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Overview

Granulocyte Colony-stimulating Factor-producing Upper Urinary Tract Carcinoma: Systematic Review of 46 Cases Reported in Japan

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Abstract

Aims: Granulocyte colony-stimulating factor (G-CSF)-producing upper urinary tract carcinoma is extremely rare, and we do not yet have a comprehensive understanding of the disease. This study was carried out to determine the characteristics of G-CSF-producing upper urinary tract carcinoma.
Materials and methods: A systematic MEDLINE and ICHUSHI WEB (Japan Medical Abstract Society) search was carried out to identify articles and conference proceedings describing patients with G-CSF-producing upper urinary tract carcinoma. The final cohort included 46 patients: eight studies were published in English, 16 in Japanese and there were 18 Japanese conference proceedings.
Results: The average age of patients was 67 years and the male to female ratio was 2.5 to 1. The mean white blood cell count was as high as 33 900/μl (range 10 000–121 000) in these patients. Pretreatment serum G-CSF levels were measured in 23 patients, all of which were higher (range 55–1220 pg/ml) than normal levels. Metastasis was detected in 29 patients (63%) and lymph node and lung metastases were well observed. The most commonly reported primary treatment was surgery (33 patients), but the median survival period for these patients was short (4.5 months). Multivariate analysis showed that lymph node and/or distant metastasis (hazard ratio 2.92, $P = 0.020$) and the absence of adjuvant therapy (hazard ratio 3.20, $P = 0.014$) were independent risk factors for mortality. A total of only seven patients survived more than 1 year and most had a history of neoadjuvant/adjuvant chemotherapy and/or radiation therapy.
Conclusion: We believe that the presence of G-CSF-induced leukocytosis represents a distinct and highly aggressive form of upper urinary tract carcinoma. However, the results of our systematic review indicate that a multidisciplinary approach including surgery, neoadjuvant or adjuvant chemotherapy and radiotherapy may have the potential to control the disease, although we cannot provide definitive recommendations from this retrospective study.

Key words: Granulocyte colony-stimulating factor; G-CSF; renal pelvis; upper urinary tract carcinoma; ureter

Statement of Search Strategies Used and Sources of Information

We searched for Japanese cases of granulocyte colony-stimulating factor (G-CSF)-producing upper urinary tract carcinoma published up to December 2013 in both English and Japanese, including conference proceedings, using MEDLINE and ICHUSHI WEB (Japan Medical Abstract Society). We used the following medical subject heading terms and/or text words: 'granulocyte colony-stimulating factor', 'leukocytosis', 'renal pelvis' and 'ureter'. We also reviewed the reference lists of the identified publications and relevant review articles for additional pertinent studies. We included only cases of upper urinary tract carcinoma with either tumour expression of G-CSF detected by immunohistochemistry or evidence of increased serum G-CSF accompanying leukocytosis without infectious disease or blood disorder. The electronic search identified 154 abstracts for review; of these, 39 articles potentially met the inclusion criteria and were retrieved for detailed examination. We added six candidate studies after reviewing the bibliographies of the relevant articles and excluded three studies that did not match our criteria. A total of 42 studies ultimately met our predefined inclusion criteria and were included in the final analyses. These studies consisted of eight published in English, 16 published in Japanese journals and 18 abstracts published in Japanese conference proceedings. These studies provided a total of 46 cases for systematic review.

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Introduction

Granulocyte colony-stimulating factor (G-CSF) is one of the haematopoietic growth factors promoting the proliferation, differentiation and maturation of haematopoietic stem cells and early progenitor cells to release granulocytes [1]. It is produced by bone marrow stromal cells, monocytes, fibroblasts and endothelial cells, but it is now known that several malignant tumours also produce G-CSF, resulting in marked leukocytosis in the absence of any acute infectious disease or blood disorder [2]. In general, most G-CSF-producing tumours are detected at an advanced stage and are associated with a detrimental clinical outcome due to highly malignant potential.

As a result of the establishment of immunohistochemistry techniques and the ability to measure serum G-CSF levels, an increasing number of G-CSF-producing non-haematopoietic malignancies have been diagnosed and reported in the lung [3], head and neck [4], thyroid [5], gall bladder [6], liver [7], stomach [8], bladder [9] and rectum [10]. However, G-CSF-producing upper urinary tract carcinoma is extremely rare. Furthermore, most reported cases have been from Japan, which is also true for other G-CSF-producing cancers. It is unknown whether these reporting differences reflect a difference in geographical prevalence or in disease recognition among societies. Some case reports of G-CSF-producing upper urinary tract carcinoma have been described in Japanese literature and almost all previous reports are limited to a single-case study. Due to a lack of systematic reports, we do not yet have a comprehensive understanding of the disease and there remains a paucity of data to serve as reference points for discussion and counselling between physician and patient. In this study we carried out a systematic review of G-CSF-producing upper urinary tract carcinoma cases reported from Japan to further clarify presentation, treatment options and prognosis.

Materials and Methods

We searched for Japanese cases of G-CSF-producing upper urinary tract carcinoma published up to December 2013 in both English and Japanese, including conference proceedings, using MEDLINE and ICHUSHI WEB (Japan Medical Abstract Society). We used the following medical subject heading terms and/or text words: 'granulocyte colony-stimulating factor', 'leukocytosis', 'renal pelvis' and 'ureter'. We also reviewed the reference lists of the identified publications and relevant review articles for additional pertinent studies. We included only cases of upper urinary tract carcinoma with either tumour expression of G-CSF detected by immunohistochemistry or evidence of increased serum G-CSF accompanying leukocytosis without infectious disease or blood disorder. After a full-text review and evaluation of appropriate references and conference proceedings, 42 studies fulfilled the inclusion criteria. These studies consisted of eight published in English [11–18], 16 published in Japanese journals [19–34] and 18 abstracts published in Japanese conference proceedings. These studies provided a total of 46 cases for systematic review. Table 1 provides a list of all references.

The collected clinical data included gender, age, symptoms, laboratory data, clinical and pathological diagnosis, type of therapy and clinical outcomes. The cases in which clinicopathological data were not available were excluded from specific data analysis. Values are presented as the mean ± standard deviation.

The difference in continuous measurements between two groups was analysed with a Mann–Whitney test, and among three groups with a Kruskal–Wallis test. A two-sided Fisher's exact test was used to determine if there were non-random associations among categorical variables. For time-course variables the starting point of this study was the time of operation for patients who underwent surgery, and that of clinicopathological diagnosis for patients who were not treated with an initial surgical approach. The end point was overall survival for all cases. To determine the risk factors for overall survival, a multivariate analysis was carried out using the Cox proportional hazards model with stepwise forward selection. Variables with missing values for more than half the observations were excluded from this analysis. The cumulative overall survival rate curves were constructed using the Kaplan–Meier method. Differences among the groups were analysed using the Log-rank test. In all analyses, $P < 0.05$ was considered statistically significant. These analyses were carried out with SPSS software, version 20 (SPSS Inc, Chicago, IL, USA), and R, version 3.0.2.

Results

The demographics of the reviewed cases are summarised in Table 2. The mean patient age was 67 years (range 39–88 years). The male to female ratio was 2.5 to 1. Common complaints were gross haematuria (54%), systemic symptoms including anorexia, general fatigue and fever (49%) and flank pain (41%). The average tumour size was 7.6 cm (range 2.5–17 cm). The mean white blood cell (WBC) count at diagnosis was extremely high (33 900/μl). Pretreatment serum G-CSF levels were measured in 23 patients, all of which were higher (range 55–1220 pg/ml) than normal levels (<39 pg/ml). Urothelial carcinoma was the most common histology (52%), followed by squamous cell carcinoma (SCC) (17%) and undifferentiated carcinoma (9%). Of the 46 total patients, 29 (63%) were noted to reveal positive G-CSF immunohistochemical staining and the other 17 were diagnosed by elevated serum G-CSF levels accompanying leukocytosis without infectious disease or blood disorder. Seventeen patients (37%) were found to have no metastasis at the time of diagnosis. Of these patients the exact primary tumour stage (T category) was not reported for six cases, four were diagnosed as T1-3 disease and the remaining seven patients had locally advanced disease (T4). Metastasis was detected in the other 29 patients (63%) and lymph node and lung metastases were well observed.

The treatment for the disease was unknown in only one patient. The most commonly reported primary treatment