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Review Article

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Xanthogranulomatous pyelonephritis

W. D. D. Prasanni and **A. P. Malalasekera**
Department of Anatomy, Faculty of Medicine, University of Colombo, Sri Lanka.

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Introduction

Xanthogranulomatous pyelonephritis (XGPN) is a rare chronic inflammatory disease of the kidney, characterized by gradual destruction and invasion of renal parenchyma by inflammatory cells resulting in a non-functional kidney. It was first described as "staphylococcosis" by Schlagenhaufer in 1916, owing to its common association with *E.coli* and *Proteus* infection (1). The name xanthoganulomatous pyelonephritis was introduced by Oberling in 1935 (2).

XGPN commonly affects middle aged females (3-6), especially during the fourth to sixth decades of life (7). But in children it has a male preponderance and mostly affects those under the age of 10 years (8). It is mostly unilateral (5,6,8) and equal incidence is reported in right and left sides (9).

Only a handful of cases of XGPN have been successfully treated medically, while the cornerstone of management is nephrectomy (7,10,11). Perioperative diagnosis of XGPN is challenging as it is frequently misdiagnosed as other inflammatory and neoplastic conditions of the kidney, due to its indefinite clinical presentation and indistinguishable imaging (12). Previously, diagnosis was confirmed histologically following nephrectomy, but with the advancement of radiological imaging, accurate preoperative diagnosis may be possible in patients with clinical suspicion of the disease (10,13). Accurate diagnosis before surgery can help in planning goal directed treatment and providing conservative management or to perform nephron sparing surgery whenever possible especially in patients with focal XGPN. The purpose of this article is to summarize clinical, pathological, radiological features of XGPN and to identify common diagnostic and therapeutic challenges encountered by surgeons when managing these patients.

Aetiology

The incidence of this disease is still unknown, but approximately 0.6% of nephrectomy patients with chronic pyelonephritis have histologically proven evidence of XGPN (14). The aetiology for XGPN is still debatable. However it is primarily due to recurrent urinary tract infections following chronic obstruction of the urinary tract (5,12). Urinary calculi are the most common reason for the obstruction, being the cause in 70%-100% of patients, but they are not essential in making the diagnosis (3,4). Majority of renal calculi in XGPN are staghorn calculi, and are found in 50% of patients (3). Rarely neuromuscular pelviureteric junction obstruction or a tumour can be the reason for the obstruction (3,12). Abnormal metabolism of lipids also plays a role in the pathogenesis (15). Some authors suggest inadequate host defenses against subacute bacterial infections may be the reason for recurrent urinary tract infections (15). Malnutrition is observed among these patients, and has been suggested to be another aetiological factor as it leads to a state of immune deficiency (10,15,16). But successful recovery and the lack of documented recurrences following surgery makes immune deficiency unlikely to be an aetiological factor. Therefore malnutrition can be considered as secondary to XGPN, rather than its aetiological factor (16). In two case series high prevalence of obesity was observed among the patients with XGPN. This association is not statistically proven yet but warrants further investigation (3,17). *Escherichia coli* and *Proteus mirabilis* are the commonest organisms isolated in urine culture (4,5,7). But in a minority, Pseudomonas, Klebsiella, anaerobic organisms (3,6-8), and fungal species (4,5) are isolated. A polymicrobial growth is also reported in 15-25% of cases (5, 6).

Pathology

Pathologically this disease entity resembles the features of chronic pyelonephritis. It can affect any part of the kidney. In ninety percent there is diffuse involvement of the kidney and focal involvement is seen in only 10% of cases (13). Chronic suppurative inflammation of the pelvicalyceal system and renal parenchyma is seen with formation of inflammatory masses referred to as pseudo-tumorous lesions, due to their ability to

invade and destroy the surrounding tissues. The kidney is grossly enlarged with markedly dilated calyces filled with pus, stones or sometimes both (7,9). Sometimes associated structural anomalies of the pelvicalyceal system can be identified (12,15).

Macroscopically, single or multiple inflamed irregular yellow to orange nodules can be seen (7, 12). The renal capsule is thickened and cortex is thin and diffusely scarred (8). In severe cases, areas of localized abscesses with central necrosis, extending in to the adrenal gland, diaphragm, spleen, intestine, perinephric fat and retroperitoneal structures can be identified (12,15).

Foamy histiocytes (xanthoma cells) in a background of acute and chronic inflammatory cells are pathognomic for XGPN (12). These changes can be focal or diffuse and in severe cases extending to perirenal tissues. Foamy appearance of the cytoplasm is due to abundant lipid deposition in the cytoplasm of the histiocytes (12). Variable number of xanthoma cells, neutrophils, lymphocytes, plasma cells and multinucleate giant cells can be seen in the infiltrate (12). In addition parenchymal calcification, variable degree of tubular atrophy and dilatation, interstitial fibrosis and haemorrhagic lesions can be identified. Glomerulosclerosis and intimal thickening with narrow lumen resembling endarteritis obliterans are two other findings described in the literature (9, 12, 15).

XGPN is known as a great mimicker, as it is commonly misdiagnosed with several neoplastic and inflammatory conditions of the kidney (Table 1). Histologically XGPN can mimic malignant lesions such as leiomyosarcoma and clear, papillary and sarcomatoid renal cell carcinoma (RCC) (12). Fine needle aspiration cytology of XGPN shows typical appearance of cells with abundant clear cytoplasm with a prominent nucleolus. This clear cell appearance of XGPN is similar to clear cell carcinoma of the kidney (12,15). Occasionally papillary renal cell carcinomas which contain many foamy cells can cause diagnostic confusion. But in XGPN, cells are usually diffusely positive for CD 68 and in RCC cells are positive for CD 10 and epithelial membrane antigen. Therefore by using immunohistochemical methods accurate differentiation can be made. Malakoplakia and megalocytic interstitial nephritis are two benign conditions which commonly cause diagnostic dilemma. Characteristically both lesions contain periodic acid-Schiff diastase-positive material in the cytoplasm of histiocytes. Among them renal malakoplakia macroscopically and histologically closely resembles XGPN but the Michaelis-Gutmann bodies in malakoplakia helps to differentiate the two (Figure 1). Other inflammatory conditions such as renal tuberculosis (TB) and abscesses also cause diagnostic difficulty. But characteristic tuberculous granulomas with Langhans type giant cells and acid-fast positive bacilli in TB direct towards a correct diagnose (18). Depending on the tissue involvement, in 1978, Malek and Elder proposed a classification for XGPN (19) (Table 2).

Table 1. Differential diagnosis of XGPN

Neoplastic	Benign conditions
Renal cell carcinoma • Clear cell carcinoma • Papillary cell carcinoma • Sarcomatoid cell carcinoma Transitional cell carcinoma of renal pelvis Leiomyosarcoma Willm's tumor	Renal/ perinephric abscess Renal tuberculosis Renal malacoplakia Megalocytic interstitial nephritis

Table 2. Staging of XGPN

Stage	Tissue involvement
Stage I	Disease confined to the kidney
Stage II	Infiltration of Gerota's space
Stage III	Infiltrate perinephric space and retroperitoneal structures

Clinical presentation

Clinical symptoms of XGPN are very nonspecific and onset is usually subacute or chronic. Generally these patients are chronically ill and almost always symptomatic. Most patients complain of more than one symptom (4). Flank/ abdominal pain and fever are the commonest symptoms and are present in almost all patients (4,5). Gross haematuria, abdominal mass, voiding symptoms and other constitutional symptoms such as loss of appetite, loss of weight are frequently documented in case series. Symptoms of chronic kidney disease are uncommon due to compensatory function of the opposite kidney (5). If the disease progresses for an adequate time patients can develop serious complications. One third of patients with XGPN are reported to have complications at the time of presentation (12). Psoas abscesses (20), emphysematous pyelonephritis (4), splenic abscesses (3,6,20) nephro cutaneous (6,8) nephrocolonic fistula (3,6) and great vessel involvement are few reported complications in the literature.

Preoperative diagnosis

Accurate preoperative diagnosis of this condition is challenging and ranges between 19%-22% in two case series as there are no conclusive clinical features, laboratory markers or imaging available (4,5). Therefore traditionally, the diagnosis is obtained at histological assessment following nephrectomy (5). Routine lab investigations are also inconclusive. But 60-80% of patients with XGPN had elevated WBC count and low haemoglobin indicating the systemic effects of the disease (4-6). Some patients had elevated ESR, CRP and liver enzymes. The raised AST/ALT usually resolve following surgery and is believed to be due to reactive hepatitis (5) or hepato-renal syndrome (15). Urine analysis often reveals proteinuria, bacteriuria and pyuria (15). Urine culture are positive in approximately 60-80%, *E. coli* and *Proteus mirabilis* being the commonest organisms implicated (4,6-8). Renal function tests are normal unless there is bilateral impairment of kidneys (15).

Imaging studies are shown to be useful in preoperative diagnosis. Preoperative diagnostic value of USS in XGPN is limited but can be used for initial evaluation (6). Enlarged kidney with thin parenchyma, multiple hypoechoic areas due to hydronephrosis, renal stones, parenchymal and perirenal calcifications in a background of inflammation is suggestive of diffuse XGPN (10). Even though radiological investigations are not 100% diagnostic (15), when available, characteristic CT findings improve the ability of diagnosis in XGPN preoperatively (20). CT can be considered as the current gold standard in preoperative diagnosis of XGPN (4). In diffuse XGPN, unilateral enlargement of kidney and evidence of renal parenchymal inflammation was present in all patients in a case series described by Rajesh et al (20). Dilated calyces and localized pus collections can be seen as areas of low attenuation and calculi also can be identified on CT scan (6,12,20). Contracted pelvis and low attenuating dilated calyces with multi-loculated appearance resemble a paw of a bear in cross sectional imaging (The Bear's paw sign – Figure 2) (21, 22). Margins of these low attenuation areas comprising of compressed renal parenchyma and highly vascular granulation tissues show enhancement with IV contrast on CECT (6,20). Unilateral renal enlargement, calculi in renal pelvis and nonfunctioning / poorly functioning kidney form a classic triad seen on CT scan in XGPN (21). Extra-renal extension of inflammation is seen as thickening of renal fascia and stranding of perinephric and para renal fat space (20). In addition to the diagnosis, these findings help to stage the disease. Xanthomas can also be seen in CT but are observed in only 29% of patients (20). Xanthomas may be present in other focal renal pathologies such as liposarcomas and angio-myolipomas as well. Therefore usefulness of this finding is still debatable (20).

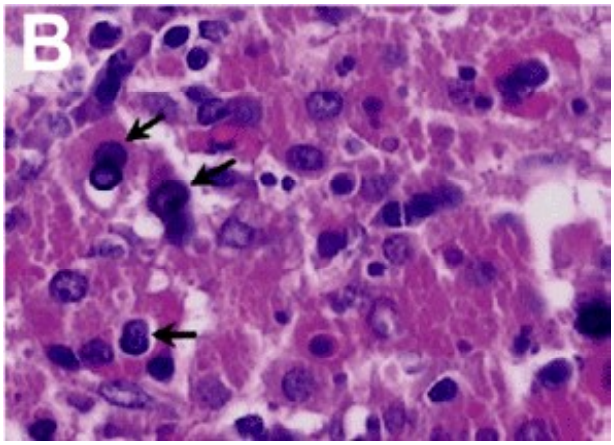

Figure 1. *Rounded concentrically layered, target or ring like structures that were interpreted as Michaelis-Gutmann bodies within the histiocytes as well as extracellularly in the stroma.*

(With permission from Cury José et al. Renal parenchymal malacoplakia with pleural effusion. Clinics [Internet]. 2007 Feb; 62(1): 87-88).

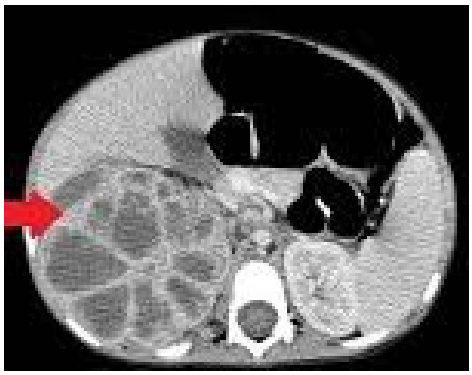

Figure 2. *Selected image of the contrast enhanced CT of the abdomen. The typical Bear's paw sign is demonstrated (arrow).*

(With permission from Valerie Said Conti et al. Xanthogranulomatous pyelonephritis: the case of a perplexing kidney. BMJ Case Reports 2014: published online 19 September 2014, doi:10.1136/bcr-2014-206172).

Unlike diffuse XGPN, CT and USS appearance of focal XGPN often confuse with other focal renal pathologies unless it is associated with features of obstruction (5, 8). Place of MRI in diagnosing focal XGPN is discussed

in the literature, but has not been shown to be effective (20). MRI confirm the findings of CT scan, but fail to provide additional information beyond CT. X-ray KUB, IVP are also not commonly performed due to the same reason. Therefore currently CT scan is considered superior to other imaging modalities in diagnosing XGPN (4,7,10).

Tc^{99m} MAG3 or DMPA scintigraphy imaging is necessary to determine whether the affected kidney has any residual function. Global loss of unilateral function indicates diffuse XGPN and kidney with residual function usually associate with focal XGPN (10,15).

Treatment

Almost all patients with XGPN are managed surgically (7,10,11,23,24). But nephrectomy is difficult in XGPN because the chronic inflammation of the perirenal tissues and the hilum leads to fibrotic adhesions and distortion of the normal architecture (4,11,23). The aim is to remove all affected granulomatous tissues with the kidney to prevent fistula formation in the future (4). Nephrectomy can be done as either open nephrectomy (ON) or laparoscopic nephrectomy (LN). Individual surgical approach is determined by the extent of the disease, preference and experience of the surgeon (23).

When performing ON the surgeon can access the kidney either trans-abdominally or via a flank incision (4,6,11,23,25). Flank incision allows surgery without entering the peritoneum, but adequate access to the entire abdominal cavity and direct access to the aorta for pedicle control favours trans-abdominal approach (3).

The role of laparoscopic surgery in this category of patients is still controversial. Laparoscopic nephrectomy is widely performed due to its advantages of minimally invasive surgery over open surgery (4,11,26). LN for XGPN is more difficult compared to nephrectomy for non-inflammatory conditions and the usual benefits of LN were not demonstrated initially in patients with XGPN (23,24,26). Initial case series reported 30-50% of conversion rates (4,11). Therefore authors concluded that conventional ON should be considered in XGPN (27). But recently several case series reported favourable outcomes in LN in contrast to the previous studies (11,23-26,28). These retrospective analyses of cases showed typical advantages of laparoscopic surgery such as minimal blood loss, shorter hospital stay, early recovery and minimal analgesia in XGPN patients also. These studies reported conversion rates of 7-20% which is much lower than the previous studies (23-26). More recently in a case series of 11 patients, none of the patients needed open conversion (28). Failure of progression due to extensive adhesions (23, 25,26), diaphragmatic and renal vein damage (11,26) were common reasons for conversion. In two case series similar postoperative complications were reported among the LN and ON groups (11,23). 80% success rate of LN reported in two further series, could be due to improved technology and skills in laparoscopic surgery (25,26). Studies show that during difficult nephrectomies, hand assisted laparoscopy (HAL) reduces incidence of conversion to ON (25,28,29). Therefore it is recommended HAL should be considered prior to converting to open surgery in order to offer the benefits of minimally invasive surgery. Evidence suggest LN for XGPN can be completed safely, therefore remains as a reasonable option in the hands of well experienced surgeons. But if there is any difficulty encountered during surgery, always need to consider HAL or failing that convert to open surgery. However further large randomized controlled trials are needed to arrive at a better conclusion.

Almost all patients with diffuse XGPN and focal XGPN with extensive tissue involvement need total nephrectomy (15). There are no reported cases of conservative management of diffuse XGPN (15). In focal XGPN, if the lesion is well localized and there is reasonable function in the affected kidney, there is a place for nephron-sparing surgery (5,8,15). Cases of young patients with focal XGPN have rarely been successfully managed with antibiotics only (15). The uncommon association of XGPN and malignancy also contribute to the unpopularity of medical management (11,30,31). Patients who are offered conservative management need to be followed up carefully and if not improving surgical options needs to be considered (16).

There are cases of focal XGPN which have been managed with simple drainage only. But this should be followed by decompression of the system if any obstruction is evident (15). Recent evidence recommends surgical or USS guided drainage of abscess prior to definitive surgery with adequate pre and postoperative antibiotic coverage. These measures have improved the postoperative outcomes in these patients (8). Multidisciplinary approach including both medical and surgical teams are crucial for management of these patients. Especially in cases of nephro-colonic, nephrocutaneous fistulae and great vessel involvement which needs extensive preoperative preparation and surgical expertise, all subspecialties need to play a vital role to provide best care for the patient.

Follow up and prognosis

The prognosis of patients with XGPN is good. As the surgery is notoriously difficult, visceral and vascular

injuries have been reported. Although it is associated with high morbidity, mortality from this disease is relatively uncommon. Following surgery laboratory investigations come back to normal, including the liver functions. There are no reported cases of recurrence of XGPN in the healthy contralateral kidney.

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