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ARTICLE

Bladder cancer patients hospitalized in a medicine ward including three fuo cases following bacillus calmette-guérin immunotherapy

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Objectives: *Bladder cancer (BC) is a prevalent malignancy with evolving treatment strategies and an increasingly aging patient population, resulting in a growing and complex burden of hospitalizations that extends beyond urological care and remains insufficiently characterized in real-world Internal Medicine settings. This study aimed to analyze the clinical data and outcomes for patients with BC admitted to the medicine ward. Additionally, this research presents three cases of fever of unknown origin, which all exhibited identical clinical and laboratory findings but ultimately resulted in different disease diagnoses.*

Methods: *This retrospective case-series study included all adult patients with BC admitted to the Internal Medicine ward of a tertiary referral hospital between 1 January 2020, and 31 December 2024. Data acquisition was performed through a systematic search of electronic discharge records using the ICD-10 code C67. Data recording involved detailed review of electronic medical records to collect demographic characteristics, clinical history, cancer-related treatments, causes of hospitalization, and outcomes. Three patients previously treated with intravesical Bacillus Calmette–Guérin (iBCG) who presented with fever of unknown origin were analyzed in detail. Data analysis comprised descriptive statistics and comparative testing using Fisher's exact test and unpaired two-tailed Student's t-test, with $p < 0.05$ considered statistically significant.*

Results: *We identified 77 hospitalizations among 67 BC patients who were predominantly male, with a mean age of 75.2. A high prevalence of metabolic syndrome comorbidities and chronic obstructive pulmonary disease was documented. In addition, 31.1% of patients had metastatic BC, 22.9% had a second malignancy, 49.2% had undergone urological surgeries, and 38% had received chemotherapy or immunotherapy other than iBCG. The most common causes of hospitalization were infections, anemia/transfusions, a newly diagnosed metastatic disease, and acute renal failure. The mortality in this cohort was high (17%), with the leading cause of death again being an infection. Among patients who had previously received BCG immunotherapy, three cases of fever of unknown origin were noticed, and despite identical clinical settings, they were identified with different diseases [metastatic disease, infection caused by Bacillus Calmette-Guérin (BCGitis), and Hodgkin's lymphoma], necessitating individualized therapeutic medications.*

Conclusions: *BC patients in the Internal Medicine unit are generally older adults, often dealing with several chronic conditions and a considerable cancer burden. They are predominantly admitted due to infections, which points to the urgent need for effective infection prevention strategies for this vulnerable population. When BC patients have a fever lasting more than seven days following BCG instillation, which is the maximum duration for self-limited adverse events to occur, regardless of whether an antibiotic regimen has been prescribed, they should consult an internal medicine department for further evaluation.*

Key Words: Bladder cancer, intravesical BCG, BCGitis, fever of unknown origin, hospitalization, hodgkin's lymphoma

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Introduction

Bladder cancer (BC) ranks as the 10th most prevalent cancer globally, the 6th most common cancer in males, and the 9th major cause of cancer-related mortality in men.[1] Following transurethral resection of bladder tumor (TURBT), the intravesical administration of Bacillus Calmette-Guérin (iBCG) is currently the gold standard adjuvant treatment for patients with high-risk non-muscle invasive bladder cancer (NMIBC) and, in certain cases, of intermediate-risk NMIBC.[2] Radical cystectomy is recommended for selected high-risk NMIBC patients, particularly those with persistent high-grade T1 disease or BCG-unresponsive tumours, in whom bladder-preserving strategies are unlikely to achieve durable oncologic control.[2] The implementation of newer immunotherapies comprising the immune checkpoint inhibitors nivolumab,[3] pembrolizumab,[4] durvalumab,[5] and other immunotherapies[6] improved overall and progression-free survival in patients with high-risk muscle-invasive or metastatic BC over the last decade. Patients with muscle-invasive bladder cancer (MIBC) experience a high and predictable burden of symptoms and hospital utilization in the final year of life, with a substantial proportion of emergency admissions driven by preventable urological complications, particularly haematuria and severe urinary tract infections.[7] In addition, the age of patients with BC who were hospitalized in the urological ward and the proportion of patients aged ≥80 years significantly increased over the last decade.[8] However, the reasons for hospitalization in this patient population have not been explored in the real world.

The objective of this case-series study was to analyze the demographics, clinical characteristics, medical and urological history, causes of hospitalization, and outcomes of patients with BC admitted to the Internal Medicine ward of a tertiary referral hospital, and compared patients previously treated with iBCG immunotherapy with those receiving other treatments. Among patients previously treated with iBCG, we further focused on three individuals who presented with fever of unknown origin (FUO), attributable to distinct underlying causes, including metastatic bladder cancer, BCG-related infection (BCGitis), and Hodgkin's lymphoma (HL).

Materials and Methods

Study design and data source

The study was approved by the Institutional Review Board of the Scientific Council of Hippokration General Hospital of Athens (Approval No. 26/11142023). Due to the retrospective nature of the study, the requirement for written informed consent was waived. We aimed to investigate the causes of hospitalization for BC patients in the internal medicine ward after three such patients, who had a history of BCG immunotherapy, presented with prolonged fever at our institution. Thus, a search was performed on the electronic discharge documents of the Internal Medicine unit of our tertiary referral hospital (General Hospital of Athens "Hippokration", Athens, Greece) using the search term "C67," the ICD 10 code for "bladder cancer," covering the period from 1 January 2020, to 31 December 2024. The aforementioned period was selected because recent immunotherapies have predominantly been integrated into clinical practice within the last five years. Inclusion criteria were all adult patients identified through electronic data retrieval using the search term "C67" in the electronic discharge records during the period from 1 January 2020, to 31 December 2024, irrespective of the cause of hospitalization. Exclusion criteria were not applied; therefore, no patients meeting the inclusion criteria were excluded from the study. The primary aim of the study was to document the three cases of FUO, and the secondary objective was to examine the characteristics and causes of hospitalization among BC patients in our medicine ward.

Study population

This computer-based study identified 77 hospitalizations involving 67 distinct patients. The medical records of these patients were analyzed, and several variables were documented in tables. These variables included age, sex, medical history (which encompassed bladder cancer diagnoses and treatments), presenting symptoms, hospital course, outcomes, duration of hospitalization, and discharge diagnoses. In three cases of prolonged fever, a comprehensive recording was conducted, including blood tests, radiographic studies, additional diagnostic investigations for fever of unknown origin (FUO), and histologic analyses.

Statistical analysis

Mean values and standard deviations were presented for continuous variables, whereas categorical variables were expressed in terms of frequencies and percentages. The Fisher's exact test was utilized for qualitative value comparisons, while the two-tailed unpaired Student's *t*-test was employed for numerical value comparisons. A *p*-value of less than 0.05 was considered significant. Analyses were conducted utilizing the Microsoft Office Home and Student 2021 (Microsoft Corporation, One Microsoft Way, Redmond, WA 98052-6399, USA).

Results

Whole patient cohort

During the study period, we identified 67 patients with BC who had been hospitalized a total of 77 times in the Internal Medicine ward. The majority of

TABLE 1. **Patients' characteristics and medical history, including demographic data, medical history comorbidities, previous cancer burden, bladder cancer treatments, and outcomes**

Variable	Whole cohort patients (n = 67)	Previously iBCG treated patients (n = 15)	Not previously iBCG treated patients (n = 52, available history n = 46)	*p* value
Total hospitalizations (n)	77	19	58	
Age (years) (mean ± SD)	75.2 ± 9.34	70.4 ± 9.38	76.58 ± 9.04	0.024
Duration of hospitalization (days) (mean ± SD)	9.47 + 7.90	12.05 + 7.07	8.62 + 8.04	0.100
Mortality (n, %)	13 (16.9%)	0 (0%)	13 (22.4%)	0.030
Gender, male (n, %)	54 (80.6%)	11 (73.3%)	43 (82.7%)	0.055
Comorbidities				
Heart diseases (n, %)	21 (36%)	2 (13.3%)	19 (41.3%)	0.063
Hypertension (n, %)	19 (32%)	6 (40%)	13 (28.3%)	0.522
Diabetes mellitus (n, %)	17 (29%)	6 (40%)	11 (23.9%)	0.320
Atrial Fibrillation/Other arrhythmias (n, %)	14 (24%)	3 (20%)	11 (23.9%)	>0.99
Dyslipidemia (n, %)	13 (22%)	6 (40%)	7 (15.2%)	0.067
Neurological/psychiatric disorders (n, %)	12 (20%)	3 (20%)	9 (19.6%)	>0.99
Chronic obstructive pulmonary disease (n, %)	8 (14%)	4 (26.7%)	4 (8.7%)	0.098
Renal Failure (n, %)	11 (16.4%)	0	11 (23.9%)	0.051
Cirrhosis/HBV infection (n, %)	7 (12%)	0	7 (15.2%)	0.177
Other comorbidities (n, %)	9 (15%)	3 (20%)	6 (13%)	0.675
Cancer burden				
Coexisting cancers (n, %)	14 (22.9%)	1 (6.7%)	13 (28.3%)	0.154
Metastatic BC (n, %)	19 (31.1%)	2 (13.3%)	17 (36.9%)	0.114
BC treatments				
TURBTs (n, %)	67 (100%)	15 (100%)	46 (100%)	
Previous iBCG therapy (n, %)	15 (25%)	15 (100%)	0	
Treatments other than TURBTs (n, %)	38 (62.3%)	5 (33.3%)	31 (67.4%)	0.033
Chemotherapies/radiotherapies/immunotherapies (n, %)	20 (32.8%)	1 (6.7%)	19 (41.3%)	0.013
Local radiation (n, %)	3 (5%)	0	3 (6.5%)	0.568
Urological interventions				
Nephrectomy/nephrostomy/pigtail placement (n, %)	15 (24.6%)	2 (13.3%)	13 (28.3%)	0.317
Cystectomy/cystoprostatectomy/ureterostomy (n, %)	14 (22.9%)	2 (13.3%)	12 (26.1%)	0.483

Note. Comparisons refer to iBCG-treated vs. non iBCG-treated BC patients. Mortality rate and duration of hospitalization were calculated for n = 77 hospitalizations. Heart diseases: coronary artery diseases, angina pectoris, myocardial infarction, chronic heart failure, valvular disease. Neurological/psychiatric disorders: stroke, transient ischaemic attack, Parkinson's diseases, dementia, psychosis. Renal failure: chronic renal failure 4 cases; acute renal failure 3 cases; acute on chronic renal failure two cases; renal dialysis two cases. Other medical history: hypothyroidism four cases; abdominal aorta aneurysm: three cases; deep vein thrombosis: two cases. Other cancers: renal four cases; prostate three cases; hematological two cases; thyroid, gynaecological, ENT, liposarcoma, and gastrointestinal cancer accounted for one case each. Statistical analysis was performed using either two-tailed *student's t*-test or Fisher's exact test. *p*-values < 0.05 were considered statistically significant. BC: bladder cancer; iBCG: intravesical BCG immunotherapy. SD: standard deviation; TURBT: transurethral resection of bladder tumor.

TABLE 2. **Discharge diagnoses in the total cohort of BC patients in those who recovered from hospitalization (n = 64/77)**

Discharge diagnosis	n (%)
Infections	38 (59.4%)
Anemia/transfusions	15 (23.4%)
Newly diagnosed metastatic BC	10 (15.6%)
ARF/RD	7 (10.9%)
Obstructive uropathy/pigtails/nephrostomy	6 (9.4%)
BC treatment-related adverse events	6 (9.4%)
Electrolyte abnormalities	6 (9.4%)
Chemo/immunotherapy induced cytopenias	4 (6.3%)
GI disorders	4 (6.3%)
Heart disorders	3 (4.7%)
Severe hematuria	3 (4.7%)
FUO	3 (4.7%)
Other diagnoses	3 (4.7%)

Note. Other diagnoses: immune thrombocytopenia, deep vein thrombosis, and intubation/ICU admission accounted for one case each. The total number of discharge diagnoses may differ from sum of hospitalizations (n = 64) as discharge documents may include more than one diagnosis. ARF: acute renal failure; BC: bladder cancer; FUO: fever of unknown origin; GI: gastrointestinal; RD: renal dialysis.

these patients were male (80.6%), with a mean age of 75.2 years. Their comorbidities, detailed in Table 1 (with comprehensive history data available for 61 patients), primarily included cardiovascular diseases, hypertension, diabetes mellitus, and dyslipidemia. Approximately a quarter of patients had a second malignancy in addition to their BC (22.9%), while nearly a third presented with metastatic BC (31.1%). All NMIBC patients had been previously subjected to TURBTs and local treatment (either with iBCG or local chemotherapy). Thirty-eight percent of patients had been treated with chemotherapies/immunotherapies and/or local radiation, besides those (24.6%) treated with iBCG instillations. In addition, almost half of patients (49.2%) had been subjected to urological interventions comprising cystectomy, cystoprostatectomy, ureterostomy, pigtail placement, nephrectomy, and nephrostomy (Table 1).

The most common reasons for hospitalization, according to their discharge diagnoses, were infections (59.4%), followed by anemia (23.4%), newly diagnosed metastatic disease (15.6%), acute renal failure (ARF, 10.9%), obstructive uropathy requiring placement of pigtails and/or nephrostomy (9.4%), anticancer treatment-related adverse events (9.4%), and electrolyte abnormalities (9.4%) (Table 2). The types of infections and their corresponding bacterial pathogens identified in discharge documents are presented in Table 3. The mean duration of hospitalization for recovering patients was 8.6 days (median: 7 days). The mortality rate during 77 hospitalizations was 16.9% (n = 13), with the most common cause being infections (77%), followed by advanced/metastatic BC (31%) and obstructive uropathy/ARF (15%).

TABLE 3. **Types of infections and related bacteria in discharge diagnosis documents (n = 38) across the entire cohort of hospitalized bladder cancer patients who recovered (n = 64)**

Type of infection/pathogens (n = 38)	Number of infection types reported in the total of discharge diagnosis documents in those who recovered (n = 64) (n, %)
UTI	16 (25%)
E. coli	5
Enterococci spp.	3
Klebsiella pneumoniae (ESBL/VIM)	3
MRSA	2
Proteus mirabilis	1
Candida albicans	1
Enterobacter	1
Bacteraemia	6 (9%)
MSSA	2
Enterococci spp.	2
Klebsiella pneumoniae	1
E. coli	1
Pneumonia	5 (8%)
Diarrhea	3 (5%)
Sepsis/septic shock	3 (5%)
Pelvis abscess	2 (3%)
BCGitis	2 (3%)
Other infections	5 (8%)

Note. Other infections: osteomyelitis, *E. coli* cholangitis, oropharynx mycosis, herpes-zoster, SARS-COV-2, accounted for one case each. The total number of infections may differ from the sum of infection types as a discharge diagnosis document may include more than one diagnoses.

Patients previously treated with iBCG (n = 15) including three FUO cases

Among the 67 hospitalized patients with BC, we identified 15 patients (19 hospitalizations, 25%) who had previously been treated with iBCG. Those were

mostly males (73.3%), and they were significantly younger compared to the rest of the group. They also had a higher prevalence of hypertension, diabetes, dyslipidemia, chronic obstructive pulmonary disease (COPD), and a lower incidence of heart diseases compared to those not previously treated with iBCG (Table 1). In addition, patients being treated with BCG instillations had a lower incidence of metastatic disease, coexistence of other cancers, and therapeutic interventions (urological, chemotherapy, immunotherapy, and local radiation). Among the hospitalized patients, we identified three with FUO, all having previously been treated with iBCG. These patients overall had a longer duration of hospitalization compared to the rest of the patients (median: 19 days, $p = 0.0005$; two-tailed student's t-test).

Patient 1:

An 80-year-old woman was admitted with a daily fever reaching a maximum of 38.5°C over the past 3 weeks, accompanied by abdominal pain, unresponsive to common antibiotics. She had a history of BC, which had been treated with multiple TURBTs and iBCG 6 years ago. The clinical examination was unremarkable, while laboratory tests revealed elevated inflammatory markers (Table 4). The patient was started on empirical antibiotic therapy with piperacillin/tazobactam. However, multiple blood and urine cultures as well as serological testing for atypical microbes and viruses were returned negative. Additionally, Ziehl-Nielsen stains and Lowenstein-Jensen cultures of urine and gastric fluid were negative. QuantiFERON TB Gold testing and PCR detection for mycobacteria in urine samples also yielded negative findings. A chest and abdomen CT revealed lymphadenopathy around the abdominal aorta and right common iliac chain, which were inaccessible to biopsy. She was initially given parecoxib and low-dose

TABLE 4. **Comparative laboratory results at presentation and other laboratory studies in the three cases with FUO**

Laboratory parameters (normal range)	Patient 1: Metastatic BC	Patient 2: Disseminated BCGitis	Patient 3: Hodgkin's Lymphoma
WBC (5.2–12.4 × 10^3/μL)	9.34	8.13	18.24
Hb (12–18 g/dL)	10.6	14.5	9.1
MCV (80–99 fL)	89.8	84	78.3
PLT (130,000–400,000/μL)	495,000	293,000	693,000
Urea (18–55 mg/dL)	24	38	64
Creatinine (0.72–1.25 mg/dL)	0.5	1	1.1
LDH (125–220 U/L)	463	265	375
AST/ALT (<45 U/L)	24/18	41/56	26/44
ALP (40–150 U/L)	57	173	86
CRP (0–5 mg/L)	156	49	138
ESR (3–10 mm/h)	75	47	141
Ferritin (22–275 ng/mL)	457	185	356
Fibrinogen (200–400 mg/dL)	617	513	870
D-dimers (<500 μg/L)	1738	2825	1985
Autoimmune disorders autoantibodies screening	negative	negative	negative
Serological screening for viruses: *(HAV, HBV, HCV, CMV, EBV, HIV)*	negative	negative	negative
Serological detection for other pathogens: *Brucella* spp., *Rickettsia* spp., *Borrelia burgdorferi, Coxiella burnetii, Leishmania* spp., *Chlamydia* spp., *Mycoplasma* spp., *Legionella* spp.	negative	negative	negative

Note. AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase; CMV: cytomegalovirus; CRP: c-reactive protein; EBV: Epstein-Barr virus; ESR: erythrocyte sedimentation rate; HAV: hepatitis A virus; Hb: hemoglobulin; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; LDH: lactate dehydrogenase; MCV: mean corpuscular volume; PLTs: platelets.

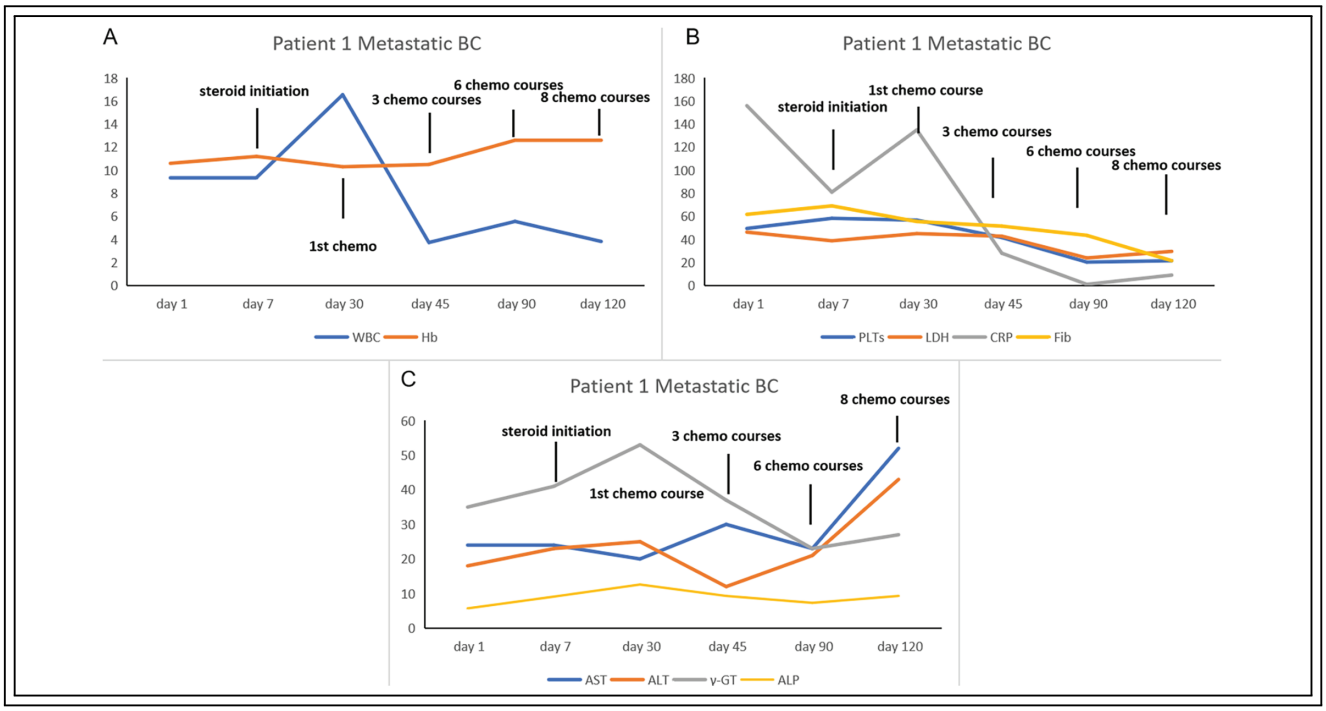

FIGURE 1. The time trends of blood test results for patient 1 from admission (day 1) through follow-up, including the treatment interventions administered. (A): Hematological indices (WBC, Hb); (B): inflammatory markers (CRP, PLTs, fibrinogen) and LDH; (C): liver biochemistry (AST, ALT, ALP, and γ-GT). BC: Bladder cancer; WBC: white blood cells; Hb:hemoglobulin; PLTs: platelets; LDH: lactate dehydrogenase; CRP: c-reactive protein; Fib: fibrinogen; AST: aspartate transaminase; ALT: alanine transaminase; γ-GT: g-glutamyl transferase; ALP: alkaline phosphatase

methylprednisolone for symptomatic relief. A PET-CT scan later in her hospital stay confirmed lymphadenopathy with increased uptake of a left supraclavicular lymph node. The cytology of the lymph node revealed infiltration by numerous squamous and papillary clusters of neoplastic epithelial cells, which were of moderate size and predominantly subround in shape. These cells exhibited central or eccentric hyperchromatic nuclei, coarse chromatin, irregular nuclear membranes, and scant dense cytoplasm. Additionally, clear intranuclear inclusions were noted in some of the cells. Numerous diffusely distributed spindle-shaped cells, binucleated and syncytial forms, as well as frequent atypical mitotic figures, were noted. The background contained abundant necrotic material and remnants of lymph node tissue. The cytological findings indicated secondary involvement of the lymph node by urothelial carcinoma. A definitive diagnosis was made 45 days after the onset of symptoms. The patient received chemotherapy, including cisplatin, paclitaxel, and gemcitabine, followed by immunotherapy. Figure 1 illustrates the dynamic laboratory trends observed during her hospitalization and in follow-up, both prior to and after therapeutic interventions.

Patient 2:

A 62-year-old male with a history of BC diagnosed 3 years ago was admitted to the hospital with a high-grade fever (up to 40°C) for 10 days right after his last iBCG instillation. He had been receiving iBCG for the last year. He was initially given ciprofloxacin for a suspected urinary tract infection for five days without a response. On presentation, he was febrile, and his laboratory tests revealed elevated inflammatory markers and slightly impaired liver biochemistry (Table 4). Urinalysis demonstrated pyuria and hematuria. Multiple blood and urine cultures for common pathogens were negative. Ziehl-Nielsen stains, Lowenstein-Jensen cultures, and PCR for detection of mycobacteria in urine, sputum, and gastric fluid were also negative. The CT scans of the chest and abdomen were unremarkable. During hospitalization, the patient experienced a persistent high fever, with early morning spikes reaching 40–40.5°C

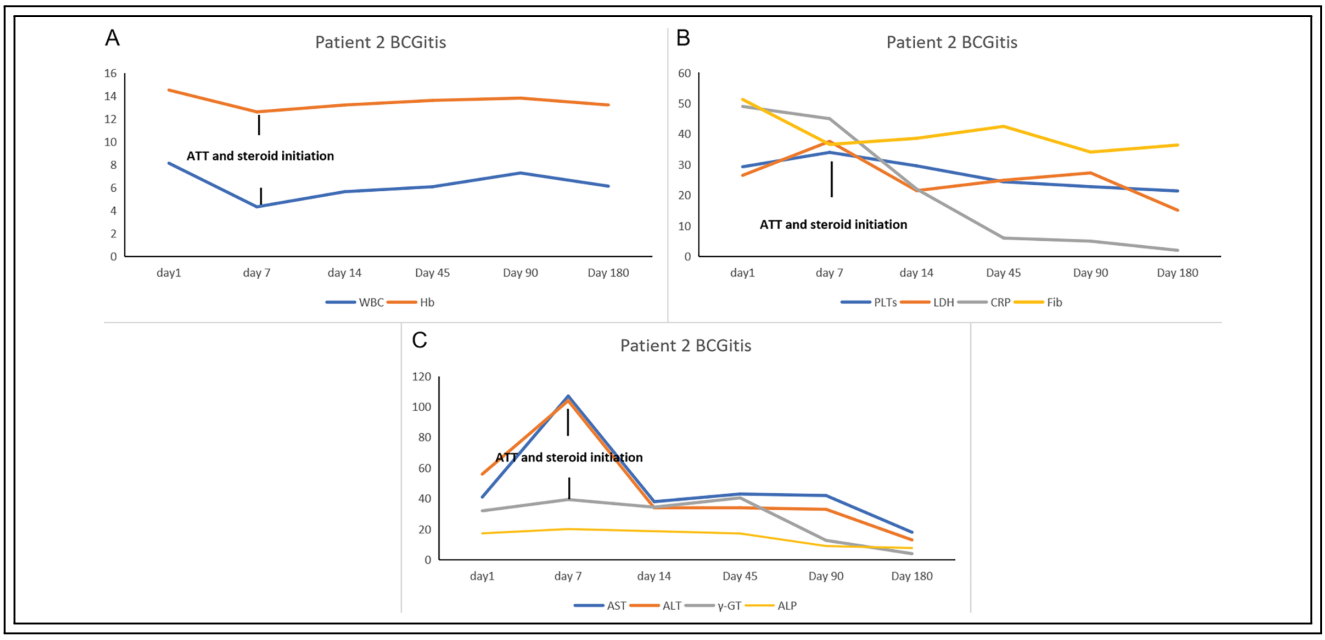

FIGURE 2. The time trends of blood test results for patient 2 from admission (day 1) through follow-up, including the treatment interventions administered. (A): Hematological indices (WBC, Hb); (B): inflammatory markers (CRP, PLTs, fibrinogen) and LDH; (C): liver biochemistry (AST, ALT, ALP, and γ-GT). BCGitis: infection caused by Bacillus Calmette–Guérin; ATT: anti-tuberculous treatment; WBC: white blood cells; Hb: hemoglobulin; PLTs: platelets; LDH: lactate dehydrogenase; CRP: c-reactive protein; Fib: fibrinogen; AST: aspartate transaminase; ALT: alanine transaminase; γ-GT: g-glutamyl transferase; ALP: alkaline phosphatase

between 4:00 and 6:00 a.m., which was unresponsive to common antibiotics. Given a high suspicion of BCGitis, the patient underwent a liver and bone marrow (BM) biopsy. He was also started on empirical anti-tuberculous therapy (ATT), which included isoniazid, rifampin, and ethambutol, along with glucocorticoids (methylprednisolone). Over the coming days, his fever gradually subsided, and the inflammatory markers and cholestatic enzymes began to decrease. The histology results of both the liver and BM revealed granulomatous inflammation, with epithelioid histiocytes and multinucleated giant cells surrounded by lymphocytes. In BCGitis, pathology findings reveal granulomas that are predominantly non-caseating in liver and bone marrow (BM) tissue due to the rich reticuloendothelial system present in these organs,[9] as observed in this case. The presence of non-caseating granulomas is strongly suggestive of BCGitis. Consequently, the diagnosis of disseminated BCGitis with liver and BM involvement was established 35 days after the onset of fever. He was discharged with continued ATT, while corticosteroids were tapered and discontinued within 2 weeks. Three months post-discharge, the patient remained asymptomatic while receiving ATT treatment. Figure 2 displays the longitudinal trends of his blood tests during hospitalization and follow-up.

Patient 3:

A 73-year-old male presented with a fever for two weeks (up to 37.8°C) and worsening fatigue. He had been diagnosed with BC two years before, and he had been managed with TURBTs followed by 9 iBCG instillations. On clinical examination, he had enlarged, painless inguinal lymph nodes bilaterally. Laboratory workup revealed leukocytosis, anemia, and elevated inflammatory markers (Table 4). The patient was given empirical piperacillin-tazobactam therapy without response. Multiple blood and urine cultures, serological testing for atypical pathogens, and a QuantiFERON TB Gold test returned negative. Ziehl-Nielsen stains, Lowenstein-Jensen cultures, and PCR for the detection of mycobacteria in urine, sputum, and gastric fluid were negative. An abdominal CT scan showed lymphadenopathy extending from the para-aortic space to the right inguinal region. A PET-CT scan revealed multiple, enlarged, hypermetabolic lymph nodes (<1 cm in size) below the diaphragm, as well as in the left supraclavicular region. During hospitalization, he exhibited 1–2 daily

fever spikes (up to 39°C). A biopsy of an inguinal lymph node confirmed the diagnosis of Hodgkin's lymphoma (HL) with mixed cellularity. This diagnosis was established 42 days after the onset of fever. Subsequently, he was transferred to the Hematology Unit of our department. Following 4 courses of chemotherapy, which included vinblastine, chlorambucil, procarbazine, and steroids, the patient went into remission (Figure 3).

Discussion

In this case series, we present real-world data on the characteristics of patients with BC who were hospitalized in a Medicine ward of a tertiary referral hospital. The majority of BC patients were elderly, with a mean age of 75.2 years. A study investigating age trends in hospitalized patients with urological cancer revealed that the average age of these individuals rose from 2005–2013 to 2014–2021.[8] Common comorbidities observed in our cohort included cardiovascular disease, hypertension, diabetes mellitus, dyslipidemia, and COPD, which aligns with findings from previous studies for BC patients.[10,11] Several meta-analyses have suggested that individuals with diabetes,[12–14] hypertension,[15] and other metabolic syndrome components[15] may have an increased risk for BC. In addition, COPD has been reported as a prevalent comorbidity in BC cohorts and is associated with increased mortality and poorer prognosis.[11,16] Interestingly, one-quarter of patients had a second primary malignancy, a proportion slightly higher than that reported in the literature for BC patients.[17,18] Furthermore, nearly one-third had advanced BC at the time of admission to the internal medicine ward, while in 15% of them, new metastases were identified during hospitalization. These findings indicate an increased cancer burden in this patient population.

Infections were the most common cause (~60%) of hospitalization in admitted BC patients, mainly from the urinary tract. This could be due to several factors, including their advanced age, local anatomical factors, comorbidities, overall cancer burden, and anti-cancer therapies. Among those who died during hospitalization (17%), the leading cause of death was again an infection (77%). Conclusively, our data

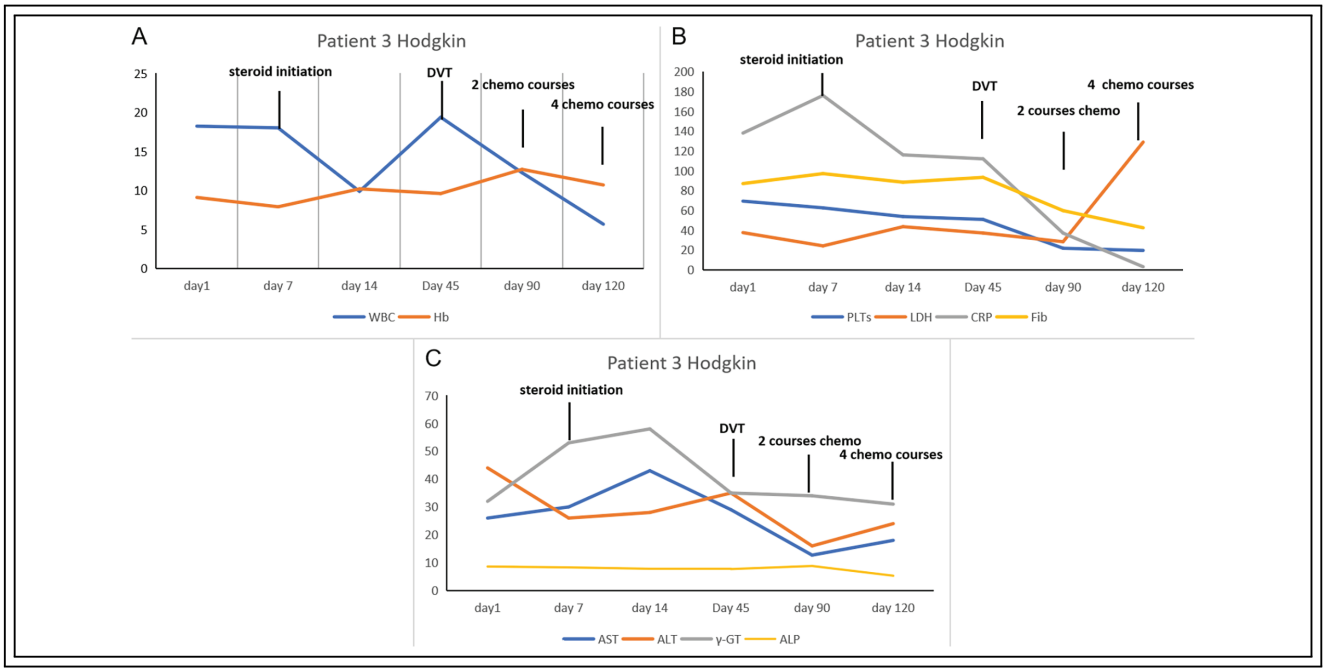

FIGURE 3. The time trends of blood test results for patient 3 from admission (day 1) through follow-up, including the treatment interventions administered. (A): Hematological indices (WBC, Hb); (B): inflammatory markers (CRP, PLTs, fibrinogen) and LDH; (C): liver biochemistry (AST, ALT, ALP, and γ-GT). DVT: deep vein thrombosis; WBC: white blood cells; Hb: hemoglobulin; PLTs: platelets; LDH: lactate dehydrogenase; CRP: c-reactive protein; Fib: fibrinogen; AST: aspartate transaminase; ALT: alanine transaminase; γ-GT: g-glutamyl transferase; ALP: alkaline phosphatase.

indicates the unmet need for better strategies in infection protection and management in this vulnerable patient population.

In the present study, iBCG-treated patients were younger with lower mortality rates compared to the rest of the cohort. Those differences could be attributed to the fact that the subgroup of BC patients subjected to BCG immunotherapy are diagnosed in earlier disease stages (NMIBC, Ta) compared to those diagnosed with MIBC or metastatic BC. On the other hand, the high incidence of comorbidities in iBCG-treated patients, such as diabetes, hypertension, dyslipidemia, heart diseases, and COPD, is consistent with literature,[9,19] while the differences estimated in this descriptive study compared to those not previously treated with iBCG are statistically non-significant. Furthermore, iBCG-treated patients experienced longer hospital stays compared to other BC patients. This finding can be explained by the inclusion of three cases of FUO in the iBCG-treated group, which represents approximately 4.5% of our hospitalized BC patients. These cases necessitated extensive diagnostic workups to determine their underlying causes. Despite significant advancements in medical diagnostics and imaging, FUO continues to be a complex clinical condition, with its etiology evolving over time. Noninfectious inflammatory diseases and infections are currently the predominant causes, followed by connective tissue disorders and malignancies.[20] Unexpectedly, despite the identical clinical settings, each of our three patients with FUO had distinct diagnoses, requiring tailored management strategies. In the first case, metastatic BC was diagnosed in a patient with a remote history of iBCG therapy who presented with lymphadenopathy. In the literature, urinary tract cancer has been listed as a potential cause of FUO, finally diagnosed 1–12 months after fever onset,[21] as in our case. The second case was a typical BCGitis that developed shortly after iBCG treatment. BCGitis is a well-documented adverse event of iBCG immunotherapy.[9] The patient had histological evidence of liver and bone marrow granulomas, which, despite the absence of *Mycobacterium bovis* in the tissue and body fluid samples, indicated BCGitis. His symptoms and laboratory abnormalities completely resolved with prolonged ATT therapy.

The diagnosis in the third case of a 73-year-old man with a history of BC was rather unexpected, as was HL. In a literature case, a mediastinal mass that tested positive for BCG was suspected to be lymphoma.[22] Additionally, in another case following iBCG treatment, bilateral adrenal and testicular tumors were diagnosed as diffuse large B-cell lymphoma.[23] To our knowledge, this is the first reported case of Hodgkin lymphoma (HL) diagnosed in a patient with BC who had previously undergone treatment with iBCG. Some literature suggests a potential association between BCG vaccination and HL,[24] while other studies contradict this claim.[25] Hodgkin and Reed-Sternberg (HRS) cells are germinal center B lymphocytes that have transformed during maturation, losing the ability to express immunoglobulins and other characteristics of normal B cells.[26] HRS cells have developed mechanisms to survive by escaping immune surveillance.[27] Many of the complex immune modulation mechanisms that are engaged in the treatment of iBCG are also implicated in the pathophysiology of HL. iBCG activates Th2 immune responses, which, via secretion of IL-4, IL-10, and TGF-β, induces macrophage M2 polarization and their transformation into tumor-associated macrophages, thereby promoting pro-tumoral activities.[28,29] The secretion of IL-10 and TGF-β is one mechanism implicated in the immune escape of HRS cells by inhibiting the activation of cytotoxic T lymphocytes and antigen-presenting cells (APCs).[27,30] Furthermore, Th2 induction from iBCG instillations may also result in both the induction of regulatory T cells (Tregs) and the secretion of IL-13, which attracts monocytes within the tumor microenvironment, transforming them into monocyte-myeloid-derived suppressor cells that inhibit T cell proliferation.[31] The recruitment of immunosuppressive Tregs and myeloid-derived suppressor cells into the classic HL microenvironment represents another mechanism by which these cells evade immune surveillance.[32] After BCG ingestion by APCs, various mycobacterial cell wall molecules (PAMPS) are released both intracellularly and extracellularly, which subsequently regulate the NF-kB signaling pathway through MyD88 and other intracellular messengers, leading to the secretion of Th1 proinflammatory cytokines.[33,34] PAMPS also induce a metabolic shift toward glycolysis via the protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway, which involves epigenetic histone modifications such as methylation, resulting in increased access to the promoter regions of genes associated with differentiation, proliferation, inflammation, and apoptosis.[9] A damage-associated molecular pattern molecule, IL-1-α, which is also induced by BCG, interacts with the IL-1 receptor (IL-1R) to regulate intranuclear transcription factors (TFs) through MAPK/ERK signaling pathways, subsequently affecting cell differentiation, proliferation, inflammation, and apoptosis.[34,35] In the pathogenesis of HL, the activation of the NF-kB and MAPK/ERK

signaling pathways is essential for the evasion of apoptosis, enabling HRS cells to circumvent programmed cell death.[36] Given that the aforementioned immunomodulatory mechanisms involved in BCG treatment overlap with those that help HRS cells evade immune surveillance, it can be suggested that BCG treatment may enhance the survival of HRS cells by aiding their evasion of immune detection and apoptosis, provided that mutated HRS cells are already present. From a clinical perspective, when BC patients experience a fever lasting more than seven days after BCG instillation, which exceeds the typical course of the very common self-limited adverse events—defined as short-term, mild reactions resolving spontaneously or with symptomatic treatment—beyond which more severe BCG-related complications may occur,[9] they should be referred to an internal medicine department for further evaluation, regardless of whether an antibiotic regimen has been prescribed.

Limitations of the study

This is a single-centre, retrospective analysis that selected patients based on an examination of computerized health data; hence, a selection bias may be present. Furthermore, some individuals may have been overlooked in case the search term "C67" was not included in the discharge diagnoses documents, as they could have been hospitalized for many other medical conditions, leading to a residual confounding. The limited number of patients in the analysis constrains its statistical power. The study's five-year duration, during which newer immunotherapies for BC patients were more extensively utilized, may have resulted in the omission of hospitalization trends and outcomes from prior decades, thereby diminishing generalizability.

Conclusions

This study investigates the reasons for hospitalizations among BC patients in an internal medicine ward. Due to the implementation of new management strategies, BC has evolved into a "chronic disease," leading to an increase in the frequency of patient admissions to internal medicine wards. In our patient population, infections constituted the leading cause of both admission and mortality, indicating the need to develop improved prevention and treatment strategies for infectious complications. The subgroup of patients who were previously treated with iBCG exhibited distinct characteristics compared to the entire group, such as younger age, an increased but non-significant incidence of metabolic parameters, longer hospitalization, and lower mortality rates, which are expected due to the earlier disease stage in this subgroup. A small percentage of patients exhibited FUO, posing several diagnostic and treatment challenges for physicians. One was diagnosed with Hodgkin's lymphoma, a previously unreported association. We propose possible mechanisms via which BCG immunotherapy could interfere with Reed-Sternberg cells to escape immune surveillance and develop into Hodgkin's lymphoma. In conclusion, a comprehensive evaluation and a multidisciplinary approach are typically necessary for these patients to attain an accurate diagnosis, and they should probably be hospitalized in a medicine ward.

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Author Contributions

George Liatsos: Writing of the draft manuscript and conception of the idea for the study; Kalliopi Zioutou, Konstantinos Vamvakaris: data collection, preparation of tables; Konstantinos Avramidis, Maria Potamiti-Komi: data process, statistical analysis; Dimitrios Vassilopoulos: supervising of the study, correction of the final version of the manuscript. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials

The data that support the findings of this study are available from the Corresponding Author, George Liatsos, upon reasonable request

Ethics Approval

The study was approved by the Institutional Review Board of the Scientific Council of Hippokration General Hospital of Athens (Approval No. 26/11142023). Due to the retrospective nature of the study, the requirement for written informed consent was waived.

Conflicts of Interest

The authors declare no conflicts of interest.

Abbreviations

WBC	White blood cells (count/μL $\times 10^{-3}$)
Hb	Hemoglobulin (g/dL)
PLTs	Platelets (count/μL $\times 10^{-4}$)
CRP	C-reactive protein (mg/L)
LDH	Lactate dehydrogenase (IU/L $\times 10^{-1}$)
Fib	Fibrinogen (mg/dL $\times 10^{-1}$)
AST	Aspartate transaminase (IU/L)
ALT	Alanine transaminase (IU/L)
γ-GT	G-glutamyl transferase (IU/L). In diagram 1B γ-GT is shown in IU/L $\times 10^{-1}$ for a better diagram visualization
ALP	Alkaline phosphatase (IU/L $\times 10^{-1}$)
ATT	Anti-tuberculous treatment
DVT	Deep venous thrombosis

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