

A Retrospective Review of Xanthogranulomatous Pyelonephritis - Our Experience at a Tertiary Care Center Located in Dharwad District, Karnataka

Pramod Jagadeesh Makannavar¹, Srinivas Kalabavi², Revanasiddappa Kanagali³,
Bhuvanesh Aradhya⁴, Sangamath⁵

^{1, 2, 3, 4, 5} Department of Urology, S.D.M. College of Medical Sciences and Hospital, Dharwad, Karnataka, India.

ABSTRACT

BACKGROUND

Xanthogranulomatous pyelonephritis (XGP) is an uncommon form of chronic pyelonephritis that is characterized by extensive enlargement and destruction of the involved kidney which ultimately results in non-functioning kidney. It often mimics other inflammatory or neoplastic renal disorders. Unlike chronic pyelonephritis, it spreads to the perinephric space with formation of multiple abscesses and fistulas. It is now being recognized as an important cause of renal morbidity and mortality worldwide.

METHODS

This is a case series undertaken in a tertiary care center. Clinical data was collected from last 6 years. Clinical features, radiological findings, treatment, and its outcome were analysed and presented.

RESULTS

A total of 23 cases diagnosed clinically were included in our study. The disease is more prevalent in females than in males with ratio of 1.8 : 1, with mean age of 47.04 years. Most of the patients presented with flank pain and fever. 2 patients had unusual presentations that are nephrocutaneous fistula and necrotising fasciitis of flank region. In our study, disease was associated with urolithiasis in 43.47 % and diabetes mellitus (DM) in 60.8 %. *E. coli* was the most commonly grown organism in urine culture. Most of the patients underwent initial percutaneous nephrostomy (PCN) or double-J (DJ) stenting followed by definitive treatment that is nephrectomy (21 patients, 2 patients lost to follow up). Extraperitoneal flank approach was most commonly chosen compared to subcostal transperitoneal approach. Excess blood loss was the most common complication encountered during surgery; 8 patients required post-operative blood transfusion. 5 patients required intensive care unit (ICU) care with inotropic support post-operatively. 6 patients had post-operative superficial surgical site infection.

CONCLUSIONS

XGP is a rare form of chronic pyelonephritis resulting in enlarged non-functioning kidney. UTI (urinary tract infection) and urolithiasis are the most important factors involved in pathogenesis. Prompt diagnosis and treatment is essential. Initial antibiotic treatment with drainage procedure (PCN or DJ stenting) followed by nephrectomy is treatment of choice. Early diagnosis and treatment may limit the disease process and associated morbidity, thus leading to good outcome.

KEYWORDS

Xanthogranulomatous Pyelonephritis, UTI (Urinary Tract Infection), Urolithiasis, Nephrectomy

Corresponding Author:

*Dr. Srinivas Kalabavi,
Department of Urology,
S.D.M. College of Medical College
Dharwad, Karnataka, India.
E-mail: srinivas.kalabhavi@gmail.com*

DOI: 10.18410/jebmh/2021/571

How to Cite This Article:

*Makannavar PJ, Kalabavi S, Kanagali R,
et al. A retrospective review of
xanthogranulomatous pyelonephritis -
our experience at a tertiary care center
located in Dharwad district, Karnataka. J
Evid Based Med Healthc
2021;8(33):3139-3144. DOI:
10.18410/jebmh/2021/571*

*Submission 17-04-2021,
Peer Review 23-04-2021,
Acceptance 28-06-2021,
Published 16-08-2021.*

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BACKGROUND

Chronic pyelonephritis results from repeated renal infection, which leads to renal scarring, atrophy of the kidney and subsequent renal insufficiency. The diagnosis is usually made by radiological or pathological examination rather than clinical presentation. However, there are unusual variants of chronic pyelonephritis with unique pathogenesis and clinical presentations which makes clinical diagnosis and treatment difficult. Xanthogranulomatous pyelonephritis is an uncommon type of severe, chronic infective pyelonephritis resulting in diffuse renal destruction. Most cases are unilateral resulting in non-functioning, enlarged kidney.¹ It is usually associated with urinary calculi and urinary tract infection. XGP is characterized by accumulation of lipid laden foamy macrophages, chronic inflammatory infiltration and fibrosis resulting in renal parenchymal destruction. It was first described by Schlagenhauser in 1916, which now globally accounts for 0.6 – 1 % of pyelonephritis cases.² The disease usually begins within pelvis and calyces and subsequently extends into and destroys renal parenchyma, it may even spread to perinephric tissues with formation of abscess or even fistulas. The primary factors involved in pathogenesis of XGP are nephrolithiasis, obstruction and infection. It appears that there is probably no single factor that is instrumental in the pathogenesis of this disease. Rather, there is an inadequate host acute inflammatory response within an obstructed, ischemic or necrotic kidney with associated low virulent bacterial infection.

Clinical manifestations are varied and it has been known to imitate virtually every other inflammatory disease of kidney, as well as renal cell carcinoma, on radiographic examination. XGP should be suspected in patients with recurrent UTI, unilateral enlarged non-functioning or poorly functioning kidney with a stone or a mass lesion indistinguishable from malignant tumour. There are reports of XGP being associated with renal cell carcinoma, papillary transitional cell carcinoma of pelvis or bladder and infiltrating squamous cell carcinoma of pelvis. CT (computer tomography) is probably the most useful radiological technique in evaluating patients with XGP. Fifty to eighty percent of patients show classical triad of unilateral renal enlargement with little or no function and a large renal calculus. Long term antimicrobial therapy with initial drainage procedure like double J stenting or percutaneous nephrostomy is necessary for stabilization of patient. But ultimately surgical intervention in the form of nephrectomy is the only definitive treatment.^{3,4} We retrospectively reviewed 23 cases over last 6 years at our tertiary care institute. Clinical presentations, evaluation, treatment and its outcome were evaluated and presented.

Objectives

The objectives of our case series were to collect and compile data from our tertiary care center of over last 6 years for better understanding of this relatively rare chronic renal condition. This study will help us to know various clinical presentations including unusual presentations, clinical evaluation, treatment and its outcome. This in turn will help

us to better understand the clinicopathological and treatment aspect of XGP and to develop treatment protocol with an aim to improve the outcome in future cases.

METHODS

This is a case series conducted in Department of Urology, SDM Medical College and Hospital, Dharwad, Karnataka, India. We retrospectively collected data of last 6 years from July 2014 till April 2021. Twenty-three (23) cases were included in this review, which were either diagnosed clinically or on the basis of histopathology report.

A detailed clinical history, examination findings were noted. Pre-operative work up included haematological and biochemical test, urine culture. Radiological imaging findings of ultrasonography (USG), CT scan, renogram were recorded. Intra-operative details, intra-operative and post-operative complications and outcomes and final histopathological report were noted.

Statistical Analysis

This is a case series. The collected numerical data was tabulated and described in terms of percentage, range, ratio and mean. Test of significance was not applicable

RESULTS

The study comprised of 23 cases, which were diagnosed either clinically or on final histopathological report. The disease was more prevalent in females than compared to males (15 females and 8 males), with ratio of 1.8 : 1. Youngest patient in our series was 23 years and oldest was 68 years, with mean age of 47.4 years. Highest incidence was found in 5th and 6th decade of life. All cases had unilateral involvement with right side being more common (right - 14, left - 9). The most common comorbidity associated with the disease was diabetes mellitus (60.86 %). Demographic details are summarized in table: 1.

Patient Characteristics	Findings
Age	23 years to 68 years., mean – 47.04 years
Sex	Males - 8, Females - 15 (1 : 1.8)
Laterality	Right - 14, Left - 9, Bilateral - 0
Comorbidities:	
Diabetes mellitus	14 (60.86 %)
Hypertension	5 (21.73 %)
Ischemic heart disease	1 (4.34 %)

Table 1. Patient Demographics

All patients had flank pain as main presenting complaint followed by fever (86 %), dysuria (69 %) and weight loss (13.06 %). Out of 23 patients, 2 patients had presented with sepsis and acute kidney failure, these patients were admitted under ICU and required renal replacement therapy before definitive management. One patient had presented with nephrocutaneous fistula and 1 patient with necrotising fasciitis of flank region.

On examination, renal angle tenderness was elicited in all patients, renal mass was palpable in 5 patients (21.7 %). Symptoms and examination findings are summarized in table 2.

Symptoms	Number
Flank pain	23 (100 %)
Fever	20 (86 %)
Dysuria	16 (69 %)
Weight loss	3 (13.04 %)
Renal angle tenderness	23 (100 %)
Palpable renal mass	5 (21.7 %)
Nephrocutaneous fistula	1 (4.34 %)
Sepsis with acute renal failure	2 (8.69 %)
Flank necrotising fasciitis	1 (4.34 %)
Associated with renal/ureteric calculus	10 (43.47 %), Renal - 6, Ureteric - 4

Table 2. Symptoms and Examination Findings

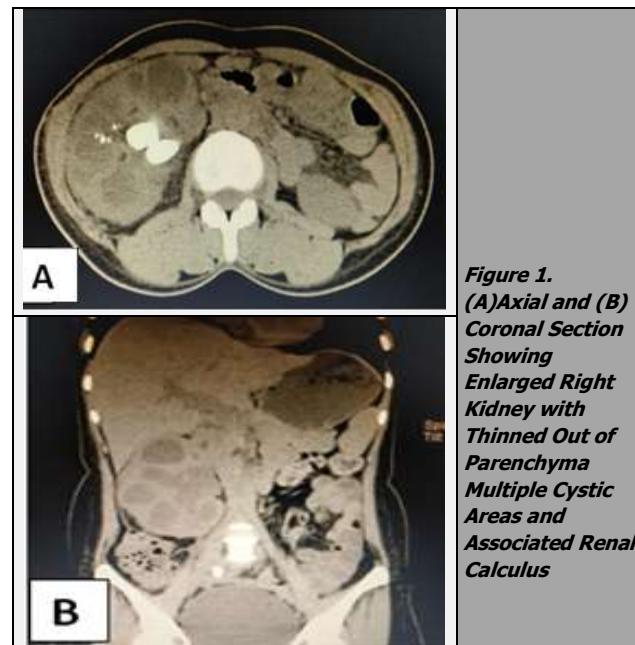
All patients underwent initial radiological evaluation with ultrasonography which showed an enlarged kidney with disappearance of its normal architecture and inhomogeneous echogenicity. Dilated pelvicalyceal system, large amorphous central echogenicity and multiple fluid filled masses and contracted pelvis was noted in most of the cases. In all cases, CT scan was done, which showed an enlarged kidney with thinned out parenchyma, thickened pelvic wall with poorly functioning or non-functioning kidney (Fig.1). Most cases also showed peripelvic, perirenal and periureteric fat stranding. The disease was associated with urolithiasis in 10 cases (43.47 %). 6 cases had renal stone and 4 cases had ureteric calculus. Diethylenetriamine pentaacetate (DTPA) renal scan was done, 19 out of 23 cases showed either non-functioning kidney or severely decreased differential renal function. Urine culture report was available for 19 cases, of which majority had grown *E. coli* (11 cases, 57.89 %) and 3 (15.7 %) had grown multiple organisms. 5 (26.3 %) patients had no growth on urine culture.

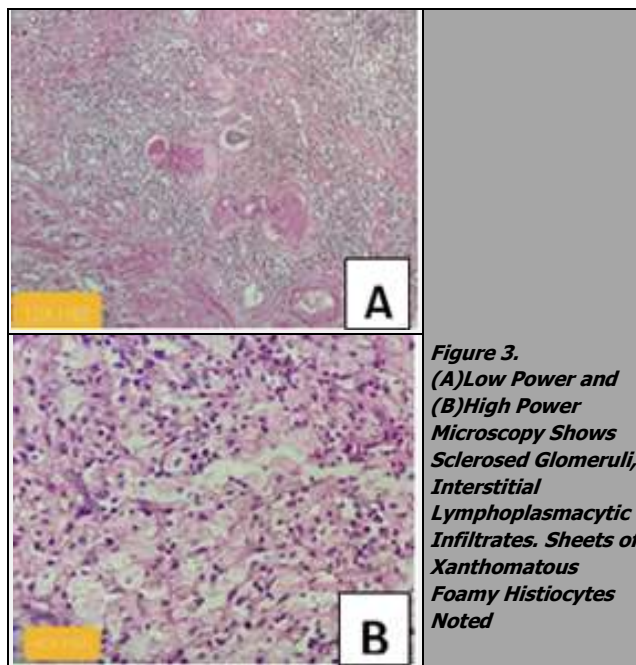
Most of the patients were initially treated with intravenous antibiotics and initial drainage procedure was done which included placement of double J stent in 8 cases (34.78 %) and percutaneous nephrostomy in 11 cases (47.82 %), 2 patients had undergone both DJS and PCN. However, 2 patients were treated with only antimicrobials without any drainage procedure. Three to four weeks later patients were taken up for definitive treatment that is nephrectomy (21 patients), 2 patients lost to follow up. In majority of cases, nephrectomy was done through extraperitoneal flank approach (16) and in 5 patient transperitoneal subcostal approach was chosen. Excess blood loss was most common complication encountered; 8 patients required post-operative blood transfusion. Post-operative tachycardia and hypotension was noted in 5 patients who required inotropic support. 6 patients had superficial surgical site infection which was managed by daily dressing and antibiotics. Treatment details summarized in table: 3.

Treatment	Number
Double J stent (DJS)	8 (34.78 %)
Percutaneous nephrostomy (PCN)	11 (47.82 %)
Both DJS and PCN	2 (8.69 %)
Nephrectomy	21 (91.30 %)
Blood transfusion	8 (34.78 %)
Surgical site infection	6 (26.08 %)

Table 3. Summary of Treatment

All the specimens were sent for histopathological examination and the reports were noted. Gross examination showed enlarged kidney and external surface scarring. Perinephric fat showed gray yellow to gray brown necrotic areas. On cut section, dilated pelvicalyceal system was noted with loss of cortico-medullary distinction. Parenchyma was replaced by multiple yellow fatty nodular areas and multiple pus-filled abscesses (Fig.2). On microscopy examination, whole of the kidney was involved, sclerosed glomeruli with thyroidisation of tubules and dense interstitial lymphoplasmacytic infiltrates with fibrosis was noted. Sheets of xanthomatous histiocytes were noted (Fig.3). None of them had concomitant renal malignancy.





DISCUSSION

Pyelonephritis is a pyogenic infection of renal parenchyma and pelvicalyceal system. It generally begins through an ascending infection that affects renal tubules, interstitium, glomeruli and vessels. The acute form manifests with fever and lumbar pain, which can be associated with inflammatory symptoms of the bladder. The chronic forms are the result of cicatricial effects and repeated infections can present as an insidious disease and can lead to end stage renal disease. XGP is an uncommon variant of chronic pyelonephritis with incidence of 1.4 cases per 100,000 populations being recorded per year. Worldwide XGP accounts for 0.6 % - 1 % of all cases of pyelonephritis. The disease is more common in females in middle age group.⁵ Similar finding were noted in our study with male to female ratio of 1 : 1.8 with mean age of 47.04 years. Although XGP is rare in the paediatric population, it is found in approximately 16 % of paediatric nephrectomy specimens. In children, XGP is more common in boys and usually affects those younger than 8 years.

The disease process mainly affects unilateral kidney, however bilateral disease has been reported rarely with fatal outcome.^{6,7} In our series, all patients had unilateral involvement with slightly more predilection for right kidney (14 cases 60.8 %).

XGP is generally a disease limited to the affected kidney, but spread to adjacent tissues have also been seen. According to the extent of involvement of adjacent tissue, Malek and Elder⁸ have classified the disease into three stages:

1. Stage 1: Nephric disease confined to renal parenchyma only.
2. Stage 2: Perinephric disease process involves renal parenchyma and extends into perinephric fat, but confined within Gerota's fascia.
3. Stage 3: Paranephric disease process extends into paranephric space, beyond Gerota's fascia and extending

into adjacent structures leading to fistula formation or diffuse spread into retroperitoneum.

XGP usually presents with flank pain, fever and chills and persistent bacteriuria. Additional vague symptom like malaise, weight loss may be present. Flank mass may be felt in up to 62 % of the cases. XGP should be suspected in patients with UTI and unilateral enlarged non-functioning or poorly functioning kidney with stone or a mass lesion indistinguishable from malignant tumour. All our cases were presented with flank pain and majority with fever and dysuria and on examination all patients had flank tenderness and 5 patients had palpable flank mass. Similar findings were noted in study conducted by R Kundu, A Baliyan et al.⁹ Two of our cases were presented with severe sepsis with acute renal failure. XGP can also present with unusual presentation, 1 patient in our series had nephrocutaneous fistula and 1 patient had presented with flank necrotising fasciitis.

The exact pathogenesis is still not known, but number of predisposing factors have been proposed, these include recurrent urinary tract infection, urolithiasis, urinary tract obstruction, altered immune response, venous occlusion, haemorrhage, renal ischemia, altered lipid metabolism and transport, diabetic mellitus.¹⁰⁻¹³ It has been proposed clinically and demonstrated experimentally that primary obstruction followed by infection with *E coli* can lead to tissue destruction and accumulation of lipid material in macrophages. These macrophages (xanthoma cells) are distributed in sheets around parenchymal abscesses and calyces and are intermixed with lymphocytes, giant cells and plasma cells. The bacteria appear to be of low virulence because spontaneous bacteraemia has rarely been described. Thus, it appears that there is probably no single factor that is instrumental in the pathogenesis of this disease. Rather, there is an inadequate host acute inflammatory response within an obstructed, ischemic, or necrotic kidney.^{11,12} In our series disease was associated with urolithiasis in 43.47 % and DM in 60.86 %. Majority of our patients had grown *E. coli* in urine culture (57.89 %).

Although review of the literature shows proteus to be the most common organism involved in XGP, *E coli* is also common. The prevalence of proteus organisms may reflect their association with stone formation and subsequent chronic obstruction and irritation. In a study conducted by Malek and Elder⁸ showed out of 23 cases, 22 cases grew bacteria on renal tissue culture. Anaerobes also have been cultured. Approximately 10 % of patients had mixed cultures. About one third of patients had no growth in their urine, probably because many patients had recently taken or were taking antimicrobial agents when cultures were obtained. The infecting organism may be revealed only by tissue cultures obtained during surgery or by percutaneous pus aspiration during initial stabilization with PCN. In our study, urine culture report was available for 19 cases, of which majority had grown *E. coli* (11 cases, 57.89 %) and 3 (15.7 %) had grown multiple organisms. 5 (26.3 %) patients had no growth on urine culture.

Various radiological studies can be employed for imaging of these patients which includes ultrasonography, CT or MRI (magnetic resonance imaging). CT abdomen is probably the

most useful radiologic technique in evaluating patients with XGP. Fifty to eighty percent of patients show classical triad of unilateral renal enlargement with little or no function and a large calculus in the renal pelvis. CT usually demonstrates diffuse enlargement of involved kidney and loss of normal architecture with multiple fluid filled masses and contracted and thickened renal pelvic wall. Majority of them had non-functioning or reduced functioning kidney. On enhanced scans, the walls of these cavities demonstrated a prominent blush owing to the abundant vascularity within the granulation tissue. The cavities themselves, however fail to enhance. Associated renal or ureteric calculus was well delineated on CT.

Ultrasonography usually demonstrates global enlargement of the kidney. The normal architecture is replaced by multiple hypoechoic fluid filled masses that corresponds to debris filled, dilated calyces or foci of parenchymal destruction. Solid mass with associated calculus in pelvis or ureter can also be made out. MRI has not yet superseded CT in the evaluation of renal inflammation, but it provides some advantages in delineating extra renal extension of inflammation. Lesions of XGP may appear as cystic foci of intermediate signal intensity on T1 weighted images and hyperintensity on T2 weighted images. In our series, none of the patients had undergone MRI. Radionuclide renal scan using ^{99m}Tc-dimercaptosuccinic acid (DMSA) or DTPA can be used to confirm and quantify the differential lack of function in involved kidney.

Various differential diagnoses have to be kept in mind. XGP in association with massive pelvic dilatation cannot be distinguished from pyonephrosis. Renal parenchymal malacoplakia may show renal enlargement with multiple inflammatory masses replacing normal renal parenchyma, but calculi are usually not found. Renal lymphoma may be associated with multiple hypoechoic masses surrounding contracted, non-dilated pelvis, but lymphoma is usually clinically obvious, and renal involvement is usually bilateral and not associated with calculi.¹³

Multiple strategies of treatment have been proposed, Leoni et al. suggested pre-operative PCN placement as a way to decrease renal size and to drain pus.¹⁴ The use of pre-operative antibiotics helps in controlling local infection and avoiding septic complication during nephrectomy. Majority will eventually require open nephrectomy. Some early studies of laparoscopic nephrectomies performed for XGP concluded that benefits of laparoscopic surgery do not extend to the treatment of this disease. However, modern XGP experience suggests that laparoscopic nephrectomy is a reasonable treatment option but with high conversion rate. In our series, majority had undergone PCN (11, 47.82 %) followed by DJS (8, 34.78 %) and both PCN and DJS (2, 8.69 %). All patients were treated with antibiotics and 3 - 4 weeks later were taken up for definitive surgery that is open nephrectomy (2 patients lost to follow up).

Pathological examination shows enlarged kidney with loss of normal contour. XGP can have diffuse or segmental involvement. In the diffuse form of the disease, entire kidney is involved, where as in segmental XGP, only the parenchyma surrounding one or more calyces or one pole of

the kidney is involved. On section, the kidney usually demonstrates nephrolithiasis and peripelvic fibrosis. The calyces are dilated and filled with purulent material, but due to peripelvic fibrosis, pelvis not dilated. Papillae are often destroyed by papillary necrosis. In advanced stages of the disease, the parenchyma is replaced by multiple abscesses with thinned out cortex. The capsule is often thickened and inflammation extends into perinephric and paranephric space. On microscopic examination, yellowish nodules show lipid laden macrophages (foamy histiocytes with small, dark nuclei and clear cytoplasm) intermixed with lymphocytes, giant cells and plasma cells. Xanthogranulomatous cells are not specific to XGP but may be present anywhere inflammation and obstruction coexists. The origin of fatty substance is disputed. Cholesterol esters that make up a part of lipid might be derived from lysis of erythrocytes after haemorrhage.¹⁵ There have been reports of concomitant renal cell carcinoma with XGP,^{16,17} but none of our patients had renal malignancy in final histopathology report.

The histomorphological differentials include renal cell carcinoma with sarcomatoid features, leiomyosarcoma, Wilms tumour, lymphoma, malakoplakia, megalocytic interstitial nephritis, pyelonephritis, tuberculosis, perinephric abscess. The benign entities, malakoplakia, megacytic interstitial nephritis can be excluded by observing cytoplasmic periodic acid Schiff-positive, diastase-resistant material in histiocytes. Michaelis-Gutmann bodies are characteristically seen in malakoplakia. A critical evaluation of sections reveals epithelial and atypical spindle cell component in sarcomatoid renal cell carcinoma and interlacing bundles of spindled tumour cells with blunted nuclei and ample eosinophilic cytoplasm in leiomyosarcoma. Mitotic activity is seen in both. Lipid-laden xanthomatous cells of XGP may mimic the clear cells of clear-cell renal cell carcinoma (RCC). Exuberant foamy histiocytes may also be seen in papillary RCC. The xanthomatous cells have a foamy cytoplasm compared with the more cleared cytoplasm of tumoral clear cells. Immunohistochemistry (IHC) may be helpful in certain cases. Sarcomatoid RCC shows at least focal positivity for cytokeratin and epithelial membrane antigen. Leiomyosarcoma is diffusely positive for desmin and smooth muscle actin. Clear-cell and papillary RCC show good positivity for CD10 and epithelial membrane antigen. The xanthomatous cells and macrophages in XGP show positive cytoplasmic staining for lysozyme, diffuse positivity for CD68, and vimentin. IHC is extremely useful in cases with coexistence of XGP and tumours which is a rarity.

CONCLUSIONS

XGP though rare form of chronic pyelonephritis, is often encountered in clinical practice. Definitive pathogenesis is still not clear but the disease is usually associated with UTI and urolithiasis. XGP usually results in progressive loss of renal parenchyma and ultimately non-functioning kidney. Early diagnosis and prompt treatment plays a crucial role in minimizing morbidity and mortality. A definitive clinical diagnosis can be made with help of clinical symptoms and radiological imaging mainly CT scan. Initial stabilization of

cases with intravenous antibiotics and drainage procedures like PCN or DJ stenting is essential. Most cases will eventually require nephrectomy. With early diagnosis and protocol-based treatment, the prognosis is generally good with most patients recovering without any major morbidity.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

Financial or other competing interests: None.

Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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