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Contents

Semimonthly Volume 8 Number 19 October 6, 2020

OPINION REVIEW

- 4280 Role of monoclonal antibody drugs in the treatment of COVID-19
Ucciferri C, Vecchiet J, Falasca K

MINIREVIEWS

- 4286 Review of simulation model for education of point-of-care ultrasound using easy-to-make tools
Shin KC, Ha YR, Lee SJ, Ahn JH
- 4303 Liver injury in COVID-19: A minireview
Zhao JN, Fan Y, Wu SD

ORIGINAL ARTICLE

Case Control Study

- 4311 Transanal minimally invasive surgery vs endoscopic mucosal resection for rectal benign tumors and rectal carcinoids: A retrospective analysis
Shen JM, Zhao JY, Ye T, Gong LF, Wang HP, Chen WJ, Cai YK
- 4320 Impact of *mTOR* gene polymorphisms and gene-tea interaction on susceptibility to tuberculosis
Wang M, Ma SJ, Wu XY, Zhang X, Abesig J, Xiao ZH, Huang X, Yan HP, Wang J, Chen MS, Tan HZ

Retrospective Cohort Study

- 4331 Establishment and validation of a nomogram to predict the risk of ovarian metastasis in gastric cancer: Based on a large cohort
Li SQ, Zhang KC, Li JY, Liang WQ, Gao YH, Qiao Z, Xi HQ, Chen L

Retrospective Study

- 4342 Predictive factors for early clinical response in community-onset *Escherichia coli* urinary tract infection and effects of initial antibiotic treatment on early clinical response
Kim YJ, Lee JM, Lee JH
- 4349 Managing acute appendicitis during the COVID-19 pandemic in Jiaying, China
Zhou Y, Cen LS
- 4360 Clinical application of combined detection of SARS-CoV-2-specific antibody and nucleic acid
Meng QB, Peng JJ, Wei X, Yang JY, Li PC, Qu ZW, Xiong YF, Wu GJ, Hu ZM, Yu JC, Su W
- 4370 Prolonged prothrombin time at admission predicts poor clinical outcome in COVID-19 patients
Wang L, He WB, Yu XM, Hu DL, Jiang H

- 4380** Percutaneous radiofrequency ablation is superior to hepatic resection in patients with small hepatocellular carcinoma

Zhang YH, Su B, Sun P, Li RM, Peng XC, Cai J

- 4388** Clinical study on the surgical treatment of atypical Lisfranc joint complex injury

Li X, Jia LS, Li A, Xie X, Cui J, Li GL

- 4400** Application of medial column classification in treatment of intra-articular calcaneal fractures

Zheng G, Xia F, Yang S, Cui J

Clinical Trials Study

- 4410** Optimal hang time of enteral formula at standard room temperature and high temperature

Lakananurak N, Nalinthassanai N, Suansawang W, Panarat P

META-ANALYSIS

- 4416** Meta-analysis reveals an association between acute pancreatitis and the risk of pancreatic cancer

Liu J, Wang Y, Yu Y

SCIENTOMETRICS

- 4431** Global analysis of daily new COVID-19 cases reveals many static-phase countries including the United States potentially with unstoppable epidemic

Long C, Fu XM, Fu ZF

CASE REPORT

- 4443** Left atrial appendage aneurysm: A case report

Belov DV, Moskalev VI, Garbuzenko DV, Arefyev NO

- 4450** Twenty-year survival after iterative surgery for metastatic renal cell carcinoma: A case report and review of literature

De Raffe E, Mirarchi M, Casadei R, Ricci C, Brunocilla E, Minni F

- 4466** Primary rhabdomyosarcoma: An extremely rare and aggressive variant of male breast cancer

Satală CB, Jung I, Bara TJ, Simu P, Simu I, Vlad M, Szodorai R, Gurzu S

- 4475** Bladder stones in a closed diverticulum caused by *Schistosoma mansoni*: A case report

Alkhamees MA

- 4481** Cutaneous ciliated cyst on the anterior neck in young women: A case report

Kim YH, Lee J

- 4488** Extremely rare case of successful treatment of metastatic ovarian undifferentiated carcinoma with high-dose combination cytotoxic chemotherapy: A case report

Kim HB, Lee HJ, Hong R, Park SG

- 4494** Acute amnesia during pregnancy due to bilateral fornix infarction: A case report
Cho MJ, Shin DI, Han MK, Yum KS
- 4499** Ascaris-mimicking common bile duct stone: A case report
Choi SY, Jo HE, Lee YN, Lee JE, Lee MH, Lim S, Yi BH
- 4505** Eight-year follow-up of locally advanced lymphoepithelioma-like carcinoma at upper urinary tract: A case report
Yang CH, Weng WC, Lin YS, Huang LH, Lu CH, Hsu CY, Ou YC, Tung MC
- 4512** Spontaneous resolution of idiopathic intestinal obstruction after pneumonia: A case report
Zhang BQ, Dai XY, Ye QY, Chang L, Wang ZW, Li XQ, Li YN
- 4521** Successful pregnancy after protective hemodialysis for chronic kidney disease: A case report
Wang ML, He YD, Yang HX, Chen Q
- 4527** Rapid remission of refractory synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome in response to the Janus kinase inhibitor tofacitinib: A case report
Li B, Li GW, Xue L, Chen YY
- 4535** Percutaneous fixation of neonatal humeral physeal fracture: A case report and review of the literature
Tan W, Wang FH, Yao JH, Wu WP, Li YB, Ji YL, Qian YP
- 4544** Severe fundus lesions induced by ocular jellyfish stings: A case report
Zheng XY, Cheng DJ, Lian LH, Zhang RT, Yu XY
- 4550** Application of ozonated water for treatment of gastro-thoracic fistula after comprehensive esophageal squamous cell carcinoma therapy: A case report
Wu DD, Hao KN, Chen XJ, Li XM, He XF
- 4558** Germinomas of the basal ganglia and thalamus: Four case reports
Huang ZC, Dong Q, Song EP, Chen ZJ, Zhang JH, Hou B, Lu ZQ, Qin F
- 4565** Gastrointestinal bleeding caused by jejunal angiosarcoma: A case report
Hui YY, Zhu LP, Yang B, Zhang ZY, Zhang YJ, Chen X, Wang BM
- 4572** High expression of squamous cell carcinoma antigen in poorly differentiated adenocarcinoma of the stomach: A case report
Wang L, Huang L, Xi L, Zhang SC, Zhang JX
- 4579** Therapy-related acute promyelocytic leukemia with FMS-like tyrosine kinase 3-internal tandem duplication mutation in solitary bone plasmacytoma: A case report
Hong LL, Sheng XF, Zhuang HF
- 4588** Metastasis of esophageal squamous cell carcinoma to the thyroid gland with widespread nodal involvement: A case report
Zhang X, Gu X, Li JG, Hu XJ

- 4595** Severe hyperlipemia-induced pseudoerythrocytosis - Implication for misdiagnosis and blood transfusion: A case report and literature review
Zhao XC, Ju B, Wei N, Ding J, Meng FJ, Zhao HG
- 4603** Novel brachytherapy drainage tube loaded with double 125I strands for hilar cholangiocarcinoma: A case report
Lei QY, Jiao DC, Han XW
- 4609** Resorption of upwardly displaced lumbar disk herniation after nonsurgical treatment: A case report
Wang Y, Liao SC, Dai GG, Jiang L
- 4615** Primary hepatic myelolipoma: A case report and review of the literature
Li KY, Wei AL, Li A
- 4624** Endoscopic palliative resection of a giant 26-cm esophageal tumor: A case report
Li Y, Guo LJ, Ma YC, Ye LS, Hu B
- 4633** Solitary hepatic lymphangioma mimicking liver malignancy: A case report and literature review
Long X, Zhang L, Cheng Q, Chen Q, Chen XP
- 4644** Intraosseous venous malformation of the maxilla after enucleation of a hemophilic pseudotumor: A case report
Cai X, Yu JJ, Tian H, Shan ZF, Liu XY, Jia J
- 4652** Intravesically instilled gemcitabine-induced lung injury in a patient with invasive urothelial carcinoma: A case report
Zhou XM, Wu C, Gu X
- 4660** Bochdalek hernia masquerading as severe acute pancreatitis during the third trimester of pregnancy: A case report
Zou YZ, Yang JP, Zhou XJ, Li K, Li XM, Song CH
- 4667** Localized primary gastric amyloidosis: Three case reports
Liu XM, Di LJ, Zhu JX, Wu XL, Li HP, Wu HC, Tuo BG
- 4676** Displacement of peritoneal end of a shunt tube to pleural cavity: A case report
Liu J, Guo M
- 4681** Parathyroid adenoma combined with a rib tumor as the primary disease: A case report
Han L, Zhu XF

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Peer-reviewer of *World Journal of Clinical Cases*, Prof. Adrián Ángel Inchauspe, obtained his MD in 1986 from La Plata National University (Argentina), where he remained as Professor of Surgery. Study abroad, at the Aachen and Tübingen Universities in Germany in 1991, led to his certification in laparoscopic surgery, and at the Louis Pasteur University in Strasbourg France, led to his being awarded the Argentine National Invention Award in 1998 for his graduate work in tele-surgery. He currently serves as teacher in the Argentine Acupuncture Society, as Invited Foreigner Professor at the China National Academy of Sciences and Hainan Medical University, and as editorial member and reviewer for many internationally renowned journals. (L-Editor: Filipodia)

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Eight-year follow-up of locally advanced lymphoepithelioma-like carcinoma at upper urinary tract: A case report

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Author contributions: Yang CH was the reviewer of medical charts of this case and responsible for the original draft; Weng WC was the patient's urologist, reviewing the literature; Ou YC provided comments to the original draft; Lin YS and Huang LH were responsible to the follow-up; Lu CH was responsible for the literature searching and the rationale on writing; Hsu CY and Tung MC were responsible for the important intellectual content and supervisor; Informed consent was conducted by Weng WC and the document was signed under the confirmation of the duty doctor.

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Abstract

BACKGROUND

Urinary tract lymphoepithelioma-like carcinoma is rarely seen. Although it is termed after lymphoepithelioma at the nasopharynx, it behaves more like high grade urothelial carcinoma by immunohistochemical features. Most published literatures focused on its rarity but few discussed results of long-term follow-ups. As no available guidelines are applicable, we postulated that principles should be similar to that of urothelial carcinoma at urinary tract. As of now, this work features the longest follow-up of this cancer at the upper urinary tract.

CASE SUMMARY

A 63-year-old female had a chief complaint of intermittent left flank pain for 2 mo, along with accompanying symptoms including vomiting and body weight loss, about 7 kg over 2 mo. Laboratory data showed normocytic anemia, mildly poor renal function, and hyperparathyroidism. Urine analysis showed mild hematuria. Computed tomography showed a 4.2-cm-width irregular mass over left renal pelvic and enlarged lymph node at the left renal hilum. Whole-body bone scan was negative of active bone lesions. Biopsy from ureteroscopy showed urothelial carcinoma. Specimen from laparoscopic nephroureterectomy with bladder cuff resection showed lymphoepithelioma-like carcinoma with muscular invasion (pT3). She took adjuvant chemotherapies of 2 cycles and full courses of radiation therapy. No recurrence was observed with designed investigative programs.

CONCLUSION

Locally advanced urinary tract lymphoepithelioma-like carcinoma could benefit from nephroureterectomy and bladder cuff excision in terms of recurrence-free survival.

Key Words: Urologic neoplasms pathology; Kidney pelvis; Tomography X-ray computed;

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Core Tip: Although urinary tract lymphoepithelioma-like carcinoma is rarely seen and no published guideline can be offered, we could still outline feasible principles from immunohistochemical evidence. In our previous experience, guideline of urothelial carcinoma at urinary tract can provide us a promising result. The case in this work comprises of most of the worst scenarios, including mixed histological type, muscular invasion, and involvement of lymph node. However, with left nephroureterectomy with bladder cuff resection and postoperative radiation therapy, our result stands superior to those other published literatures. Thus, in our experiences, the operative methods play the definite roles on patients' prognosis.

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INTRODUCTION

Urinary tract lymphoepithelioma-like carcinoma (LELC) is termed after lymphoepithelioma (LE) at the nasopharynx but is actually a variant of urothelial carcinoma (UC). LELC is infrequently, 2% occurrence, identified at both upper and lower urinary tract. Malignancy is constituent of epithelial parts and inflammatory cells, such as myeloid cells or lymphoid cells under hematoxylin and eosin stain, making chemotherapy feasible. Immunohistochemical analysis differentiates urinary tract LELC from LE at the nasopharynx. No hybridization to Epstein-Barr virus, which is thought to be essential in cell expression and maintenance in LE of the nasopharynx, could be found in urinary tract LELC^[1]. On the other hand, other characteristics such as presence of p53 make urinary tract LELC more resembling to high grade UC. In our previous published literature^[2], we deliberated our postulation on urinary tract LELC, applying the same therapeutic principle as UC. From our experiences^[2], nephroureterectomy with bladder cuff excision without adjuvant therapies on urinary tract LELC showed no recurrence within one year after surgery. However, most published literatures tend to have more discussion on the lower and few on the upper urinary tract. Among case studies of upper urinary tract LELC, few had discussions on long-term follow-ups. Furthermore, compared to stages T1 and T2 upper urinary tract LELC, stage T3 is proved to be worse in terms of overall survival^[3]. To date, this documentation has the longest investigations on the locally advanced upper urinary tract LELC.

CASE PRESENTATION

Chief complaints

On July 2012, a 63-year-old female came to the urology office with symptoms of intermittent left flank pain for 2 mo.

History of present illness

The pain was described to be localized at left flank. Neither precipitating factors nor exaggerating factors were mentioned. It occurred randomly without any special time or occasions, and can be suppressed by painkillers. Accompanying symptoms include vomiting and body weight loss, about 7 kg over 2 mo. She denied having visible red color urine, neither fever. Appetite was not changed. Neither specific travel histories nor cluster histories were mentioned.

History of past illness

She had uterine prolapse diagnosed 2 years before this episode, but did not have any interventions about it.

Physical examination

Her temperature was 35.9 °C, and heart rate was 74 bpm. Respiratory rate was 17 breaths per minute, and blood pressure was 127/81 mmHg. Oxygen saturation in room air was 98%. She ranked the pain subjectively 4 out of 10 on visual analog scale pain score. No knocking pain was examined at costovertebral angle, neither the tenderness on abdomen.

Laboratory examinations

Normocytic anemia was seen on complete blood cell (White blood cell: 4 500/UL, Red blood cell: 3370000/UL, Hemoglobin: 10.4 g/DL, Mean corpuscular volume: 93.5 fL). Mildly insufficiency was seen on renal functions tests (Creatinine: 1.4 mg/DL, Blood urea nitrogen: 16.2 mg/DL). Elevated Intact parathyrin (EIA/LIA) was 245 pg/ML. Free T4 (EIA/LIA) was 1.070 ng/DL, and TSH (EIA/LIA) was 1.5 UIU/ML. Tumor markers of carcino-embryonic antigen, CA-199, and alpha-fetoprotein were all within normal limits. Urine examination showed hematuria (red blood cell 5-10/HPF) and pyuria (white blood cell: 10-20/HPF). Urine cytology was gained, but no atypical cells were examined.

Imaging examinations

Left side hydronephrosis was evident on ultrasound. Intravenous pyelography showed a non-enhanced left kidney (Figure 1) and then computed tomography urogram was arranged (Figure 2) for comprehensive studies, which showed an enlarged lymph node close to the left renal pedicle and one irregularly ill-defined 4.2-cm width mass at the left renal pelvic.

Further diagnostic work-up

Ureteroscopy was arranged and biopsy was done to this 4.2-cm mass at left renal pelvis. Pathology from the biopsy was proved to be high-grade (grade III) UC, which is invasive to lamina propria.

FINAL DIAGNOSIS

The final diagnosis of this case is upper urinary tract UC with clinical stage of T3N1Mx at left renal pelvis.

TREATMENT

A whole-body bone scan showed a negative finding (Figure 3). After securing informed consent, the patient underwent laparoscopic left nephroureterectomy with bladder cuff excision.

A tumor size of 3 cm × 2.5 cm × 2.5 cm from left nephroureterectomy with bladder cuff resection was examined as undifferentiated LELC (Figure 4), high grade (undifferentiated type, grade IV), and invasive into muscle at renal pelvis and peripelvic fat (pT3). Surgical margin, Gerota's fascia, ureter, and resected bladder cuff were all free of tumor. No lymph node was identified from the specimen. Tissues from the other non-tumor kidney displayed chronic pyelonephritis with focal global sclerosis.

OUTCOME AND FOLLOW-UP

She received two cycles of gemcitabine (1000 mg/m²) and cisplatin (35 mg/m²) chemotherapy after the operation but stopped due to unbearable adverse effects, which was assessed to be grade I nausea and vomiting on World Health Organization criteria. Palliative radiation therapy (RT) was targeted to the enlarged lymph node at the left renal pedicle which had no proven pathologies. A total dosage of 5580 cGy was divided into 31 doses. However, 2 mo later, she suffered from low back pain and

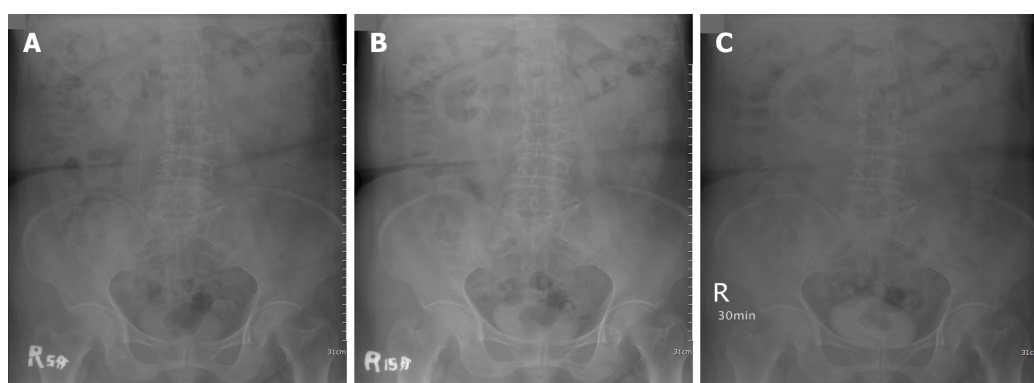


Figure 1 Intravenous pyelography. No enhancement of urinary tract at 5 min (A), 15 min (B) and 30 min (C) after administration of the contrast.

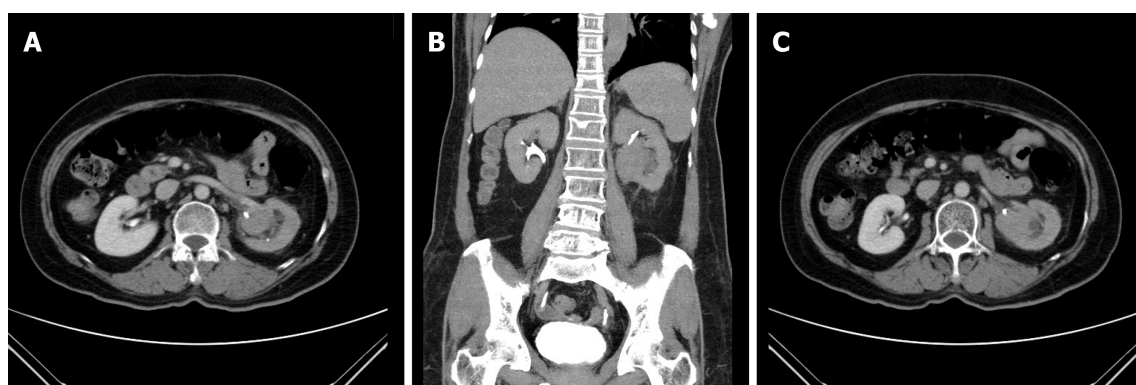


Figure 2 Computed tomography urogram. One 4.2 cm irregular mass was seen occupying the left renal pelvis on computed tomography urogram (A) (B); One enlarged lymph node was observed at the left renal pedicle (C).

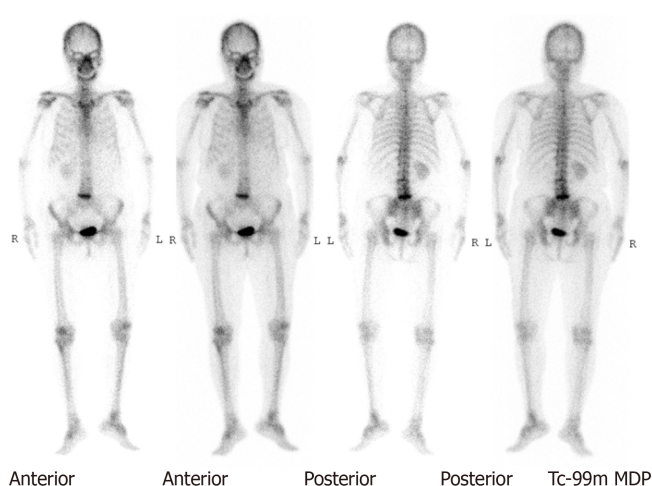


Figure 3 No observed active lesions were demonstrated on whole-body bone scan.

osteoporotic compression fractures were shown on X-ray and magnetic resonance imaging (Figure 5) of the L-spine (L2 and L5), which was a suspicious pathological change secondary to LELC. A second whole-body bone scan revealed no new onset changes compared to the preoperative one. The orthopedist performed palliative resection of the bone lesions and fixation with cages for symptomatic treatment. Fortunately, the specimen taken from bones showed null of metastatic cancer. Active follow-ups with urine cytology and cystoscopy every three months were planned. Computed tomography scan was done every six months postoperatively in the succeeding five years. After five years, biannual cystoscopy and annual computed

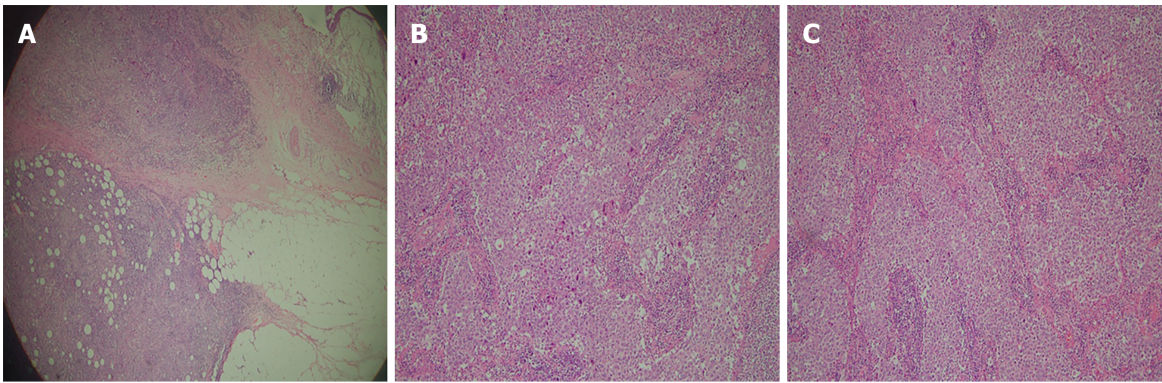


Figure 4 Hematoxylin and eosin stain. A: Generally, with hematoxylin and eosin stain the tumor was seen with invasion to muscular layer; B and C: Under augmentation (400 ×), the tumor was examined with epithelial cells and lymphoid cells.

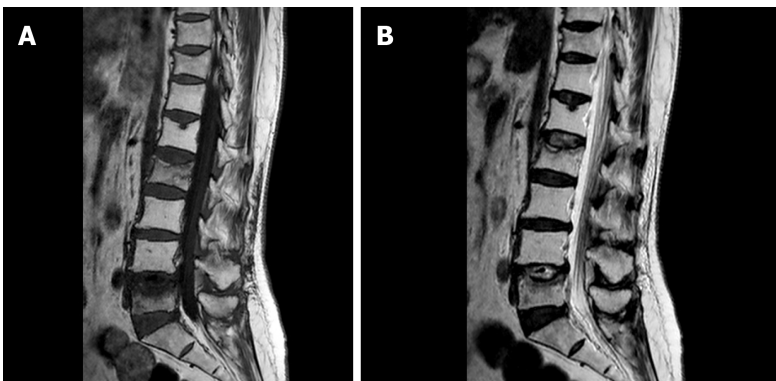


Figure 5 Magnetic resonance imaging. T1-weight (A) and T2-weight (B) image revealed destructive L2 and L5 spine. Related involvement of nearby spinal cord was also noted.

tomography scan were done. She has no evidence of tumor recurrence postoperatively for 8 years till now. In conclusion, this pathological T3N1Mx mixed LELC with two cycles' adjuvant chemotherapy and a full dose of palliative RT can lead to a recurrence-free survival up to 8 years after left nephroureterectomy with bladder cuff excision.

DISCUSSION

Generally speaking, urinary tract LELC can be categorized into pure (100% LELC) or mixed type (predominant: > 50% LELC), and pure type is reported to have more favorable prognosis. The case, described in this article, comprises of some of the worst scenarios of LELC at the upper urinary tract, with muscular invasion, lymph node involvement, and undifferentiated mixed type histology. Lopez-Beltran *et al*^[3] issued the largest series of follow-ups on upper urinary tract LELC^[3] with a maximal 4.8-year span. Their data suggests that the overall survival rate is comparable to conventional UC at the upper urinary tract (about 60% survival rate and 40% cancer-related death) across all stages. However, in their statistics, all cancer-related deaths are at pT3 stage. They also find that prognosis will be influenced by T stage, and T3 stage (time before cancer-related death: 15 ± 16.2 mo; median: 8.5 mo; range: 4-39 mo) will significantly be worse than T1 and T2. The other related reports about LELC at the upper urinary tract in the past 20 years are listed in Table 1^[3-11].

Among most publications, very few are documented with follow-ups long enough to represent meaningful survival analysis^[3,4,8,10,11]. In article by Lopez-Beltran *et al*^[3], radical nephrectomy with adjuvant chemotherapy is performed to all pT3N1 predominant LELC, which is similar to our case, at renal pelvis but they all die from cancer within 7 ± 3 mo. Judging from our case, literature from Lopez-Beltran *et al*^[3] and case reports from Valverde *et al*^[8] and Tamas *et al*^[11], patients can benefit more from the operative method of nephroureterectomy than nephrectomy in terms of recurrence-

Table 1 Published literatures of upper urinary tract lymphoepithelioma-like carcinoma

Ref.	Case amount	Gender, Age	Site and pathological TNM stage	LELC type	Treatment	Documented follow-up period
Lopez-Beltran <i>et al</i> ^[3]	10	68 yr old (Range: 54-85); male: 8; female: 2	All high grade; T stage: pT1: 2 (20%) pT2: 2 (20%) pT3: 6 (20%); renal pelvis: 4 (pT3N1: 3); ureter: 6 (pT3N1: 2, pT3N0: 1)	Pure type: 3 (pT3: 1); predominant type: 7 (pT3: 5)	Radical nephrectomy + adjuvant chemotherapy: 4 (all pT3); radical nephrectomy: 1; nephroureterectomy+ chemotherapy: 1(pT3); nephroureterectomy:2(pT3:1); ureterectomy: 2; all pT3N1predominant LELC at renal pelvis received radical nephrectomy+ adjuvant chemotherapy	Maximal 4.8 yr; cancer-related death: 4 (40%) (all pT3); overall survival of pT3N1 predominant LELC at renal pelvis: 7 ± 3 mo (range: 4-10 mo)
Haga <i>et al</i> ^[4]	1	75-year-old female	Left renal pelvis; pT1N1M0	Pure	Laparoscopic nephroureterectomy; no adjuvant therapies	3 yr, no recurrence
Yamada <i>et al</i> ^[5]	1	75-year-old female	Left renal pelvis; pT3N0M0	Not mentioned	Left nephrectomy; no adjuvant therapies	6 mo; no recurrence
Modi <i>et al</i> ^[6]	1	75 year-old female	Right renal pelvis; pT3N1M0	Mixed; predominant	Right radical nephroureterectomy; no adjuvant therapies	6 mo; no recurrence
Ahn <i>et al</i> ^[7]	1	65-year-old female	Right renal pelvis; pT3N0M0	Mixed; predominant	Laparoscopic right radical nephroureterectomy; no adjuvant therapies	6 mo; no recurrence
Valverde Martínez <i>et al</i> ^[8]	2 (one is at low urinary tract)	74-year-old female	Left renal pelvis; pT4N1M0	pure	Left radical nephrectomy + adjuvant chemotherapy(cisplatin, gemcitabine)	Recurrent at the 5 th yr
Wen <i>et al</i> ^[9]	1	64-year-old male	Right middle ureter	Mixed, predominant	Rght radical nephroureterectomy with bladder cuff excision; no adjuvant therapies	6 mo; no recurrence
Teraï <i>et al</i> ^[10]	1	73-year-old male	Right ureter; pT2N0M0	Pure	Right laparoscopic nephroureterectomy; no adjuvant therapies	30 mo; no recurrence
Tamas <i>et al</i> ^[11]	30 (only 1 at renal pelvis; the rests are at low urinary tract)	Not mentioned	Renal pelvis; pT3Nx	Mixed	Radical nephrectomy + adjuvant chemotherapy	34 mo; no recurrence

LELC: Lymphoepithelioma-like carcinoma.

free survival and overall survival. Adjuvant chemotherapy and palliative RT, by comparing our case with T1 from Haga *et al*^[4] and T2 from Teraï *et al*^[10], might provide beneficial credits to prolong the recurrence-free survival for those with unfavorable advanced stage. However, there are still some examples with radical nephrectomy and adjuvant chemotherapy^[8] that demonstrated patients could live without recurrence to a maximal 5-year interval. This phenomenon of prognostic variations might imply that some other factors will further affect recurrence-free survival.

CONCLUSION

From our experiences and published literature, operative methods still possess definite roles, and locally advanced LELC at the upper urinary tract could benefit from nephroureterectomy and bladder cuff excision over nephrectomy in terms of recurrence-free survival and overall survival. Adjuvant chemotherapy and palliative RT might have positive roles for locally advanced LELC at upper urinary tract to extend the recurrence-free survival parallel to those with T1 and T2 ones, but a large-scale analysis is necessary to further prove the hypothesis.

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