

A RARE GASTROINTESTINAL AND PANCREATIC IMMUNE-RELATED ADVERSE EVENT DURING PEMBROLIZUMAB THERAPY IN TRIPLE NEGATIVE BREAST CANCER – A CASE REPORT

REDAK SLUČAJ GASTROINTESTINALNE I PANKREATIČNE IMUNOPOSREDOVANE NEŽELJENE REAKCIJE TOKOM PRIMENE PEMBROLIZUMABA U LEČENJU TROSTRUKO-NEGATIVNOG KARCINOMA DOJKE – PRIKAZ SLUČAJA

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Case report

Prikaz slučaja

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Abstract

Introduction. Immune checkpoint inhibitors have improved outcomes in triple-negative breast cancer but may trigger immune-related adverse events involving multiple organs. Pancreatic toxicity is uncommon but clinically important, and its recognition is challenging because of broad differential diagnoses. **Case Report.** We report the case of a 44-year-old woman with a first relapse of triple-negative breast cancer after seven years of disease-free follow-up. Germline testing revealed a mutation in the breast cancer susceptibility gene 1. First-line systemic therapy with pembrolizumab combined with weekly paclitaxel was initiated, resulting in a radiologically confirmed partial response. During the fifth treatment cycle, the patient developed upper abdominal discomfort, and endoscopy identified fibrin-covered “kissing” duodenal bulb ulcers, suggestive of possible immune-mediated duodenitis. Symptoms improved with proton pump inhibitors and supportive care. After reintroduction of therapy, the patient subsequently presented with recurrent symptoms. Laboratory evaluation revealed markedly elevated pancreatic enzymes, while imaging confirmed acute pancreatitis. Alternative aetiologies were excluded. Pembrolizumab was permanently discontinued, and corticosteroid therapy was initiated, resulting in gradual clinical and biochemical recovery. Maintenance therapy with a poly adenosine diphosphate-ribose polymerase inhibitor was introduced. At 10 months of follow-up, the patient remained asymptomatic, with preserved pancreatic function and sustained partial response. **Conclusion.** This case highlights an uncommon presentation of pembrolizumab-associated pancreatic and duodenal toxicity in a patient with triple-negative breast cancer. Awareness of rare irAEs is crucial to ensure timely diagnosis and effective management. Multidisciplinary collaboration and individualised therapeutic planning enabled both toxicity resolution and continued oncological disease control in this patient.

Key words: Breast Neoplasms; Triple-Negative Breast Neoplasms; Antibodies, Monoclonal, Humanized; Antineoplastic Agents, Immunological; Drug-Related Side Effects and Adverse Reactions; Gastrointestinal Diseases; Pancreatic Diseases; Immunotherapy; Immune Checkpoint Inhibitors; Patient Care Team

Sažetak

Uvod. Imunološki inhibitori kontrolnih tačaka značajno su unapredili ishode lečenja trostruko negativnog karcinoma dojke. Istovremeno njihova primena može izazvati neželjene događaje koji zahvataju više organskih sistema. Pankreatitis predstavlja retku, ali klinički relevantnu manifestaciju, čije prepoznavanje može biti otežano zbog nespecifičnih simptoma i širokog spektra diferencijalno-dijagnostičkih mogućnosti. **Prikaz slučaja.** Pacijentkinji starosti 44 godine, koja je nakon sedam godina remisije razvila prvi relaps trostruko negativnog karcinoma dojke, u lečenje je uvedena prva linija terapije pembrolizumabom u kombinaciji sa nedeljnim paklitakselom što je dovelo do radiološki potvrđenog parcijalnog odgovora. Germinativno testiranje potvrdilo je prisustvo mutacije gena predispozicije za karcinom dojke 1. Tokom petog ciklusa lečenja kod pacijentkinje se javljao bol u gornjem delu abdomena; endoskopijom su uočeni fibrinom prekriveni *kissing* ulkusi u bulbusu duodenuma, koji su ukazivali na imunoposredovani duodenitis i koji je saniran nakon primene inhibitora protonске pumpe. Nakon ponovnog uvođenja terapije registrovan je povratak simptoma. Laboratorijski nalazi pokazali su povišene pankreasne enzime, a radiološkim ispitivanjem potvrđen je akutni pankreatitis. Alternativni uzroci su isključeni. Pembrolizumab je trajno obustavljen i započeta je kortikosteroidna terapija koja je dovela do postepenog kliničkog i biohemijskog poboljšanja. Uvedena je terapija održavanja inhibitorom poliadenozin difosfat-riboza polimeraze. Nakon deset meseci praćenja, pacijentkinja je bez simptoma, sa očuvanom pankreasnom funkcijom i održanim parcijalnim odgovorom na primenjenu terapiju. **Zaključak.** Ovaj slučaj prikazuje pojavu pankreasne i duodenalne toksičnosti povezane sa primenom pembrolizumaba kod pacijentkinje sa karcinomom dojke. Poznavanje retkih imunoposredovanih neželjenih reakcija ključno je za pravovremeno prepoznavanje i adekvatno lečenje. Multidisciplinarni pristup i individualizovano planiranje terapije omogućili su istovremeno saniranje toksičnosti i kontrolu bolesti.

Ključne reči: tumori dojke; trostruko negativni tumori dojke; humanizovana monoklonska antitela; imunološki antineoplastični agensi; neželjena dejstva i neželjene reakcije povezane sa lekovima; gastrointestinalne bolesti; bolesti pankreasa; imunoterapija; inhibitori imunskih kontrolnih tačaka; multidisciplinarni tim

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Abbreviations

BRCA1	– breast cancer susceptibility gene 1
CTCAE	– common terminology criteria for adverse events
CPS	– combined positive score
EGDS	– oesophagogastrroduodenoscopy
ER	– oestrogen receptor
HER-2	– human epidermal growth factor receptor 2
ICI	– immune checkpoint inhibitor
irAE	– immune-related Adverse Event
MRI	– magnetic resonance imaging
MSCT	– multislice computed tomography
PARP	– poly (adenosine diphosphate-ribose) polymerase
PD-1	– programmed Cell Death Protein 1
PD-L1	– Programmed Death Ligand 1
PPI	– proton pump inhibitor
PR	– progesterone receptor
RECIST	– Response Evaluation Criteria in Solid Tumours
TNBC	– triple-negative breast cancer
NCCN	– National Comprehensive Cancer Network Guidelines

Introduction

Immune checkpoint inhibitors (ICIs) are immunomodulatory immunoglobulin-based agents designed to restore antitumour T cell activity by targeting inhibitory immune checkpoint pathways, most commonly programmed death receptor-1 (PD-1), programmed death ligand-1 (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and have revolutionised cancer care. More recently, lymphocyte activation gene-3 (LAG-3) has also emerged as a clinically validated checkpoint target, while other inhibitory receptors such as T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), V-domain Ig suppressor of T-cell activation (VISTA), B- and T-lymphocyte attenuator (BTLA), T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) remain under active investigation [1]. In this report, we focus on pembrolizumab, an anti-PD-1 antibody, because it was the agent used in our patient. However, activating the immune system through ICIs results in a high burden of toxicities, known as immune-related adverse events (irAEs), which can become chronic and even life-threatening [2,3]. Among breast cancer subtypes, triple-negative breast cancer (TNBC) that is defined by the absence of oestrogen (ER) and progesterone (PR) receptor expression, as well as the lack of human epidermal growth factor receptor 2 (HER-2) overexpression or amplification and frequently high proliferative activity commonly assessed by the Ki-67 index, remains one of the most challenging to treat due to its intrinsic genomic instability, common association with germline BRCA mutations, lack of actionable receptor targets, and typically aggressive clinical behaviour [4,5]. Over the past several years, integrating PD-1/PD-L1 blockade has opened a new therapeutic avenue

for selected patients with early-stage and metastatic TNBC, offering the potential for improved survival in disease settings where progress had long been marginal [4,6]. As the use of ICIs expands in routine clinical practice, recognition of their distinct toxicity profile has become increasingly important, particularly given the potential for immune-mediated effects to involve nearly any organ system [3,7,8]. Similarly, rare oncological presentations and atypical clinical manifestations remain diagnostically challenging and are best documented through carefully reported case reports and literature reviews [9]. We report a rare case of acute pancreatitis accompanied by “kissing” duodenal bulb ulcers arising as an irAE of pembrolizumab therapy. This unusual presentation expands the spectrum of gastrointestinal toxicity associated with ICIs and emphasises the importance of early recognition and tailored multidisciplinary management.

Case Report

A 44-year-old female patient was diagnosed with a first relapse of previously treated invasive ductal carcinoma, triple-negative phenotype (ER 0, PR 0, HER-2: immunohistochemistry score 2+ with negative dual silver in situ hybridisation (dualSISH-), Ki67 30%). After 7 years of follow-up, a first local relapse with observed capsular and muscular infiltration, and supraclavicular and parasternal lymphadenopathy was detected. Core-needle biopsy reconfirmed the triple-negative phenotype (invasive ductal carcinoma, ER 0, PR 0, HER-2: 2+, dualSISH-, Ki67 45%, PD-L1 positive with a combined positive score (CPS status: ≥ 10)). At the same time, additional testing identified presence of the germline BRCA1 mutation. Therefore, the first-line systemic treatment with pembrolizumab in combination with weekly paclitaxel was introduced according to multidisciplinary tumour board recommendation. The first three initial cycles were well tolerated, with a registered partial response on multislice computed tomography (MSCT) per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1 PR). During the fifth cycle, the patient reported upper abdominal discomfort with dyspeptic symptoms. There was no history of prolonged or regular nonsteroidal anti-inflammatory drug use before symptom onset. Oesophagogastroduodenoscopy (EGDS) revealed hyperaemic and oedematous duodenal mucosa with fibrin-covered kissing ulcers in the duodenal bulb, which do not strongly support, yet are not incompatible with immune-mediated duodenitis. Further diagnostics showed a negative *Helicobacter pylori* test. Symptom-oriented treatment was initiated, including proton-



Figure 1. T2 blade FS sequence: abdominal MRI demonstrates diffuse enlargement and T2 hyperintensity of the pancreatic head and body with surrounding inflammatory fat stranding and small volume peripancreatic fluid, without biliary duct dilation

pump inhibitors (PPIs) and mucosal protective agents, with gradual clinical improvement. After a one-month interruption in antineoplastic treatment, combined immuno-chemotherapy was reinitiated for one additional cycle, after which ICI monotherapy was continued with close monitoring. After the seventh cycle, the patient presented with recurrent epigastric pain, nausea and anorexia but remained haemodynamically stable, with preserved renal function and no evidence of respiratory compromise. Laboratory testing revealed markedly elevated serum lipase 533 U/L (8-57 U/L) and pancreatic amylase 303 U/L (27-102 U/L), complemented by imaging findings (abdominal MRI demonstrated diffuse enlargement and T2 hyperintensity of the pancreatic head and body with surrounding inflammatory fat stranding and small volume peripancreatic fluid, without biliary duct dilation) consistent with acute pancreatitis (**Figure 1**). There was no prior history of gallstone disease, alcohol use, hypertriglyceridaemia or other secondary causes, suggesting a high likelihood of immune-mediated aetiology. According to the Common Terminology Criteria for Adverse Events (CTCAE v5.0) and the National Comprehensive Cancer Network Guidelines (NCCN), the patient developed grade 3 immune-related pancreatitis. In accordance with irAE management guidelines, pembrolizumab was discontinued. An EGDS showed, which showed no signs of recurrent or active duodenal ulceration. Systemic corticosteroids (methylprednisolone 0.5 mg/kg/day) were commenced, followed by the transition to oral prednisone once grade 1, <3x ULN (CTCAE v5.0) pancreatic enzyme levels were attained, with a gradual taper of 5 mg per week over approximately 1 month in consultation with gastroenterology/pancreatic subspecialist. Supportive symptomatic care included analgesia, intravenous hydration, bowel rest and continuous proton pump inhibitors (PPIs). Over the following four months, pancreatic enzyme values steadily normalised, with full clinical recovery and

resolution of abdominal symptoms. Due to the severity of the immune-related pancreatic toxicity, immunotherapy was not reintroduced. Given the presence of a BRCA1 Mutation, poly (ADP-ribose) polymerase (PARP) inhibitors were instituted as maintenance therapy. At the most recent follow-up, 10 months after PARPi initiation, the patient remained clinically stable and asymptomatic from a gastrointestinal standpoint, with laboratory parameters within reference ranges. From the oncological perspective, the previously achieved RECIST 1.1 PR was sustained.

Discussion

TNBC represents an aggressive breast cancer subtype with limited targeted therapeutic options and generally poorer clinical outcomes [4,5]. The incorporation of ICIs has reshaped the therapeutic paradigm for metastatic TNBC. In particular, the phase III KEYNOTE-355 trial showed that adding pembrolizumab to chemotherapy significantly improves progression-free and overall survival in patients whose tumours express PD-L1 with CPS ≥ 10 . CPS represents the ratio of PD-L1 positive tumour and immune cells to the total number of viable tumour cells and is used as a predictive biomarker for immunotherapy response in TNBC, thereby establishing pembrolizumab plus chemotherapy as a standard first-line regimen in appropriately selected patients [4–6]. This combination was adopted into routine clinical practice in Serbia in 2024, aligning national treatment standards with contemporary international guidelines. Pembrolizumab exerts antitumour effects by blocking PD-1 on activated T lymphocytes, restoring anti-tumour immune surveillance. However, by enhancing immune activation, PD-1 inhibition can also disrupt peripheral tolerance, leading to a spectrum of irAEs [2,3,7,8]. The present case illustrates several clinically important aspects of ICI-associated GI toxicity. First, the patient achieved a sustained partial oncological response to pembrolizumab-based therapy, consistent with data from the KEYNOTE-355 trial demonstrating clinical benefit in PD-L1 positive TNBC with CPS ≥ 10 . Tumour response was assessed using RECIST 1.1 criteria, consistent with the response assessment methodology used in the KEYNOTE-355 study [4]. However, despite favourable tumour control, treatment was complicated by sequential upper gastrointestinal (GI) and pancreatic irAEs, highlighting the complex balance between antitumour efficacy and immune-mediated toxicity during PD-1 blockade. Gastrointestinal (GI) toxicities such as colitis and hepatitis are well-recognised, whereas immune-mediated pancreatic involve-

ment is relatively uncommon but clinically significant. Recent reports also highlight the duodenum as a possible site of immune-related injury, with histology demonstrating villous blunting and intraepithelial lymphocytosis. Such upper-small-intestinal involvement underscores the need to broaden clinical vigilance beyond typical enterocolitis, particularly when patients under ICI present with epigastric pain or upper GI symptoms [10,11]. The estimated incidence of immune-related pancreatic enzyme elevation with PD-1 inhibitors is approximately 1–2%, and clinically overt pancreatitis is reported in ~1–2% of cases [7,8]. Pharmacovigilance registry data indicate a median symptoms onset within the first 2–3 months of treatment and a non-negligible risk of morbidity [7,8]. Mechanistically, ICI-induced pancreatitis is driven by the activation and clonal expansion of cytotoxic T-cells with loss of tolerance to pancreatic self-antigens. This leads to T-cell infiltration of pancreatic parenchyma, cytokine-mediated acinar cell damage, and premature activation of digestive enzymes, resulting in pancreatic autodigestion [7,8,12]. In the present case, the clinical course was consistent with this immune-driven pathology, according to CTCAE v5.0 criteria and NCCN guideline, the patient developed grade 3 immune related pancreatitis with significant pancreatic enzyme elevation and radiologically confirmed pancreatic inflammation, evidenced by the absence of classical aetiological factors (gallstones, alcohol, hypertriglyceridaemia) and the favourable response to systemic corticosteroids, with subsequent complete clinical and biochemical recovery [13–15]. An additional dimension in this case is the presence of a germline BRCA1 mutation. BRCA1-associated TNBC is characterised by heightened genomic instability, increased neoantigen load, and elevated tumour-infiltrating lymphocytes, fea-

tures that contribute to enhanced intrinsic immunogenicity [16–18]. Although current data do not demonstrate increased irAE risk in BRCA1 mutation carriers, a more immune-reactive tumour microenvironment could plausibly contribute to amplified immune activation during ICI therapy, potentially explaining the severity of pancreatic toxicity observed in this patient [16]. Following guideline-based management, pembrolizumab was permanently discontinued due to the development of grade ≥ 3 pancreatitis, while chemotherapy was temporarily held and later resumed [13–15]. The transition to maintenance therapy with a PARP inhibitor represented an evidence-based (supported by the OlympiAD trial) and biologically rational continuation strategy, given the patient's BRCA1 mutation [19]. Notably, the partial radiological response achieved during pembrolizumab-based therapy was sustained throughout follow-up, consistent with emerging evidence suggesting that irAEs may be associated with more durable antitumour immune responses [20].

Conclusion

This case underscores the importance of prompt recognition and management of immune-related pancreatic toxicity during immune checkpoint inhibitor therapy, particularly as these agents become increasingly integrated into triple-negative breast cancer treatment pathways. While rare, pancreatitis must be considered in patients presenting with upper abdominal pain, dyspepsia, or unexplained pancreatic enzyme elevation during immunotherapy. Close multidisciplinary collaboration between oncology and gastroenterology teams is essential to ensure timely diagnosis, appropriate corticosteroid administration, and safe treatment modification.

References

1. Andrews LP, Yano H, Vignali DAA. Inhibitory receptors and ligands beyond PD-1, PD-L1 and CTLA-4: breakthroughs or backups. *Nat Immunol.* 2019;20(11):1425–34.
2. Martins F, Sofiya L, Sykietis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol.* 2019;16(9):563–80.
3. Wan G, Chen W, Khatlab S, Roster K, Nguyen N, Yan B, et al. Multi-organ immune-related adverse events from immune checkpoint inhibitors and their downstream implications: a retrospective multicohort study. *Lancet Oncol.* 2024;25(8):1053–69.
4. Cortes J, Rugo HS, Cescon DW, Im SA, Yusof MM, Gallardo C, et al. Pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. *N Engl J Med.* 2022;387(3):217–26.
5. Garrido-Castro AC, Lin NU, Polyak K. Insights into molecular classifications of triple-negative breast cancer: improving patient selection for treatment. *Cancer Discov.* 2019;9(2):176–98.
6. Simmons CE, Brezden-Masley C, McCarthy J, McLeod D, Joy AA. Positive progress: current and evolving role of immune checkpoint inhibitors in metastatic triple-negative breast cancer. *Ther Adv Med Oncol.* 2020;12:1758835920909091.
7. Shatila M, Zhang HC, Shirwaikar Thomas A, Machado AP, Naz S, Mittal N, et al. Systematic review of immune checkpoint inhibitor-related gastrointestinal, hepatobiliary, and pancreatic adverse events. *J Immunother Cancer.* 2024;12(11):e009742.
8. Tong L, Yuan Y, He W, Yang W, Pan X. Adverse events associated with acute pancreatitis caused by immune checkpoint inhibitors: a pharmacovigilance analysis of the FDA adverse event reporting system (FAERS) database. *Expert Opin Drug Saf.* 2025:1–9.
9. Marjanović M, Đurić A, Radić J, Petrović N, Stanulović N, Ignjatović Kresoja M. Large bowel obstruction due to metastasis of pancreatic cancer – case report and literature review. *Med Pregl.* 2024;77(9–12):331–7.

10. Johncilla M, Grover S, Zhang X, Jain D, Srivastava A. Morphological spectrum of immune check-point inhibitor therapy-associated gastritis. *Histopathology*. 2020;76(4):531-9.

11. Wang Q, Yu M, Zhang S. Peptic ulcer induced by immune checkpoint inhibitors successfully treated with glucocorticoids: a report of three cases and a literature review. *Exp Ther Med*. 2024;28(5):410.

12. Shirwaikar Thomas A, Chari ST. Immune checkpoint inhibitor-induced (Type 3) autoimmune pancreatitis. *Curr Gastroenterol Rep*. 2023;25(10):255-9.

13. National Cancer Institute. Common terminology criteria for adverse events (CTCAE) Version 5.0. Bethesda, MD: U.S. Department of Health and Human Services; 2017.

14. Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, et al. NCCN guidelines insights: management of immunotherapy-related toxicities, Version 1.2020. *Natl Compr Canc Netw*. 2020;18(3):230-41.

15. Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunothera-

py: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(Suppl 4):iv119-42.

16. Zhou Z, Li M. Evaluation of BRCA1 and BRCA2 as indicators of response to immune checkpoint inhibitors. *JAMA Netw Open*. 2021;4(5):e217728.

17. Fu X, Tan W, Song Q, Pei H, Li J. BRCA1 and breast cancer: molecular mechanisms and therapeutic strategies. *Front Cell Dev Biol*. 2022;10:813457.

18. Xu J, Bao H, Wu X, Wang X, Shao YW, Sun T. Elevated tumor mutation burden and immunogenic activity in patients with hormone receptor-negative breast cancer. *Oncol Lett*. 2019;18(1):449-58.

19. Indini A, Di Guardo L, Cimminiello C, Prisciandaro M, Randon G, De Braud F, et al. Immune-related adverse events correlate with improved survival in patients undergoing anti-PD1 immunotherapy for metastatic melanoma. *J Cancer Res Clin Oncol*. 2019;145(2):511-21.

20. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med*. 2017;377(6):523-33.

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