Case Report

Bladder cancer metastasis producing beta-human chorionic gonadotropin, squamous cell carcinoma antigen, granulocyte-colony stimulating factor, and parathyroid hormone-related protein

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Abbreviations & Acronyms
β-hCG = beta human chorionic gonadotropin
CT = computed tomography
G-CSF = granulocyte-colony stimulating factor
L/D = laboratory data
PTHrP = parathyroid hormone-related protein
SCC = squamous cell carcinoma
TURBT = transurethral resection of bladder tumor
UC = urothelial cancer
WBC = white blood cell

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Introduction: In urothelial cancer, several paraneoplastic syndromes can be triggered by the aberrant expression of hormones, growth factors or lymphokines by tumor cells.
Case presentation: A 71-year-old female patient underwent radical cystectomy for muscle-invasive urothelial cancer. Shortly after the operation, the patient presented with a leukemoid reaction and hypercalcemia. Computed tomography scans revealed a rapidly progressing tumor on the left pelvic side, and serum levels of granulocyte-colony stimulating factor, parathyroid hormone-related protein, and beta human chorionic gonadotropin were elevated. The patient also tested positive for serum squamous cell carcinoma antigen. Hypercalcemia was successfully treated with denosumab. However, the patient's leukocyte counts steadily increased, her condition deteriorated and she passed away.
Conclusion: To the best of our knowledge, this is the first report of urothelial cancer that tested positive for four tumor markers. The findings support the idea that poorly differentiated bladder carcinomas can ectopically secrete multiple proteins causing pleiotropic paraneoplastic syndromes.

Key words: bladder cancer, granulocyte-colony stimulating factor, human chorionic gonadotropin β, parathyroid hormone-related protein, urothelial carcinoma.

Keynote message

Poorly differentiated UC can secrete multiple cytokines, hormones and proteins of different classes, causing paraneoplastic syndromes. Manifestation of paraneoplastic syndromes may suggest the need for more aggressive management of bladder cancer.

Introduction

Elevations of various tumor markers have been reported in UC patients. Notably, systemic effects resulting from the secretion of cytokines, growth factors or hormones by tumor cells can cause paraneoplastic syndromes. Tumor cells or surrounding cells may express receptors for multiple cytokines and hormones produced by tumor cells, which act as growth factors on the cells. In this way, the growth factors can operate in a paracrine and/or autocrine manner.[1] This can explain why paraneoplastic syndromes are usually associated with high-grade aggressive tumors.

Leukemoid reactions and hypercalcemia are common signs of a malignancy. They are triggered by the aberrant expression of G-CSF and PTHrP, which are secreted by tumor cells. Tumors resulting in paraneoplastic syndromes typically present with a highly malignant phenotype and are associated with a poor prognosis. Here, we report a case of UC associated with the production of G-CSF, PTHrP, and β-hCG. To the best of our knowledge, this is the first report of bladder cancer producing β-hCG, PTHrP, and G-CSF.

Case presentation

A 71-year-old female patient underwent multiple TURBT for recurrent UC from January 2016 (Table 1). On 29 July 2017, the patient underwent a TURBT and the pathological diagnosis was muscle-invasive high-grade UC. The tumor was small and no lymph node metastasis was detected on a CT scan. Thus, no neoadjuvant chemotherapy was administered. Extraperitoneal radical cystectomy with bilateral ureterocutaneostomy was performed on 16 August 2017. Pathological diagnosis of the resected bladder tumor was high grade UC, pT2, v−, ly+, pN0 (0/6). Based on the results of the pathological examination no adjuvant chemotherapy was considered. One month after the operation the patient presented with a high fever and severe leukocytosis without obvious infection. At that time, a CT scan revealed a mass on the left pelvic side (Fig. 1). Hypercalcemia (18.6 mg/dL serum calcium) was also present. Hypercalcemia and leukocytosis were suspected to be manifestations of paraneoplastic syndrome due to ectopic expression of PTHrP and G-CSF, respectively. On 18 October 2017, several tumor markers were examined. It was found that PTHrP (24.4 pmol/l; normal level, <1.1 pmol/l), SCC (45.3 ng/mL; normal level, <1.5 ng/mL) and β-hCG (4.3 ng/mL; normal level, <0.1 ng/mL) were elevated; however, carcinoembryonic antigen, carbohydrate antigen 19-9, α-fetoprotein, neuron-specific enolase and progastrin-releasing peptide were within the normal range. G-CSF was also elevated to 198 pg/mL (normal level, <30 pg/mL). Furthermore, the WBC count was increased to 37 000/μL (Fig. 2) and neutrophils accounted for 96% of all

Table 1 Timeline of the disease

Date	Diagnosis/treatment	Findings
January 2016	TURBT 1	UC, high grade,† pTa
June 2016	TURBT 2	UC, high grade, pTa
March 2017	TURBT 3	UC, high grade, pTa
May 2017	TURBT 4	UC, high grade, pTa
July 2017	TURBT 5	UC, high grade, pT2
25 August 2017	Total cystectomy	UC, high grade, pT2a, pN0 (0/6), ly1, v0, INFb, RM0
23 September 2017	High fever (°C)	39°C
26 September 2017	CT	Left pelvic mass was detected. Differential diagnosis between abscess and recurrence.
4 October 2017	L/D	WBC 37 040/μL, calcium 5.28 mg/dL
10 October 2017	CT	Left pelvic soft tissue mass was progressively growing.
18 October 2017	L/D	PTHrP 24.4 pmol/L, SCC 45.3 ng/mL, β-hCG 4.3 ng/mL, G-CSF 198 pg/mL, WBC 104 620/μL, calcium 18.6 mg/dL
19 October 2017	Denosumab, 120 mg	
1 November 2017	L/D	Calcium 8.7 mg/dL
10 November 2017	CT	Left pelvic soft tissue mass was rapidly progressing.
11 November 2017	L/D	WBC 122 000/μL, calcium 9.9 mg/dL
12 November 2017		The patient passed away.

†Grading according to the 2016 World Health Organization classification of tumors.

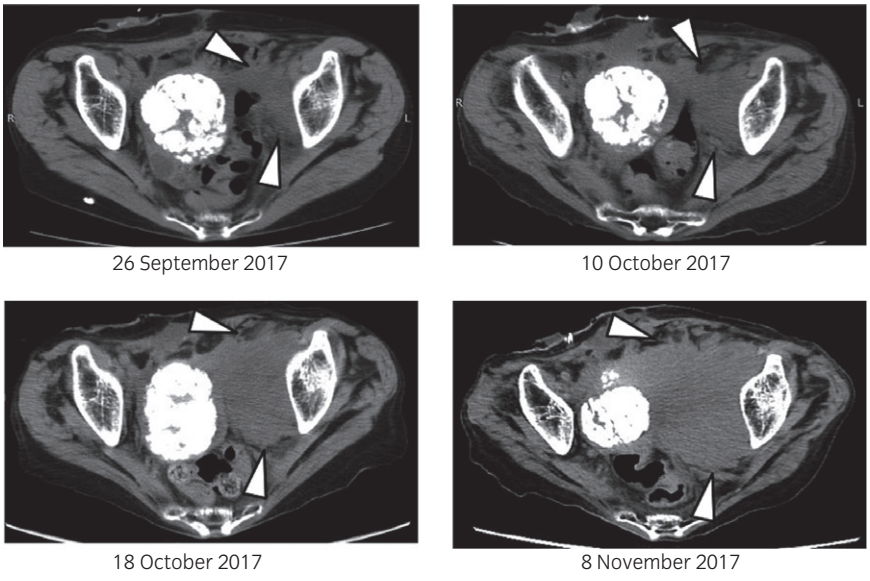

Fig. 1 CT scan taken at the indicated time points. Soft tissue mass on the left pelvic side (indicated by arrowheads) was rapidly progressing.

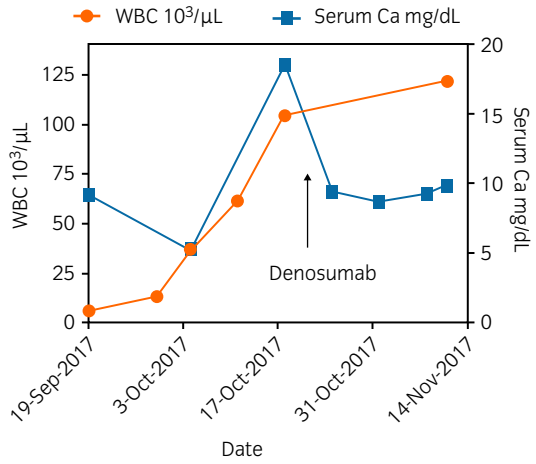

Fig. 2 The graph demonstrated changes in WBC and serum calcium.

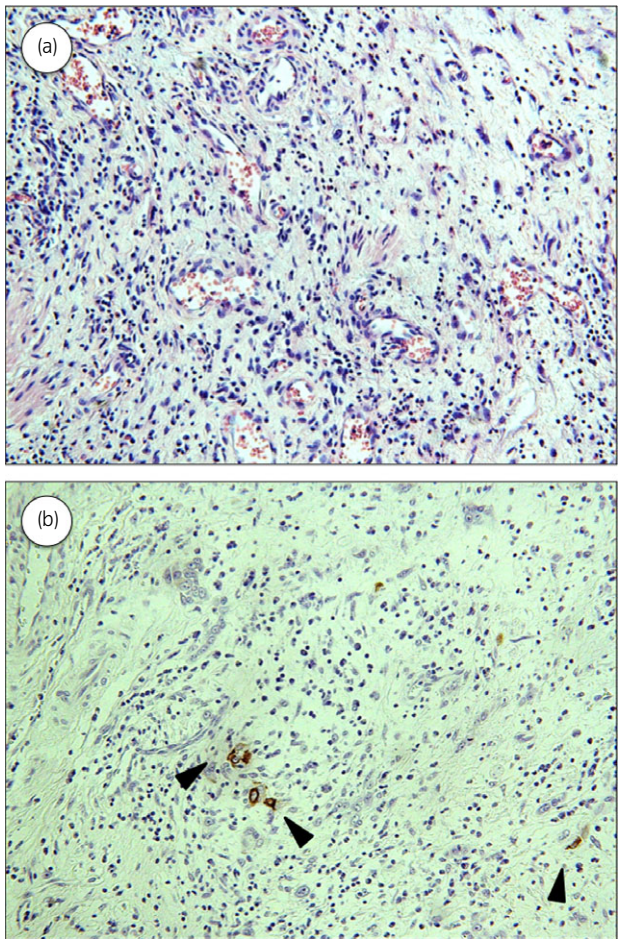

Fig. 3 Total cystectomy tissue sample. Hematoxylin and eosin staining (a) and immunohistochemical staining with the anti-hCG antibody (b). Positive staining of the tumor cells was detected (indicated by arrowhead).

leukocytes. Hypercalcemia was successfully treated with 120 mg denosumab. Serum calcium levels were gradually decreased (Fig. 2). However, leukocytes reached 122 440/μL (Fig. 2). In addition, the mass volume had increased steadily on the left pelvic side (Fig. 1). The patient died on 12 November 2017 (<3 months after radical cystectomy). The time course of the disease is summarized in Table 1.

Immunohistochemical staining of the specimens obtained during TURBT and radical cystectomy (Fig. 3) revealed positive staining for β-hCG.

Discussion

Hypercalcemia is the most common paraneoplastic syndrome, which is usually caused by PTHrP. Hypercalcemia can be treated with bisphosphonates. However, it can also be more efficiently treated with the anti-RANKL antibody (denosumab), which was performed in the present case.

In one-third of UCs with paraneoplastic syndromes, hypercalcemia coexists with leukemoid reactions induced by G-CSF.[2] Leukemoid reactions are typically present in aggressive types of cancer.[3] Furthermore, it has been reported that the cause of leukemoid reactions can be due to autocrine cell growth induced by G-CSF.[3]

hCG plays a role in cell transformation, angiogenesis, metastasis and immune evasion, which are key processes of carcinogenesis.[4] Non-trophoblastic malignancies dedifferentiate and produce a hyperglycosylated free β subunit of hCG. Ectopic expression of hCG and its β subunit by UC has been recognized as a relatively common observation.[5] Previous findings have reported the expression of hCG by a bladder cancer cell line with multiple cytokines, including G-CSF and G-CSF receptors.[6] A previous study suggested that hCG production may be an indicator of radioresistance, advanced disease, and poor prognosis.[7] Notably, secretion of cytokines and hormones by a tumor commonly occurs in metastasis. Metastasis formation is associated with the clonal selection process, and is strongly associated with dedifferentiation and formation of less mature and more aggressive metastatic tumors.

A MEDLINE database search revealed that there have been seven reported cases of UC producing G-CSF and PTHrP.[8–14] There were two female and five male patients (ages ranged from 38 to 83 years old; three patients were <70 years old). Transurethral resection or a biopsy was performed in three, total cystectomy in four, and chemotherapy in two patients. Although treatment was aggressive, the disease progressed rapidly and resulted in the death of six patients. Only one patient was disease free at 40 months following intra-arterial chemotherapy and total cystectomy.[8]

In the present case, SCC antigen (45.3 ng/mL, normal <1.5 ng/mL) was elevated without obvious pathological signs of SCC in tumor tissues. SCC antigens are a group of glycoproteins that belong to a family of serine/cysteine protease inhibitors.[15] Inhibition of proteases by SCC can affect tumor cell motility, invasiveness, proliferation and apoptosis. Although the tumor tissues in the present case lacked the typical findings of SCC, the patient's serum SCC antigen was elevated. A similar observation was indicated by Kato *et al.*[10] It is possible that dedifferentiated UC cells produce various antigens, including SCC, without manifestation of typical morphological squamous cell features. This also might be a case of UC with diffuse squamous transdifferentiation.[16]

Surgical resection is considered to be the most effective treatment for G-CSF-producing UC.[10,17] Chemotherapy may be an option in non-resectable tumors; however, taking into account the decreased renal function (on 18 October, creatinin was 1.34 mg/dL and estimated glomerular filtration rate was 30 mL/min) and rapid deterioration of the general condition of the patient, it was decided that the patient was not fit for standard systemic chemotherapy (methotrexate, vinblastine, doxorubicin and cisplatin or gemcitabine and cisplatin).

To the best of our knowledge, this is the first report of a bladder cancer producing multiple cytokines/hormones and SCC antigen. Undifferentiated, highly aggressive UCs tend to express multiple cytokines and hormones, causing paraneoplastic syndromes. The present findings suggest that detection of hCG in UC may be indicative that more aggressive management of the cancer is necessary.

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Conflict of interest

The authors declare no conflict of interest.

References

1 Nicolson GL. Paracrine and autocrine growth mechanisms in tumor metastasis to specific sites with particular emphasis on brain and lung metastasis. *Cancer Metastasis Rev.* 1993; **12**: 325–43.
2 Turalic H, Deamant FD, Reese JH. Paraneoplastic production of granulocyte colony-stimulating factor in a bladder carcinoma. *Scand. J. Urol. Nephrol.* 2006; **40**: 429–32.
3 Tachibana M, Murai M. G-CSF production in human bladder cancer and its ability to promote autocrine growth: a review. *Cytokines Cell. Mol. Ther.* 1998; **4**: 113–20.
4 Sisinni L, Landriscina M. The role of human chorionic gonadotropin as tumor marker: biochemical and clinical aspects. *Adv. Exp. Med. Biol.* 2015; **867**: 159–76.
5 Grammatico D, Grignon DJ, Eberwein P, Shepherd RR, Hearn SA, Walton JC. Transitional cell carcinoma of the renal pelvis with choriocarcinomatous differentiation. Immunohistochemical and immunoelectron microscopic assessment of human chorionic gonadotropin production by transitional cell carcinoma of the urinary bladder. *Cancer* 1993; **71**: 1835–41.
6 Tachibana M, Miyakawa A, Nakashima J *et al.* Constitutive production of multiple cytokines and a human chorionic gonadotrophin beta-subunit by a human bladder cancer cell line (KU-19-19): possible demonstration of totipotential differentiation. *Br. J. Cancer* 1997; **76**: 163–74.
7 Venyo AK-G, Herring D, Greenwood H, Maloney DJL. The expression of beta human chorionic gonadotrophin (beta-HCG) in human urothelial carcinoma. *Pan Afr. Med. J.* 2010; **7**: 20.
8 Hirasawa K, Kitamura T, Oka T, Matsushita H. Bladder tumor producing granulocyte colony-stimulating factor and parathyroid hormone related protein. *J. Urol.* 2002; **167**: 2130.
9 Kamai T, Arai G, Takagi K. Granulocyte colony-stimulating factor and parathyroid hormone related protein producing bladder cancer. *J. Urol.* 1999; **161**: 1565–6.
10 Kato T, Yasuda K, Iida H *et al.* Trousseau's syndrome caused by bladder cancer producing granulocyte colony-stimulating factor and parathyroid hormone-related protein: a case report. *Oncol. Lett.* 2016; **12**: 4214–8.
11 McRae SN, Gilbert R, Deamant FD, Reese JH. Poorly differentiated carcinoma of bladder producing granulocyte colony-stimulating factor and parathyroid hormone related protein. *J. Urol.* 2001; **165**: 527–8.
12 Tsuchiya F, Ikeda I, Kanda F, Fukuoka H. A case of bladder tumor producing granulocyte-colony stimulation factor and parathyroid hormone-related protein. *Hinyokika Kiyo* 2001; **47**: 873–6.
13 Ueno M, Ban S, Ohigashi T *et al.* Simultaneous production of granulocyte colony-stimulating factor and parathyroid hormone-related protein in bladder cancer. *Int. J. Urol.* 2000; **7**: 72–5.
14 Vaidyanathan S, Mansour P, Ueno M *et al.* Problems in early diagnosis of bladder cancer in a spinal cord injury patient: report of a case of simultaneous production of granulocyte colony stimulating factor and parathyroid hormone-related protein by squamous cell carcinoma of urinary bladder. *BMC Urol.* 2002; **2**: 8.
15 Suminami Y, Kishi F, Sekiguchi K, Kato H. Squamous cell carcinoma antigen is a new member of the serine protease inhibitors. *Biochem. Biophys. Res. Comm.* 1991; **181**: 51–8.
16 Gaisa NT, Braunschweig T, Reimer N *et al.* Different immunohistochemical and ultrastructural phenotypes of squamous differentiation in bladder cancer. *Virchows Arch.* 2011; **458**: 301–12.
17 Matsuzaki K, Okumi M, Kishimoto N *et al.* A case of bladder cancer producing granulocyte colony-stimulating factor and interleukin-6 causing respiratory failure treated with neoadjuvant systemic chemotherapy along with sivelestat. *Hinyokika Kiyo* 2013; **59**: 443–7.