CASE REPORT
ONCOLOGY

Diseases & Research

Chemotherapy-Induced Fever: A Case Report of Metastatic Urothelial Cancer

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Abstract: Chemotherapy-induced fever (CIF) is a significant non-hematological side effect of chemotherapeutic medications, with Gemcitabine being one of the most common agents that cause this type of fever. CIF is determined as a diagnosis of exclusion when a comprehensive clinical and laboratory evaluation fails to find the specific cause for the patient's fever. An old-age male with a history of metastatic urothelial cancer presented with CIF after treatment with a single-agent Gemcitabine. Clinicians should maintain a high index of suspicion for CIF to avoid unnecessary treatments and superfluous investigations.

Keywords: Chemotherapy; Gemcitabine; Fever; Urothelial carcinoma.

Introduction

CIF is defined as a temperature of ≥ 37.5 °C that persists for ≥ 1 hour following the administration of a chemotherapeutic medication[1]. It is typically considered a diagnosis of exclusion when no specific cause of fever is identified after a thorough clinical and laboratory assessment[2,3].

Different chemotherapeutic drugs can cause this type of fever, with Gemcitabine being one of the most common culprits[1]. A retrospective multicenter study reported that the incidence of Gemcitabine-related fever is 20%[1], whereas two manufacturers of Gemcitabine (Pfizer and Lilly) reported that the incidence is 37.3% and 41%, respectively, in patients treated with single-agent Gemcitabine[4,5].

When antibiotics are prescribed due to the worry of infection in the case of CIF, the patient's fever frequently will not subside and could result in unwanted outcomes, including a prolonged hospital admission, additional costly tests, unnecessary treatments, and the potential development of drug-resistant bacteria. Although CIF is a very important issue for clinicians, it remains underexplored in the clinical studies[1].

In this case study, we presented an old-age male patient with metastatic urothelial cancer who experienced attacks of fever during chemotherapy treatment.

Case Presentation

A 74-year-old male smoker presented in January 2022 with painless hematuria that lasted for 1 week. Vitally, he was stable with unremarkable history and physical examination apart from a significant weight loss over the last 2 months. He had neither a past medical history nor a family cancer history. In January 2022, contrast-enhanced computerized tomography (CT) scans of the abdomen and pelvis were conducted (Fig. 1) and showed a 5 × 3.5 cm mass in the left renal pelvis extending to the ureter, alongside multiple para-aortic lymphadenopathies and two soft tissue lesions on the anterior and posterior walls of the urinary bladder (measuring 2.6 × 0.7 cm and 2 × 1 cm, respectively).

In that same month, he underwent left radical nephroureterectomy with para-aortic lymph node dissection as well as transurethral resection of bladder tumors, with the histopathology result revealing: synchronous multifocal high-grade papillary urothelial carcinoma of the renal pelvis, ureter, and urinary bladder (Fig. 2).

In March 2022, post-operative assessment CT scans of the chest and abdomen were performed and showed multiple bilateral pulmonary metastatic nodules (Fig. 3) with a clear operative bed.

According to the 8th edition of the TNM classification of malignant tumors[6], our patient has stage IV disease (metastatic disease). The novel therapeutic agents recommended for metastatic upper tract urothelial carcinoma (UTUC) like immunotherapy and others were not available in our cancer center, and the patient couldn't afford the cost, so the treatment plan for our patient was to start palliative chemotherapy with follow-up. He received 6 cycles of Carboplatin + Gemcitabine (administered every 21 days) with a stable disease observed by the CT scan assessment. Due to Carboplatin being a nephrotoxic drug and the patient having slightly elevated renal function tests as well as having a solitary kidney, Carboplatin was discontinued, and the patient proceeded with only Gemcitabine. In the 2nd and 3rd cycles of Gemcitabine, the patient complained of fever attacks (a sustained fever of ≥ 38 °C lasting approximately five hours) that began on the 3rd day after Gemcitabine administration and persisted for a 3-day duration, then subsided (see Fig. 4).

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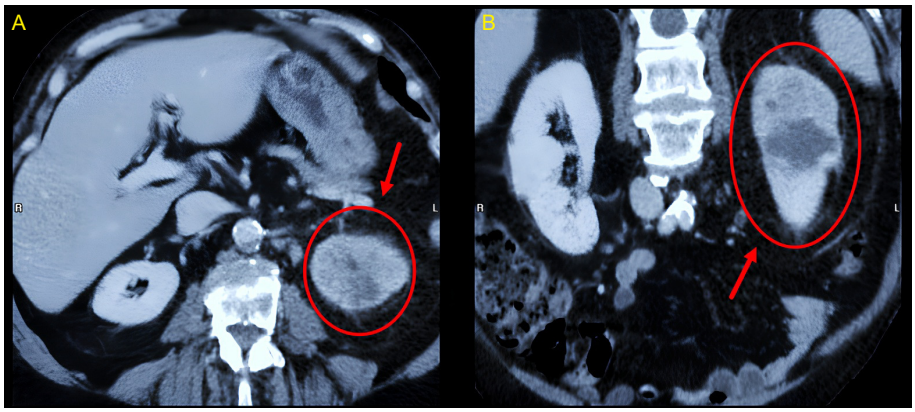

Fig. 1. Contrast-enhanced CT scan.
A. Coronal section.
B. Sagittal section, showing the primary lesion in the left upper urinary tract with enhancement (arrows).

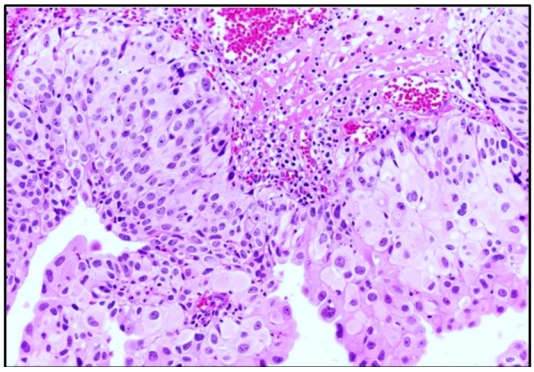

Fig. 2. High-grade papillary urothelial carcinoma of the upper urinary tract showing atypical cells with high nuclear grade and mitotic features.

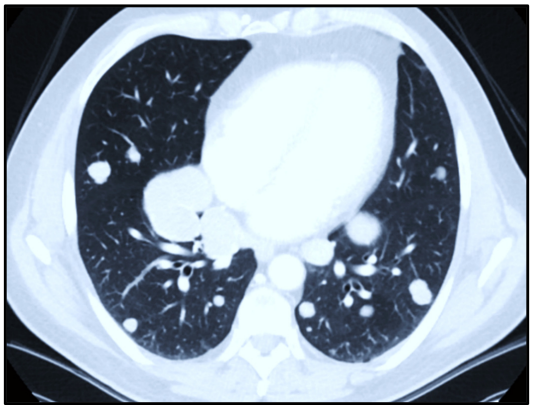

Fig. 3. Contrast-enhanced CT scan showing multiple bilateral lung metastatic nodules.

This fever was relieved by antipyretic medications (Acetaminophen). See Fig. 5. for a timeline summary of the clinical course of the patient's condition.

Throughout the fever time, the patient remained clinically stable and had no symptoms or signs of systemic or local infections, and his laboratory investigations were unremarkable regarding infections (C-reactive protein, complete blood count with differential, erythrocyte sedimentation rate, viral screen, urine, and blood cultures). Chest X-ray, followed by chest and abdominopelvic CT scans, didn't reveal any occult source of infection. Additionally, he didn't receive granulocyte-colony stimulating factor (G-CSF), which can induce fever as a side effect, nor blood transfusion given. Based on all these results and findings, it was determined that this fever is chemotherapy-induced.

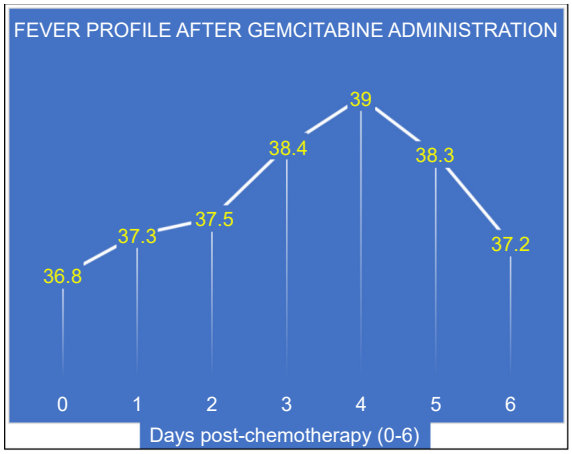

Fig. 4. Fever profile after Gemcitabine administration.

Discussion

UTUC is a rare disease that accounts for 5–10% of urothelial cancers. Despite the several similarities between UTUC and bladder cancer, UTUC has a more aggressive course[7,8].

According to the international guidelines, contrast-enhanced CT scans of the abdomen and pelvis are the recommended initial diagnostic test for the work-up of suspicious UTUC. Cystoscopy + /- ureteroscopy with urine sampling examination are further investigations that are added occasionally in the work-up assessment. To rule out organ and lymph node metastasis, whole-body contrast-enhanced CT scans are enough. Although it is less sensitive and specific, magnetic resonance (MR) with urography followed by renal ultrasound can be used for the diagnosis and staging of UTUC in case of contraindications to contrast-enhanced CT scan, whilst 18F-Fluorodeoxyglucose positron emission tomography/CT (PET/CT) scan is preferred to assess nodal metastasis[9].

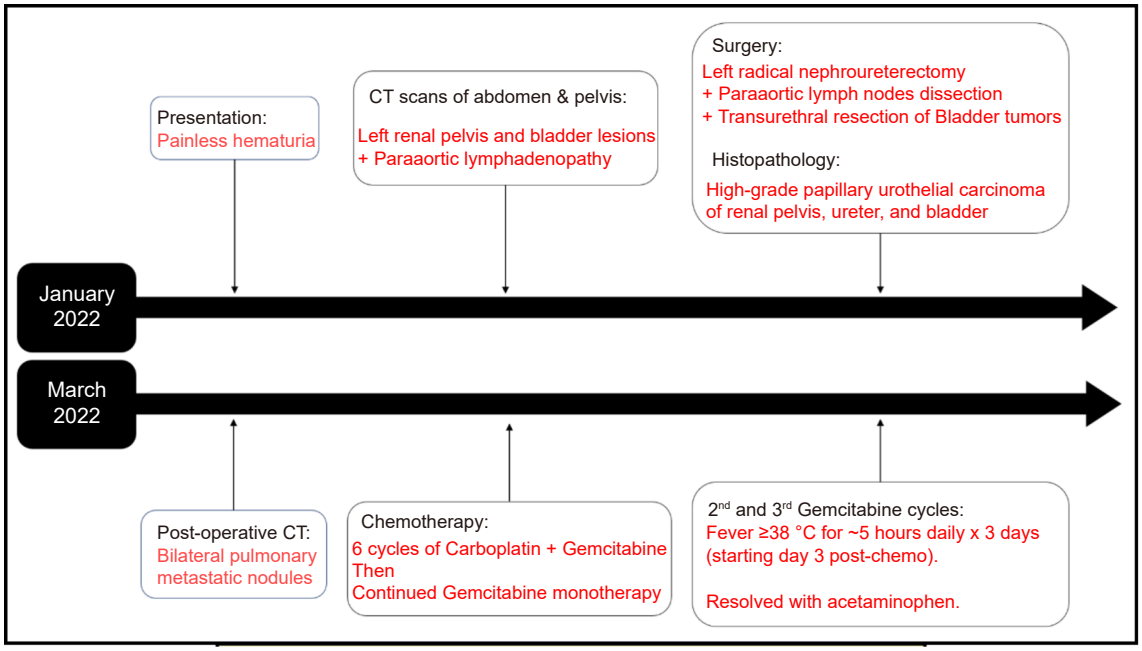

Fig. 5. Chronological summary of the patient's condition.

Patients with cancer disease may develop fever that could be related to different causes and factors. Infections (bacterial, viral, or fungal) are the most common causes of fever among cancer patients, primarily due to neutropenia resulting from the administration of immunosuppressant cytotoxic treatments[10]. Cancer-related fever is another etiology of fever in cancer patients. The mechanism of neoplastic fever production involves cytokines such as tumor necrosis factor (TNF), interleukin 1 and 6 (IL-1, IL-6), and interferon (IFN), which are produced either by the host macrophages in response to the tumor or sometimes by the cancer itself. The cytokines stimulate the production of prostaglandins, which act on the hypothalamus, causing a change in the thermoregulatory set point[11,12]. Additionally, fever in such condition can be one of the clinical features of paraneoplastic syndrome. It is thought to result from the release of endogenous pyrogens (i.e., lymphokines or tissue pyrogens). Fever may also be related to necrotic-inflammatory phenomena of the tumor and/or to alterations in liver function and consequent disorders of steroidogenesis[13,14]. Furthermore, transfusion-related reactions, mainly the nonhemolytic febrile reactions, can cause fever in cancer patients who require blood-product transfusions. Cytokines and other normal constituents of leukocytes, platelets, or plasma accumulate in blood components during storage. When blood components are transfused, some recipients experience varying generalized symptoms, with fever being the most common[15,16]. Drugs like antibiotics or cytotoxic drugs can sometimes cause fever. Chemotherapy is thought to promote the production of cytokines[13].

Gemcitabine is one of the pyrimidine-derived antimetabolites, which are a group of chemotherapeutic agents that disrupt DNA synthesis and exert cytotoxic effects on cancer cells[17]. Gemcitabine can be used as a single agent or in combination with other chemotherapeutic agents for the treatment of various solid cancers, particularly pancreatic cancer, small and non-small cell lung cancers, bladder cancer, ovarian cancer, and breast cancer[18–20].

Although Gemcitabine is generally well tolerated when used as a single-agent therapy, its toxicity can vary depending on the administration schedule and dosage[19]. The common adverse effects of Gemcitabine include myelosuppression, nausea and vomiting, elevated liver enzymes, and fever[5,21]. The exact mechanism and clinical significance of Gemcitabine-induced fever remain unclear[21]; however, the potential mechanisms of drug-related fever include hypersensitivity reactions[22], drug pyrogenicity[23], drug effect on the thermoregulatory center[24], and the release of endogenous pyrogenic cytokines from the tumors during their breakdown[25]. Gemcitabine may trigger cytokine release (e.g., IL-1, IL-6, TNF-α, IFN), possibly through tumor necrosis or immune activation, which eventually induces fever[21]. In vitro studies confirm that Gemcitabine enhances cytokine release in colorectal cancer cells[26]. Additionally, fever following Gemcitabine administration reflects a systemic inflammatory response triggered by the tumor and is suggested to be related to tumor activity[21].

Gemcitabine-related fever is usually mild to moderate (grade 1 or 2), is easily managed, lasts for a short period, and rarely results in dose-limiting[8]. Fever in our presented patient ranged from mild to moderate grades (38–39 °C), persisted for a short duration (3–5 hours per day and resolved after 3 days), was easily relieved with simple antipyretics (Acetaminophen), and never led to a Gemcitabine-dose reduction or omission.

The incidence of Gemcitabine-related fever typically peaks on day 3 post-treatment[1]. Fever occurring on days 3 or 4 post-treatment is usually considered a drug-induced fever because chemotherapy-related myelotoxicity is not usually observed during this period[1]. This was comparable to the presentation of our patient, where fever began on day 3 post-Gemcitabine administration, which supports the diagnosis of chemotherapy-related fever.

There is no definitive method to diagnose chemotherapy-induced fever when a cancer patient is febrile. A provisional diagnosis of this fever type should only be considered after ruling out other serious conditions. Therefore, evaluating such a clinical condition requires a detailed medical history and physical examination to help identify the source of the fever. Although laborat-

ory tests or imaging may be useful, clinicians should remember that no single result can confirm or rule out chemotherapy-induced fever. Identifying the responsible drug can be challenging when multiple medications are being used[27].

Healthcare providers are usually worried about fever during chemotherapy in cancer patients. However, they have to consider the possibility of CIF, and if suspected on days 3 or 4 post-treatment, they can focus on symptomatic management[1]. Further clinical and investigational studies are required to better understand CIF, as it is a somewhat under-explored important issue.

Conclusion

CIF is a diagnosis of exclusion, and Gemcitabine is one of the common drugs causing this type of fever. Clinicians, particularly oncologists, should be aware of CIF in patients who have a fever without an identifiable cause. This mindfulness can avoid the escalated inappropriate use of antibiotics as well as the use of unnecessary costly tests.

Abbreviations

°C, Celsius; CIF, Chemotherapy-Induced Fever; CT, Computerized Tomography; DNA, Deoxyribose Nucleic Acid; G-CSF, Granulocyte-Colony Stimulating Factor; IFN, Interferon;IL, interleukin; MR, Magnetic Resonance; PET, Positron Emission Tomography; TNF, Tumor Necrosis Factor; TNM, Tumor Node Metastasis; UTUC, Upper Tract Urothelial Carcinoma.

Ethics approval and consent to participate

After a thorough evaluation and gathering of information from the patient and his guardian, written consent was obtained to present his condition for publication. A copy of the consent form is available upon request. The ethical committee approval was required and obtained from the ethical committee of the health department.

Conflict of Interest

The author declares that there is no conflict of interest.

Authors' contributions

The only author of this case report wrote, organized, and reviewed the whole article.

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