



## Case Report

# A case of mixed tumor formed by metastasis of urothelial carcinoma and malignant lymphoma to the same lymph nodes

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### Abbreviations & Acronyms

FDG = fluorodeoxyglucose  
GC = gemcitabine and cisplatin  
H&E = hematoxylin and eosin  
PET/CT = positron emission tomography/computed tomography  
RP = retrograde pyelography

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**Introduction:** Mixed tumor in the same lymph nodes is extremely rare and no previous reports have described mixed tumor comprising urothelial carcinoma and malignant lymphoma.

**Case presentation:** A 71-year-old woman visited a local clinic with a main complaint of hematuria. Imaging revealed right hydronephrosis and a mid-ureter tumor shadow. Positron emission tomography-computed tomography showed high uptake of fluorodeoxyglucose in para-aortic lymph nodes. Abdominal para-aortic lymph node biopsy was performed. Pathology showed urothelial carcinoma and malignant lymphoma in the same lymph nodes, where a mixed tumor was diagnosed.

**Conclusion:** We encountered a case of mixed tumor of urothelial carcinoma and Hodgkin lymphoma, which metastasized to the same tissues.

**Key words:** malignant lymphoma, mixed tumor, urothelial carcinoma.

## Keynote message

Mixed tumor in the same lymph nodes is extremely rare in urological malignancies. The accurate diagnosis of mixed tumor by imaging is extremely difficult due to the lack of specific features. Treatment for mixed tumor was difficult because of the nature of the pathology as a double cancer. In the diagnosis and treatment of cancer patients, when the clinical course is atypical, such as standard therapies proving ineffective or pathology not able to be explained by a single tumor, we should consider for possible mixed tumor.

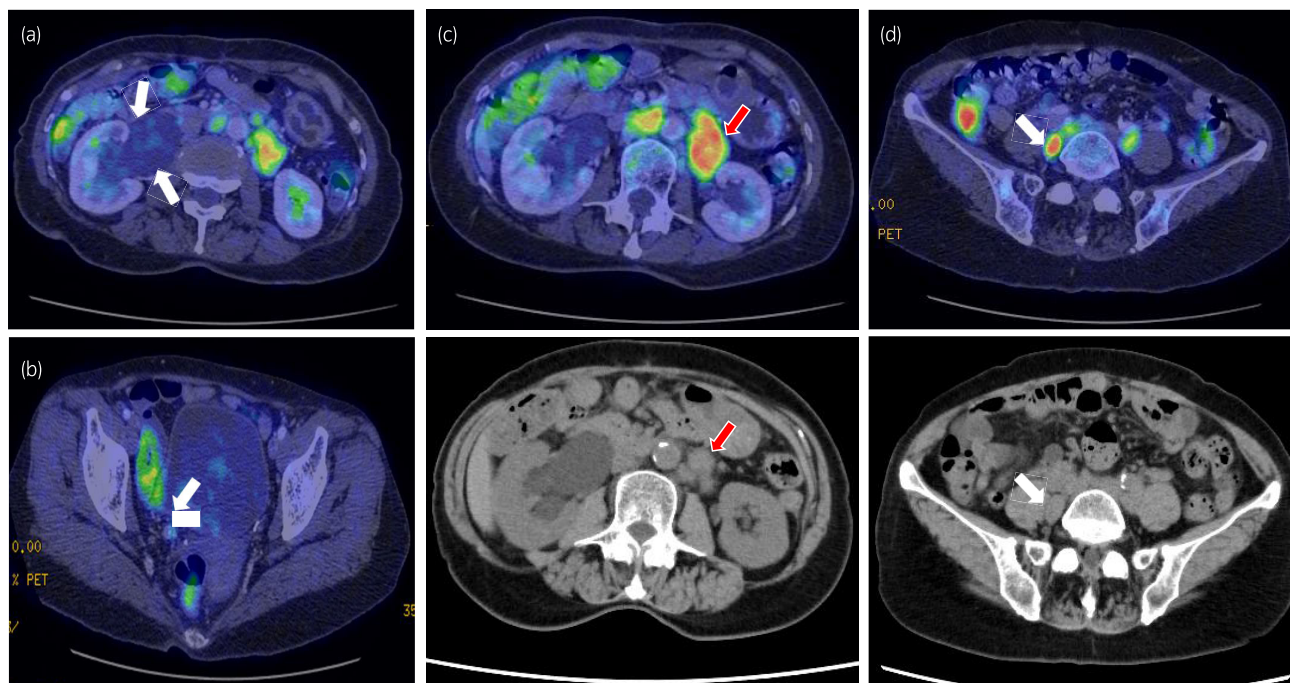
## Introduction

The incidence of double cancer is in fact increasing slightly because of advances in diagnostic technologies and therapeutic methods for malignant tumor. However, mixed tumor in the same lymph nodes is extremely rare and no previous reports have described mixed tumor comprising urothelial carcinoma and malignant lymphoma. We report herein a case of double cancer of urothelial carcinoma, malignant lymphoma, and mixed tumor and these malignancies in lymph nodes.

## Case presentation

A 71-year-old woman was referred by her local physician in 2018 for gross hematuria. Chronic rheumatoid arthritis had been treated with methotrexate since 2006. She visited our hospital for further examination and treatment.

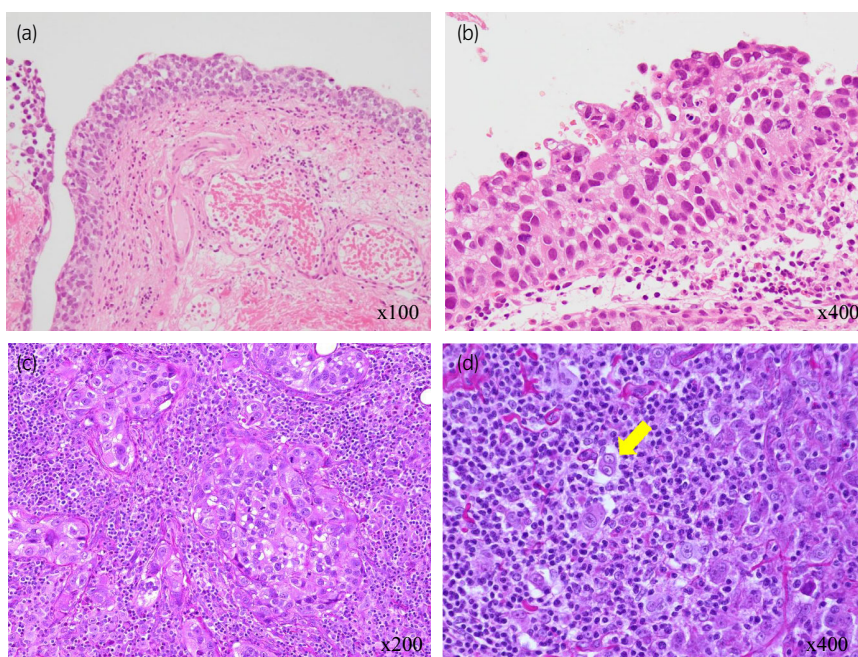
Abdominal-pelvic ultrasound scan and CT scan revealed right hydronephrosis. Laboratory data showed mild anemia (Hb 10.0 g/dL/Ht 30.9%). Urine cytology showed malignant (class IV). Soluble interleukin-2 receptor was elevated (1886 U/mL [normal; <582]). The other all tumor markers remained within the range of normal. Diuretic contrast-enhanced PET-CT revealed right hydronephrosis and hydroureter (Fig. 1a). Circumferential thickening of the wall showing a contrast effect was observed in the area slightly cranial to the right ureteral



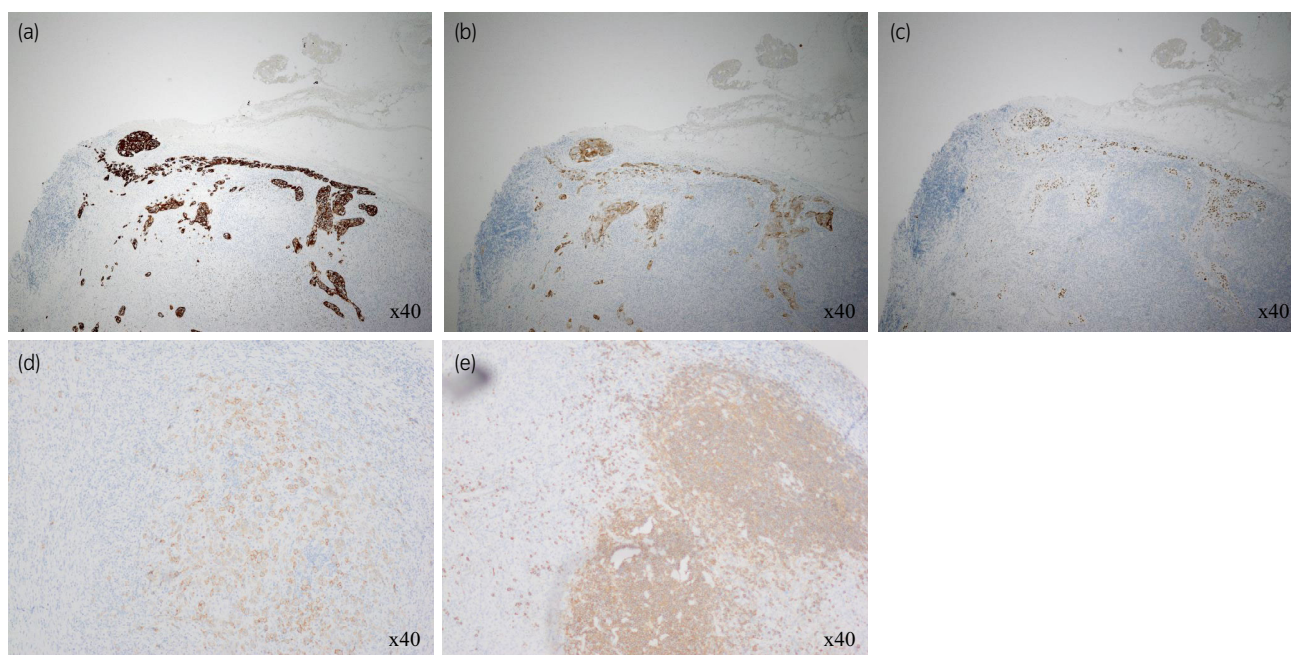
**Fig. 1** Imaging findings of PET/CT scan. PET/CT scan of the right ureter lesion and regional lymph node metastatic lesion. (a) Right hydronephrosis. (b) FDG accumulation of the right ureteric lesion (arrow). (c) FDG accumulation of abdominal para-aortic lymph nodes (arrow). (d) FDG accumulation of pelvic lymph nodes (arrow).

opening to the bladder (Fig. 1b). FDG uptake was noted in this site, with a SUVmax of 3.1. A number of swollen lymph nodes and FDG uptake in the same area (Fig. 1c,d) were observed in abdominal para-aortic and bilateral internal iliac areas. RP revealed no clear ureteric stenosis, and selective urine cytology showed class V in the right urinary tract. A papillary tumor

was observed in the lower ureter, and biopsy was performed in ureterorenoscopy. Edematous and rough bladder mucosa was also observed in the area around the right ureter opening, and biopsy was performed in cystoscopy. Histopathologic examination revealed noninvasive papillary urothelial carcinoma/pTa for the ureteral tumor and urothelial carcinoma in situ for the



**Fig. 2** Histopathological examination in the bladder, ureter, and para-aortic lymph node. H&E staining showed urothelial carcinoma in situ for the bladder tumor (a) and noninvasive papillary urothelial carcinoma for the ureter tumor (b). Para-aortic lymph node was composed of nets of atypical cells (component of urothelial carcinoma) and large cells with enlarged nuclei (component of lymphoma) (c). Reed-Sternberg cell was also found among large cells (d) (arrow).



**Fig. 3** Immunohistochemistry of para-aortic lymph node. The atypical cells in lymph node were positive for CK20 (a), uroplakin (b), and GATA3 (c). Large cells in lymph node were positive for CD30 (d) and CD20 (e).

bladder tumor (Fig. 2a,b). The patient herself did not wish for treatment for an apprehensiveness of adverse events of nephroureterectomy, and the decision was made to continue with follow-up alone. After performing biopsy in the ureter and bladder, swelling of the para-aortic lymph nodes was found to have worsened in PET-CT performed 3 months later, and abdominal para-aortic lymph node biopsy was performed with open surgery. In H&E staining of the para-aortic lymph nodes (Fig. 2c,d), a number of nets of atypical cells with enlarged nuclei indicating a urothelial carcinoma were observed. Immunostaining for CK7, CK20 (Fig. 3a), p63, uroplakin 2 (Fig. 3b), and GATA3 (Fig. 3c) were all positive.

Large cells with multiple enlarged nuclei were also observed. Results from immunostaining of these cells were CD30 (+) (Fig. 3d), PAX-5 ( $\pm$ ), CD15 (-), CD20 (-) (Fig. 3e), and ALK (-). Small CD3-positive lymphocytes were distributed diffusely and somewhat sparsely. Small CD20-positive lymphocytes tended to be distributed around large cells in a nodular manner. Based on these results, nodular sclerosis classical Hodgkin lymphoma was diagnosed. The histopathology of samples from ureterorenoscopic tumor biopsy and abdominal para-aortic lymph node biopsy resulted in the diagnosis of a mixed tumor comprising upper tract urothelial carcinoma (10%) and classical Hodgkin lymphoma (90%), which had occurred as double cancer, in same lymph nodes. Upper tract urothelial carcinoma and multiple lymph node metastases were treated first by chemotherapy with GC. After 2 cycles of GC therapy, PET-CT showed that para-aortic lymph nodes tended to shrink and FDG uptake was decreased. After 3 cycles of GC therapy, the patient developed malaise and inappetence. PET-CT confirmed increases in multiple lung metastases, multiple liver metastases, and multiple bone metastases. Chemotherapy was discontinued and the disease

rapidly exacerbated. The patient died 12 months after abdominal lymph node biopsy.

## Discussion

The incidence of double cancer is increasing slightly because of advances in diagnostic technologies and therapeutic methods for malignant tumor. Warren and Gates defined multiple primary malignant tumors as the tumors meeting the three following criteria: (i) each tumor shows a different malignant image; (ii) the tumors are separated from each other; and (iii) one tumor is not a metastasis of the other.<sup>1</sup> The present case was considered a double cancer, meeting all these criteria. The incidence of double cancer has been reported as 3.7% by Warren and Gates,<sup>1</sup> 2.5% by Watson,<sup>2</sup> 1.54% by Fried,<sup>3</sup> and 4.6% (clinical cases) and 10.6% (autopsy cases) by Moertel *et al.*<sup>4</sup>

Rodriguez-Abreu *et al.*<sup>5</sup> reported the incidence of Hodgkin lymphoma as 2.7 per 100 000 population, and Bray *et al.*<sup>6</sup> reported that Hodgkin lymphoma accounted for 0.4% of all new cancer cases. Bray *et al.*<sup>6</sup> also reported that bladder cancer accounted for 3% of the new cancer cases. Considering this, urothelial carcinoma and Hodgkin lymphoma occurring in the same patient as double cancer can be considered rare.

Internal and external factors have been considered to be involved in double cancer. In our case, no external factors such as radiotherapy were found in the treatment history. We think that the use of methotrexate for rheumatoid arthritis appears likely to have been involved. The patient had been using methotrexate and tocilizumab for the treatment of rheumatoid arthritis. Wadstrom *et al.*<sup>7</sup> reported that tocilizumab did not contribute to any increase in the incidence of malignant tumor. A possible increase in the risk of Hodgkin lymphoma caused by methotrexate use has been pointed out

by Kojima *et al.*<sup>8</sup> For our case, we speculate that the use of methotrexate for rheumatoid arthritis is likely to have been involved in the onset of Hodgkin lymphoma.

Based on her medical history and the above reports, we speculate that the patient first developed rheumatoid arthritis followed by Hodgkin lymphoma, and cancer cells of urothelial carcinoma showed the distant metastasis to extra regional lymph node beyond regional lymph node, and incidentally existed in the same lymph nodes as Hodgkin lymphoma cells.

In our case, the onset of urothelial carcinoma resulted in the detection of malignant lymphoma. Treatment was difficult because of the nature of the pathology as a double cancer. In clinical practice, when lymphadenopathy occurs during the treatment of known malignant tumor, it tends to be considered to represent distant metastasis of the tumor under treatment. However, the possibility of double cancer as shown in our case cannot be ruled out. What was extremely distinctive in this patient was that different types of cancer, occurring as double cancer, were found in the same lymphoid tissue. This made the treatment difficult. In the diagnosis and treatment of cancer patients, when the clinical course is atypical, such as standard therapies proving ineffective or a pathology finding not able to be explained by a single tumor, examination of not only the local areas, but also the whole body should be considered for possible double cancer.

## Conflict of interest

The authors declare no conflict of interest.

## Approval of the research protocol by an institutional review board

The Ethics Review committee of Kochi medical school does not require ethical approval for reporting individual case.

## Editorial Comment

### Editorial Comment to A case of mixed tumor formed by metastasis of urothelial carcinoma and malignant lymphoma to the same lymph nodes

The current article by Kobayashi *et al.* reported a rare case of a mixed tumor in a para-aortic lymph node that comprised a metastatic urothelial carcinoma and Hodgkin lymphoma.<sup>1</sup> To our best knowledge, the coexisting metastases of urothelial carcinoma and Hodgkin lymphoma in the same lymph node have never been reported. This article has potential importance for daily clinical practice.

We read the article with great interest because of the extremely rare phenomenon of a mixed tumor derived from

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## Informed consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

## Registry and the registration no. of the study/trial

Not applicable.

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different origins. Hypothetical mechanisms in the development of mixed tumors have been described.<sup>2</sup> One important hypothesis concerns changes in the surrounding microenvironment induced by a primary tumor that lead to increased risk of a secondary tumor. Some cancer cells have also been reported to produce chemokines that induce lymphocytic migration.<sup>3</sup> In the reported case, the pathogenesis of the composite tumor consisting of carcinoma and lymphoma could be attributed to both hypothetical mechanisms, although it is also possible that the mixed tumor occurred coincidentally.

Methotrexate (MTX)-associated lymphoproliferative disorders (LPDs) can be considered in patients undergoing long-term MTX treatment, because these patients have a relatively high risk of lymphoma.<sup>4</sup> The patient in this case had chronic