

Case Report

Serum G-CSF May Be a More Valuable Biomarker than Image Evaluation in G-CSF-Producing Urothelial Carcinoma: A Case Report

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Keywords

Granulocyte colony-stimulating factor · Image evaluation · Tumor marker · Therapy ·
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Abstract

Granulocyte colony-stimulating factor (G-CSF)-producing urothelial carcinomas (UCs) are rare and have a poor prognosis. According to the literature, treatment for G-CSF-producing UCs is very difficult. We experienced 2 cases of UC presenting with leukocytosis. In these cases, serum G-CSF levels were higher than the reference value with leukocytosis at diagnosis, and the resected specimens were positive for anti-G-CSF immunostaining. One case had a good prognosis and the other case died after 9 months from diagnosis. A change in serum G-CSF levels was reportedly an effective tumor marker in several reports. In the present cases, evaluation of serum G-CSF levels was found to be more sensitive than computerized tomography. The treatment and outcomes of UC-producing G-CSFs and the efficacy of serum G-CSF as a tumor marker are discussed based on our cases and a review of the literature.

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Introduction

Leukocytosis is often seen in patients with paraneoplastic syndromes and is related to granulocyte colony-stimulating factor (G-CSF) production. Lung cancer is the most common G-CSF-producing cancer, and, in urology, bladder cancer is reportedly the highest G-CSF producer [1]. G-CSF-producing cancers have a poor prognosis, and most cases are difficult to treat.

To date, 122 cases of G-CSF-producing urothelial carcinomas (UCs) have been reported, including the present cases. However, none of the previous reports has focused on the value of serum G-CSF as a tumor marker compared to image evaluation. It is easier and much inexpensive to evaluate serum G-CSF than it is to use computerized tomography (CT). In this report, the pathological background, treatment, and efficacy of serum G-CSF as a biomarker are discussed from the viewpoint of the present cases, and a review of the literature is provided.

Case Report

Case 1

A 74-year-old man noticed asymptomatic macrohematuria and visited our hospital in October 2014. Cystoscopy showed no tumor, and a full-body CT scan showed a left renal pelvic tumor with no lymph node metastasis or visceral metastasis (Fig. 1a). Urine cytology showed UC. Blood tests showed leukocytosis (WBC 14,800/ μ L) without specific cause as infection. His serum G-CSF level was 147 pg/mL (reference value <37 pg/mL). Hence, a diagnosis of left renal pelvic G-CSF-producing cancer, cT3N0M0 cStage III, was made. Neoadjuvant chemotherapy with 2 courses of gemcitabine/cisplatin (GC) was administered starting in December 2014. Despite the 2 courses of GC, CT showed enlargement of the primary tumor, although the serum G-CSF levels decreased to 115 pg/mL. Hence, the chemotherapeutic agent was changed to methotrexate/epirubicin/cisplatin (MEC) in February 2015. After 1 course of MEC, the primary tumor enlarged even further, although there was no obvious metastasis on CT (Fig. 1b). Furthermore, serum G-CSF decreased to 89 pg/mL. Since CT showed the chemotherapy to be ineffective, left nephroureterectomy with para-aortic lymphadenectomy was performed in March 2015. A pathological examination of the resected specimen showed invasive UC, pT3bN0M0, pStage III, that was positive for anti-G-CSF immunostaining (Fig. 2). Since the primary tumor demonstrated widespread necrosis, it appeared that the chemotherapies had, in fact, been effective, as seen on pathological examination.

Although serum G-CSF was \leq 19.5 pg/mL before discharge, it increased to 92.8 pg/mL by May 2015. However, there was no obvious recurrence on CT. MEC was administered as adjuvant chemotherapy. After 2 courses of MEC, serum G-CSF decreased to 30.4 pg/mL. The patient has been followed up for 24 months after diagnosis without any evidence of recurrence on CT and with serum G-CSF levels remaining stable within the reference range (Fig. 3).

Case 2

A 62-year-old man visited our hospital for macrohematuria and dysuria in June 2015. Cystoscopy showed multiple nodular tumors, and transurethral biopsy revealed UC. With full-body CT scanning and magnetic resonance imaging, we diagnosed his tumor as urinary

bladder cancer, cT3N0M0, cStage III (Fig. 4a). Blood tests showed leukocytosis (WBC 22,530/ μ L) without specific cause as infection. His serum G-CSF level was 83.9 pg/mL. We administered GC as neoadjuvant chemotherapy. After 3 courses of GC, the tumor size decreased on CT (Fig. 4b) and cystoscopy, while serum G-CSF increased to 185 pg/mL. We thereafter performed cystectomy in October 2015. A pathological examination of the resected specimen revealed a sarcomatoid variant of invasive UC, pT4aN0M0, pStage IV, that was positive for anti-G-CSF immunostaining. The primary tumor had slight necrosis.

However, subcutaneous and multiple liver metastases appeared 1 month after surgery, and the patient died 9 months after diagnosis.

Discussion

It has been reported that G-CSF-producing cancers are relatively rare and have a poor prognosis [1]. As the reason for this, it is thought that tumor cells express G-CSF, which in turn increases the number of tumor cells by autocrine signaling, and immature monocytes and myeloblasts, which suppress tumor immunity, are induced [2]. Several papers reported that serial changes in serum G-CSF levels were effective as a tumor marker [2–4]. In case 1, serum G-CSF decreased after chemotherapy despite the image evaluation showing tumor enlargement. Since the pathological examination showed widespread necrosis of the tumor, serum G-CSF levels reflected the condition of the disease better than did CT. After surgery, serum G-CSF levels increased despite the absence of recurrence on CT, and administration of adjuvant chemotherapy led to prevention of recurrence and normal serum G-CSF levels up to 24 months. On the other hand, in case 2, serum G-CSF levels increased after chemotherapy despite tumor reduction on image evaluation. As a result, there was recurrence soon after surgery. Based on the present cases, serum G-CSF might be a more sensitive biomarker of G-CSF-producing UCs than is imaging evaluation.

To date, a total of 122 G-CSF-producing UC cases have been reported [1–10]. In the histopathological classification of tumor types of G-CSF-producing UCs, the pathological type was UC in 72 cases (59.0%), UC with squamous cell carcinoma (SCC) differentiation in 15 cases (12.3%), UC with adenocarcinoma in 1 case (0.8%), UC with a sarcomatoid variant in 9 cases (7.4%), SCC in 14 cases (11.5%), undifferentiated carcinoma in 7 cases (11.5%), and unknown in 4 cases (3.3%). There are many more variant types among G-CSF-producing UCs than among non-G-CSF-producing UCs. In cases in which the stage was specified at diagnosis, most were diagnosed at an advanced stage: stage I, 6 cases; stage II, 6 cases; stage III, 28 cases; and stage IV, 42 cases. Chemotherapy was administered in 53 cases, since most cases were diagnosed at an advanced stage. Only 24 cases had no recurrence 12 months after diagnosis. Regarding tumor stage in the survivors, 4 cases had stage I, 1 case had stage II, 10 cases had stage III, and 9 cases had stage IV disease. None of the surviving stage IV cases had lymph node or visceral metastases. There were no significant differences with respect to whether or not chemotherapy was administered.

The poor prognosis of G-CSF-producing UCs may be due to poor response to chemotherapy. Of the 53 patients who received chemotherapy, only 14 (26.4%) demonstrated partial response or stable disease. Although several chemotherapeutic agents such as GC, MEC, methotrexate/vinblastine/Adriamycin/cisplatin (M-VAC), gemcitabine/nedaplatin (GN), gemcitabine/paclitaxel (GP), paclitaxel/ifosfamide/nedaplatin (TIN), and intra-arterial injection chemotherapy with epirubicin/cisplatin have been reported, none of them have been found to be effective. In addition to aggressive progression of tumor, this could be due to the

diverse histopathological backgrounds of these tumors, since UC accounted for only 59.0% of the reported cases, while 38.5% of them were variant type UC or SCC. However, there are probably other factors related to the lack of responsiveness to chemotherapy, since there are many UC cases that are not sensitive to chemotherapy.

Recently, neoadjuvant chemotherapy has often been administered for improvement of overall survival in advanced UC cases. Although the combination of surgery with neoadjuvant chemotherapy was also used in many cases of G-CSF-producing UC, the majority of them recurred soon after surgery. Considering the poor response rate to chemotherapy, surgery might be performed as soon as possible in these cases if there is no obvious metastasis. When choosing neoadjuvant chemotherapy as in the present cases, frequent examination of serum G-CSF levels is more valuable and easier to evaluate than imaging evaluation, and treatment should be considered with reference to changes in serum G-CSF levels.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare no conflict of interest in association with this article.

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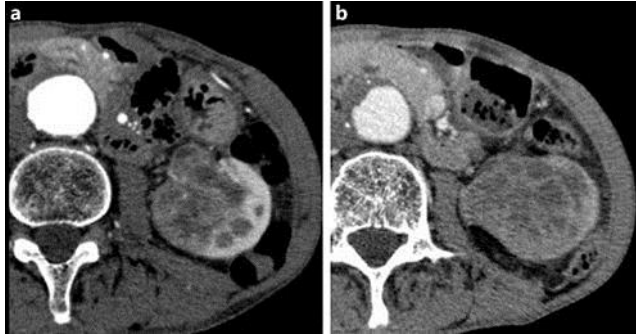


Fig. 1. Serial computerized tomography (CT) images of case 1. **a** The full-body CT scan shows left pelvic cancer with no lymph node or visceral metastases at diagnosis. **b** The left pelvic cancer has enlarged in size despite 2 courses of gemcitabine/cisplatin and 1 course of methotrexate/epirubicin/cisplatin.

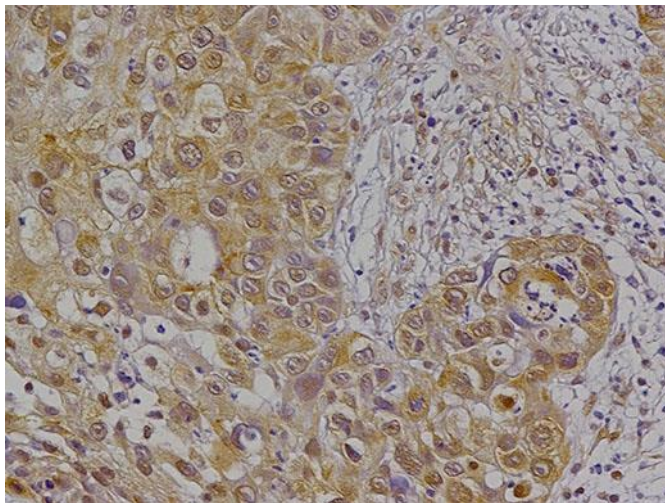


Fig. 2. Pathological examination of the left nephroureterectomy specimen from case 1 in March 2015 shows that it is positive for anti-G-CSF immunostaining. $\times 100$.

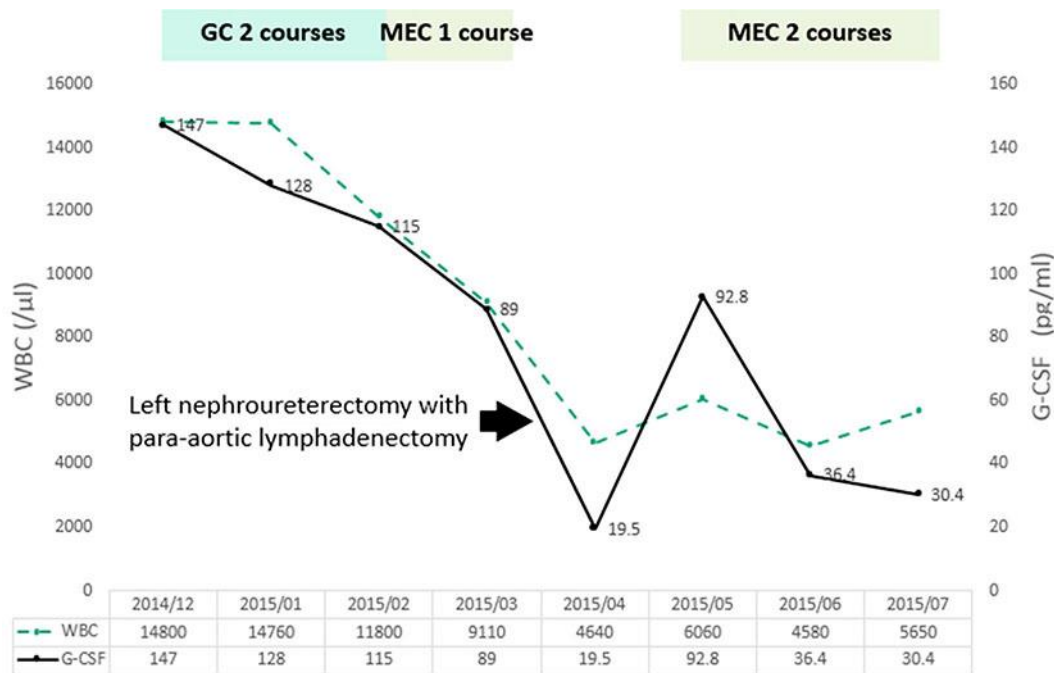


Fig. 3. Clinical course and changes of leukocyte and G-CSF levels.

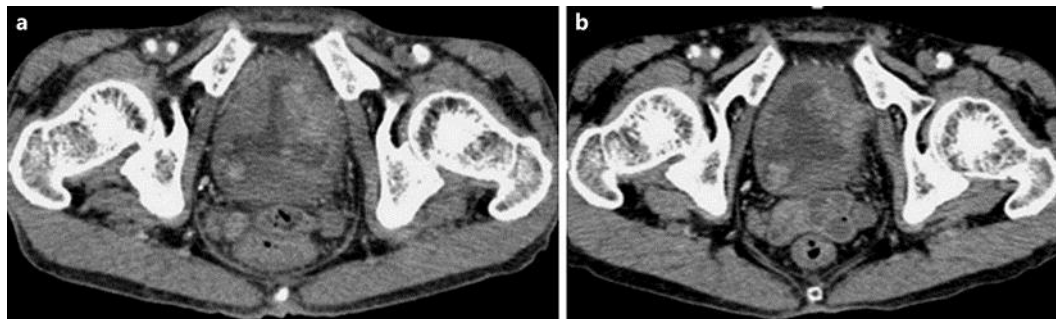


Fig. 4. Serial computerized tomography (CT) images of case 2. **a** The full-body CT scan shows multiple bladder cancer with no lymph node or visceral metastases at diagnosis. **b** The bladder cancer has reduced in size after 3 courses of gemcitabine/cisplatin.