Identification and Characterization of a Single-Center Cohort of Patients With Refractory or Relapsing Immune Checkpoint Inhibitor-Induced Colitis

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INTRODUCTION

Immune checkpoint inhibitors (ICIs) are the latest development in the fight against cancer. ICI-induced colitis is seen frequently, in 8.7% to 54% of individuals undergoing ICI therapy.[1-2]

The pathogenesis of ICI-colitis appears to arise from increased CD8+ tissue resident T cells activation in colonic mucosa, which is distinct from the immunological changes seen in traditional inflammatory bowel disease.[3-4]

Treatment for ICI-induced toxicities relies on immunosuppressants such as corticosteroids and biologic therapy. These treatments are not always sufficient, and recent meta-analysis found that corticosteroids were only effective in 59% of cases.5

We sought to characterize and describe the disease and treatment course of those individuals who suffer prolonged courses of ICI colitis. Predicting which patients are susceptible to either a second episode of colitis or refractory colitis would allow providers to better tailor colitis-directed treatment, resume ICI therapy sooner, and ultimately reduce cancer mortality.

MATERIAL AND METHODS

Retrospective chart review was performed across a multisite health system. To identify cases of ICI-induced colitis we utilized the hospital system's Unified Data Platform. Cases were identified for medication administrations of FDA-approved immune checkpoint inhibitors prior to December 1st 2021. Cases were then narrowed based on UDP search of clinical notation identifying "colitis."

Clinical documentation was abstracted to determine the duration of ICI therapy, duration of symptoms, diagnostic evaluation, and treatment course. Colitis was defined clinically based on CTCAE V5 criteria for colitis.[6]

Cases were subdivided into four different groups. "Responsive" cases were those with a single episode of colitis that responded to treatment without relapse or recurrence. "Refractory" cases were those with no symptom improvement after more than 30 days of definitive treatment but with eventual symptom resolution. "Second colitis" cases had complete resolution of their symptoms but then proceeded to develop a second *de novo* episode of colitis. "Unresolved" cases never had symptom resolution at the time of last follow up.

Data was abstracted and imported into Bluesky statistical software. The statistical analysis utilized BlueSky Statistics software v. 7.10 (BlueSky Statistics LLC, Chicago, IL, USA). Categorical variables across different groups were analyzed by Chi-Squared analysis, and numerical variables were analyzed by ANOVA in BlueSky. To evaluate for predictive factors for refractory recurrent colitis logistic regression or cox proportional hazards analysis were performed.

RESULTS

Table 1A, Demographics of Patients Developing ICI-induced Colitis

	Single Episode, Responsive Symptoms N=61	Single Episode, Refractory Symptoms N=53	Second Episode of Colitis N=19	Unresolved Symptoms N=15	All Cases n=148
Gender f (%)	28 (45.9%)	30 (56.6%)	6 (31.6%)	9 (60.0%)	73 (49.3%)
Age at first ICI median, years (median, IQR)	66.6 (57.4-72.5)	67.9 (58.4-71.7)	66.1 (56.8-71.3)	70.3 (68.3-75.7)	67.4 (57.6-72.4)
Median Follow Up After Symptom Onset, years (median, IQR)	1.04 (0.46-1.86)	1.44 (0.66-2.04)	1.93 (0.75-2.69)	0.22 (0.12-0.45)	1.08 (0.46-1.99)
Malignancy					
Melanoma	27 (44.3%)	25 (47.2%)	9 (47.4%)	3 (20.0%)	64 (43.2%)
Lung Cancer-NSCLC	12 (19.7%)	13 (24.5%)	3 (15.8%)	3 (20.0%)	31 (20.9%)
Renal cell carcinoma	5 (8.2%)	4 (7.5%)	2 (13.3%)	2 (13.3%)	16 (10.8%)
Other	17 (28%)	11 (21%)	3 (16%)	7 (47%)	37 (25%)
Prior Bowel Resection	6 (10.5%)	4 (8.0%)	**6 (31.6%) ***	3 (20.0%)	19 (13.5%)
Causative Immune Checkpoint inhibitor					
Pembrolizumab	27 (44.3%)	21 (39.6%)	8 (42.1%)	7 (46.7%)	63 (42.6%)
Nivolumab	5 (8.2%)	11 (20.8%)	5 (26.3%)	0 (0.0%)	21 (14.2%)
Ipilimumab + Nivolumab	24 (39.3%)	14 (26.4%)	3 (15.8%)	6 (40.0%)	47 (31.8%)
Other	5 (8.2%)	7 (13.2%)	3 (15.8%)	2 (13.3%)	17(11.5 %)
ICI doses prior to colitis, n (median, IQR)	6 (2-11)	6 (3-10.250)	6 (2.500-11)	6 (3.500-8)	6 (3-10.500)
Duration of symptoms, days (median, IQR)	59 (24-102)	**137 (74-225) *****	65 (24.5-102.5)	80 (43-163)	80.500 (30.8-146.5)
Hospitalized for event	30 (49.2%)	26 (49.1%)	9 (47.4%)	**12 (80.0%) ***	77 (52.0%)
Deceased	25 (41.0%)	15 (28.3%)	7 (36.8%)	**13 (86.7%)****	60 (40.5%)
Time from event to death, days (median, IQR)	332 (168-496)	332 (141-660.5)	521.5 (272.8-612.5)	60 (41-123)	274 (110-529)

Values given are n, % unless otherwise specified
P<0.05, ** p< 0.01, *** p<0.001
†Ongoing refers to at time of last follow up

Figure 1: CTCAE Grade By Disease Presentation

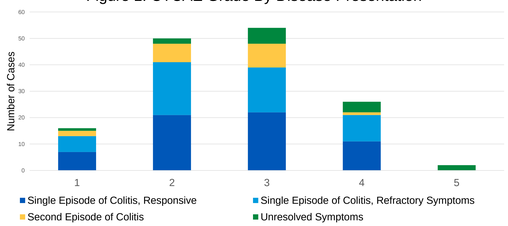

Table 1B Evaluation and Treatment of Colitis

	Single Episode, Responsive Symptoms N=61	Single Episode, Refractory Symptoms N=53	Second Episode of Colitis N=19	Unresolved Symptoms N=15	All Cases n=148
Colonoscopy obtained	13 (21.3%)	**24 (45.3%) ****	3 (15.8%)	4 (26.7%)	44 (29.7%)
Sigmoidoscopy obtained	15 (24.6%)	17 (32.1%)	8 (42.1%)	4 (26.7%)	44 (29.7%)
Fecal calprotectin elevated	6 (75.0%)	16 (88.9%)	2 (66.7%)	3 (75.0%)	27 (81.8%)
Treatment					
Duration of symptoms after starting systemic steroids, days (median, IQR)	43.500 (20-83.8)	**119 (61-192) *****	30 (9-87.8)	NA	65 (22-118)
Systemic Steroids ongoing for colitis †	10 (17.5%)	16 (30.2%)	4 (22.2%)	7 (46.7%)	37 (25.9%)
Duration of budesonide treatment, days (median, IQR)	138 (70.5-244.3)	165.5 (107-317.8)	137 (119.5-281)	131 (104.5-157.5)	155 (97-280)
Duration of symptoms after starting budesonide, days (median, IQR)	42 (14-79)	94 (49.8-157)	56.5 (21.5-89.8)	NA	64.500 (21-134.5)
Budesonide ongoing	6 (25.0%)	9 (29.0%)	3 (33.3%)	4 (66.7%)	22 (31.4%)
Treatment with biologic	5 (8.2%)	**18 (34.0%) *****	2 (10.5%)	2 (13.3%)	27 (18.2%)
Duration of symptoms after starting biologic	29 (27-62)	68.5 (42-115.8)	23.5 (13.3-33.8)	NA	
Biologic ongoing†	1 (20%)	9 (50%)	2 (66.7%)	2 (100.0%)	14 (50.0%)
Suppressive treatment to continue ICI?	9 (25.0%)	**19 (63.3%) ****	8 (47.1%)	5 (83.3%)	41 (46.1%)

Figure 2: Treatment of Colitis by disease presentation

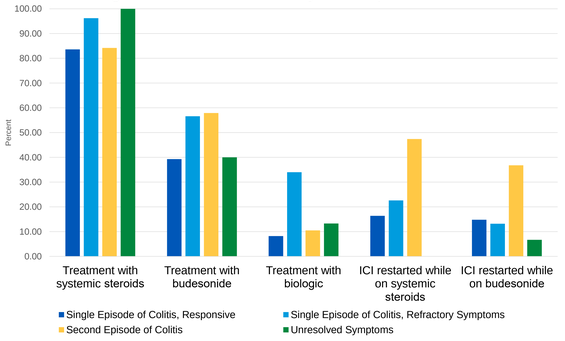

Table 2: Risk Factors for Refractory Colitis (calculated via logistic regression)

Variable	OR (95% CI)
Melanoma	0.80 (0.32-1.99)
Lung Cancer-NSCLC	0.87 (0.41-1.82)
Prior Chemotherapy	1.31 (0.65-2.63)
Any Additional Adverse Event	1.48 (0.74-2.98)
Combination of ICI + Chemotherapy	1.50 (0.72-3.15)
Multiple ICI Therapy	0.7 (0.32-1.5)
Number of ICI Doses	1.01 (0.97-1.06)
Pembrolizumab	0.84 (0.41-1.7)
Ipilimumab + Nivolumab	0.7 (0.32-1.5)

Table 3A: Symptoms of Second Event of ICI-Colitis

Immune Checkpoint Inhibitor	
Colitis on systemic steroid treatment	5 (26.3%)
Colitis on enteral steroid treatment	5 (26.3%)
Colitis on biologic treatment	1 (5.3%)
Time from ICI reintroduction to second episode, days (median, IQR)	59.5 (13.5-154)
CTCAE Grade	
1	2 (10.5%)
2	2 (10.5%)
3	11 (57.9%)
4	2 (10.5%)
5	2 (10.5%)
Hospitalized	9 (47.4%)
Mortality	2 (10.5%)
ICI held due to colitis	18 (100%)
ICI held permanently	12 (66.7%)
Switched to another ICI	3 (16.7%)
Treatment	
Systemic Steroids	15 (78.9%)
Budesonide	11 (57.9%)
Biologic	7 (36.8%)

Table 3B: Risk Factors for Second Event of ICI Colitis

Variable	HR (95% CI)
Melanoma	0.66 (0.26-1.94)
NSCLC	0.64 (0.17-2.49)
Prior Chemotherapy	0.13 (0.37-2.38)
Prior Radiation	**2.50 (1.31-9.36)***
Combination ICI Plus Chemotherapy	0.48 (0.30-2.08)
ICI	
Pembrolizumab	0.79 (0.57-3.76)
Nivolumab	1.07 (0.20-1.61)
Ipilimumab and Nivolumab	1.69 (0.84-10.21)
Switched to another ICI	0.59 (0.20-2.39)
ICI Doses	1.06 (0.91-1.03)
Previous Treatment	
Systemic Steroids	0.94 (0.16-1.92)
Budesonide	0.23 (0.45-2.80)
Biologics	1.27 (0.09-1.69)

DISCUSSION

- Of 148 cases of ICI-induced colitis, 36% experienced refractory colitis and 13% experienced a second episode of colitis.
- Management of ICI-colitis frequently required systemic and enteral steroids and required holding ICI therapy in 87.2% of cases.
- Regression analysis for risk factors for refractory colitis (table 2) demonstrated the difficulty predicting colitis course.
- Refractory colitis more often required biologic therapy compared to other clinical presentations of colitis.
- Cases experiencing a second episode of colitis trended towards being more likely to have restarted ICI while on enteral or corticosteroids.
- Second episodes of colitis were severe, with 2/19 cases suffering mortality. Prior radiation was the most significant risk factor associated with a second episode of colitis (p=0.01).

CONCLUSIONS

- We describe a comprehensive and complex cohort assessing symptom duration and treatment course of ICI-colitis, with a focus on those developing prolonged or recurrent colitis.
- ICI-induced colitis frequently results in hospitalization and often requires prolonged systemic or enteral steroid courses.
- Predictive factors for individuals who will develop prolonged or recurrent colitis remain to be identified.
- When symptoms remain refractory to systemic and corticosteroids, biologic therapy may be needed to induce clinical improvement.

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