four researchers screened the potentially relevant content. For each included article, two researchers independently screened the title, abstract, and full article for inclusion evaluation. All disagreements were agreed upon by consensus. All data entered by one researcher into the data file was reviewed by another researcher to confirm data accuracy. The search yielded 2,109 articles with 212 case reports and 19 case series meeting criteria representing 251 patients (see Fig. 1).

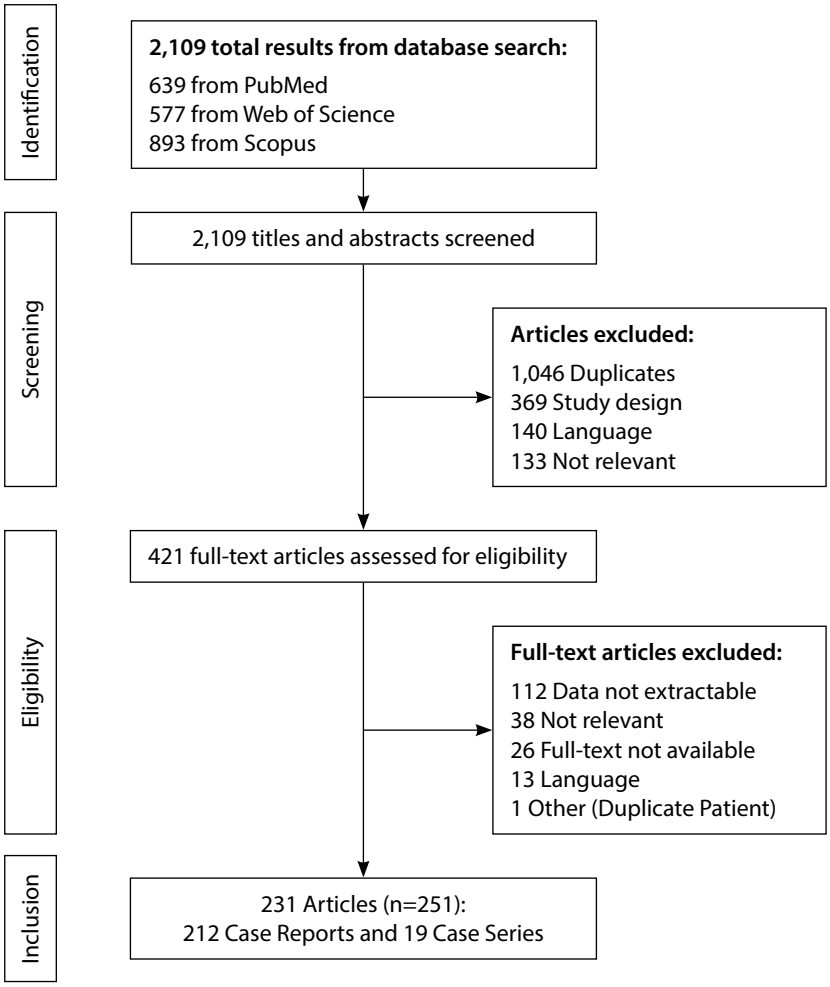

Fig. 1. PRISMA Flow Diagram.
Note: PRISMA — Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Variables

Demographic variables were age (years) and sex (male/female). History was urinary tract infection (UTI) (no/yes). Presenting symptoms were fever, flank pain/discomfort, weight loss, dysuria, and urinary frequency all recorded as no or yes. Findings of pyuria, hematuria, renal stones, and cancer were recorded as no or yes. Also, findings included kidney involvement which was recorded as left, right or both/horseshoe. XGP type was recorded as diffuse, focal, segmental, mixed, and not described. Diagnosis and management variables were pre-operative diagnoses, intensive care unit admission, and dialysis required, all recorded as no or yes. Also, we recorded antibiotics treatment (yes, no, or unknown), operative treatment (nephrectomy only, nephrostomy/nephrostomy + nephrectomy, unknown/no surgery), and microbes (multi-organism, E. coli, Proteus sp.,

Pseudomonas, Staph aureus, Enterococcus, Candida sp., Klebsiella, other, not described). The primary outcome variable was a negative composite outcome of recovery with post-surgery complications, partial recovery, death, or chronic kidney disease (no versus yes). The secondary outcome variables were any presentation or treatment complication, and also each specific presentation or treatment complication of renal fistula, sepsis, postoperative infection, and abscess, all measured as no or yes.

Statistical Analysis

Mean and standard deviation was used to describe the continuous variable of age. Frequency and percentage were used to describe the categorical variables. Multivariate logistic regression was used to analyze the outcome variables. IBM SPSS Statistics version 26 was used for all analyses (IBM Corporation, Armonk, NY, 2019). All p-values were two-tailed. The alpha level was $p < 0.05$.

Results

Table 1 shows the sample characteristics. The mean age was above 36 years, and more than half were female. Almost one-third had a history of urinary tract infection. Fever was the greatest percentage (55.0%) for symptoms. Renal stones were the greatest percentage (53.8%) for findings. XGP type was not described in 88.8%. There were 62.2% who received antibiotics treatment and 72.9% who underwent nephrectomy. E. coli (20.7%) was the greatest percentage for microbes. For the outcome variables, there were 15.5% for the composite outcome of recovery with either post-surgery complications, partial recovery, death, or CKD. There were 51.0% with any presentation or treatment complications. For specific presentation or treatment complication types, there were 19.1% with a renal fistula, 23.1% with sepsis, 6.4% with postoperative infection, and 27.1% with an abscess.

Table 2 shows the multivariate logistic regression analysis for the composite outcome of recovery with either post-surgery complications, partial recovery, death, or CKD. Increased age ($p = 0.03$), kidney of both/horseshoe ($p = 0.048$), dialysis required ($p = 0.002$), and operative treatment of nephrostomy or nephrostomy + nephrectomy ($p = 0.01$) were each significantly associated with increased odds for the composite outcome. None of the history or symptoms variables were significantly associated with the composite outcome.

Table 3 shows the multivariate logistic regression analysis for any presentation or treatment complications. Fever ($p < 0.001$) and renal stones ($p = 0.004$) were each significantly associated with increased odds for any presentation or treatment complications. Additional analyses were conducted for each of the specific presentation or treatment complications (data not shown). Increased age (OR:1.02, 95% CI:1.01, 1.04, $p = 0.01$) and renal stones (OR:6.67, 95% CI:2.50, 17.78, $p < 0.001$) were each significantly associated with increased odds for renal fistula. Dysuria (OR:3.69, 95% CI:1.15, 11.83, $p = 0.03$), ICU admission (OR:6.97, 95% CI:1.12, 43.43, $p = 0.04$), and operative treatment of nephrostomy or nephrostomy + nephrectomy (OR:3.06, 95% CI:1.16, 8.08, $p = 0.02$) were each significantly associated with increased odds for sepsis. UTI infection history (OR:0.39, 95% CI:0.17, 0.93, $p = 0.03$) was significantly associated with decreased odds for sepsis. Antibiotics treatment (OR:2.82, 95% CI:1.06, 7.47, $p = 0.04$) was significantly associated with increased odds for an abscess. None of the demographics, history, symptoms, findings, and diagnosis/management variables were significantly associated with postoperative complications.

Table 1. Sample Characteristics of 251 Patients with Xanthogranulomatous Pyelonephritis.

Variables	M (SD) or Frequency (Percentage)
Demographics	
Age (years) [mean]	36.1 (25.01)
Sex (female)	144 (57.4)
History	
Urinary tract infection (yes)	77 (30.7)
Symptoms	
Fever (yes)	138 (55.0)
Flank pain (yes)	111 (44.2)
Weight loss (yes)	52 (20.7)
Dysuria (yes)	28 (11.2)
Urinary frequency (yes)	17 (6.8)
Findings	
Pyuria (yes)	113 (45.0)
Hematuria (yes)	53 (21.1)
Renal stones (yes)	135 (53.8)
Kidney	
Right	112 (44.6)
Left	116 (46.2)
Both/Horseshoe	23 (9.2)
Cancer (yes)	19 (7.6)
XGP type	
Not described	223 (88.8)
Focal	19 (7.6)
Segmental	0 (0.0)
Diffuse	8 (3.2)
Mixed	1 (0.4)
Diagnosis and Management	
Pre-operative diagnosis (yes)	66 (26.3)
ICU admission (yes)	10 (4.0)
Dialysis required (yes)	15 (6.0)
Antibiotics treatment	
No	42 (16.7)
Yes	156 (62.2)
Unknown	53 (21.1)
Operative treatment	
Nephrectomy	183 (72.9)
Nephrostomy/nephrostomy + nephrectomy	40 (15.9)
Unknown/no surgery	28 (11.2)

Variables	M (SD) or Frequency (Percentage)
Microbes	
Multi-organism	24 (9.6)
E. coli	52 (20.7)
Proteus sp.	39 (15.5)
Pseudomonas	7 (2.8)
Staph aureus	5 (2.0)
Enterococcus	3 (1.2)
Candida sp.	1 (0.4)
Klebsiella	7 (2.8)
Other	13 (5.2)
Not described	100 (39.8)
Outcomes	
Recovery with post-surgery complications/partial recovery/death/ CKD (yes)	39 (15.5)
Presentation/treatment complications (any)	128 (51.0)
Presentation/treatment complications (renal fistula)	48 (19.1)
Presentation/treatment complications (sepsis)	58 (23.1)
Presentation/treatment complications (post-operative infection)	16 (6.4)
Presentation/treatment complications (abscess)	68 (27.1)

Note: SD — standard deviation, XGP — xantho granulomatosis pyelonephritis, ICU — intensive care unit, and CKD — chronic kidney disease. Recovery with post-surgery complications (n = 22), partial recovery (n = 5), death (n = 8), and CKD (n = 4).

Table 2. Multivariate Logistic Regression Analysis for Recovery with Post-surgery Complications, Partial Recovery, Death, or Chronic Kidney Disease.

Variables	OR (95% CI)	p-value
Demographics		
Age (years)	1.02 (1.002, 1.04)	0.03
Sex (female)	0.86 (0.36, 2.04)	0.73
History		
Urinary tract infection (yes)	1.67 (0.68, 4.13)	0.27
Symptoms		
Fever (yes)	2.00 (0.79, 5.11)	0.15
Flank pain (yes)	1.15 (0.51, 2.60)	0.74
Weight loss (yes)	0.75 (0.25, 2.25)	0.60
Dysuria (yes)	1.08 (0.28, 4.19)	0.92
Urinary frequency (yes)	1.34 (0.27, 6.63)	0.72
Findings		
Pyuria (yes)	1.05 (0.41, 2.69)	0.93
Hematuria (yes)	0.42 (0.13, 1.33)	0.14
Renal stones (yes)	0.54 (0.22, 1.33)	0.18
Kidney		
Right	1.00	
Left	2.00 (0.80, 5.02)	0.14
Both/Horseshoe	3.86 (1.01, 14.73)	0.048
Cancer (yes)	2.40 (0.61, 9.53)	0.21
Diagnosis and Management		
Pre-operative diagnosis (yes)	1.78 (0.63, 5.03)	0.27
ICU admission (yes)	1.97 (0.38 10.40)	0.42
Dialysis required (yes)	8.64 (2.27, 32.94)	0.002
Antibiotics treatment		
No	1.00	
Yes	0.93 (0.21, 4.04)	0.92
Unknown	2.70 (0.60, 12.05)	0.19
Operative treatment		
Nephrectomy	1.00	
Nephrostomy/nephrostomy + nephrectomy	4.57 (1.58, 13.17)	0.01
Unknown/no surgery	1.63 (0.47, 5.66)	0.44

Note: OR — odds ratio, CI — confidence interval, and ICU — intensive care unit.
Nagelkerke R Square = 0.30.

Table 3. Multivariate Logistic Regression Analysis for any Presentation or Treatment Complications.

Variables	OR (95% CI)	p-value
Demographics		
Age (years)	1.00 (0.99, 1.02)	0.56
Sex (female)	1.07 (0.58, 1.96)	0.83
History		
Urinary tract infection (yes)	0.73 (0.38, 1.41)	0.35
Symptoms		
Fever (yes)	3.04 (1.63, 5.67)	<0.001
Flank pain (yes)	0.97 (0.54, 1.75)	0.92
Weight loss (yes)	0.57 (0.28, 1.17)	0.13
Dysuria (yes)	0.70 (0.27, 1.84)	0.47
Urinary frequency (yes)	0.89 (0.26, 3.05)	0.85
Findings		
Pyuria (yes)	0.98 (0.52, 1.86)	0.95
Hematuria (yes)	0.59 (0.28, 1.27)	0.18
Renal stones (yes)	2.55 (1.35, 4.81)	0.004
Kidney		
Right	1.00	
Left	0.73 (0.40, 1.34)	0.31
Both/Horseshoe	0.55 (0.19, 1.62)	0.28
Cancer (yes)	0.70 (0.21, 2.35)	0.57
Diagnosis and Management		
Pre-operative diagnosis (yes)	1.29 (0.64, 2.62)	0.48
ICU admission (yes)	8.49 (0.83, 87.12)	0.07
Dialysis required (yes)	1.06 (0.29, 3.88)	0.93
Antibiotics treatment		
No	1.00	
Yes	1.62 (0.70, 3.74)	0.26
Unknown	1.34 (0.53, 3.42)	0.53
Operative treatment		
Nephrectomy	1.00	
Nephrostomy/nephrostomy + nephrectomy	1.91 (0.79, 4.60)	0.15
Unknown/no surgery	0.69 (0.26, 1.85)	0.46

Note: OR — odds ratio, CI — confidence interval, and ICU — intensive care unit.
Nagelkerke R Square = 0.25.

Discussion

This study pooled data from 251 patients with XGP to identify clinical presentations and findings. The mean age was above 36 years with greater than half being of female sex. Almost one-third had a history of urinary tract infection. Fever was the most common symptom at 55.0%. Renal stones were the most common finding at 53.8%. Greater than 60% received antibiotics treatment and greater than 70% required nephrectomy. Increased age, kidney of both/horseshoe, dialysis required, and operative treatment of nephrostomy or nephrostomy followed by nephrectomy were each significantly associated with increased odds for the composite outcome. Fever and renal stones were each significantly associated with increased odds for any presentation or treatment complications.

The multivariate logistic regression analysis for the composite outcome showed that increased age, both/horseshoe kidney, dialysis requirement, and operative treatment with nephrostomy or nephrostomy followed by nephrectomy were each significantly associated with increased odds for the composite outcome of recovery with either post-surgery complications, partial recovery, death, or CKD. A meta-analysis showed that the increased age of the patient was not associated with an increased risk of complications after radical and partial nephrectomy [10]. Although our findings with XGP for age differ from this pattern, in our study age had an odds ratio of 1.02 which indicates only a slight association. Horseshoe kidney is associated with UTIs and urolithiasis due to impaired emptying of the kidneys [11]. A recent meta-analysis found that 36% of individuals with horseshoe kidneys will develop nephrolithiasis which can increase the risk of chronic kidney disease in patients with horseshoe kidneys [12]. Our findings for XGP are similar to this pattern. We suggest that the impaired emptying and increased infection rates associated with horseshoe kidneys likely influenced the poorer outcomes in patients with XGP. Additionally, impairment of renal function of both kidneys with XGP prevents compensation by one healthy kidney likely causing poorer outcomes. A meta-analysis of elective surgeries showed that patients on dialysis have a significantly increased risk of poorer surgery outcomes compared to patients not on dialysis across all surgical subspecialties [13]. Also, dialysis patients were at an increased risk for postoperative complications, postoperative acute kidney injury, urinary complications, and longer hospital stays [14]. Our findings for XGP are similar to this pattern. Renal failure is associated with accelerated vascular calcification, anemia, increased oxidative stress, and impaired immunity [13]. We hypothesize that this could be the reason why dialysis patients with XGP had increased odds for complications. Nephrectomy, in this setting, is known to be associated with complication rates ranging from 19–36% [15]. The increased complication rate found within our sample of XGP patients who underwent nephrostomy, or nephrostomy followed by nephrectomy may be due to the potential additive impact of complications associated with nephrostomy.

We found that the presence of either fever or renal stones were significantly associated with increased odds for any complication. Temperatures about 40°C are associated with mortality increases suggesting the organ and cellular impact of such temperatures may outweigh the potential benefits of hyperpyrexia in combating infection [16]. Furthermore, in ICU admissions, a temperature greater than 37.5°C at any point is associated with worse outcome, and those greater than 38.5°C becomes significantly associated with worse outcomes [16]. Our findings for XGP are consistent with this research. We suggest that cellular and organ biological dysfunction associated with fever may be the cause of increased complications in patients with XGP.

Chronic infection, especially prevalent in renal stone disease, can lead to complications such as renocutaneous fistula [17], renocolic fistula [6], renogastric fistula [18], or nephron-psoas fistula [19] Similarly, XGP can be complicated by abscesses such as perinephric abscess [20], hepatic abscess [21], subcutaneous [22], or retroperitoneal abscess [22]. Our findings for XGP are consistent with this pattern. We suggest that renal stone presence may be a precipitating factor of complication development in patients with XGP, due to their association with fistula and abscess development.

We found that increased age was significantly associated with increased odds for renal fistula. Previous studies identified kidney stones, xanthogranulomatous pyelonephritis, and renal tuberculosis as positively associated with nephrocutaneous fistula [23]. We speculate that fistula formation may be a chronic process of XGP and more likely to occur after long-standing disease and thus associated with older age.

We found that dysuria, ICU admission, and operative treatment of nephrostomy or nephrostomy followed by nephrectomy were significantly associated with increased odds for sepsis. Dysuria is typically associated with UTIs which are one of the most common infections in adults [24]. UTIs can cause sepsis and acute kidney injury and are the etiology of 20–30% of sepsis in patients [25]. Our findings for XGP are similar to this pattern. Persistent dysuria can be associated with complicated UTIs which may include nephrolithiasis or anatomical or functional abnormalities of the urinary tract [26]. We speculate that the presence of dysuria is associated with a greater chance of an underlying complicated UTI, which in turn may increase the odds for sepsis.

A meta-analysis found that 24% of sepsis cases were acquired in the ICU [27]. We suggest that patients admitted to the ICU with XGP have an increased risk of ICU-acquired sepsis. Sepsis is a rare but potentially fatal complication of percutaneous nephrostomy [28]. Our findings indicate that this can occur for XGP. We found that UTI history was significantly associated with decreased odds for sepsis. We speculate that this may be due to early treatment of UTI and thus reducing the risk of sepsis.

We found that antibiotic treatment was significantly associated with increased odds for an abscess. A study of patients with renal abscesses found that all patients received antibiotic treatment [29]. We suggest that among XGP patients it is likely that patients with abscesses are empirically treated with antibiotics.

This study has several limitations. First, we included only published cases, thus our study is inherently associated with publication bias. Second, the lack of extractable data in some published case reports excluded certain cases. There are some areas for future research. As most patients were diagnosed postoperatively after biopsy, research should be conducted to analyze the accuracy of pre-operative imaging and other diagnostic testing for early diagnosis. Early diagnosis with prompt treatment may reduce the complications and the negative composite outcome associated with XGP.

Conclusions

In conclusion, kidney of both/horseshoe, dialysis required, and operative treatment of nephrostomy or nephrostomy followed by nephrectomy were each significantly associated with increased odds for the composite outcome. Fever and renal stones were each significantly associated with increased odds for any presentation or treatment complications. Clinicians treating XGP patients with involvement of both or horseshoe kidneys, dialysis requirements, or operative treatment of

nephrostomy or nephrostomy followed by nephrectomy may require more aggressive treatment, such as early nephrectomy, to mitigate poor patient outcomes. Clinicians treating patients with fever and renal stones may need to consider heightened surveillance and more aggressive treatment to mitigate these complications.

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Author Contribution Statement

The authors confirm contribution to the paper as follows: study conception and design: A.P., Z.K., and J.F.; data collection: A.P., A.T., D.G., K.P., H.P., and H.B.; analysis and interpretation of results: All authors; draft manuscript preparation: All authors. All authors reviewed the results and approved the final version of the manuscript.

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Ethics Statement: This manuscript reflects the authors' own research and analysis in a truthful and complete manner. This study did not require institutional or ethical review board approval. Principles of the Helsinki Declaration were followed.

Conflict of interest

None declared.

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