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# A Case Report of Immune Checkpoint Inhibitor-Associated Acute Pancreatitis Presenting as Mixed DKA/HHS: Histopathological and Radiological Findings

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## Case Description

- 88 y/o M with history of CAD, atrial fibrillation on warfarin, and stage IV bladder cancer s/p TURBT 08/2022
- Initially presented with several days of worsening fatigue, confusion, irritability, lightheadedness, abdominal pain, back pain, loose stools, polydipsia
- Initial labs significant for: corrected Na 158, glucose 1086, bicarb 16, AG 23, K 6.5, Cr 1.4, lactate 2.5, venous pH 7.32, serum osmolality 351, small serum ketones, UA 3+ glucose and 2+ ketones, corrected Ca 13, ionized calcium 1.67
- Admitted to the ICU for management of DKA/HHS
- Met criteria for acute pancreatitis with epigastric/RUQ tenderness on exam and serum lipase 988
  - LFTs and triglycerides within normal limits
  - RUQ US: no gallstones, cholecystitis (fig. 1A), or CBD dilatation. Pancreas appeared grossly normal (fig. 1B).
  - Family denied history of tobacco or alcohol use
- NPO, DKA protocol, aggressive IVF resuscitation
- Patient had been receiving pembrolizumab (PD-1 receptor antagonist) every 3 weeks outpatient over the past several months for his metastatic bladder cancer
- No history of DM; A1c had increased from 5.6% (07/29/2022) to 8.5% on admission (09/18/2022)
- Baseline CT A/P (04/2022): A few punctate calcifications within the pancreatic parenchyma suggestive of chronic pancreatitis. No peripancreatic inflammatory change or mass
- No additional CT scan was done during this hospitalization

## Discussion

- With other common causes of pancreatitis ruled out and only a moderate hypercalcemia, pembrolizumab was believed to be the culprit of pancreatitis leading to DKA/HHS in this patient's case
- Hirota et. al. (05/2022): Histopathological appearance of pembrolizumab-induced pancreatitis (fig. 3)
  - Neutrophil infiltration (seen in type 2 AIP)
  - Acinar-ductal metaplasia
  - Non-specific fibrosis
  - Fat deposition
    - No fat necrosis (seen in AP)
  - CD8+ T-cell infiltrates
    - No IgG4-positive plasma cells (seen in type 1 AIP)
    - No CD4+ T cells (seen in classic T1DM)

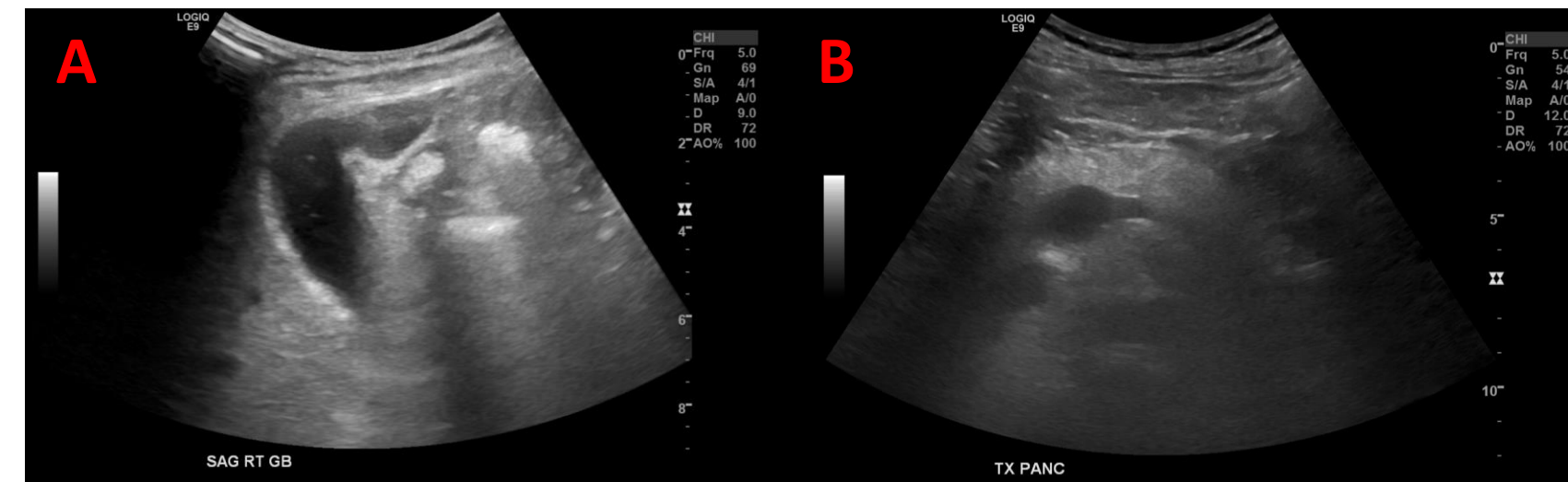


Figure 1: RUQ ultrasound after admission to rule out gallstone pancreatitis. A) Gallbladder with minimal sludge, no stones, no cholecystitis, and no CBD dilatation. B) The pancreas appeared grossly normal.

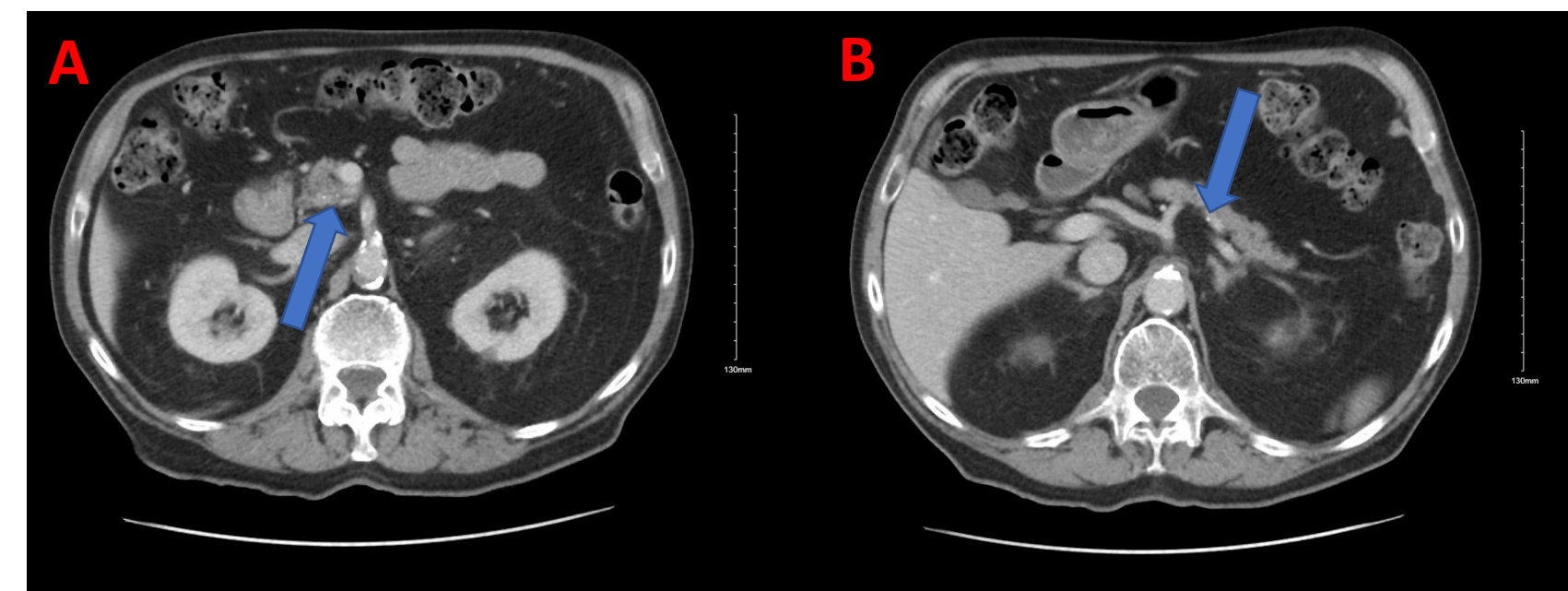


Figure 2: CT abdomen/pelvis from April 2022 showing several punctate calcifications in the A) head and B) body of the pancreas.

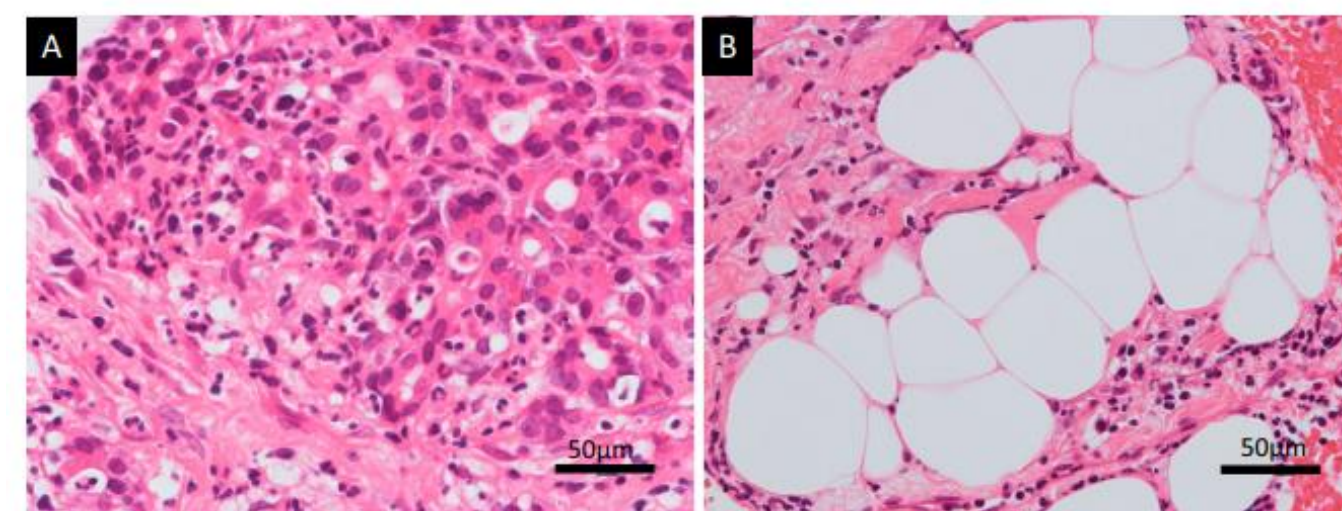


Figure 3 (Hirota et. al. (05/2022): Unique histopathological appearance of pembrolizumab-induced pancreatitis with lack of typical findings for acute pancreatitis. A) Neutrophil infiltration and acinar-ductal metaplasia without IgG4-positive plasma cells. B) Fat deposition without fat necrosis.

## Discussion (continued)

- Pembrolizumab binds the PD-1 receptor on T-cells, preventing their inactivation by tumor cells
- Decreased T-cell regulation appears to lead to autoimmune-like pattern of pancreatic injury which may affect endocrine or exocrine function
- Immune checkpoint inhibitor (ICI)-associated pancreatitis is uncommon; <1% incidence of moderate to severe pancreatitis in most clinical trials
- ICI-associated pancreatitis is usually asymptomatic with incidentally discovered elevations in serum lipase
- Management involves holding the ICI in these cases
- In severe cases, steroids are recommended in addition to the standard IVF, pain control, bowel rest
  - Typically 0.5–1 mg/kg/day prednisone/methylprednisolone with a 4-6 week taper. In severe cases, a double daily dose may be given
- Imaging findings related to ICI pancreatitis include pancreatic enlargement, decreased attenuation, and surrounding fat stranding. PET/CT may show increased FDG uptake
- ICIs are also rarely associated with new T1DM with reported incidence of <0.5%
- Wide range in the time of onset: as early as a single cycle of ICI treatment. Average onset after 20 cycles of immunotherapy
- The majority of these patients presented with DKA

## Conclusion

- This case is unusual in that the patient presented with a mixed DKA/HHS picture in addition to acute pancreatitis. Loose stools may indicate exocrine gland dysfunction; if so, this is a very unique presentation of both endocrine and exocrine pancreatic dysfunction caused by pembrolizumab
- Despite its rarity, clinicians should be aware of adverse effects of ICIs including new onset DM (which often presents as DKA) and acute pancreatitis
- More research is needed to further characterize histopathology and determine optimal treatment guidelines

## References

- Available upon request

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