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Immunotherapy in Metastatic Pancreatic Adenocarcinoma with DNA Repair Deficiency: A Narrative Review of Current Evidence and Therapeutic Perspectives

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1. Abstract

Metastatic pancreatic adenocarcinoma is a highly lethal neoplasm with limited response to conventional chemotherapy. However, in a small subset of patients with high microsatellite instability (MSI-H) or DNA mismatch repair deficiency (dMMR), there is enhanced sensitivity to immunotherapy, especially immune checkpoint inhibitors. This article critically reviews the literature on the use of pembrolizumab in these patients, highlighting clinical and molecular data and future perspectives. It emphasizes the value of predictive biomarkers, challenges to implementation, and discusses the immunobiological rationale for the complete responses observed in selected cases.

2. Introduction

Pancreatic ductal adenocarcinoma is the seventh leading cause of cancer death worldwide and has a 5-year survival rate of less than 10%. Even with intensive regimens such as FOLFIRINOX or gemcitabine plus nab-paclitaxel, response rates remain limited and progression-free survival is short. In this context, immunotherapy emerges as a promising strategy for specific molecular subgroups, particularly tumors with high microsatellite instability (MSI-H) or deficient mismatch repair (dMMR).Early studies such as KEYNOTE-158 and KEYNOTE-164 showed that MSI-H tumors, regardless of the site of origin, respond better to PD-1 inhibition. In pancreatic cancer, although rare (<2%), such cases have demonstrated durable responses and, in some reports, even complete pathological responses, including in patients who failed prior chemotherapy.

3. Immunobiological Mechanism of Response in dMMR/MSI-H

MMR deficiency promotes the accumulation of frameshift mutations and tumor neoantigens, enhancing recognition by T cells. PD-L1 expression, associated with tumor inflammation, allows immune escape via the PD-1/PD-L1 pathway. PD-1 inhibitors like pembrolizumab restore antitumor immune response. This rationale led to the tumor-agnostic approval of pembrolizumab by the FDA and ANVISA in 2017 for any MSI-H/dMMR tumor.

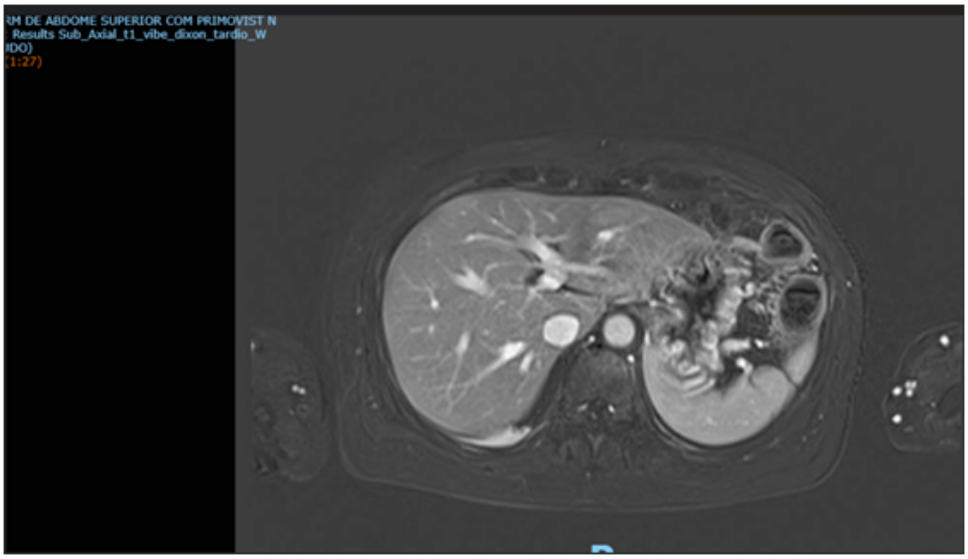

Figure 1: Current resonance maintaining the complete pathological response to immunotherapy treatment.

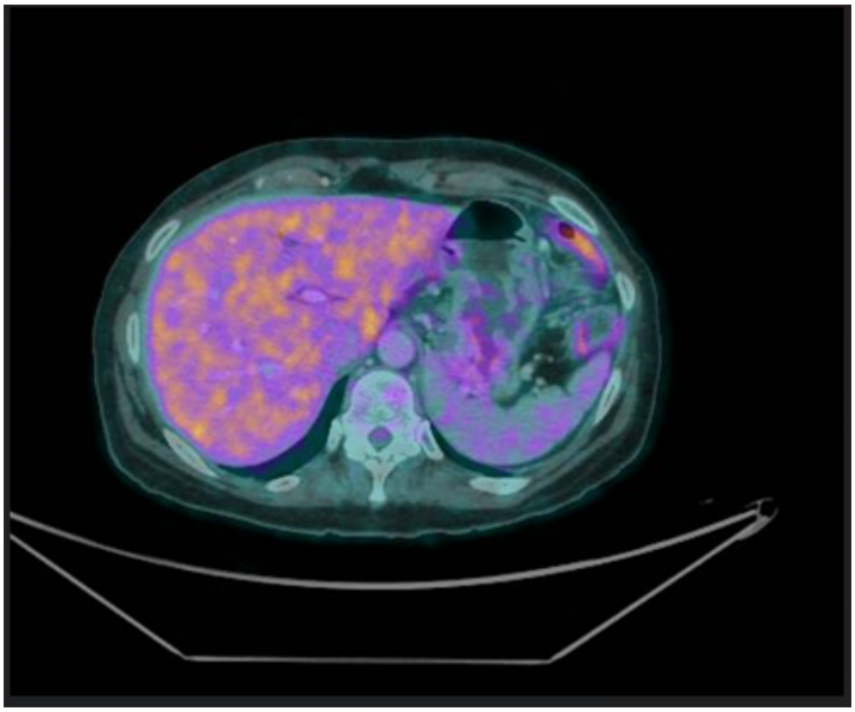

Figure 2: one year of treatment with complete metabolic response.

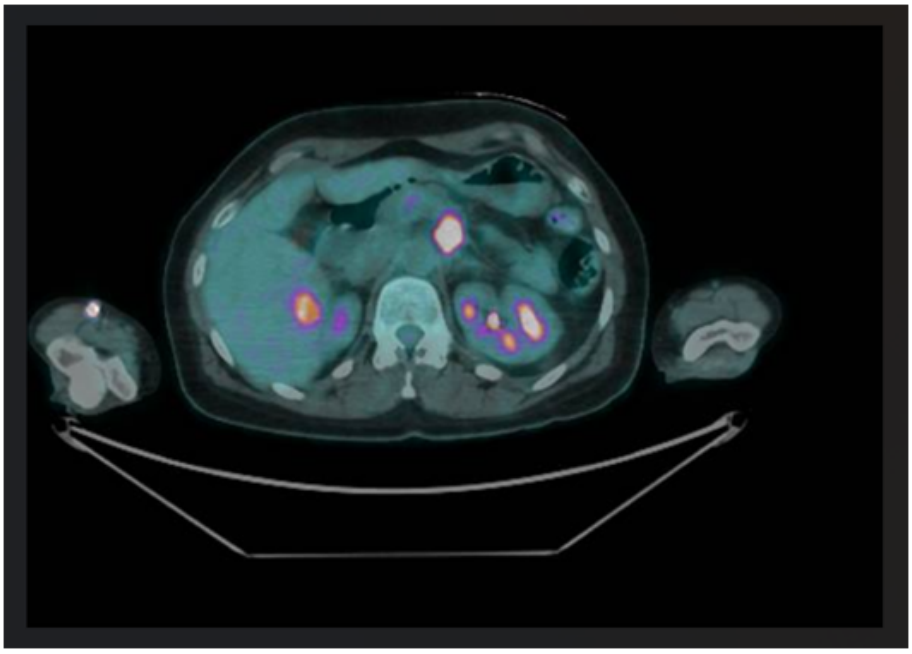

Figure 3: Pretreatment with immunotherapy.

4. Current Clinical Evidenc

4.1. KEYNOTE-158

Multicenter phase II trial of pembrolizumab in MSI-H tumors. The pancreatic cancer subgroup (n=22) had an objective response rate (ORR) of 18.2%, with a median duration of response of 13.4 months and overall survival of 13.1 months [1].

4.2. KEYNOTE-164

Included patients with colorectal and other MSI-H tumors. Similar results were seen in the pancreatic cancer subgroup, with disease stabilization in a significant proportion of patients [2].

4.3. Case Reports and Small Series

Reports published between 2019 and 2024 describe complete responses with immunotherapy in MSI-H pancreatic cancer, though most show partial responses or disease control. Complete pathological response remains rare [3,4].

5. Lynch Syndrome and Pancreatic Cancer

Lynch syndrome is caused by germline mutations in MMR genes (MLH1, MSH2, MSH6, PMS2). Although pancreatic cancer is not the most frequent tumor type, its cumulative risk by age 70 is estimated at 3 to 5%. In these patients, active surveillance and genetic profiling have direct therapeutic implications.

6. Current Barriers and Future Directions

6.1. Barriers

- Low prevalence of MSI-H (<2%) in pancreatic cancer.
- Underuse of molecular testing in public and private healthcare systems.
- High cost of immunotherapy.

6.2. Perspectives

- Routine use of NGS panels in all pancreatic adenocarcinoma cases.
- Combination strategies with immunotherapy and chemotherapy or epigenetic agents.
- Investigation of ctDNA as a biomarker for response.

7. Final Considerations

Despite the rarity of MSI-H/dMMR pancreatic tumors, the response to immunotherapy can be robust and durable. Reports of complete pathological responses with pembrolizumab are encouraging but require validation in prospective studies. Expanding access to molecular profiling is essential for early identification of eligible patients.Practical recommendation: All patients with pancreatic adenocarcinoma should undergo MSI-H/dMMR testing, regardless of age or family history.

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