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Case Series

Diagnosis, Treatment, and Prognosis of Urachal Carcinoma: A Case Series of Eleven Patients

Han Yang[1,2], Zhonggui Hu[2], Pan Gao[2], Dabin Tan[3], Xinyu Li[2], Yuanming Sui[1], Xueyu Li[1], Dan Du[2], Tianzhen He[4] and Ke Wang[1*]

[1]Department of Urology, The Affiliated Hospital of Qingdao University, Qingdao, China; [2]Department of Urology, The Second People's Hospital of Yichang, The Second People's Hospital of China Three Gorges University, Yichang, China; [3]Department of Neurosurgery, Yiling Hospital, Yichang, China; [4]Nantong University, Institute of special environmental medicine, Nantong, China

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Abstract

Background and objectives: Urachal carcinoma (UC) cases are rare but aggressive that pose significant diagnostic and therapeutic challenges. To summarize the diagnostic features of UC, we report our case findings.

Methods: Retrospectively analyzed the clinical features of patients with UC between 2010 and 2020 at our center. Patient demographics, clinical history, treatment, and follow-up information were obtained.

Results: All 11 UC patients with a mean age of 54.2 years, including 8 men and 3 women. The initial symptom in 7 cases was painless gross hematuria, followed by urinary tract irritation and abdominal pain. Pathological findings revealed malignancies in all patients, including three mucinous UC, six moderate differentiated UC, one poorly differentiated UC, and one undifferentiated typed UC. Most of the patients underwent extended partial cystectomy. In addition, the majority of patients (82%) had a short duration of follow-up (2–36 months), and 18% of patients were lost to follow-up. As a result, the average postoperative follow-up time was 19.7 months and the 2-year survival rate was 54.5%.

Conclusions: The incidence of UC is concealed and patients often complain about hematuria and mucinuria. There is a lack of effective systemic treatment, and the prognosis of UC is poor.

Introduction

Urachal carcinoma (UC) is a rare type of malignant epithelial tumor. In 1930, Begg first described UC.[1] The urachus is a cannular structure that connects the bladder to the allantois. The incidence rate of UC accounts for 0.35~0.7% of all bladder-associated malignancies and about 22~35% of bladder adenocarcinomas.[2] Some retrospective studies from some centers have reported the clinical features. UC is usually considered a bad prognosis.[3,4] However, the experience of handling UC needs to be further understood. In this study, we retrospectively analyzed the clinical features of UC patients, and comprehensively reviewed the clinical manifestations, examination methods, diagnostic criteria, and treatment methods of UC.

Methods

We retrospectively analyzed the clinical features of patients with UC between 2010 and 2020 at the Affiliated Hospital of Qingdao University and the Second People's Hospital of Yichang. These data of UC patients are recorded, including sex, age, lower uri-

Keywords: Diagnosis; Hematuria; Prognostic; Treatment; Urachal carcinoma.
Abbreviations: UC, urachal carcinoma; CT, computed tomography; MRI, magnetic resonance imaging.
[*]**Correspondence to**: Ke Wang, Department of Urology, The Affiliated Hospital of Qingdao University. No. 1677 Wutaishan Road, Qingdao 266003, China. ORCID: https://orcid.org/0000-0002-5073-4200. Tel: +86 17853287619, Fax: +86-532-8291 9529, E-mail: wangke@qdu.edu.cn
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Table 1. The clinical features of UC patients

Items	Cases (%)
Gender	
Male	8 (72.7)
Female	3 (27.3)
Sheldon staging	
II	2 (18.2)
III	6 (54.5)
IVA	3 (27.3)
Accessory examination	
CT	11 (100)
Cystoscopy	11 (100)
Ultrasonography	1 (9)
Clinical symptoms	
Painless gross hematuria	7 (63.6)
Lower abdominal pain	2 (18.2)
Mucinuria	1 (9)
Asymptomatic	1 (9)
Follow-up (2years)	
OS	6 (60)
PFS	5 (50)

nary tract symptoms (frequency, urgency, and dysuria), hematuria, lower abdominal pain or tenderness, and mucinuria. Besides, we diligently obtained patients' demographics, clinical history, treatment methods, and follow-up information. Furthermore, we carefully reviewed these UC patients' tumor size and location from the pathology reports or operation records.

This study received ethical approval from the institutional review board of the Affiliated Hospital of Qingdao University and the Second People's Hospital of Yichang, and was performed per the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and the accompanying images. A copy of the written consent is available for review by the editorial office of this journal. This study was reported according to the recommendation of the CARE guideline (Supplementary File 1).

Results

A total of 11 UC cases with an average of 54.2 years (range from 36 to 69 years), including 8 males and 3 females. The clinical symptoms of these UC patients are shown below. 7 cases were painless gross hematuria, 2 cases were lower abdominal pain, 1 case had mucinuria and 1 patient had accidentally identified an abdominal mass which was examined by health ultrasonography. The general information about the patients is summarized in Table 1. Although the physical examination shown no obvious abnormality, computed tomography (CT) examination showed a solid mass in the anterior wall of the bladder with a size of 3–7 cm (Fig. 1). And magnetic resonance imaging (MRI) showed that the anterior wall of the bladder was agglomerated and infiltrated. In addition,

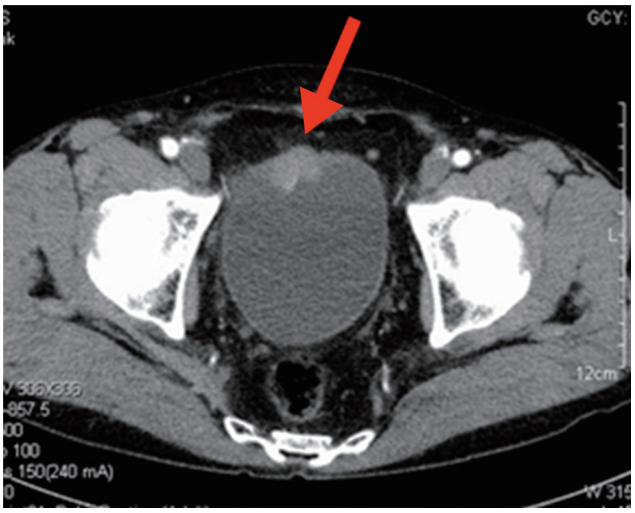

Fig. 1. The typical CT image showed an enhanced solid mass in the anterior wall of the bladder dome. CT, computed tomography.

diffusion-weighted imaging showed high signal intensity and low signal intensity (Fig. 2). Cystoscopy further showed a solid tumor with no pedicle on the top of the bladder, accompanied by necrosis or mucus (Fig. 3).

Furthermore, the pathology reports of these 11 cases were reviewed and showed that they are all adenocarcinoma, including 3 cases of mucinous adenocarcinoma, 6 cases of moderate to poorly differentiated adenocarcinoma, one case of poorly differentiated adenocarcinoma, and one case of undifferentiated typed adenocarcinoma. In UC, the immunohistochemical markers CK20, CDX-2, MUC2, and MUC5AC were infiltrated in tumors and showed strongly positive stain, 50% of CK7 was positively stained (Fig. 4). And β-catenin was markedly expressed in the cytoplasm and cell membrane.

After diagnosis, three treatment strategies were used in our center. Firstly, two patients who received radical cystectomy and pelvic lymph node dissection underwent ileal conduit or cutaneous ureterostomy. One of the two patients died of postoperative complications 3 months after surgery. the other case was followed up for 2 years without recurrence or metastasis. Then, eight patients underwent extensive partial cystectomy with umbilical resection. Of these eight patients, one patient had tumor recurrence, progressed 8 months after surgery, and died 5 months later. One patient developed lung metastasis 1 year after surgery and survived 2 years after radiotherapy. One patient developed extensive intra-abdominal metastasis after 8 months, refused chemotherapy, and died 5 months later (Fig. 5). Meantime, the CEA value of this patient significantly increased more than tenfold, compared with the normal one (>100 ng/mL, normal value 0–6). One patient was lost to follow-up. The other four patients were followed up for 24 months without recurrence. Finally, one case in stage IVb received palliative radiotherapy without surgery, and he died six months later.

Discussion

The umbilical tube is the leftover part of the main secretory organ in the early fetus. It is located at the Retziu gap (the gap between the peritoneum and the transverse abdominal fascia). It stretches

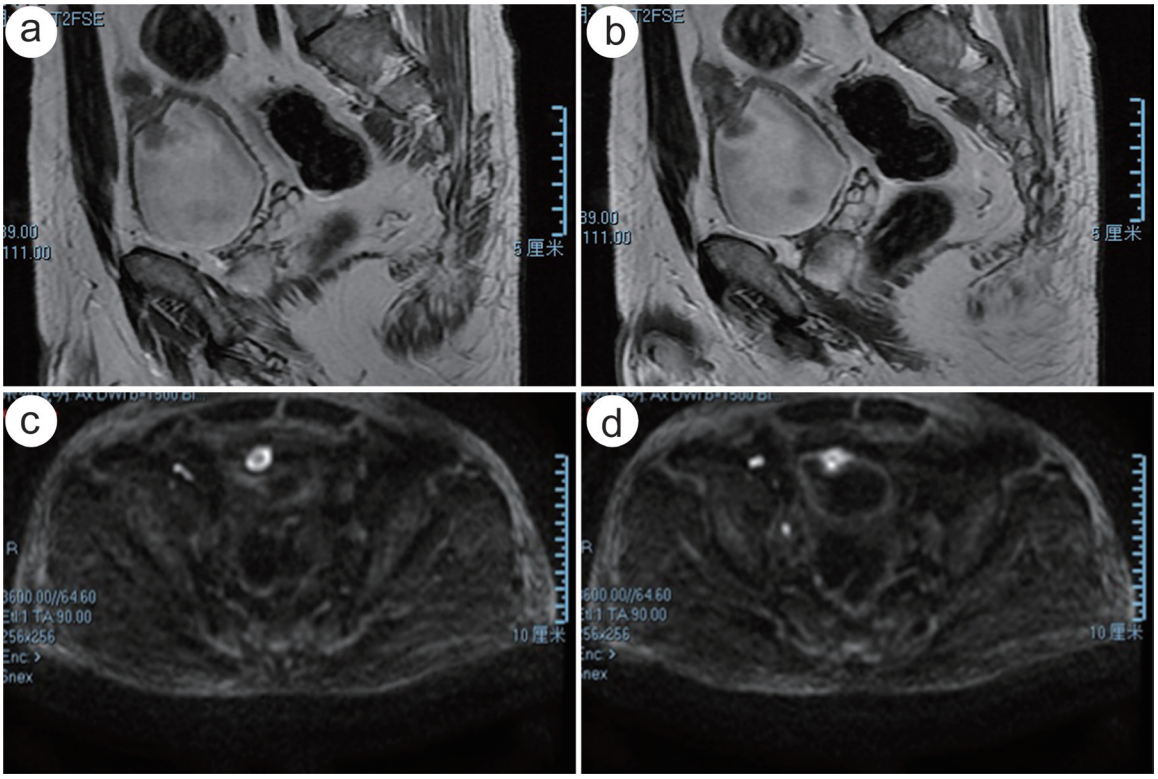

Fig. 2. MRI showed that it was located at the junction of the bladder and urachal, showing infiltrative growth (a, b). It was a predominantly high signal on diffusion-weighted imaging images with a low signal shadow visible within it (c, d). MRI, magnetic resonance imaging.

from the top of the bladder to the umbilicus. The urachus is divided into three parts, namely the upper part of the bladder, the muscle layer, and the mucosa. The wall is divided into three layers from the inside to the outside: the inner layer is the cubic epithelial layer which is the transitional epithelium, the middle is the submucosa and the outer layer is smooth muscle.[5] The urachus gradually become fibrosis and atresia after birth. UC mostly occurs in unclosed urachus probably due to transitional epithelial metaplasia. The tumor site often occurs on the anterior wall of the top of the bladder, the bladder mucosa has no glandular or cystic cystitis, the tumor is found in the muscle layer of the bladder or deeper tissues, and the urachus remains are visible.[6] Most of them are mucinous adenocarcinoma. The rare ones are signet ring cell carcinoma, papillary carcinoma, squamous cell carcinoma, transitional epithelial carcinoma, and sarcoma.

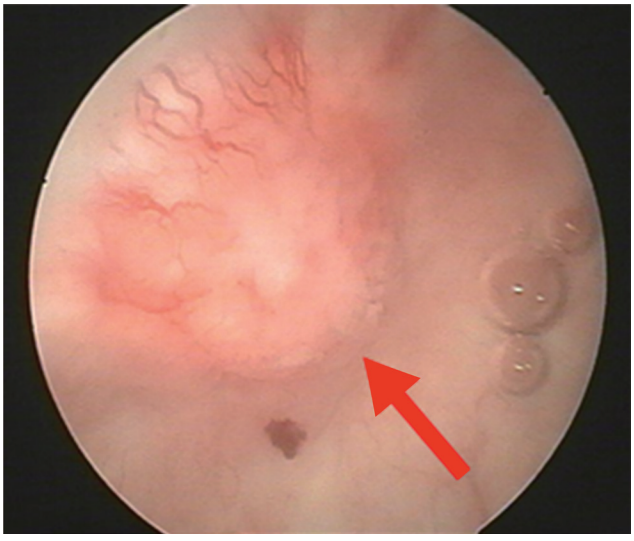

Fig. 3. Cystoscopy showed a solid tumor at the top of the bladder without a pedicle.

The pathogenesis is not very clear at present. Perhaps, mucosal metaplasia caused the development of urachal adenocarcinoma.[2,7] Previous reports showed that the dormant intestinal cells in the urinary tube could revert to an undifferentiated state, and form a glandular epithelium that secretes mucus.[8] Some studies suggested that transitional metaplasia in UC leads to adenocarcinoma. The common clinical symptoms of urachal adenocarcinoma are hematuria, mucinuria, and suprapubic masses. Besides, these rare symptoms are urinary irritation and purulent or bloody discharge from the umbilical cord.[9–12] In our study, there are seven cases of gross hematuria and one case with mucus urine.

UC is a highly malignant epithelial cancer and is difficult to diagnose in the early time.[13] Previous studies showed that men over 50 years old tend to suffer UC more than women.[14] Consistent with those previous reports, our study showed that the average age of these UC patients was 54.2 years old.

The diagnostic criteria for UC were first proposed by Wheeler *et al*.[15] Later, Sheldon *et al*.[16] modified the diagnostic criteria for UC and were widely adopted by scholars at present (Table 2). The Mayo staging system was used to divide patients into 4 stages: Stage I, tumors confined to the urachus and/or bladder; Stage II, tumors extending beyond the muscular layer of the urachus and/or the bladder; Stage III, tumors infiltrating the regional lymph

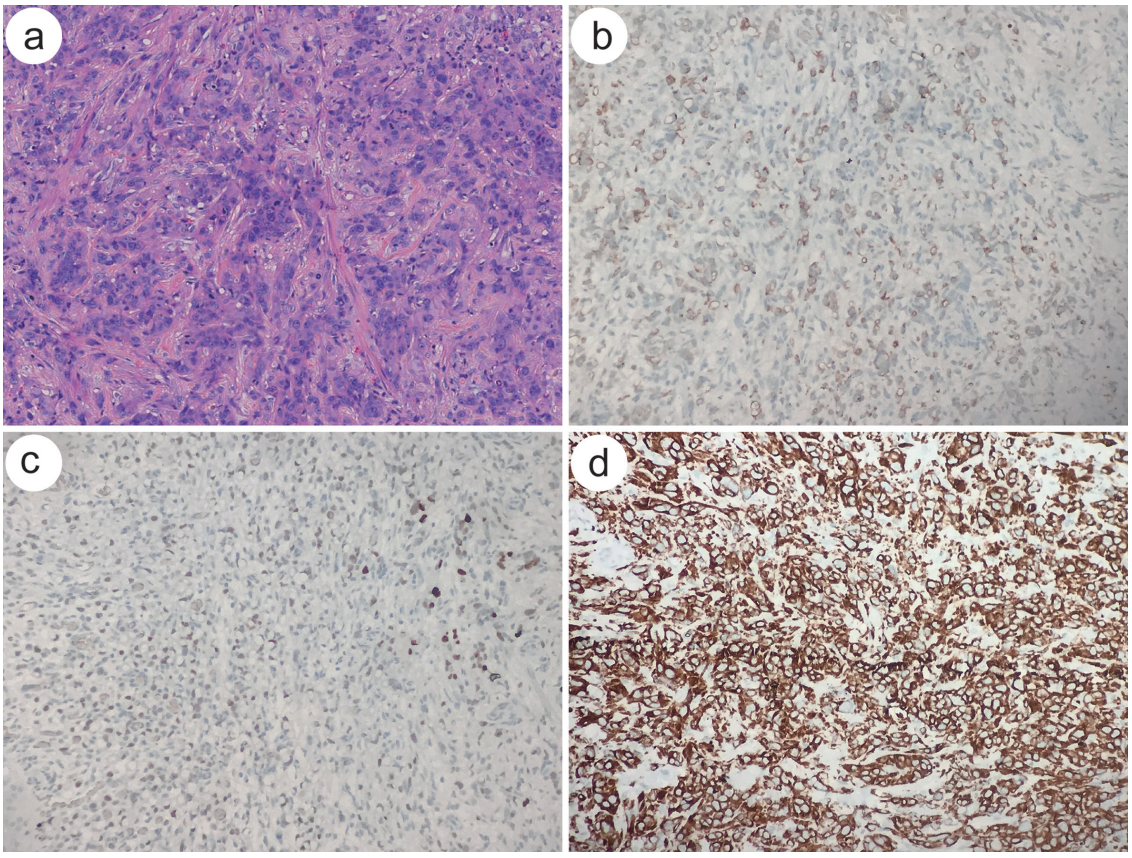

Fig. 4. Pathological and immunohistochemical findings. The diagnosis of UC was histopathologically confirmed based on hematoxylin and eosin staining (a). Representative immunohistochemical staining images that are positive for CK20, CDX-2, and CK7 in the tumoral cells, respectively (b, c, d). UC, urachal carcinoma.

nodes; and Stage IV, tumors infiltrating nonregional lymph nodes or other distant sites.[17]

Imaging examinations are very important for the diagnosis of UC. We observe the structure of the tumor and its relationship with surrounding tissues from multiple angles and levels and even determine whether there is distant lymphatic metastasis by using CT or MRI. CT features show low-density signals, extending to the umbilicus along the Retzius gap, often accompanied by calcification among the rectus abdominis and the anterior wall and (/or) top of the bladder.[18,19] Some scholars also believe that calcification is a characteristic imaging manifestation of UC.[20] Enhanced scans mostly show uneven enhancement. MRI showed residual urachal structure, the solid part showed slightly lower T1 signal, slightly longer T2 signal, cystic part showed long T1 signal, and changed long T2 signal. After enhanced scanning, the cystic part of the cyst wall and local flocculent enhancement or no reinforcement, but the actual part is reinforced.[21] Except for medical history and physical examination, cystoscopy is very useful to identify the position of the tumor in the dome. Cystoscopy and biopsy are of great significance in UC diagnosis.[17,22]

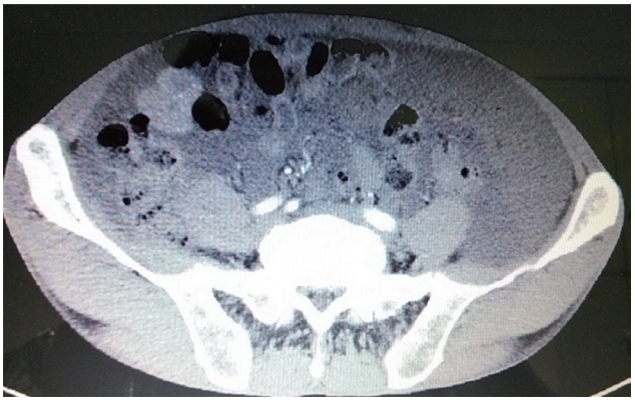

Fig. 5. The tumor metastasized widely in the abdominal cavity.

Surgery is the currently recommended treatment for nonmetastatic UC. Some studies suggested that extended partial cystecto-

Table 2. : The Sheldon staging systems for Urachal cancer

Stage	Definition
I	No invasion beyond urachal mucosa
II	Urachal cancer invasion confined to urachus
IIIA	Local extension into the bladder
IIIB	Local extension into the abdominal wall
IIIC	Local extension into the peritoneum
IIID	Local extension into viscera other than bladder
IVA	Metastasis to the regional lymph node
IVB	Metastasis to distant sites

my, the bladder dome, transverse abdominal fascia, umbilical urinary arm, and partial peritoneum with tumor resection, were used as the primary surgical method for UC.[23,24] In addition, complete removal of residual urachal and the umbilical cord is an effective way to prolong the survival of patients.[25]

Previous reports showed that platinum chemotherapy drugs are an effective treatment strategy for 71% of patients with metastatic UC.[26] A Meta-analysis of 1,010 UC cases showed that the 5-FU combined with cisplatin provided similar response rates and had lower progression rates, compared with 5-FU monotherapy. They summarized the most effective option for UC patients was the therapy of the 5-FU combined with cisplatin, which was better than cisplatin-based therapies. Hence, the therapy of the 5-FU combined with cisplatin seems to provide the highest benefit for UC patients.[12,27] There were few studies on targeted therapies for UC. At present, targeted drug therapies for UC are also based on the epidermal growth factor receptor (EGFR) inhibitors commonly used in colorectal cancer, including gefitinib, cetuximab, and panimab. Patients' responses to drugs are predicted by analyzing the EGFR pathway.[28]

The main prognostic factors were tumor stage, lymph node or distant metastasis, positive surgical margin, and complete removal of residual urachal.[29] Ke *et al*.[30] found that the positive expression rate of CEA in blood was 33% (>5 ng/mL), CA19-9 was 33% (>34 u/mL), and CA724 was 11.1% (>6.9 u/mL), the expression of tumor markers was very high in UC patients in the later stage. And the expression of tumor markers will be decreased after operation or chemotherapy, which is associated with tumor staging and treatment response. These tumor markers are expected to be used to monitor and evaluate the prognosis of UC.[31] Most of the patients had tumor recurrence from half a year to two years after surgery, including bladder, abdominal wall, and surgical incision. Some patients were treated with surgery or radiotherapy and chemotherapy, which can improve the survival rate of patients.[32]

Needless to say, small samples and retrospective studies make our study very limited. In particular, not all patients had completed CT or MRI, and the not very standardized follow-up made some of our patients' information missing, leading to limitations in the reliability of our results.

Hypothesis

Nowadays, with the increasing health awareness, many people are starting to undergo a standard routine health check, which to some extent allows for early diagnosis and treatment. It is hypothesized that if markers with high specificity and sensitivity are found, UC can be accurately and timely determined, and then patients can be given timely and accurate treatment. Of course, the advent of the era of targeted therapy and immunotherapy has brought great benefits to patients with many kinds of tumors. Assuming that a breakthrough can be made in targeted therapy or immunotherapy for UC, the prognosis of patients may be better.

Conclusion

In summary, UC has an insidious onset, lacks obvious clinical manifestations in the early stage, and the tumor is often at an advanced stage when patients come to the outpatient department. There is a lack of effective systemic treatments, consequently, the prognosis of patients is poor. Therefore, early diagnosis is very important. Accurate clinical staging and comprehensive treatment may improve the curative effect and prognosis. In addition to multi-center prospective clinical research, exploring new targeted drugs or immunotherapy methods may lead to higher effects in UC treatment.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/ERHM.2022.00007.

Supplementary File 1. CARE Checklist.

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None.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Study concept and design (HY, ZGH, KW), acquisition of data (YMS, PG), analysis and interpretation of data (XYL, YMS, XYL, ZGH), drafting of the manuscript (HY, DBT), critical revision of the manuscript for important intellectual content (DD, TZH, KW), administrative, technical, or material support (PG), and study supervision (DD, TZH, KW). All authors have made a significant contribution to this study and have approved the final manuscript.

Ethical statement

This study received ethical approval from the institutional review board of the Affiliated Hospital of Qingdao University and the Second People's Hospital of Yichang, and was performed per the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and the accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Data sharing statement

No additional data are available.

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