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WORD COUNT

2209

TIME SUBMITTED

23-MAY-2024 03:24PM

PAPER ID

109161333

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Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 95115

Manuscript Type: CASE REPORT

Primary large cell neuroendocrine carcinoma of the bladder: A case report

Bai LL *et al.* LCNEC of the bladder

Abstract

BACKGROUND

Large cell neuroendocrine carcinoma (LCNEC) is a rare non-urothelial tumor of the bladder. The treatment of LCNEC of the bladder is different from that of urothelial carcinoma (UC); therefore, early and accurate diagnosis is particularly important. As LCNEC of the bladder is rare and its clinical symptoms and radiographic features are similar to those of urothelial tumors, the clinical diagnosis of the disease remains challenging.

CASE SUMMARY

We report a 72-year-old female patient who presented with gross hematuria for 3 months. A solitary tumor located in the anterior wall of the bladder was found by cystoscopy. Pathological examination after biopsy suggested UC of the bladder in the absence of immunohistochemical assessment. The patient underwent partial cystectomy and was finally diagnosed with LCNEC (pT2bN0M0) based on the results of postoperative immunohistochemical examination. During the ten-month follow-up, we found no signs of tumor recurrence or metastasis.

CONCLUSION

Immunohistochemical examination is essential for diagnosing LCNEC of the bladder. Accurate diagnosis and multidisciplinary treatment in the early stage of the disease are crucial for improving the prognosis.

Key Words: Large cell neuroendocrine carcinoma; Bladder tumor; Pathology; Immunohistochemistry; Partial cystectomy; Case report

Bai LL, Guo YX, Song SY, Li R, Jiang YQ. Primary large cell neuroendocrine carcinoma of the bladder: A case report . *World J Clin Cases* 2024; In press

Core Tip: Large cell neuroendocrine carcinoma (LCNEC) of the bladder is a rare non-urothelial tumor of the bladder. As LCNEC is a rare disease and its clinical symptoms and radiographic features mimic those of urothelial tumors, it may be misdiagnosed as urothelial carcinoma. We reported a patient with LCNEC of the bladder, who was not accurately diagnosed due to the absence of immunohistochemical examination before surgery. In this article, we summarize the methods for diagnosing and treating LCNEC of the bladder and highlight the importance of early diagnosis and multimodal treatment.

INTRODUCTION

Neuroendocrine carcinoma (NEC) is commonly found in the lung and gastrointestinal tract but rarely found in the urinary system [1]. NEC of the bladder accounts for less than 1% of bladder tumors [2], and LCNEC is the rarest subtype [3,4]. Few cases of LCNEC of the bladder have been reported previously, and studies on its biological and clinicopathological features are lacking. We report a patient with LCNEC of the bladder, who was not accurately diagnosed due to the absence of immunohistochemical examination before surgery. The treatment process and clinical data can improve clinicians' awareness of LCNEC of the bladder and facilitate its accurate diagnosis and treatment.

LCNEC of the bladder ¹ has a poor prognosis, with the majority of patients being diagnosed at an advanced stage [5,6]. However, due to the rarity of the disease, there is currently no standard treatment. The treatment of UC of the bladder is not applicable to this disease. In the existing studies, the most commonly used treatment was comprehensive treatment including surgery [2,5]. The therapeutic effect of new antineoplastic drugs, such as targeted drugs and immune checkpoint inhibitors, on this disease is still uncertain [5,7,8]. More data are needed to develop guidelines for the diagnosis and treatment of this disease.

As the clinical symptoms and radiographic features of LCNEC of the bladder are similar to those of urothelial tumors, it may be misdiagnosed as UC; thus, clinicians

cannot choose the appropriate treatment in a timely manner. The diagnosis of this disease is challenging for clinicians. This article summarizes the diagnostic and treatment approaches for LCNEC of the bladder. We suggest that attention should be paid to the identification of rare pathological types of bladder tumors before surgery to adopt timely and appropriate treatment.

CASE PRESENTATION

Chief complaints

A 72-year-old female patient who had experienced intermittent gross hematuria in the last 3 months came to our hospital.

History of present illness

The patient experienced gross hematuria 3 months before her visit, with obvious terminal hematuria accompanied by a burning sensation in the lower abdomen, without frequency or urgency. After treatment with oral cefixime for 1 wk, there was no change in hematuria; therefore, she came to the Department of Urology at the Hebei Medical University Third Hospital for treatment. Ultrasonography revealed a hypoechoic mass in the anterior wall of the bladder.

History of past illness

The patient had no history of chronic diseases or other diseases.

Personal and family history

The patient was exposed to leather tanning reagents for more than 10 years. The patient did not mention any family history.

Physical examination

Physical examination showed no obvious positive signs.

Laboratory examinations

Urine analysis showed that RBC count was 418.40/ul and WBC count was 46.50/ul.

Imaging examinations

Contrast-enhanced CT revealed that the tumor involved almost the whole layer of the bladder wall and exhibited mild enhancement, similar to what is observed in common infiltrative UC of the bladder (Figure 1A, B).

FINAL DIAGNOSIS

LCNEC of the bladder (pT2bN0M0).

TREATMENT

After admission, cystoscopy revealed a pink mass with a maximum diameter of approximately 2 cm on the anterior wall of the bladder (Figure 2A). A small amount of tumor tissue was obtained by cystoscopy and sent for pathological examination. The pathological section showed pronounced atypia, large and differently shaped cells and nuclei, and deeply stained nuclei (Figure 2B). Tumor cells invaded the muscularis layer. The pathologist diagnosed a malignant tumor of the bladder, suggesting an invasive UC. The patient was unwilling to pay for immunohistochemical examination; thus, the pathologists could not determine the origin of the tumor. The preliminary clinical diagnosis was bladder UC (cT2N0M0). As the patient wished to retain her bladder, we opted for laparoscopic partial cystectomy rather than radical cystectomy. During the operation, no tumor invasion or adhesions were found in the adipose tissue outside the bladder wall. Pathological examination of the complete tumor showed that the tumor invaded the deep muscular layer rather than the vessels or nerves, and no tumor tissue was found at the incisional margin or base. The morphology of the cells revealed large nuclei, coarse-grained chromatin, a nucleolus, mitosis, and trabecular growth patterns (Figure 3A). Immunohistochemical examination revealed that the cells were positive for chromogranin-A (CgA) and synaptophysin (Syn) (Figure 3B, C) and negative for CD56.

The Ki-67 index reached 70% (Figure 3D). The patient was finally diagnosed with LCNEC of the bladder (pT2bN0M0) based on the results of immunohistochemical examination.

OUTCOME AND FOLLOW-UP

The patient refused further chemotherapy after the surgery. During the ten-month follow-up, we detected no indications of tumor recurrence or metastasis.

DISCUSSION

The tissue origin of LCNEC of the bladder is still unclear. Recent studies have suggested that the metaplasia of neuroendocrine cells, pluripotent stem cells, or urothelial cells beneath the bladder mucosa are possible origins [9]. Since nearly half of all LCNECs in the bladder contain tumor cells from other tissue types, such as UC, small cell carcinoma, or adenocarcinoma [2,10], pluripotent stem cells have become popular because of their origin. Recent studies have identified mutations of multiple genes, such as P53, RB1, NTRK, RET, and BRAF, in LCNEC of the bladder. Inactivation of TP53 and RB1 is the most common genetic mutation in the LCNEC of the bladder, but unfortunately, neither of these genes can be a target for precision therapy [11]. Future studies on gene targets may bring new treatment options for patients with LCNEC of the bladder.

The average age at diagnosis of LCNEC of the bladder is 61.5 years, and the male-to-female ratio is approximately 4:1 [2]. Smoking and personal or family history of cancer are risk factors for this cancer [4], but our patient did not mention any of these factors. However, whether her exposure to leather tanning chemicals contributed to her disease development remains unclear. Hematuria is the most common clinical symptom of LCNEC of the bladder [2,10]. At the time of diagnosis, most patients have muscle layer invasion or distant metastasis [2,10], which may be related to its high invasiveness and lack of early symptoms.

CT and MRI can help the diagnosis and staging of LCNEC of the bladder. Some studies have recommended 18F-FDG-PET/CT scanning to measure the systemic change in 18F-FDG uptake since tumor cells in NEC have high metabolic activity and high 18F-FDG uptake [3,5]. As a functional imaging modality, 18F-FDG-PET/CT is more reliable than CT or MRI for staging the disease [11]. This advanced method is not available in most hospitals and cannot be fully applied.

Currently, the diagnosis of LCNEC relies on histopathological examination and immunohistochemical staining. The pathomorphological characteristics of LCNEC of the bladder include large cells with pleomorphism, abundant cytoplasm, coarse granular chromatin, and prominent nucleoli. In addition, LCNEC of the bladder sometimes shows special structures, such as rosettes, palisading pattern, and trabecular architecture [8,10,11]. The most important method for diagnosing NEC is immunohistochemical examination. The expression of Syn, CgA, and CD56 and a Ki-67 index > 40% indicate high sensitivity and specificity for detecting NEC compared to UC [5,8-10]. In the present case, palisade-like structures, large nuclei, coarse granular chromatin, and nucleoli were observed in the surgically resected tumor tissue (Figure 3A), and immunohistochemical staining showed positive Syn and CgA and a Ki-67 index of 70% all supporting the diagnosis of LCNEC (Figure 3B-D), even though CD56 was negative. For this patient, the pathological sections of the tissue obtained during cystoscopy showed the general characteristics of malignant tumor cells, including large cells and nuclei, deep staining of nuclei, and lack of cell polarity. Rosette and palisade-like structures were not observed possibly because the tissue amount was too small and could not represent most of the diseased tissue. It is difficult to make an accurate diagnosis based on limited histological and morphological information. Immunohistochemical examination serves as a reliable method to distinguish NEC from other tumors. Cystoscopy and urine cytology are common methods to obtain pathological specimens. Urine cytology has a relatively high false negative rate, even though it is a non-invasive test. In comparison, cystoscopy is a more reliable method. However, in certain scenarios, such as when imaging examination confirms the

presence of bladder tumors, cystoscopy may be bypassed. Although UC is the most common type of bladder tumor, the differential diagnosis of rare tumors should not be overlooked. Patients with bladder tumors confirmed by imaging examination should undergo cystoscopic biopsy to accurately determine the origin and stage of the tumor. Accurate diagnosis is crucial, as non-urinary epithelial tumors necessitate different treatment modalities compared to urothelial cancer.

Currently, there is no standard treatment for LCNEC of the bladder. The common clinical treatments include surgery, chemotherapy, and radiotherapy. Compared to surgery alone, multimodal treatment is more conducive to prolonging survival [4,10,12]. There was no significant difference in overall survival between patients who underwent radical cystectomy and patients who underwent bladder-sparing surgery [2]. The same chemotherapy regimens used for small cell neuroendocrine carcinomas of the lung, such as etoposide and platinum drugs, are adopted for treating LCNEC of the bladder. Cisplatin combined with etoposide or carboplatin combined with etoposide is the treatment choice [9]. A study showed that cisplatin-based chemotherapy was superior to carboplatin in terms of prolonging the survival time [13]. For our patient, preoperative imaging revealed no extravesicular invasion or metastasis. Compared to radical surgery, bladder-sparing surgery may lead to similar survival times but has less impact on the quality of life. Our patient refused postoperative chemotherapy or radiotherapy. Single-modal treatment may be a risk factor for poor prognosis. We conducted a review of the follow-up data of patients with bladder LCNEC, comparing the prognosis of various surgical procedures. We observed that similar to those undergoing partial cystectomy, 33% of patients treated with radical cystectomy suffered from metastasis or recurrence during follow-up. Patients treated with trans-urethral resection of the bladder tumor had the worst prognosis, with 50% having metastasis or recurrence during follow-up [5]. We recommend radical surgery combined with platinum chemotherapy for patients with LCNEC of the bladder. For localized tumors that can be completely removed from the bladder, partial cystectomy may be an alternative option, particularly for patients refusing radical surgery. However,

currently, few patients undergo partial cystectomy whose reliability needs more studies. Our patient had a relapse-free survival of 10 months after partial cystectomy, without any additional treatments. She had a favorable prognosis, showing the value of partial cystectomy. We will continue to closely monitor her condition.

The overall prognosis of LCNEC of the bladder is poor, with a 1-year survival rate of less than 55% and a 3-year survival rate of less than 25%. The average survival time of patients with metastasis is less than 3 months. The postoperative survival time of patients with this disease is closely related to the T stage at the time of diagnosis. The median survival times of patients with T1-2 and T3-4 tumors are 23.9 months and 16.0 months, respectively [2]. Early diagnosis is therefore particularly important for survival.

CONCLUSION

Primary LCNEC of the bladder is an extremely rare malignant bladder tumor. Immunohistochemical examination is indispensable for diagnosing LCNEC of the bladder. For patients whose tissue biopsy has been obtained before surgery, we recommend immunohistochemical examination to determine the source of the tumor. Early diagnosis and multimodal treatment are highly important for prolonging patients' survival.

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