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Xanthogranulomatous pyelonephritis: an overview and management guide for clinicians

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Abstract

Xanthogranulomatous pyelonephritis is a rare and chronic form of pyelonephritis. Patients can present with an array of signs and symptoms including flank pain, fever and weight loss. The insidious nature of its clinical presentation means that it can mimic a neoplastic process. Kidney stone disease, diabetes and female gender are the most common associated factors. Early diagnosis can be difficult, but is vital to avoid sequelae such as abscess formation and involvement of surrounding structures. Management requires a multidisciplinary approach. Definitive resolution can only be achieved through nephrectomy. This article provides an overview and guide to diagnosis, investigation and management.

Key words: Infection; Inflammation; Kidney diseases; Xanthogranulomatous pyelonephritis

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Introduction

First described by Schlagenhaufer (1916), xanthogranulomatous pyelonephritis is a rare and atypical form of chronic pyelonephritis. Over time, it can lead to a complete loss of function in the affected kidney as well as becoming a nidus responsible for recurrent infection, which is frequently associated with multiple hospital admissions for treatment of sepsis. Recurrent infection and obstruction, which may be caused by kidney stones, leads to replacement of the renal parenchyma with granulomatous tissue. Xanthogranulomatous pyelonephritis accounts for approximately 0.6–1% of cases of chronic pyelonephritis (Goyal et al, 2011). Histological evaluation is required to establish a definitive diagnosis. In secondary care, patients can present under the admitting care of both medical and surgical specialities. Given the insidious clinical presentation, delayed diagnosis is not uncommon and this further supports the natural history of cases presenting to different specialities. An understanding and awareness of this clinical phenomenon is therefore important for doctors in training across all subspecialities. Diagnosis mandates a multidisciplinary approach, with involvement of microbiology, radiology, urology and diabetic specialists. This holistic model is mirrored in the clinical management pathway that is required. This article gives an overview and clinical guide to this condition.

Clinical presentation

Common presenting symptoms include dysuria, flank pain (non-colicky), haematuria, fever, chills, unintentional weight loss, loss of appetite and malaise. Detailed questioning may further reveal a history of recurrent urinary tract infections. Examination can reveal a palpable loin mass. This symptom profile means that the presentation can often mimic a malignant process. Differential diagnosis includes malignant disease such as renal cell carcinoma as well as tuberculosis, renal abscess, angiomyolipoma, extrapulmonary sarcoidosis and actinomycosis (Schlagenhaufer, 1916). Xanthogranulomatous pyelonephritis can also affect renal allografts. Delays to diagnosis can result in disease complications, principally as a result of local extension to neighbouring structures. Fistulation is one of the hallmarks of xanthogranulomatous pyelonephritis. Adverse sequelae can include psoas abscess as well as communication with the gastrointestinal tract. Patients can therefore also present with signs and symptoms related to these superimposed complications such as shortness of breath as a result of empyema caused by intrathoracic communication (Figure 1) or discharging sinus from the flank wall as a result of renocutaneous fistulation.

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Pathogenesis

Xanthogranulomatous pyelonephritis is more common in women, with a male to female ratio of 1:4 (Kundu et al, 2019). The group most commonly affected is women between 50 and 60 years of age. It nearly always affects a single kidney at one time. There has been limited advancement in the understanding of the underlying cause. Over 80% of cases are associated with underlying kidney stone disease and therefore chronic obstruction is very likely to contribute to the disease process (Figure 2). Aetiological factors postulated to play a role including obesity, immunosuppression, dyslipidaemia and diabetes mellitus. The latter is present in approximately 10% of cases and if it is poorly controlled, the clinical picture is worsened (Kundu et al, 2019).

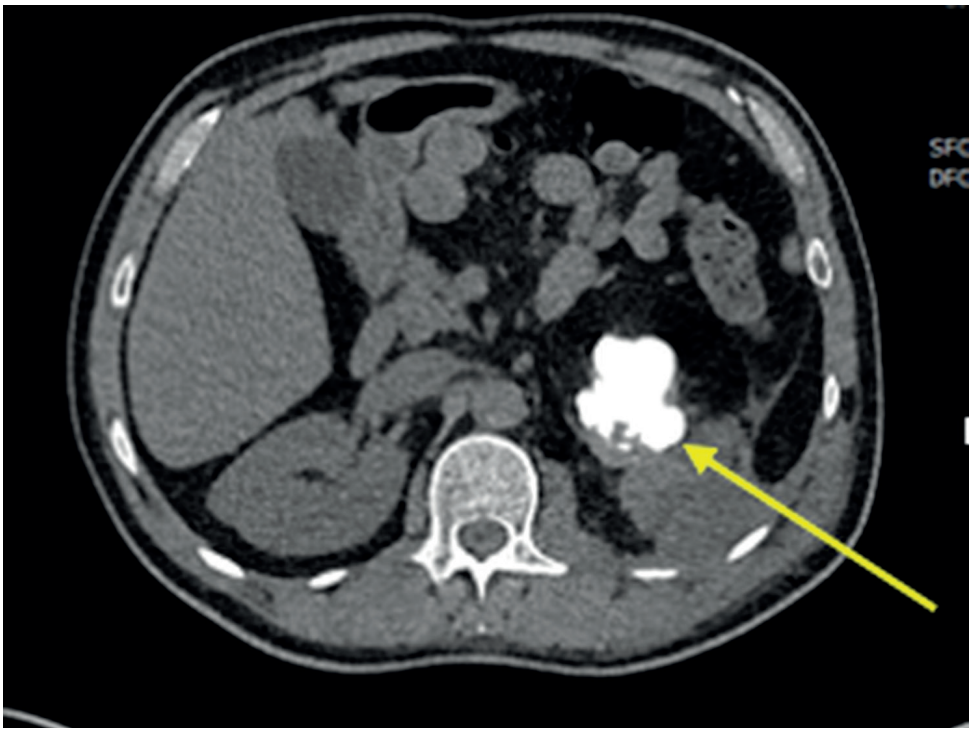

Figure 1. Staghorn calculus and associated psoas abscess.

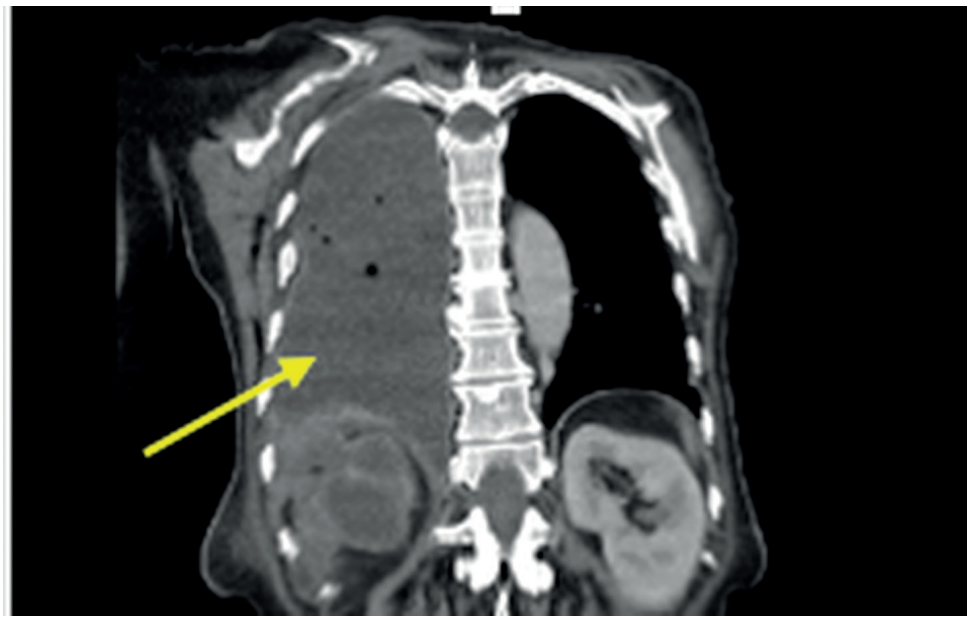

Figure 2. Pleural collection caused by intrathoracic extension of disease.

Diagnosis

Investigations

After clinical history and physical examination has been performed, blood tests should be obtained. At the least these should include full blood count, C-reactive protein and renal function. White cell count and levels of inflammatory markers are usually raised, including erythrocyte sedimentation rate. Xanthogranulomatous pyelonephritis can lead to chronic deterioration of renal function. Liver function tests can be deranged as result of nephrogenic hepatic dysfunction. Clotting screen will also be required if an interventional radiology procedure is under consideration. Urine should be sent for culture and sensitivity testing and the sample should ideally be collected before antibiotic therapy is commenced. Patients with signs of sepsis should be managed as per local sepsis protocol and this will include blood cultures too. All patients with suspected xanthogranulomatous pyelonephritis should be screened for diabetes. In cases of poor diabetic control, the NHS Diabetes guideline recommends referral to the specialist team if glycosylated haemoglobin (HbA_{1c}) is >69 mmol/mol in patients being managed perioperatively (Dhatariya et al, 2012). Given the association with immunosuppression, patients should also be tested for human immunodeficiency virus.

Imaging

Computed tomography is the most valuable imaging choice if available (Loffroy et al, 2008). Interestingly, before the advent of computed tomography the reported accuracy for correct preoperative diagnosis was only 5–15% (Varma et al, 1985). Use of contrast, if renal function allows, and a dedicated renal protocol adds valuable information. Computed tomography may reveal parenchymal inflammation, diffuse kidney enlargement, calculus and hydronephrosis. It will also help characterise any extrarenal extension. A characteristic radiological finding is the 'bear paw' sign (Figure 3), which is the result of multiple low attenuation, pus-filled cavities and the high vascularity of the surrounding walls (Xiang et al, 2018). However, it is not seen in all cases of xanthogranulomatous pyelonephritis. There is marked physiological uptake of fluorodeoxyglucose in the affected kidney if positron emission tomography–computed tomography has been performed, for example in select cases of pyrexia of unknown origin.

While ultrasound offers a more readily available and radiation-free alternative, the diagnostic yield for xanthogranulomatous pyelonephritis is much lower. Magnetic resonance imaging has a more limited role, although it is recommended in certain populations, for

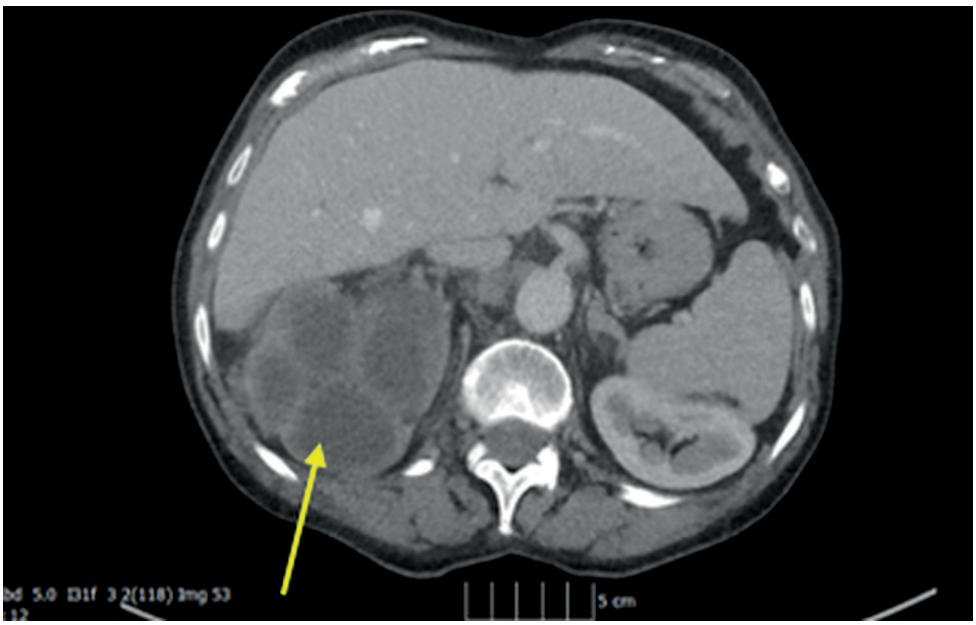

Figure 3. Radiological 'bear paw' sign.

example during pregnancy. While magnetic resonance imaging is less sensitive for confirming the presence of calculi than computed tomography, it is able to show hydronephrosis, oedema, abscesses and fluid collections.

Imaging alone cannot always differentiate between xanthogranulomatous pyelonephritis and a malignant process, particularly in cases of focal xanthogranulomatous pyelonephritis. It has also been reported to mimic recurrence after previous partial nephrectomy (Vernuccio et al, 2020). Cases of synchronous xanthogranulomatous pyelonephritis and renal cancer have also been reported (Goulding and Moser, 1984).

Classification and grading

Xanthogranulomatous pyelonephritis can be classified according to whether it is focal, segmental or diffuse. In focal xanthogranulomatous pyelonephritis (only 15.4% of cases), the disease is limited to the renal cortex and there is no involvement of the renal pelvis (Loffroy et al, 2008). A three-level grading system was devised by Malek and Elder (1978) to evaluate and stratify severity. Level 1 refers to cases where xanthogranulomatous pyelonephritis is confined to the kidney only, level 2 involves the peri-nephric fat (up to 70% of cases) and level 3 refers to spread to the retroperitoneum.

Treatment

While xanthogranulomatous pyelonephritis is acknowledged as a 'special type' of renal infection in the European Association of Urology guidelines, no further recommendation is provided to direct treatment (Bonkat et al, 2020). Pyuria and positive urine culture are reported in 95% and 60–88.9% of cases respectively (Dwivedi et al, 2006). *Escherichia coli*, *Proteus mirabilis* and *Klebsiella* spp. are the most commonly isolated pathogens. Patients with systemic symptoms require inpatient admission and starting on parenteral intravenous antibiotics. Choice of agent should be dictated by local resistance rates and susceptibility results when available. According to the International Clinical Practice Guidelines, an example of a regimen to initiate would be an extended use penicillin, with or without an aminoglycoside (Gupta et al, 2011). Response to antibiotics should be closely monitored and early involvement of the microbiologist is recommended.

Interventional radiology

Antibiotic therapy alone will not definitively treat the patient. Drainage of the upper tract is required in the presence of pyonephrosis. This can be achieved through percutaneous nephrostomy or cystoscopy and ureteral stent insertion. The decision regarding the method of decompression is typically made on a case-by-case basis and also largely influenced by the local setting, for example whether an interventional radiology service is available. Percutaneous nephrostomy has a higher success rate and is can be performed under local anaesthetic, which is an added advantage if the patient is in extremis or has a high anaesthetic risk. Confirmation of the anticoagulation status and correction if needed is required in these patients.

Surgical

Decompression of the upper urinary tract system is only a temporising measure. Patients may have multiple presentations to hospital with repeat infection as well as nephrostomy issues such as blockage, leakage and dislodgement among others. In addition to this, the ongoing quality of life is impaired as a result of having a nephrostomy. Once the infected system has been drained, extirpative surgery in the form of a simple nephrectomy is therefore warranted, which is the definitive treatment method. Patients may require preoperative optimisation, similar to that required for major oncological surgery, and dietician input should be considered. The functional status of the kidneys can be assessed using a dimercapto succinic acid radionuclide scan, which is a static nuclear medicine study (Hierholzer and Hierholzer, 1997). This can confirm the relative lack of function of the affected kidney and further support rationale for surgical removal. It may also demonstrate compensatory hypertrophy of the contralateral kidney.

A prolonged course of antibiotics (at least 4 weeks) is recommended in the lead up to surgery; studies have shown this to be associated with a shorter postoperative stay and a reduced rate of complications (Xie et al, 2020). Such is the complexity associated with the chronic inflammatory process that an open surgical approach is the standard technique. This provides a larger operative field, which holds advantages given the lack of clear planes; the kidney is typically stuck down and careful dissection is required as a result. The removed organ will often feel woody on palpation. Such is the distorted appearance of the kidney as a result of the obliterative disease process that it may need to be bi-valved at the time of surgery to confirm it is indeed the kidney. The pathophysiology of xanthogranulomatous pyelonephritis also results in increased vascularity and therefore a greater risk of intraoperative bleeding. Difficulties can ensue and the need for additional theatre time should be factored in. The operating team will require an experienced surgeon, which may consist of a dual consultant team. Forewarning other surgical specialities, such as vascular or gastrointestinal surgery, regarding the possible need for their involvement is advised. This level of planning is even more important when fistulation with intimately related structures has taken place. Major intraoperative complications including aortic injury, inferior vena cava and lumbar vein avulsion have been recorded (Xie et al, 2020).

Patients should be counselled regarding planned need for admission to intensive care postoperatively, which should be booked in advance rather than left as an afterthought. High volume, tertiary referral centres for complex surgery may consider a minimally invasive approach such as laparoscopic or robot-assisted surgery (Barboza et al, 2020). Cases where xanthogranulomatous pyelonephritis is radiologically organ confined and there is no fistulation are considered more suitable for this, but a low threshold for conversion should be upheld. Where a significant interval (for example several months) has passed since previous imaging, up-to-date cross-sectional imaging is strongly recommended before surgery in order to optimise procedural planning and help determine if a minimally invasive approach is even feasible. Arvind et al (2011) recorded outcomes of 19 patients undergoing nephrectomy for xanthogranulomatous pyelonephritis at a tertiary centre. Laparoscopic surgery was successfully performed in 14 patients, but conversion to open surgery was required in five cases as a result of failure to progress satisfactorily, bleeding or diaphragmatic injury. The mean operative time was 284 minutes (range 181–340 minutes). Three patients suffered major complications during laparoscopic surgery (collection in renal fossa, bowel obstruction and pancreatitis causing multiorgan failure).

Histological finding

Inspection of an affected kidney at a macroscopic level reveals gross architectural distortion of the parenchymal tissue and/or collecting system as well as possibly the surrounding fat depending on the degree of extension (Goyal et al, 2011). Overall, the scarring leads to morphological effacement. Yellow nodules may be seen, which can contain central areas of necrosis. Microscopically, peripherally to necrotic areas, there is granulation tissue with a mixed inflammatory cell infiltrate, including plasma cells, lymphocytes and lipid-laden histiocytes (xanthoma cells) (Muta et al, 1997). Neutrophils and occasional multinucleated giant cells can be seen (Figure 4).

Special populations

Xanthogranulomatous pyelonephritis has been reported in both the neonatal and paediatric setting, albeit the prevalence is even lower than in adults (less than 300 cases published) (Samuel et al, 2011). Wilms tumour and mesonephric blastoma are the key differentials in these age groups. Stoica et al (2018) reported the largest series in children (n=66, mean age 4.84 years) to date. Disease extended outside of the kidney in 79% of the cohort. All were treated successfully with surgery, but five cases required colonic resection as a result of gastrointestinal involvement.

There are reports of xanthogranulomatous pyelonephritis occurring in pregnancy (Ferreira et al, 2015). This can add difficulty to the standard management pathway. Similar to the surgical management of kidney stone disease in pregnancy, in cases of xanthogranulomatous

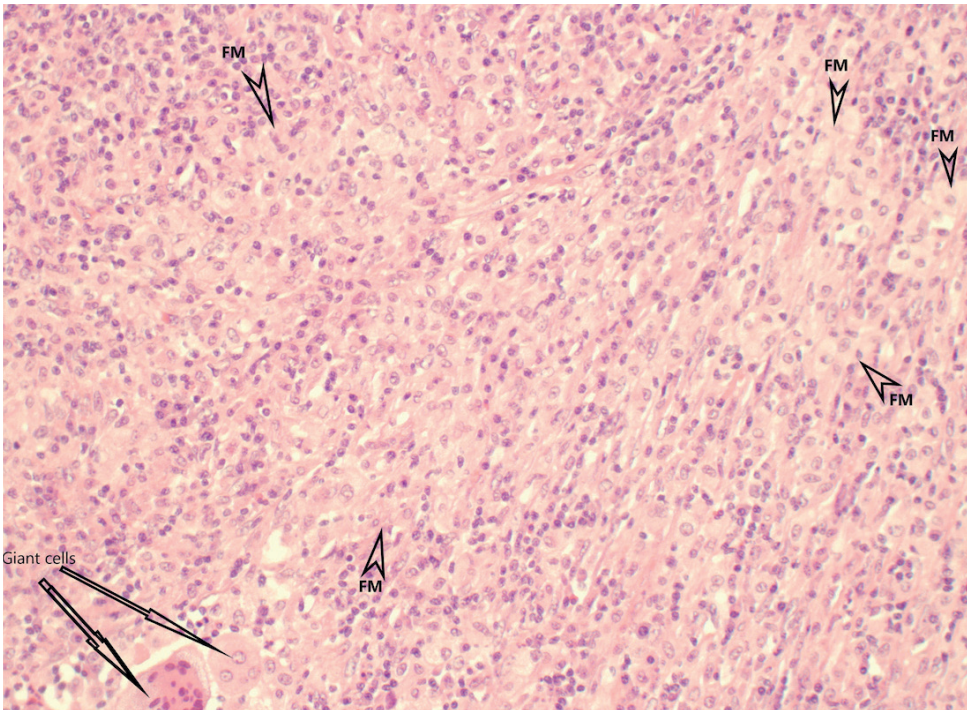

Figure 4. Microscopic view revealing foamy macrophages (FM) and giant cells.

pyelonephritis in pregnancy, the aim is to defer definitive surgery until delivery has taken place (Somani et al, 2017). In patients with severe xanthogranulomatous pyelonephritis where this is not safe and/or not possible, there are reports of nephrectomy being safely performed in pregnancy (Figueroa et al, 1996). However, this is an end of the line strategy and every effort to deliver a treatment plan, which renders the best outcomes for mother and baby, should be upheld. Loffroy et al (2007) reported their experience with a case of diffuse xanthogranulomatous pyelonephritis complicated by psoas abscess where caesarean delivery was performed at 32 weeks followed by extended nephrectomy.

Prognosis and further considerations

Surgery is considered curative for xanthogranulomatous pyelonephritis and review of the literature reveals no disease recurrence after surgery has been (finally) performed. No long-term follow up is therefore mandated in adults. The overall prognosis is much more favourable compared to other subtypes of renal infections such as emphysematous pyelonephritis (Aboumarzouk et al, 2014). The final histology report can deliver unexpected results such as concomitant amyloidosis or malignancy. In these cases, follow up is tailored accordingly. Failure to execute surgery will result in recurrent presentations of acute on chronic infection, which necessitate hospital admission and contribute further to the patient's decline in performance status. The mortality rate is low, and all reported cases are attributed to postoperative sepsis. Strict adherence to preoperative planning, including a tailored preoperative antibiotic regimen, are key recommendations from a meta-analysis of deaths recorded after kidney stone disease-related surgery (Whitehurst et al, 2019). The occurrence of bilateral xanthogranulomatous pyelonephritis is more likely to be associated with a fatal outcome. Given that the prevalence of kidney stone disease, diabetes and obesity is increasing, it is plausible that the number of cases of xanthogranulomatous pyelonephritis will follow the same trend, which further supports the importance of the clinician's awareness and understanding of it.

Conclusions

Xanthogranulomatous pyelonephritis is an atypical and chronic form of pyelonephritis, which can present with an array of non-specific symptoms. Early diagnosis is key to minimising development of sequelae such as abscess formation and extension to neighbouring viscera.

Key points

- Xanthogranulomatous pyelonephritis is an atypical and chronic form of pyelonephritis, which can present with an array of non-specific symptoms.
- Over 80% of cases are associated with underlying kidney stone disease.
- Xanthogranulomatous pyelonephritis can be classified according to whether it is focal, segmental or diffuse.
- Drainage of the upper urinary tract followed by nephrectomy is the recommended standard of care.
- Surgery is considered curative for xanthogranulomatous pyelonephritis.

Curriculum checklist

This article addresses the following requirements from the general internal medicine training curriculum:

- Managing an acute unselected take
- Managing an acute specialty-related take
- Managing medical problems in patients in other specialties and special cases
- Managing end of life and applying palliative care skills

A multidisciplinary treatment approach can deliver excellent outcomes. Drainage of the upper urinary tract followed by nephrectomy is the recommended standard of care. Careful preoperative planning and a multidisciplinary approach is of paramount importance given the complexity of such cases.

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Conflicts of interest

The authors declare no conflicts of interest.

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