CASE REPORT
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Diseases & Research

PD-1 Inhibitor and GM-CSF in Oligometastatic Gallbladder Adenosquamous Carcinoma: A Case Report

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Abstract: Gallbladder adenosquamous carcinoma is a rare and aggressive malignancy. In patients with microsatellite-stable (MSS) and low tumor mutational burden (TMB) biliary tract tumors, PD-1/PD-L1 monotherapy yields limited responses, necessitating low-toxicity combination strategies to enhance efficacy. In this case report, an 85-year-old female with postoperative relapse of gallbladder adenosquamous carcinoma (pT2bN0M0, AJCC 8th edition, Stage IIB) presented with new oligometastatic lesions in the posterior mediastinum, supraclavicular region, and right adrenal gland after prior para-aortic radiotherapy. The patient declined chemotherapy. A 'point-and-field' regimen was implemented: stereotactic body radiotherapy (SBRT) to a dominant posterior mediastinal lymph node (95% PTV 30 Gy in 5 fractions), combined with pembrolizumab (200 mg every 3 weeks) and recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF; 150 μg subcutaneously on days 1–7 of each cycle). Abdominal pain resolved completely and Karnofsky Performance Status (KPS) improved. Serum CA19-9 levels declined from 237 U/mL to 15.4 U/mL. A 6-month follow-up PET/CT scan demonstrated a complete metabolic response of all metastatic lesions. Peripheral blood immune profiling revealed increases in $CD45^+$, $CD3^+$, $CD8^+$ T cell, and natural killer (NK) cell counts, with a transient decrease in the $CD4^+/CD8^+$ ratio. Treatment-related adverse events were limited to grade 1 anemia, grade 1 nausea, and a grade 2 angioma-like rash. No grade ≥ 3 or late toxicities were observed. The patient passed away in June 2023 due to disease progression, having achieved a progression-free survival of 25 months and an overall survival of 29 months from treatment initiation. In this elderly patient with chemotherapy-refractory oligometastatic gallbladder adenosquamous carcinoma, we observed a durable complete metabolic response on PET/CT following treatment with SBRT, a PD-1 inhibitor, and GM-CSF, with a manageable toxicity profile in this single case. These observations generate the hypothesis that further prospective evaluation of this multimodal immunomodulatory approach may be warranted.

Keywords: Gallbladder adenosquamous carcinoma; SBRT; PD-1 inhibitor; GM-CSF; Abscopal effect; Immunotherapy.

Introduction

Gallbladder adenosquamous carcinoma represents a rare yet highly aggressive histological subtype, accounting for only 1–5% of all gallbladder malignancies and characterized by a substantially higher recurrence risk and poorer prognosis compared to conventional adenocarcinoma[1]. Management challenges are particularly pronounced in elderly patients, who often exhibit limited tolerance to standard platinum-based chemotherapy and may decline cytotoxic systemic therapy. The therapeutic landscape for biliary tract cancers has historically been constrained, with most tumors demonstrating microsatellite stability (MSS) and low tumor mutational burden (TMB)-features that have been associated with modest response rates to single-agent programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors[2]. This underscores the need for innovative, low-toxicity combination strategies designed to enhance tumor immunogenicity while maintaining an acceptable safety profile[3].

Recent advances in immuno-oncology have highlighted the potential of radiotherapy, particularly stereotactic body radiotherapy (SBRT), to function as an in situ vaccine by inducing immunogenic cell death and activating innate immune signaling pathways such as cGAS-STING, thereby enhancing tumor antigen presentation and priming tumor-specific T-cell responses[4]. When delivered to oligometastatic lesions, SBRT has been reported to be associated with systemic, or “abscopal”, tumor regression when combined with immune checkpoint inhibitors (ICIs), an effect that has been attributed to synergistic immunomodulatory effect[5,6]. Preclinical models suggest that radiation-induced immunogenic modulation may create a favorable microenvironment for ICIs to counteract T-cell exhaustion and restore anti-tumor immunity.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) plays a pivotal role in dendritic cell maturation, migration, and antigen cross-presentation, potentially amplifying the systemic immune response initiated by SBRT and sustained by PD-1/PD-L1 blockade[7,8]. Preclinical and early clinical evidence suggests that GM-CSF may potentiate abscopal effects when combined with radiotherapy[7], and its addition to ICI regimens has shown promise in enhancing antitumor responses[9,10]. The combination of these three modalities-SBRT, PD-1 inhibition, and GM-CSF-

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bas been proposed as a "point-and-field" strategy, wherein focal radiation to a dominant metastatic lesion ("point") is combined with systemic immunotherapy ("field") to maximize both local control and systemic immune activation[11,12].

Despite encouraging signals from SBRT-ICI combinations in various solid tumors[6,13,14], and preliminary evidence supporting GM-CSF-ICI combinations[8,10], clinical experience applying this triple-modality approach to gallbladder adenosquamous carcinoma remains exceptionally scarce. Furthermore, data regarding the safety and efficacy of such intensive immunomodulatory regimens in elderly patients are limited[15]. In this context, we present the case of an 85-year-old patient with oligometastatic gallbladder adenosquamous carcinoma who, after declining chemotherapy, achieved a durable complete metabolic response on PET/CT following treatment with SBRT, pembrolizumab, and GM-CSF. This report aims to provide a detailed description of this single-case experience and to generate the hypothesis that further exploration of this multimodal strategy in biliary tract cancers may be warranted[16].

Case presentation

Clinical history and initial diagnosis

An 85-year-old female (Eastern Cooperative Oncology Group Performance Status 1) presented with a medical history significant for bilateral carotid artery plaques and gastric carcinoma in situ treated with endoscopic submucosal dissection four years prior, with no evidence of recurrence. There was a family history of colorectal cancer in her father and sister. On January 4, 2019, she underwent laparoscopic cholecystectomy with common bile duct exploration and T-tube drainage for gallbladder cancer. Histopathological examination revealed a poorly differentiated adenosquamous carcinoma, staged as pT2bN0M0 (American Joint Committee on Cancer, 8th edition, Stage IIB). No adjuvant therapy was administered postoperatively, based on shared decision-making considering the patient's age and preferences.

Disease course and prior therapy

The patient's disease course was characterized by sequential metastatic progression, with initial para-aortic lymph node involvement identified on PET/CT in August 2019, followed by palliative radiotherapy to the para-aortic region (50 Gy in 25 fractions) between August and September 2020, which effectively alleviated pain. However, despite this local intervention, subsequent imaging in October 2020 demonstrated new metastatic involvement of posterior mediastinal lymph nodes, and by January 2021, the disease had progressed further, with metastases detected in the left supraclavicular lymph node, posterior mediastinal lymph nodes, and the right adrenal gland.

Time of intervention

Upon presentation in January 2021, the patient reported abdominal pain. Physical examination revealed a firm, poorly mobile left supraclavicular lymph node measuring approximately 2 cm. Routine laboratory parameters were within normal limits. Elevated tumor markers were noted: CA-125 at 134 U/mL and CA19-9 at 237 U/mL (carcinoembryonic antigen was normal at 2.89 ng/mL). Immunohistochemical analysis of available tumor tissue confirmed poorly differentiated adenosquamous carcinoma (CK5/6 partially positive, KI-67 positive, CK8/18 positive). Testing for microsatellite instability (MSI), tumor mutational burden (TMB), and programmed death-ligand 1 (PD-L1) expression was not performed, representing a limitation of this study. A comprehensive PET/CT scan confirmed hypermetabolic lesions in the left supraclavicular region, posterior mediastinum, porta hepatis/para-aortic chain, and right adrenal gland (Fig. 1). The final diagnosis was recurrent and metastatic poorly differentiated adenosquamous carcinoma of the gallbladder in an oligometastatic state. The patient explicitly declined conventional chemotherapy and requested a low-toxicity therapeutic alternative.

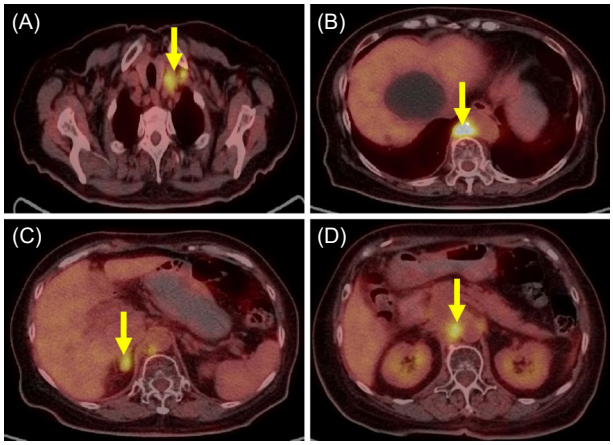

Fig. 1. Pre-treatment PET-CT scans showing multiple metastatic sites at the time of disease progression in January 2021.
A. Left supraclavicular lymph node metastasis (arrow).
B. Posterior mediastinal lymph node metastasis (arrow).
C. Right adrenal gland metastasis (arrow).
D. Retroperitoneal lymph node metastasis (arrow).

Treatment

Given the patient's age of 85 years, a comprehensive geriatric assessment was considered. After extensive discussion regarding the goals of care, the patient expressed a strong preference for active anti-tumor treatment over best supportive care. The decision to proceed with this immunomodulatory regimen was reached through a shared decision-making process, weighing the potential risks against the patient's desire for disease control and acceptable performance status. Based on clinical scenario, a novel "point-and-field" therapeutic strategy was conceptualized and implemented, combining localized stereotactic body radiotherapy (SBRT) with systemic immunotherapy. As data on the toxicity and optimal timing of this combining are limited[17], close clinical monitoring was prioritized. In this case, immunotherapy was initiated the day after the last fraction of SBRT, as per a predefined close monitoring protocol with rigorous clinical and laboratory assessments. The irradiated lesion-a dominant posterior mediastinal lymph node metastasis- was selected based on its progressive metabolic activity and anatomic suitability for safe high-dose radiotherapy, with the goal of achieving local tumor control and potential immunogenic cell death induction. SBRT was prescribed at 30 Gy in 5 daily fractions, covering 95% of the

planning target volume (PTV), defined as the gross tumor volume expanded by 5 mm (Fig. 2). Systemic immune modulation was delivered concurrently with pembrolizumab (200 mg intravenously every 21 days) and recombinant human GM-CSF (150 μg subcutaneously on days 1–7 of each 21-day cycle), initiated immediately following SBRT and continued thereafter. A total of 7 cycles pembrolizumab and GM-CSF were completed. A detailed schematic timeline of the treatment was presented in Table 1.

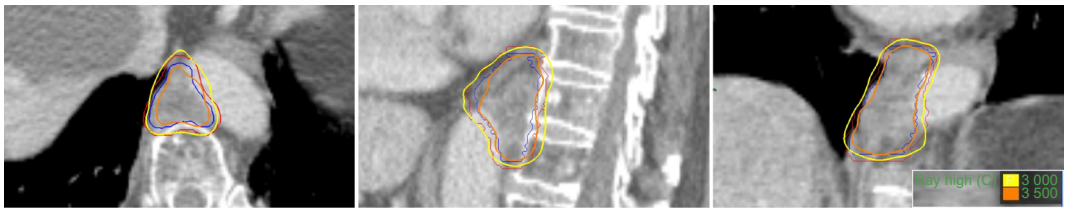

Fig. 2. SBRT treatment plan.
Axial, sagittal, and coronal views of the dose distribution for the posterior mediastinal lymph node metastasis. The red line denotes the planning target volume (PTV), and the prescribed isodose line (30 Gy in 5 fractions) is shown in yellow.

Table 1. Treatment timeline.

Cycle	Day(s)	SBRT (30 Gy/5 fx)	Pembrolizumab (200 mg IV)	GM-CSF (150 μg SC)
—	1–5	√	—	—
C1	6	—	Cycle 1	START
	6–12		—	Days 1–7
	13–26			—
C2	27	—	Cycle 2	START
	27–33		—	Days 1–7
	34–47			—
C3	48	—	Cycle 3	START
	48–54		—	Days 1–7
	55–68			—
C4	69	—	Cycle 4	START
	69–75		—	Days 1–7
	76–89			—
C5	90	—	Cycle 5	START
	90–96		—	Days 1–7
	97–110			—
C6	111	—	Cycle 6	START
	111–117		—	Days 1–7
	118–131			—
C7	132	—	Cycle 7	START
	132–138		—	Days 1–7

SBRT was delivered on Days 1-5. Pembrolizumab 200 mg IV was administered every 21 days for 7 cycles (Days 6, 27, 48, 69, 90, 111, 132). GM-CSF 150 μg SC was given on Days 1-7 of each cycle. IV, Intravenous; sc, Subcutaneous.

Outcomes and follow-up

Clinical and biochemical response

The patient experienced rapid symptomatic improvement, with complete resolution of abdominal pain and an increase in Karnofsky Performance Status (KPS). Serial monitoring of the tumor marker CA19-9 showed an obvious and sustained decline: from a baseline of 237 U/mL to 175 U/mL, and subsequently to 20.7 U/mL, 17.2 U/mL, and finally 15.4 U/mL over approximately 6–8 months (Fig. 3). Disease progression was subsequently documented in February 2023. During the preparation of this manuscript, we learned that the patient passed away in June 2023. She achieved a progression-free survival (PFS) of 25 months and an overall survival (OS) of 29 months from the start of the described treatment.

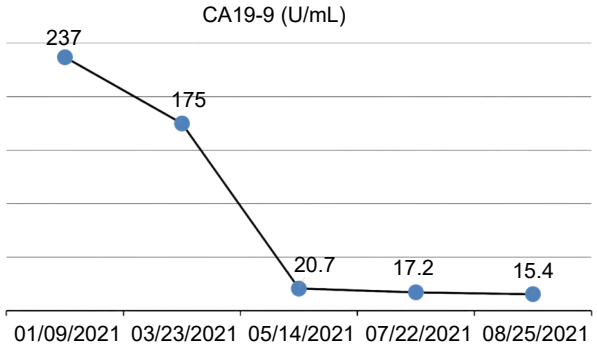

Fig. 3. Serum CA19-9 kinetics during treatment.
A rapid and sustained decline in CA19-9 levels was observed following initiation of the combined SBRT and immunotherapy regimen.

Imaging response

A follow-up PET/CT scan performed 6 months after treatment initiation demonstrated a complete metabolic response. All previously identified hypermetabolic metastases-in the supraclavicular, posterior mediastinal, para-aortic, and adrenal sites-showed complete resolution of fluorodeoxyglucose (FDG) avidity, with no evidence of new disease (Fig. 4). At the time of the 6-month imaging assessment, the patient had achieved progression-free survival (PFS) exceeding 6 months from treatment initiation.

Immune profiling

Peripheral blood mononuclear cell subsets were analyzed at baseline and during follow-up (Table 2, Fig. 5), revealing descriptive immunomodulatory changes: a substantial increase in total lymphocyte ($CD45^+$) count; marked expansion of cytotoxic $CD8^+$ T cells and natural killer (NK; $CD16/56^+$) cells; a more modest increase in $CD4^+$ helper T cells, which led to a transient decrease in the $CD4^+/CD8^+$ ratio from 1.62 to 1.07, followed by a partial rebound to 1.23; and a progressive increase in B cell ($CD19^+$) counts. These observations represent exploratory find-

ings and are presented descriptively, as the observed shifts may reflect pharmacodynamic effects of GM-CSF rather than definitive evidence of anti-tumor immunity. In the absence of functional immune assays or tumor-infiltrating lymphocyte data, mechanistic interpretations are not possible.

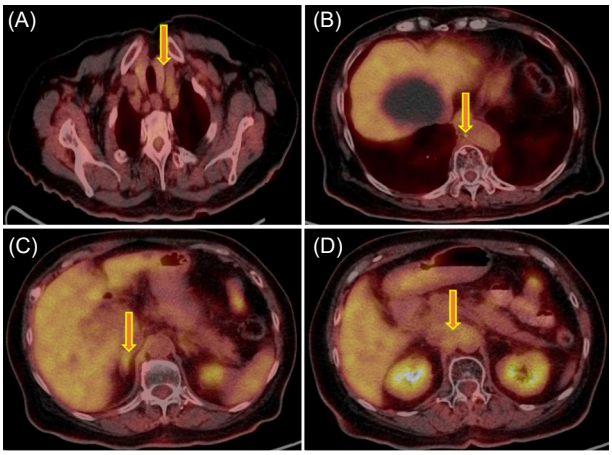

Fig. 4. Post-treatment PET/CT imaging.
A. Left supraclavicular lymph node metastasis (arrow).
B. Posterior mediastinal lymph node metastasis (arrow).
C. Right adrenal gland metastasis (arrow).
D. Retroperitoneal lymph node metastasis (arrow).
Follow-up PET/CT scan (6 months post-treatment) showing complete metabolic resolution of all previously documented metastatic lesions in A, B, C, and D.

Table 2. Longitudinal changes of immune cell subsets in peripheral blood.

Cell Population (cells/μL)	Baseline (Jan 2021)	Follow-Up (Jul 2021)	Follow-Up (Nov 2021)
$CD45^+$ (Total Lymphocytes)	380	772	760
$CD3^+$ (T Cells)	202	272	249
$CD4^+$ (Helper T Cells)	120	139	135
$CD8^+$ (Cytotoxic T Cells)	74	130	109
$CD4^+/CD8$ + Ratio	1.62	1.07	1.23
$CD19^+$ (B Cells)	46	157	195
$CD16/56^+$ (NK Cells)	123	337	308

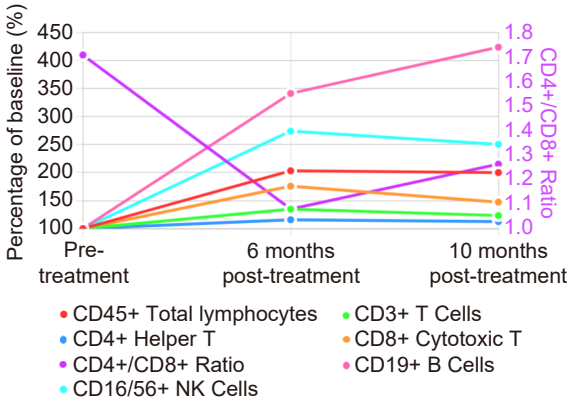

Fig. 5. Dynamic changes in key immune cell populations.
Line graphs illustrating the relative changes in $CD45^+$, $CD3^+$, $CD4^+$, $CD8^+$, and NK cell counts, alongside the $CD4^+/CD8^+$ ratio, over the treatment period.

Adverse events

The treatment regimen was well-tolerated in this single case. Adverse events were limited to grade 1 anemia, grade 1 nausea, and a grade 2 angioma-like skin rash (Fig. 6), which was managed with topical care without requiring systemic corticosteroids or treatment interruption. No immune-related adverse events (irAEs) of grade ≥ 3, radiation pneumonitis, hepatitis, colitis, endocrinopathies, or other significant late toxicities were observed during the follow-up period. No treatment-related deaths occurred. The patient ultimately passed away in June 2023 due to disease progression, as documented in the Outcomes section.

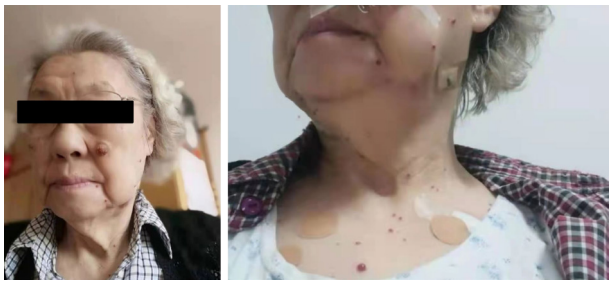

Fig. 6. Representative dermatologic adverse event.
Photograph showing the grade 2 angioma-like rash that appeared during early treatment cycles. The rash was associated with mild pruritus and resolved with conservative management.

Discussion

This case report describes a novel, low-toxicity multimodal approach administered to an r elderly patient with a rare and aggressive biliary malignancy who was unsuitable for standard chemotherapy. A complete metabolic response on PET/CT was observed, with durable PFS exceeding 25 months and OS of 29 months from treatment initiation. Peripheral blood immune monitoring revealed expansion of $CD8^+$ T cells and natural killer (NK) cells following treatment. While these observations are consistent with the hypothesized immunomodulatory effects of the combination, the absence of a control group, lack of tumor immune profiling, and single-case design preclude definitive attribution of this response to a synergistic abscopal effect[5,14]. The observed immune cell changes are presented as exploratory findings, as they may reflect pharmacodynamic effects of GM-CSF, delayed effects of prior radiotherapy, indolent tumor biology, or spontaneous variability in FDG uptake rather than definitive evidence of anti-tumor immunity. Notably, the treatment demonstrated a favorable safety profile in this 85-year-old patient, consistent with emerging real-world data suggesting the feasibility of immune checkpoint inhibitors in older populations[15]. Given that older patients often present with frailty, comorbidities, and reduced treatment tolerance, optimizing therapeutic strategies for this growing population is of critical importance. SBRT offers particular advantages in this setting due to its non-invasive nature, short treatment course, and favorable toxicity profile, making it a practical option for elderly patients with limited reserve. In this context, geriatric screening tools such as the G8 (Geriatric 8) and CCI (Charlson Comorbidity Index) may facilitate patient selection by identifying those fit enough to benefit from combined modality therapies[18,19]. These observations high-

light the need for further prospective evaluation of this approach in elderly patients with biliary tract cancers, particularly given the demographic trends toward an aging population[15].

The therapeutics rationale underlying the approach used in this case is informed by contemporary understanding of radiation immunology and tumor immunology. Preclinical studies suggest that SBRT can function as an in situ vaccine by inducing immunogenic cell death, releasing tumor-associated antigens, and activating innate immune pathways including cGAS-STING, thereby enhancing antigen presentation and priming tumor-specific T-cell responses[4,20]. When delivered to oligometastatic sites with optimal dosing and fractionation[18], SBRT has been reported to create a pro-inflammatory microenvironment that may overcome the typical immunosuppressive features of MSS/low-TMB biliary tumors[2,21]. This localized immunogenic modulation is hypothesized to synergize with PD-1 blockade, which counteracts T-cell exhaustion and sustains effector T-cell activity against tumor cells[2,20]. The addition of GM-CSF represents a third mechanistic layer, promoting dendritic cell maturation, migration to draining lymph nodes, and enhanced antigen cross-presentation-processes critical for generating durable systemic immune responses[7,8]. While these mechanisms provide a plausible framework for interpreting the observed response, definitive evidence of their operation in this case is lacking due to the absence of tumor immune profiling and functional immune assays.

This case adds to the growing body of literature examining SBRT-ICI combinations in biliary tract cancers[14,16]. While several reports have described abscopal responses with SBRT and ICIs in various solid tumors[5,6,11], experience in gallbladder adenosquamous carcinoma specifically remains extremely limited. The inclusion of GM-CSF in this regimen represents a novel element within this context, building upon foundational work demonstrating its ability to potentiate abscopal effects when combined with radiotherapy[7] and preliminary evidence supporting GM-CSF-ICI combinations in biliary cancer[10]. Peripheral immune profiling revealed expansion of CD8 + T cells and NK cells, coupled with a transient decrease in the $CD4^+/CD8^+$ ratio. These descriptive findings are presented as exploratory observations, as then may reflect pharmacodynamic effects of GM-CSF rather than definitive evidence of anti-tumor immunity. In the absence of functional immune assays and tumor-infiltrating lymphocyte data, mechanistic conclusions cannot be drawn.

Recent advances in biomarker research underscore the importance of patient selection for immunomodulatory strategies[22]. We acknowledge that comprehensive biomarker data (MSI, TMB, PD-L1) were not available in this case, which represents a significant limitation. While a durable response was observed in this patient with an MSS/low-TMB tumor phenotype (presumed based on biliary tract cancer epidemiology), the observation should be interpreted with caution. It raises the hypothesis that even MSS/low-TMB tumors could benefit from appropriately designed combination immunotherapies that effectively prime and sustain anti-tumor immunity, but definitive conclusions cannot be drawn from a single case. Future studies should integrate multiplex biomarker analyses-including tumor mutational burden, PD-L1 expression, tumor-infiltrating lymphocyte profiles, and circulating immune signatures-to identify patients most likely to benefit from such approaches[22].

Several limitations warrant consideration in interpreting these findings. As a single-case report, this study cannot establish causality or comparative efficacy compared to standard therapies. The absence of a control group and the lack of comprehensive tumor biomarker data (MSI, TMB, PD-L1 expression) constrain definitive conclusions. In addition, the individual contributions of SBRT, pembrolizumab, and GM-CSF to the observed response cannot be disentangled within this combined approach. The immune correlates derived from peripheral blood are presented as descriptive findings; while they demonstrate temporal changes in circulating immune subsets, they may not reflect dynamic processes within the tumor microenvironment, and in the absence of functional immune assays, mechanistic interpretations are not possible. We acknowledge that not all studies have demonstrated favorable outcomes with SBRT-ICI combinations. Several trials have reported negative or neutral results, highlighting the complexity of this approach and the importance of optimal patient selection, timing, and dosing. Finally, although the patient achieved durable survival, the single-case design precludes generalization of these outcomes to broader populations.

Despite these limitations, this case highlights the potential feasibility of combining SBRT with PD-1 inhibitors and GM-CSF in biliary tract cancers, and may serve as a preliminary basis for further prospective investigation. Future clinical trials should address several key questions: optimal sequencing and timing of these modalities[15], ideal SBRT dose and fractionation for maximal immunogenic effect[20], patient selection criteria based on predictive biomarkers[22], and long-term safety monitoring in elderly populations[15]. Additionally, mechanistic studies exploring the tumor microenvironment before and after treatment would provide valuable insights into the immunological changes underlying clinical responses.

Conclusions

In conclusion, the combination of SBRT, a PD-1 inhibitor, and GM-CSF was associated with a complete metabolic response on PET/CT and a favorable toxicity profile in this elderly patient with chemotherapy-refractory oligometastatic gallbladder adenosquamous carcinoma. This case provides a preliminary basis for prospective clinical trials to evaluate the efficacy and safety of this immunomodulatory strategy in biliary tract cancers, with integrated biomarker analyses to identify patients most likely to benefit.

Abbreviations

AJCC, American Joint Committee on Cancer; B cells, B lymphocytes; CA125, Cancer Antigen 125; CA19-9, Carbohydrate Antigen 19-9; $CD3^+$, CD3-positive T cells; $CD4^+$, CD4-positive helper T cells; $CD8^+$, CD8-positive cytotoxic T cells; $CD16/56^+$, Natural killer cells; $CD19^+$, B cells; $CD45^+$, Total lymphocytes; cGAS-STING, Cyclic GMP-AMP Synthase-Stimulator of Interferon Genes; CK, Cytokeratin; CT, Computed Tomography; F, Fractions; FDG, Fluorodeoxyglucose; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; GTV, Gross Tumor Volume; Gy, Gray; ICIs, Immune Checkpoint Inhibitors; irAEs, Immune-Related Adverse Events; IV, Intravenous; KPS, Karnofsky Performance Status; KI-67, Proliferation marker; LN, Lymph Node; MSI, Microsatellite Instability; MSS, Microsatellite

Stable; NK cells, Natural Killer cells; NSCLC, Non-Small Cell Lung Cancer; OS, Overall Survival; PD-1, Programmed Death-1; PD-L1, Programmed Death-Ligand 1; PET/CT, Positron Emission Tomography/Computed Tomography; PFS, Progression-Free Survival; PTV, Planning Target Volume; RT, Radiotherapy; SBRT, Stereotactic Body Radiotherapy; sc, Subcutaneous; T cells, T lymphocytes; TMB, Tumor Mutational Burden.

Ethics Approval and Consent to Participate

This case report was prepared in accordance with institutional guidelines. Written informed consent was obtained from the patient for publication of her clinical details and associated images.

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Conflicts of interest

The author declares no competing interests relevant to this work.

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Authors' Contributions

JJW: Conceptualization, project administration, writing-review & editing. YC: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, validation, visualization, writing-original draft, writing-review & editing. RHL, YPZ: Data curation, formal analysis, methodology, visualization, writing-original draft, writing-review & editing.

Availability of Data and Materials

The datasets and images supporting this case report are available from the corresponding author upon reasonable request.

Consent for Publication

The patient provided written informed consent for the publication of this case report and any accompanying images.

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