Characteristics of Appendicitis After Immune Checkpoint Inhibitors Among Cancer Patients

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Introduction

- Immune checkpoint inhibitors (ICIs) have been associated with immune-related adverse events (irAEs), with gastrointestinal (GI) irAEs among the most reported.
- Recent case reports have raised concern that acute appendicitis may be a possible irAE. Conventional appendicitis usually occurs in a younger population (age 5-45 years) and is characterized by acute right lower quadrant abdominal pain with a perforation rate of 20-30%.
- We aim to describe the disease course of appendicitis after ICI exposure and its associated complications.

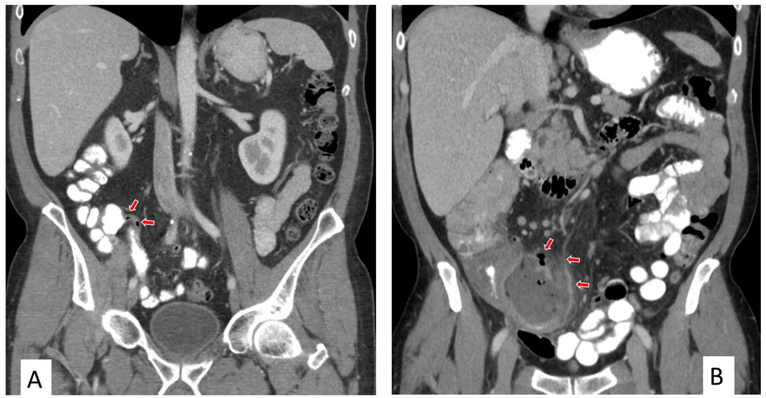
Methods

- Retrospectively studied adult patients who had an ICD code of appendicitis between their 1st dose of ICI and up to 2 years with imaging evidence of appendicitis. Patients were excluded if the appendicitis diagnosis was prior to ICI exposure.

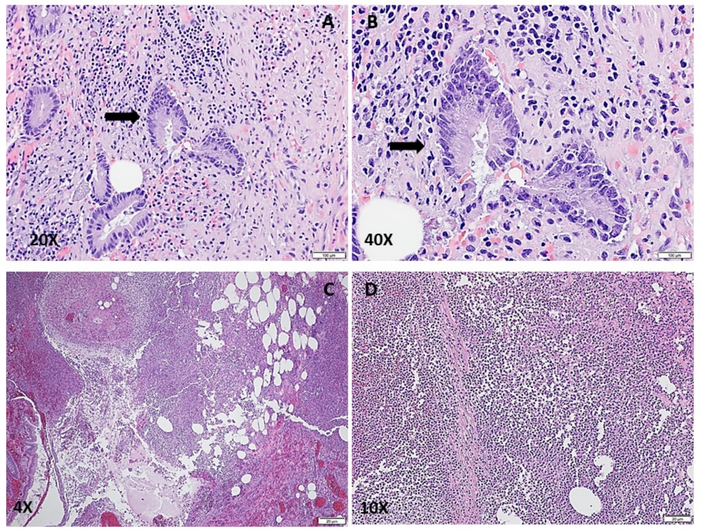
Results

- Forty-four out of the 13,991 ICI patients had the ICD diagnostic code for appendicitis during the study period, among whom 10 patients met the inclusion criteria.
- The median age at the time of appendicitis diagnosis was 59 years (IQR=55-60). Seven patients (70%) were male.
- The most common malignancies were melanoma (n=4, 40%) and genitourinary cancers (n=3, 30%).
- Nine patients (90%) had stage IV cancer.
- Most patients received treatment with anti-PD-1/L1 monotherapy (60%).
- The median time from ICI initiation to appendicitis onset was 188 days (IQR=46-386). The median doses of ICI received was 4 (IQR=2-15).
- The most common presenting symptoms were abdominal pain (70%) and fever (40%).
- Abscess was present on imaging in two patients (20%) and a perforation was found in one patient (10%). No patients had symptoms or evidence of concurrent colitis.
- All ten patients had received antibiotic treatment. Five patients (50%) required surgical or IR intervention.
- Nine patients (90%) had resolution of appendicitis symptoms after treatment. Three patients (30%) had their ICI terminated after the episode of appendicitis. However, all three of these patients resumed non-ICI cancer therapy.

Figures



Radiological Contrast-enhanced features of appendicitis and complications.
(A) CT image showing a normal-appearing appendix
(B) Contrast-enhanced CT image showing an appendix perforated by a large abscess



Pathological features of appendicitis and complications. (A and B) Markedly increased apoptosis in the epithelium of the appendiceal crypts. (C and D) Transmural acute inflammation with infiltration of neutrophils throughout the full thickness of the appendiceal wall and abscess formation

Table: Appendicitis-related characteristics of patients (n=10)

Characteristic	No. of patients (%)
Median no. of ICI doses (IQR)	4 (2-15)
Clinical symptoms	
Abdominal pain	7 (70)
Diarrhea	0
Fever	4 (40)
Nausea/vomiting	3 (30)
Loss of appetite	3 (30)
CT findings	
Appendiceal inflammation	10 (100)
Abscess/fluid collection	2 (20)
Perforation	1 (10)
Complications of appendicitis	
Abscess	2 (20)
Perforation	1 (10)
Treatment of appendicitis	
No treatment	0
Antibiotics	5 (50)
Antibiotics plus surgery/IR procedure	5 (50)
ICI therapy termination due to appendicitis	2 (20)
Cancer treatment after ICI therapy termination	
No further cancer treatment	0
Switched to other non-ICI treatment	1 (10)
Outcomes	
Hospitalization	10 (100)
Median length of hospitalization, days (IQR)	9 (2-11)
Response of appendicitis after any treatment	9 (90)
Median follow-up duration, months (IQR)	28.5 (14.0-35.5)
All-cause mortality	3 (30)

Conclusion

- Appendicitis after ICI therapy is extremely rare.
- Compared to conventional appendicitis it occurs at an older age but with similar clinical presentations and comparable complication rates.
- Management strategies are comparable to conventional appendicitis, with appendectomy being the mainstay of treatment.
- Appropriateness of continuing ICI therapy after episode of appendicitis has yet to be delineated and is often determined by clinical judgement.
- Further studies are needed to bring awareness to this clinical entity and advance understanding of its management.