Xanthogranulomatous Pyelonephritis

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Xanthogranulomatous pyelonephritis is an uncommon chronic destructive granulomatous process of renal parenchyma in association with long-term urinary tract obstruction and infection. It affects females more often than males, with a wide range of age, from newborn to elderly. Almost all patients are symptomatic and the most common symptoms are flank or abdominal pain, lower urinary tract symptoms, fever, palpable mass, gross hematuria, and weight loss. The common laboratory findings are leukocytosis and anemia. Urine cultures most often reveal *Escherichia coli* and *Proteus mirabilis*. Computed tomography is the mainstay of diagnostic imaging for xanthogranulomatous pyelonephritis. Imaging studies may demonstrate diffuse or focal form. Histologically, xanthogranulomatous pyelonephritis presents a granulomatous inflammatory infiltrate composed of neutrophils, lymphocytes, plasma cells, xanthomatous histiocytes, and multinucleated giant cells. The differential diagnosis includes clear cell renal cell carcinoma, papillary renal cell carcinoma, sarcomatoid renal cell carcinoma, leiomysarcoma, malakoplakia, and megalocytic interstitial nephritis. Both antibiotics and surgery can be treatment options depending on the patient’s disease status. (Arch Pathol Lab Med. 2011;135:671–674)

**X**anthogranulomatous pyelonephritis (XGP) is a chronic destructive granulomatous inflammation of renal parenchyma. This entity was first described by Schlagenhauer in 1916. Three forms were recognized: diffuse, segmental, and focal. Segmental XGP is characterized by segmental involvement of the disease, while focal XGP is located within the cortex with no pelvic communication. It mimics other neoplastic and inflammatory renal diseases. It is an uncommon entity, accounting for from 0.6% of histologically documented cases of chronic pyelonephritis to 19.2% of nephrectomies performed for pyelonephritis.

**AGE AND SEX**

The mean age of occurrence of XGP varies from 45 to 55.2 years; age range is 2 to 84 years. In a recent series on XGP in childhood, the age range was 1 to 3 years. Neonatal XGP has also been reported. In most series, women are affected more frequently than men, with male to female ratio ranging from 7.3 to 1.5. 

**SYMPTOMS**

In a recent series, all patients were symptomatic and the most common symptoms were flank or abdominal pain, lower urinary tract symptoms, fever, palpable mass, gross hematuria, and weight loss. In general, patients had more than one symptom. Other series reported similar symptoms, with an exceptional case that was detected during the workup for vague gastrointestinal symptoms. Complications were observed in one-third of cases in a series including psoas abscess, nephrocutaneous fistula, nephrocolonic fistula, and paraneoplastic abscess. Ischemic colitis involving transverse and descending colon owing to compression by a large mass and emphysematous pyelonephritis have also been reported.

**LABORATORY FINDINGS**

The hematologic evaluation shows leukocytosis (41%), mean white blood cell count 12,300/μL and anemia (63%), mean hemoglobin 10.4 g/dL. Urinalysis reveals pyuria in most cases (57%). The percentage of positive urine cultures ranges from 61.5% to 88.9%. Most common organisms are *Escherichia coli* and *Proteus mirabilis*. Others include *Staphylococcus aureus*, group B *Streptococcus*, *Candida*, *Klebsiella*, and *Bacteroides*. Urine culture might also grow more than one organism. Additional laboratory findings include increased erythrocyte sedimentation rate (94.4%), raised alkaline phosphatase and aspartate aminotransferase (27.8%), low albumin (27.8%), and high fasting blood sugar (22.2%).

**IMAGING FEATURES**

Computed tomography is the mainstay of diagnostic imaging for XGP. The imaging studies show diffuse disease in most cases (84.6%) and focal disease in the rest (15.4%). Computed tomography findings of diffuse XGP include hydronephrosis (90.9%), renal calculus (72.7%), pyonephrosis (45.5%), intraparenchymatous collection (45.5%), cortical renal atrophy (45.5%), nonfunctioning kidney (36.4%), abscess (36.4%), and perinephric fat accumulation (18.2%). In summary, the combination of a nonfunctioning enlarged kidney, a central calculus within a contracted renal pelvis, expansion of the calices, and inflammatory changes in the perinephric fat is strongly suggestive of XGP. Atypical findings are less common and include massive pelvic dilatation, absence of...
stones, and renal atrophy with or without accumulation of perinephric fat.1

Focal and segmental XGP can be associated with normal kidney function.2 Some of the cases demonstrate findings similar to those seen in the diffuse form, but others may show features that are difficult to differentiate from neoplasms.3

Ultrasound of diffuse XGP typically demonstrates an enlarged kidney with a large amorphous central echogenicity that corresponds to a renal pelvis staghorn calculus, multiple fluid-filled masses, and pelvic contracture. Ultrasound findings in focal XGP are nonspecific and virtually impossible to differentiate from a renal abscess or necrotic renal cell carcinoma (RCC).4,6 Abdominal x-ray shows renal calculi.5 Magnetic resonance imaging can be a valuable tool, as it is sensitive for identifying the accumulation of lipid-laden foamy macrophages as high-intensity signal on spin-echo, T1-weighted images. However, it is less useful if the lesion lacks a certain number of foamy macrophages.5

PREOPERATIVE DIAGNOSIS

Xanthogranulomatous pyelonephritis is commonly misdiagnosed preoperatively because it mimics other pathologic conditions such as pyelonephritis, tuberculosis, perinephric abscess, and RCC. No single clinical or radiologic feature is diagnostic of XGP.4 The preoperative diagnostic rates were 22%, 46.2%, and 30.76% in 3 series, respectively.2,4,10 In 1 series, up to 42.3% of cases had renal masses that were suggestive of RCC on computed tomography scan.10 In the pediatric population, the preoperative diagnosis was made at a much higher rate, up to 100% in 1 series.12

ETIOLOGY

The exact etiology of XGP is unknown, but it is generally accepted that the disease process is associated with long-term obstruction and infection. Calculi, frequently staghorn type, may be seen in 47% to 100% of the cases,4,5,8-11 although they are not a prerequisite to make a diagnosis of XGP. Additional predisposing factors are ureteropelvic junction syndrome, ureteropelvic duplication, bladder tumor, and chronic interstitial nephritis. Comorbid conditions were also noted including pregnancy, diabetes mellitus, rheumatoid arthritis, chronic viral hepatitis C, cirrhosis, and obesity.4

GROSS FEATURES

The kidney involved by diffuse XGP is typically enlarged with hydronephrosis, pelvic calculi, or some other conditions such as congenital type obstruction, radiation fibrosis, and carcinoma of the ureter. Single or multiple yellow to orange nodules are present, which can mimic tumor nodules. Other findings include central necrosis with abscess formation, involvement of perinephric fat,5 diffuse cortical scarring with effacement of the normal renal architecture,16 and cortical atrophy. In severe cases, gross destruction extends into the perinephric tissues and adrenal glands17 (Figure 1).

MICROSCOPIC FEATURES

AND IMMUNOHISTOCHEMISTRY

Xanthogranulomatous pyelonephritis is characterized by a granulomatous mixed inflammatory infiltrate with fibrosis and cholesterol clefts in the background (Figure 2). The changes diffusely or focally involve renal parenchyma and perirenal soft tissue in severe cases. The inflammatory infiltrate is composed of a variable number of xanthomatous histiocytes with foamy cytoplasm (Figure 3), neutrophils, lymphocytes, plasma cells, and multinucleated giant cells. In addition, a variable degree of renal tubular atrophy, tubular dilatation and focal squamous metaplasia of the urothelium,9 microabscesses, lymphoid aggregates with germinal center formation, and spindle cell proliferation can be observed. Acute inflammation within the tubular system may also be present. Small- to medium-sized arteries show intimal fibrosis with luminal narrowing in association with hemorrhage. The ureters can be involved by the inflammation as well.17

The lesion shows diffuse positivity for CD68 (Figure 4) and vimentin, and negativity for smooth muscle actin, desmin, and epithelial markers.16 The xanthomatous cells and macrophages show positive cytoplasmic staining for α1-antitrypsin and lysozyme.16

Three stages of XGP were proposed: stage I, the lesion is confined to the renal parenchyma; stage II, the lesion involves the perirenal space; and stage III, the lesion extends into perirenal and pararenal spaces.

CYTOLOGY FEATURES

Fine-needle aspiration cytology of XGP is characterized by individual or small clusters of xanthomatous cells and cells showing a glandlike pattern that might be from degenerative renal tubules.18 The cells had abundant clear to vacuolated fragile cytoplasm, round vesicular nucleus, and single prominent nucleolus, consistent with histiocytes. The cells may be surrounding rich branching blood vessels. Focal necrosis, mild pleomorphism, and plasma cells can be seen.19 The cytoclogic morphology of XGP can be misinterpreted as RCC, and erroneous diagnoses are commonly made.19,20 Therefore, fine-needle aspiration cytology plays an insignificant role in diagnosing XGP. Immunohistochemistry (cytokeratin, epithelial membrane antigen, and CD68) can help to make a confident diagnosis when it is possible.19

MICROSCOPIC DIFFERENTIAL DIAGNOSIS

The lipid-laden xanthomatous cells may mimic the clear cells of clear cell RCC. Foamy histiocytes may also present extensively in papillary RCC. The xanthomatous cells have a foamy cytoplasm compared with the more cleared cytoplasm of clear cells. Adequate sampling should reveal granulomatous inflammation of XGP and the papillary structures of papillary RCC. However, as more preoperative biopsies of kidney mass are performed, sampling becomes more challenging. In this situation, immunohistochemistry study can play an essential role in the differential diagnosis. Xanthogranulomatous pyelonephritis is diffusely positive for CD68. Renal cell carcinoma is usually positive for CD10 and epithelial membrane antigen. Vimentin can stain positive for both. Xanthogranulomatous pyelonephritis with prominent spindle cell proliferation may mimic sarcomatoid RCC; the differentiation relies on demonstration of markedly atypical spindle cells and coexisting epithelial cell components. Sarcomatoid RCC demonstrates at least focal positivity for cytokeratin and epithelial membrane antigen. Another spindle cell lesion, leiomyosarcoma, is also in the differential diagnosis; it demonstrates interlacing bundles of spindle cells with blunt-ended nuclei and eosinophilic
cytoplasm. These cells are positive for desmin and smooth muscle actin.16

Two benign closely related entities are malakoplakia and megalocytic interstitial nephritis. The hallmark of both lesions is the periodic acid–Schiff diastase-positive material in the cytoplasm of the histiocytes. Malakoplakia of the kidney is primarily a disease of the renal pelvis with involvement of the renal parenchyma, and Michaelis-Gutmann bodies are characteristic of the lesion.9

Other differential diagnoses include Wilms tumor in the pediatric population, other types of RCC, tuberculosis, and renal abscess. Characteristic histology and special and immunohistochemistry stains usually lead to the right diagnosis.

TREATMENT AND PROGNOSIS

For diffuse or advanced-stage disease, nephrectomy usually is the treatment option.1 Focal XGP, patients who are not candidates for surgery, or bilateral XGP can also be treated with antibiotics if the diagnosis can be established with histologic features of biopsy or combined clinical and cytologic features.21-23 Preoperative and postoperative broad-spectrum antibiotics and symptomatic management are also key factors for successful management of this condition.20 The prognosis is considered to be good after treatment.22 However, several deaths were reported including 1 of 87 patients who died directly from XGP,11 and 2 of 41 patients who died of postoperative sepsis.2
Xanthogranulomatous pyelonephritis has been shown to be associated with transitional cell carcinoma of the renal pelvis and RCC.\textsuperscript{5,7} Cases of XGP in renal allografts have also been reported.\textsuperscript{24}

**CONCLUSION**

Xanthogranulomatous pyelonephritis is an uncommon encounter on the surgical pathology bench and is associated with long-term urinary tract obstruction and infection. It mimics various benign and malignant conditions, both clinically and pathologically. It requires a combination of clinical presentation, imaging studies, fine-needle aspiration cytology, or biopsies to make a definite diagnosis preoperatively. Pathologic diagnosis relies on the characteristic morphology of XGP and immunohistochemistry studies when necessary. Treatment includes both surgical intervention and medical management.

**References**