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CT Evaluation of the Findings of Nutcracker Syndrome in Patients with Bladder Cancer after Radical Cystectomy and Ileal Neobladder Formation: A Correlation with Hematuria

근치적 방광적출 후 회장 신방광형성술을 시행받은 방광암 환자의 컴퓨터단층촬영: 호두까기 증후군 소견의 분석 및 혈뇨와의 관계

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Purpose Patients with bladder cancer may show hematuria after radical cystectomy with ileal neobladder formation, causing anxiety regarding tumor recurrence. Here, we aim to show that the nutcracker syndrome (NCS) can be a cause of hematuria post-operation, and is a common, rather than a rare syndrome.

Materials and Methods A retrospective review of contrast-enhanced abdominopelvic CT (CE-APCT) and urine analysis (UA) findings of 255 patients with bladder cancer who underwent radical cystectomy and ileal neobladder formation between 2011 and 2016 was performed. In the CE-APCT review, the left renal vein flow patterns were evaluated to determine the presence of NCS findings. In the UA review, patients were classified according to the percentage of UA tests with positive hematuria among the total number of UA tests.

Results CT findings of NCS were present in 31.9% of the 135 patients. In the positive hematuria group, there were 26% more patients with NCS findings than those without.

Conclusion NCS findings are prevalent even for bladder cancer patients after surgery, and there is a strong correlation between NCS findings and hematuria. Furthermore, the prevalence of NCS findings is much higher than urinary tract recurrence after the surgery.

Index terms Renal Nutcracker Syndrome; Renal Nutcracker Phenomenon; Hematuria; Bladder Cancer; Cystectomy; Urinary Diversion

INTRODUCTION

The nutcracker phenomenon (NCP) refers to the compression of the left renal vein (LRV) between the superior mesenteric artery (SMA) and abdominal aorta (AA). The NCP may or may not have accompanying symptom. The nutcracker syndrome (NCS) refers to when NCP is accompanied by symptoms or signs, such as hematuria (either gross or microscopic), proteinuria, or left flank pain (1, 2). Gross hematuria in NCS is caused by LRV hypertension and rupture of the thin-walled veins close to the calyceal fornices; however, the mechanisms of microscopic hematuria and proteinuria are not well known.

NCS is also called LRV entrapment syndrome; additionally, this concept of LRV entrapment was first introduced in 1950 by El-Sadr and Mina (3). Notably, the term NCS was first described in 1972 by de Schepper (4).

NCP and NCS have been known as a rare phenomenon and syndrome, respectively; however, several studies have suggested that they are quite frequent in practice.

In a recent study, a total of 1223 patients who visited a nephro-uroradiology clinic were investigated. NCP was confirmed in 30.4% of the patients by Doppler study and 49.5% of those NCP cases were found to be NCS patients (5). In other studies, 16% of children and adolescents were reported to have NCP when ultrasound was performed (6); additionally, the prevalence of NCP was 27% in a study involving CT (7).

Radical cystectomy with ileal neobladder formation is commonly used as a curative option for bladder cancer treatment. For patients who underwent this operation, regular abdominal CT is performed to monitor tumor recurrence. Hematuria can be a sign of tumor recurrence, especially in the upper urinary tract. Therefore, urologists pay attention to patients who have persistent hematuria during the follow-up period. Therefore, persistent hematuria can be very stressful to the patients as well. As previous studies have found that NCP is more common than expected, NCP needs to be considered as a possible cause of persistent microscopic hematuria in those patients.

One of the purposes of this study was to assess how often NCS finding is found on follow-up CT of bladder cancer patients who underwent radical cystectomy and ileal neobladder formation. The other purpose of this study was to investigate the correlation between NCS findings and hematuria with a hypothesis that the patients who have CT findings of NCS show hematuria more frequently than those who do not have findings of NCS on CT.

MATERIALS AND METHODS

A retrospective review of contrast-enhanced abdominopelvic CT (CE-APCT) and urine analysis (UA) findings of 255 bladder cancer patients who underwent radical cystectomy and ileal neobladder formation between 2011 and 2016 in Ewha Womans University Mokdong Hospital was performed (IRB No. 2022-07-021).

The exclusion criteria were patients who were in situations that may cause hematuria other than NCS, such as lower abdominal radiation therapy after surgery, urinary tract infections, such as pyelonephritis, renal or neobladder stone, percutaneous nephrostomy, ureteral catheter insertion, upper urinary tract tumor recurrence, urinary tract fistula, neobladder rupture, urinary tract foreign body, or reflux uropathy. Patients who underwent additional left nephrectomy and patients who were lost to follow up prior to 1 year of their surgery were also excluded.

CT PROTOCOL

A multidetector CT with 64 or 128 channels was used (Definition flash, Siemens, Munich, Germany; Sensation 64, Siemens) for follow-up CE-APCT for bladder cancer patients. Three phases with pre, venous, delayed phases (obtained 40 seconds and 5 minutes after contrast material injection for the venous and delayed phases, respectively) or four phases with precontrast, arterial, venous, and delayed phases (obtained 20 seconds after contrast material injection for arterial phase, other phases are same with three-phase CT) were taken with single breath-hold. The arterial phase was used preferentially for evaluating NCS findings if it exists or the venous phase was used otherwise.

Iopromide (concentration: 300 mg iodine/mL, injection dose: 100–120 mL) or iobitridol (concentration: 350 mg iodine/mL, injection dose: 120 mL) was used as the iodine contrast material.

CT IMAGE ANALYSIS

The CT images were retrospectively interpreted by a urogenital radiologist (K.S.H, an attending physician with an experience of 35 years) and a second-year resident of radiology (S.H.M),

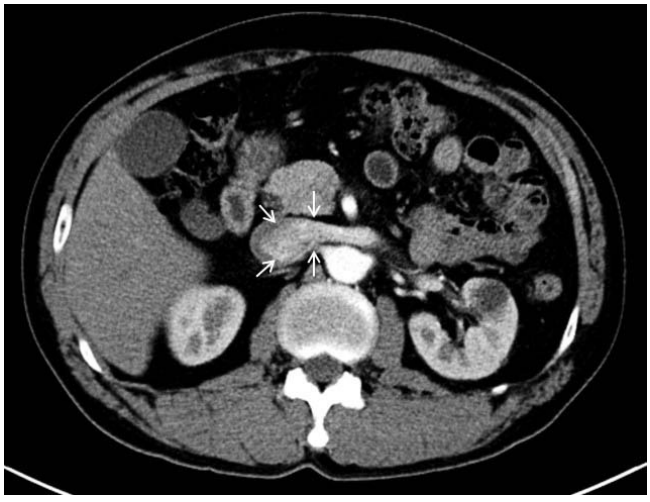

Fig. 1. Normal left renal vein plug-flow pattern. Contrast-enhanced CT image of a 56-year-old male in the early arterial phase. Normal contrast medium flow from the left renal vein is observed to fill the entire inferior vena cava lumen with a smooth margin in a plug-flow patten (arrows).

who were unaware of the clinical information to determine whether the findings suggesting NCS are present or not on the CT images. When the two interpreters disagreed, they arrived at a consensus through discussion.

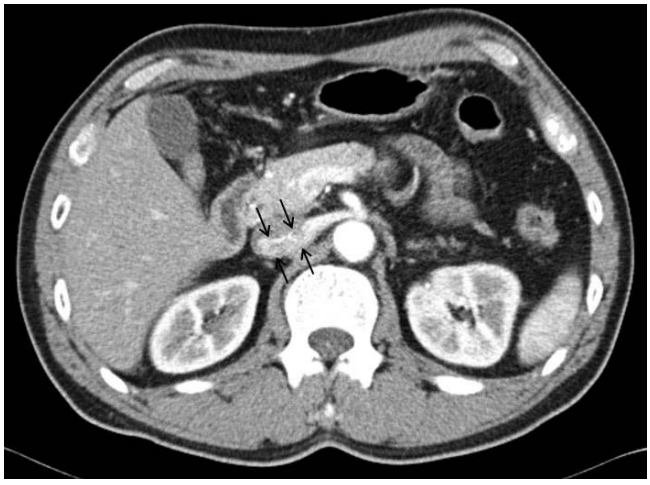

Fig. 2. Normal left renal vein preferential flow pattern. Normal preferential flow of contrast medium is observed along the posterior dependent margin of the left renal vein and inferior vena cava (arrows).

Fig. 3. Nutcracker syndrome. Contrast-enhanced CT image of a 55-year-old female in the early arterial phase. Contrast-jetting phenomenon (spouting contrast medium flow) is observed across the aortomesenteric portion of the left renal vein, suggestive of nutcracker syndrome (arrows).

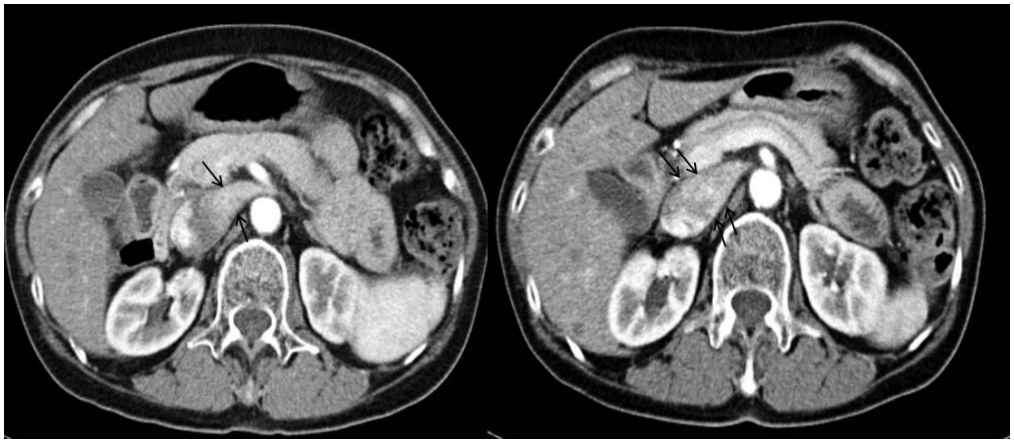

Fig. 4. Nutcracker syndrome. Contrast-enhanced CT image of a 66-year-old female in the early arterial phase. Preferential flow of contrast medium is observed along the anterior non-dependent margin of the left renal vein and inferior vena cava due to high flow velocity, suggestive of nutcracker syndrome (arrows).

The normal LRV flow pattern to the inferior vena cava (IVC) was either plug-flow (filling the entire IVC lumen with a smooth margin) (Fig. 1) or preferential flow along the posterior dependent margin of the LRV and IVC (Fig. 2). The findings suggesting NCS on CE-APCT were; 1) contrast-jetting phenomenon (spouting contrast media) across the aortomesenteric portion of the LRV (Fig. 3), or 2) preferential flow of contrast-opacified flow along the anterior or non-dependent margin of the LRV and IVC (Fig. 4). It was considered positive for NCS finding if at least one of these two CT features were seen on CE-APCT images (8).

URINE ANALYSIS

With respect to the UA to check for hematuria, only the tests from more than 1 year after the surgery were investigated because hematuria is not unusual during the immediate post-operative period. Subsequently, the patients were classified into 4 categories according to the percentage of positive UA tests for hematuria among the total UA examinations underwent; (UA-0) 0%, (UA-1) more than 0% to less than 50%, (UA-2) 50% to less than 80%, and (UA-3) more than 80% positive hematuria.

STATISTICAL ANALYSIS

We have presented the frequency and proportion of the patients having CT finding suggesting NCS among the study participants, which can be interpreted as the prevalence of NCS finding in the patients without identifiable focus for hematuria after radical cystectomy and ileal neobladder formation. To test the association between NCP and hematuria, we made a cross-tabulation contingency and performed a chi-squared test after defining UA-0 and UA-1 as negative hematuria, and defining UA-2 and UA-3 as positive hematuria. For the evaluation of the magnitude of the association, we calculated the odds ratio with a 95% confidence interval (CI) using univariate logistic regression.

The statistical test was performed on 2-sides; a p value < 0.05 was considered statistically significant. SAS version 9.4. (SAS Institute, Cary, NC, USA) were used for analysis.

RESULTS

Out of a total of 255 patients, 120 patients were excluded due to the following: follow-up loss (n = 54), lower abdominal radiation therapy (n = 12), tumor recurrence in urinary tract (n = 12), left nephrectomy (n = 9), urinary tract infection (n = 9), reflux uropathy (n = 7), renal or neobladder stone (n = 7), percutaneous nephrostomy or ureteral catheter insertion (n = 6), urinary tract fistula (n = 2), neobladder rupture (n = 1), urinary tract foreign body (n = 1), and the remaining 135 patients were included.

Table 1. Number and Proportion of Patients Showing NCSF according to the Hematuria Frequency Groups

Hematuria NCSF	UA-0 (none)	UA-1 (1%–49%)	UA-2 (50%–79%)	UA-3 (80% <)
NCSF-negative	23	59	12	4
NCSF-positive	2	56	30	12

NCSF = nutcracker syndrome findings, UA = the group by the proportion of patients positive for hematuria in urinalysis

Table 2. Contingency Table for Nutcracker Syndrome Findings and Hematuria

Chi-Squared Statistics = 10.363 *p*-Value = 0.001 Odds Ratio; 3.696 (95% CI: 1.627–8.395)	Hematuria	
	Positive Hematuria Group*	Negative Hematuria Group†
Nutcracker syndrome findings		
+	18 (54.5)	25 (24.5)
-	15 (45.5)	77 (75.5)

*Positive hematuria group (UA-2, UA-3 in Table 1).
†Negative hematuria group (UA-0, UA-1 in Table 1).
CI = confidence interval, UA = the group by the proportion of patients positive for hematuria in urinalysis

Among the included 135 patients, the findings suggesting NCS were present on the CT images of 43 patients, which is approximately 31.9% (95% CI: 24.0%–39.1%); additionally, those CT findings suggesting NCS were absent in the remaining 92 patients.

In the two categories (UA-2, UA-3) of the positive hematuria group, there were more patients with NCS finding than those without NCS finding (NCS finding-positive: 42%, NCS finding-negative: 16%). Also, the number of patients with NCS findings in the category of 0% of hematuria (UA-0) was very small (2%) (Table 1).

The contingency table analysis showed that the odds of NCS findings in the positive hematuria group are bigger than the odds of NCS findings in the negative hematuria group ($p = 0.001$), which suggested that the patients with NCS findings have a 3.696 times higher risk of hematuria than those without NCS findings (Table 2).

DISCUSSION

NCP is a phenomenon of LRV compression between SMA and AA. NCP may or may not have accompanying symptom, and it is called NCS when the NCP is accompanied by the related symptoms or signs, such as hematuria, proteinuria, or left flank pain (1).

In this study, we investigated whether the NCS finding is present or not on CE-APCT image and the relationship between NCS findings and hematuria for bladder cancer patients after radical cystectomy with ileal neobladder formation.

A definite diagnosis of NCP can be made by invasive catheterization into the LRV demonstrating a pressure gradient over 3 mm Hg at the hilar portion of LRV than IVC. However, other non-invasive imaging techniques are generally used to diagnose NCP, using ultrasonography (US), CE-APCT, or MRI (9). In this study, we used CE-APCT evaluation to detect NCS findings by LRV flow pattern to IVC. According to the basic fluid mechanics, since the patient takes a supine position when undergoing CE-APCT, non-compressed LRV in patients without NCS finding flows along the dependent portion (Fig. 2) or shows a plug-flow pattern, which fills the entire IVC lumen with a smooth margin (Fig. 1). On the other hand, compressed LRV in patients with NCS finding flows along the non-dependent portion (Fig. 4) or directly spouting to the IVC showing the 'jetting phenomenon' (Fig. 3) due to high flow velocity. In addition, the correlation with NCS findings according to these LRV patterns in CE-APCT has been statistically proven in a recent study (10).

NCS has been believed to be a rare syndrome; however, some studies have shown that NCS

is quite frequent in practice. In this study, approximately 32% of bladder cancer patients who underwent radical cystectomy with neobladder formation showed CT findings of NCS. Therefore, this study also showed that NCS can be a quite a common syndrome unlike what is known. In addition, this prevalence is very similar to the 30.4% prevalence derived from the previously mentioned study in which the sonographic investigation of NCP prevalence in 1223 patients, who visited a nephro-uroradiology clinic was studied (5). Additionally, it is similar with a prevalence of 27% derived from another study that investigated NCP prevalence on CT (7). Therefore, the prevalence of 32% derived from this study shows strong consistency with previous studies, which means that this result is very reliable and meaningful.

Furthermore, considering approximately 4.9% of upper urinary tract recurrence rate after radical cystectomy reported in a study in 2009 (11), it can be said that the prevalence of NCS findings is much higher than upper urinary tract recurrence after the surgery.

In addition, in the two categories of the positive hematuria group (UA-2 and UA-3), there were 26% more patients with NCS findings than those without. Also, only 2% of patients were positive for NCS findings in the group who never had hematuria (UA-0) (Table 1). The contingency table analysis also showed that the patients with NCS findings have a 3.696 times higher risk of hematuria than those without (Table 2). Therefore, it can be said that there is a strong correlation between NCS findings and hematuria even for bladder cancer patients who underwent radical cystectomy with neobladder formation.

However, this study has some limitations. Since this study was a retrospective study of CT and UA in bladder cancer patients, it was not possible to measure the pressure gradient between the LRV and IVC, which is the most definitive diagnosis of NCP, and there was no additional modality to ensure the diagnosis of NCP such as US doppler study.

Also, selection bias may inevitably exist since there were many patients excluded who were in situations that may cause hematuria. Lastly, reflux uropathy was included in the exclusion criteria, but its evaluation by CT may have limitations.

In conclusion, for bladder cancer patients who show persistent hematuria without identifiable cause during the follow-up period after the surgery, upper urinary tract tumor recurrence should be suspected although its prevalence is very low and it can be very stressful for both patients and doctors. In such cases, it has been observed that NCS has been overlooked as a cause of hematuria because it has been believed as a rare syndrome. However, this study showed that NCS findings are quite frequent unlike what is believed and much more frequent than upper urinary tract tumor recurrence rate, giving consistent results with other previous studies. Also, it is shown that there is a strong correlation between NCS findings and hematuria. Therefore, physicians should be aware that NCS can also be the cause of persistent hematuria in such patients considering its high prevalence. In such situations, CT images can be a clue to find the right cause for persistent hematuria of bladder cancer patients after the surgery; additionally, if NCS is thought to be more likely than tumor recurrence as a cause of hematuria, it will aid in relieving patients of their anxiety and reducing unnecessary tests.

Author Contributions

Conceptualization, S.H.M., K.S.H.; data curation, L.D.H., S.H.M.; formal analysis, S.H.M., K.S.H.; investigation, S.H.M.; methodology, S.H.M., L.J., K.S.H.; project administration, K.S.H.; resources, L.D.H.; software, L.J.; supervision, K.S.H.; validation, all authors; visualization, S.H.M.; writing—origi-

nal draft, S.H.M.; and writing—review & editing, S.H.M., K.S.H.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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근치적 방광적출 후 회장 신방광형성술을 시행받은 방광암 환자의 컴퓨터단층촬영: 호두까기 증후군 소견의 분석 및 혈뇨와의 관계

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목적 근치적 방광적출 후 회장 신방광형성술을 시행 받은 방광암 환자는 수술 후 혈뇨를 보일 수 있는데, 이는 종양 재발에 대한 불안을 유발할 수 있다. 그러나 종양 재발뿐 아니라 호두까기 증후군이 수술 후 혈뇨의 원인이 될 수 있으며, 이는 빈번한 증후군일 수 있음을 증명하려고 한다.

대상과 방법 2011년부터 2016년까지 근치적방광적출 후 회장 신방광형성술을 시행 받은 255명의 방광암 환자를 대상으로 조영증강 복부골반 컴퓨터단층촬영과 소변검사 소견을 후향적으로 분석하였다. 컴퓨터단층촬영에서 호두까기 증후군 소견의 유무는 좌신정맥 흐름 패턴을 평가하여 판단하였다. 소변분석에서는 총 소변검사에서 혈뇨가 양성인 비율에 따라 환자를 분류하였다.

결과 컴퓨터단층촬영에서 호두까기 증후군 소견은 135명의 환자 중 31.9%에서 나타났다. 혈뇨 양성 그룹에서는 호두까기 증후군의 소견이 없는 환자보다 있는 환자가 26% 더 많았다.

결론 호두까기 증후군의 소견은 수술 후 방광암 환자에게 빈번하였으며, 호두까기 증후군 소견과 혈뇨 사이에는 유의미한 상관관계가 있었다. 또한 호두까기 증후군 소견의 유병률은 수술 후 요로의 종양 재발률보다 높았다.

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