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### ► To cite this version:

Chloé Vuillamy, Jean-Philippe Arnault, Mathurin Fumery, Laurent Mortier, Sandrine Monestier, et al.. Clostridium difficile infection and immune checkpoint inhibitor–induced colitis in melanoma: 18 cases and a review of the literature. *Melanoma Research*, 2023, 10.1097/CMR.0000000000000878 . hal-04061838

**HAL Id: hal-04061838**

**<https://u-picardie.hal.science/hal-04061838>**

Submitted on 3 Jun 2024

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# *Clostridium difficile* infection and immune checkpoint inhibitor-induced colitis in melanoma: 18 cases and a review of the literature

Chloé Vuillamy<sup>a</sup>, Jean-Philippe Arnault<sup>a</sup>, Mathurin Fumery<sup>b</sup>, Laurent Mortier<sup>c</sup>, Sandrine Monestier<sup>d</sup>, Sandrine Mansard<sup>e</sup>, Guido Bens<sup>f</sup>, Anne-Bénédicte Duval-Modeste<sup>g</sup>, Elisa Funck-Brentano<sup>h</sup>, Géraldine Jeudy<sup>i</sup>, Laurent Machet<sup>j</sup>, Guillaume Chaby<sup>a</sup>, Ali Dadban<sup>a</sup> and Catherine Lok<sup>a</sup>, Groupe de Cancérologie Cutanée de la Société Française de Dermatologie

Immunotherapy has become the standard of care for several types of cancer, such as melanoma. However, it can induce toxicity, including immune checkpoint inhibitor-induced colitis (CIC). CIC shares several clinical, histological, biological, and therapeutic features with inflammatory bowel disease (IBD). *Clostridium difficile* infection (CDI) can complicate the evolution of IBD. We aimed to characterize the association between CDI and CIC in patients treated with anti-CTLA-4 and anti-PD-1 for melanoma. Patients from nine centers treated with anti-CTLA-4 and anti-PD-1 for melanoma and presenting with CDI from 2010 to 2021 were included in this retrospective cohort. The primary endpoint was the occurrence of CIC. The secondary endpoints were findings allowing us to characterize CDI. Eighteen patients were included. Eleven were treated with anti-PD-1, four with anti-CTLA-4, and three with anti-PD-1 in combination with anti-CTLA-4. Among the 18 patients, six had isolated CDI and 12 had CIC and CDI. Among these 12 patients, eight had CIC complicated by CDI, three had concurrent CIC and CDI, and one had CDI followed by CIC. CDI was fulminant in three patients. Endoscopic and histological features did not specifically differentiate CDI from CIC. Nine of 11 patients required immunosuppressive therapy when CDI

was associated with CIC. In nine cases, immunotherapy was discontinued due to digestive toxicity. CDI can be isolated or can complicate or reveal CIC. CDI in patients treated with immunotherapy shares many characteristics with CDI complicating IBD. Stool tests for *Clostridium difficile* should be carried out for all patients with diarrhea who are being treated with immunotherapy. *Melanoma Res* 33: 192–198 Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc

*Melanoma Research* 2023, 33:192–198

**Keywords:** checkpoint inhibitor colitis, *Clostridium difficile*, diarrhea, immunotherapy, inflammatory bowel disease, melanoma

Departments of <sup>a</sup>Dermatology and <sup>b</sup>Gastroenterology, CHU Amiens Picardie University Hospital, Amiens, <sup>c</sup>Department of Dermatology, Lille University Hospital, Lille, <sup>d</sup>Department of Dermatology, Marseille University Hospital (APHM), Marseille, <sup>e</sup>Department of Dermatology, Clermont-Ferrand University Hospital, Clermont-Ferrand, <sup>f</sup>Department of Dermatology, Orléans University Hospital, Orléans, <sup>g</sup>Department of Dermatology, Rouen University Hospital, Rouen, <sup>h</sup>Department of General and Oncologic Dermatology, Ambroise Paré Hospital (APHP), Boulogne-Billancourt, <sup>i</sup>Department of Dermatology, Dijon University Hospital, Dijon and <sup>j</sup>Department of Dermatology, Tours Regional University Hospital, Tours, France

Correspondence to Chloé Vuillamy, MD, Department of Dermatology, Centre Hospitalier Universitaire d'Amiens, 1 Rond-Point du Professeur Christian CABROL, 80054 Amiens Cedex, France  
Tel: +33 3 22 08 80 00; e-mail: chloe.vuillamy@chu-lille.fr

Received 28 June 2022 Accepted 19 December 2022.

## Introduction

Checkpoint inhibitor-based immunotherapy is a cornerstone in the treatment of melanoma in the adjuvant as well as metastatic settings [1–7]. The immune checkpoint inhibitors approved for melanoma are ipilimumab (Bristol-Myers Squibb, New York, New York, USA), an antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) as well as nivolumab (Bristol-Myers Squibb) and pembrolizumab (Merck Sharp & Dohme, New York, New York, USA), antibodies against a programmed cell death-ligand 1 (PD-1) [8–11].

Gastrointestinal toxicity is among the most frequent immune-related adverse events (irAEs) of these treatments [12]. It is more frequent with immunotherapy based on anti-CTLA-4 than anti-PD-1. It is also the irAE that leads to most cases of treatment discontinuation [13]. Symptoms of checkpoint inhibitor-induced colitis (CIC) are diarrhea (occurring in 92% of patients), abdominal pain (82%), hemochezia (64%), fever (46%), and vomiting (36%) [14]. Flexible sigmoidoscopy or colonoscopy with biopsies is recommended. Endoscopic lesions of anti-CTLA-4 induced colitis include loss of vascular pattern, granulation, erythematous mucosa, pus, bleeding, and ulcerations [15]. Histopathological features of anti-CTLA-4 induced colitis are the presence of intraepithelial neutrophilic leukocytes, crypt abscesses, increased transmucosal inflammatory infiltrates, and crypt irregularities [15].

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The characteristics of anti-PD-1-induced colitis are less well described than those of anti-CTLA-4-induced colitis. Collins *et al.* [16] observed four clinical and pathological patterns of colitis: acute colitis sharing similarities with anti-CTLA-4-related colitis, microscopic colitis, upper gastrointestinal tract involvement, and pseudo-obstruction.

Colitis occurs earlier and is more frequent with combined anti-CTLA-4 and anti-PD-1 agents than with either ipilimumab or anti-PD-1 [17].

Studies have shown that CIC shares many similarities with inflammatory bowel disease (IBD) [14].

*Clostridium difficile* is a spore-forming, anaerobic gram-positive intestinal pathogen transmitted among humans through the fecal-oral route [18]. *Clostridium difficile* releases two protein exotoxins (TcdA and TcdB) responsible for diarrhea and colitis [19]. Diagnosis of *Clostridium difficile* infection (CDI) is based on the detection of *Clostridium difficile* and its toxin in stools [20].

CDI is a well-known complication of IBD [21]. CDI may reveal or complicate the disease course of both Crohn's disease and ulcerative colitis, in which CDI is a surrogate marker of disease severity.

CDI has been described with CIC in several case reports [22–25].

Here, we aimed to characterize the association between CDI and CIC in patients treated with the immunotherapeutic agents anti-CTLA-4 or anti-PD-1. They were selected from a larger cohort of melanoma patients.

## Methods

### Study design

This was a retrospective multicenter study. We enrolled patients from nine French hospitals over a period from January 2010 to February 2021. We developed a questionnaire to collect patient characteristics that was completed by the referring physician of each patient. The protocol of the study was reviewed by the institutional review board or ethics committee at each center.

### Patients

Eligible patients had CDI, defined as the presence of both *Clostridium difficile* and toxin A or B in the stool. Patients had to be: (a) adults with (b) stage III or IV (American Joint Commission on Cancer eighth edition) [26] histologically confirmed melanoma (c) treated by immunotherapy with anti-CTLA-4 or anti-PD-1 in an adjuvant, locally advanced, or metastatic setting.

Patients with a history of CDI before the start of immunotherapy were excluded.

### *Clostridium difficile* infection

The severity of CDI was defined according to the Infectious Diseases Society of America (IDSA) and

Society for Healthcare Epidemiology of America [27]. Nonsevere CDI was defined as leukocytosis with a white blood cell count of 15 000 cells/ml or less and a serum creatinine level of less than 1.5 mg/dl. Severe CDI was defined as leukocytosis with a white blood cell count of at least 15 000 cells/ml or a serum creatinine level of more than 1.5 mg/dl. CDI was considered fulminant when there was hypotension or shock, ileus, or megacolon.

Therapeutic failure of CDI was defined as the persistence of symptoms after a line of treatment.

The recurrence of CDI was defined as a negative test for *Clostridium difficile* in the stool after treatment of CDI followed by new symptoms associated with the presence of *Clostridium difficile* toxin in the stool.

### Checkpoint inhibitor-induced colitis

The definition of CIC lacks precision. According to the Common Terminology Criteria for Adverse Events v5.0 classification, CIC is defined as a disorder characterized by inflammation of the colon. In this study, the diagnosis of CIC was based on compatible clinical signs confirmed by histological/endoscopic lesions or resolution after treatment with general corticosteroids or infliximab.

### Study endpoints

The primary endpoint was the occurrence of CIC. Secondary endpoints were findings allowing us to describe the CDI: patient characteristics: melanoma, immunotherapy setting, endoscopic and histopathological features, risk factors for CDI, time to onset of CDI, treatment of CDI, and patient outcome.

### Statistical analysis

Median and mean results were calculated using Microsoft Excel, Albuquerque, New Mexico, USA.

## Results

### Occurrence of checkpoint inhibitor-induced colitis

The general characteristics of the patients are presented in Table 1.

Eighteen patients were enrolled. Eight (44.4%) were female. The average age of the population was 64.4 years ( $\sigma 14.1$ ). Six had isolated CDI and 12 CDI associated with CIC. Among those with CDI associated with CIC, eight had CIC followed by CDI (patients 1–8), three had both conditions concurrently (patients 9–11), and one had CDI followed by CIC (patient 12). Patients 13–18 had isolated CDI without CIC.

### Immunotherapy treatment

Seventeen patients were treated for unresectable or metastatic melanoma. The immunotherapies used are presented in Table 1 and consisted of nivolumab, pembrolizumab, ipilimumab, or combinations of nivolumab and ipilimumab or ipilimumab and TLR9 agonists. One

**Table 1 General patient characteristics**

Patient number	Age	Sex	Immunotherapy	Treatment regimen	Line of therapy	CIC
1	72	M	Pembrolizumab	2 mg/kg every 3 weeks	2	Yes
2	45	M	Ipilimumab	3 mg/kg every 3 weeks	1	Yes
3	62	F	Nivolumab	240 mg every 2 weeks	2	Yes
4	64	F	Ipilimumab	3 mg/kg every 3 weeks	3	Yes
5	69	M	Ipilimumab + TLR9 agonists	3 mg/kg every 3 weeks	2	Yes
6	70	F	Pembrolizumab	2 mg/kg every 3 weeks	3	Yes
7	70	M	Pembrolizumab	2 mg/kg every 3 weeks	2	Yes
8	70	M	Ipilimumab	3 mg/kg every 3 weeks	1	Yes
9	20	F	Ipilimumab + nivolumab	3 mg/kg + 1 mg/kg every 3 weeks	2	Yes
10	54	M	Ipilimumab + nivolumab	3 mg/kg + 1 mg/kg every 3 weeks	1	Yes
11	61	F	Ipilimumab + nivolumab	3 mg/kg + 1 mg/kg every 3 weeks	1	Yes
12	67	M	Pembrolizumab	2 mg/kg every 3 weeks	1	Yes
13	77	F	Pembrolizumab	200 mg every 3 weeks	1	Yes
14	57	M	Nivolumab	480 mg every 4 weeks	1	No
15	73	M	Pembrolizumab	2 mg/kg every 3 weeks	1	No
16	72	F	Pembrolizumab	2 mg/kg every 3 weeks	2	No
17	81	F	Nivolumab	3 mg/kg every 2 weeks	1	No
18	75	M	Nivolumab	3 mg/kg every 2 weeks	1	No

CIC, checkpoint inhibitor-induced colitis; F, female; M, male.

patient was treated with nivolumab in the adjuvant setting (patient 14).

**Characteristics of Clostridium difficile infection**

The characteristics of the CDI cases are presented in Table 2. The median time from the start of immunotherapy to CDI diagnosis was 2.8 months [interquartile range (IQR), 0.8–5]. For patients who presented with CIC followed by CDI, the median time between the two events was 2.9 months (IQR, 2.4–3.2). When CDI occurred, six of eight patients were treated with corticosteroid therapy. For patient 12, the time from CDI to CIC was 1.9 months. Fourteen patients (77.8%) required hospitalization for CDI.

**Endoscopic and histological findings**

Digestive endoscopy was performed on half of the patients, including eight flexible sigmoidoscopies and one colonoscopy. The digestive endoscopy was normal for three patients. Endoscopic lesions consisted of erythematous mucosa (four patients), erosions (one patient), ulcerations (two patients), and pseudomembranes (two patients). Seven patients underwent biopsies. Histopathological examination showed the presence of intraepithelial neutrophilic leukocytes (four patients), crypt abscesses (one patient), basal plasmacytosis (one patient), and lymphocytic colitis (one patient).

**Treatment of Clostridium difficile infection**

Information on the treatment of CDI for patients with CIC and those with isolated CDI is presented in Tables 3–6.

No patients required a colectomy for CDI. Three patients received a fecal transplant. Two patients had CDI recurrence.

**Patient outcomes and response to immunotherapy**

Among patients with CIC, 10 of 12 discontinued immunotherapy, eight because of digestive system toxicity. Among the patients with isolated CDI, three discontinued immunotherapy, one due to a complete response and two because of digestive system toxicity.

The tumoral response to immunotherapy was complete for five patients and partial for six. Six patients showed progression of the disease.

**Discussion**

We recovered the number of patients treated with immunotherapy for melanoma in six of the nine centers. In these centers, 2144 patients were treated with anti-PD-1 or anti-CTLA-4 immunotherapy. Among them, 11 had CDI. The prevalence of CDI among patients treated with immunotherapy was 0.5% in these centers.

**Table 2** *Clostridium difficile* infection characteristics

Patient number	Time from the start of immunotherapy to CDI (months)	Time from CIC to CDI (months)	Severity	Hospitalization	Use of antibiotherapy within 3 months before
1	6	3.2	Severe	Yes	No
2	2.1	1.9	Nonsevere	Yes	No
3	0.4	2.7	Severe	Yes	No
4	2.8	0.4	Nonsevere	Yes	Yes
5	3.6	2.5	Nonsevere	No	Yes
6	0.6	3.3	Nonsevere	No	Yes
7	6.33	5.3	Fulminant	Yes	Yes
8	3.3	3	Severe	Yes	Yes
9	0.2	0	Fulminant	Yes	Yes
10	1.1	0	Nonsevere	Yes	No
11	0.7	0	Nonsevere	Yes	No
12	21	-1.9	Nonsevere	No	Yes
13	2.8		Nonsevere	No	Yes
14	5.2		Nonsevere	Yes	No
15	2		Nonsevere	Yes	Yes
16	0.3		Nonsevere	Yes	Yes
17	4.2		Severe	Yes	Yes
18	15.8		Fulminant	Yes	Yes

CDI, *Clostridium difficile* infection; CIC, checkpoint inhibitor–induced colitis.

**Table 3** Characteristics of treatment of *Clostridium difficile* infection and checkpoint inhibitor–induced colitis for patients with checkpoint inhibitor–induced colitis complicated by *Clostridium difficile* infection

Patient number	First-line treatment	Therapeutic failure or recurrence	Second-line treatment	Therapeutic failure or recurrence
1	Metronidazole Corticosteroids for CIC	Therapeutic failure	Vancomycin Corticosteroids for CIC	No
2	Vancomycin Corticosteroids for CIC	No		
3	Vancomycin + metronidazole Corticosteroids for CIC	Therapeutic failure	Infliximab for CIC	No
4	Metronidazole Corticosteroids for CIC	Therapeutic failure	Vancomycin Corticosteroids for CIC	No
5	Vancomycin Corticosteroids for CIC	No		
6	Metronidazole	Recurrence	Fidaxomicin	No
7	Metronidazole Corticosteroids for CIC	No		
8	Metronidazole	No		

CIC, checkpoint inhibitor–induced colitis.

**Table 4** Characteristics of treatment of *Clostridium difficile* infection and checkpoint inhibitor–induced colitis for patients with concurrent *Clostridium difficile* infection and checkpoint inhibitor–induced colitis

Patient number	First-line treatment	Therapeutic failure or recurrence	Second-line treatment	Therapeutic failure or recurrence	Third-line treatment	Therapeutic failure or recurrence
9	Vancomycin + metronidazole	Therapeutic failure	Fidaxomicin Corticosteroids for CIC	Therapeutic failure	Infliximab for CIC	No
10	Vancomycin Corticosteroids for CIC	Therapeutic failure	Infliximab for CIC	Therapeutic failure	Fecal transplant	No
11	Vancomycin Corticosteroids for CIC	Therapeutic failure	Infliximab for CIC	Therapeutic failure	Fecal transplant	No

CIC, checkpoint inhibitor–induced colitis.

**Table 5** Characteristics of treatment of *Clostridium difficile* infection and checkpoint inhibitor–induced colitis for the patient with *Clostridium difficile* infection followed by checkpoint inhibitor–induced colitis

Patient number	First-line treatment	Therapeutic failure or recurrence	Second-line treatment	Therapeutic failure or recurrence	Third-line treatment
12	Metronidazole	Therapeutic failure	Vancomycin Corticosteroids for CIC	Therapeutic failure	Infliximab for CIC

CIC, checkpoint inhibitor–induced colitis.

The main immunotherapy reported was ipilimumab (as monotherapy or in combination with nivolumab) when CDI was associated with CIC. No patient had received ipilimumab in the subgroup with isolated CDI. This result is consistent with those in the literature: CIC occurs more frequently with the use of anti-CTLA-4 than anti-PD-1 agents [13].

The time between the introduction of immunotherapy and the occurrence of CDI varied from a few days to almost 2 years. When CIC occurred, the time from CIC to CDI also varied from a few days to approximately 5 months. In the general population, the main risk factor for CDI is recent antibiotic exposure [28–31]. In our cohort study, most of the patients had been exposed to antibiotics in the

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**Table 6 Characteristics of treatment of *Clostridium difficile* infection among patients with isolated *Clostridium difficile* infection**

Patient number	First-line treatment	Therapeutic failure or recurrence	Second-line treatment	Therapeutic failure or recurrence	Third-line treatment	Therapeutic failure or recurrence
13	Metronidazole	No				
14	Vancomycin	Therapeutic failure	Fidaxomicin	Therapeutic failure	Tigecycline + teicoplanin	No
15	Vancomycin	No				
16	Vancomycin	No				
17	Vancomycin + metronidazole	Therapeutic failure	Vancomycin	Therapeutic failure	Fecal transplant	No
18	Fidaxomicin	Recurrence	Fidaxomicin	No		

three previous months. Three patients developed fulminant CDI and all three had received antibiotic therapy in the three previous months. In the general population, 3–8% of CDI cases are fulminant [32], which is lower than in our study. It, therefore, appears to be important to assess the risk-benefit of prescribing antibiotics in this population.

More patients had been exposed to antibiotic therapy in the three previous months in the subgroup with isolated CDI than in the subgroup with associated CIC. CIC may be a contributing factor for CDI. CDI should be considered, even in the absence of recent antibiotic exposure.

The most frequently used antibiotic treatment was metronidazole because most patients were treated before 2018. Based on current recommendations, either vancomycin or fidaxomicin has been recommended over metronidazole for an initial episode of CDI since 2018 [27,33,34].

Among patients with CIC complicated by CDI, two recovered with antibiotic therapy alone. Most (nine of 11 patients) received immunosuppressive therapy (systemic corticosteroids or infliximab). For CIC resistant to corticosteroids, infliximab, vedolizumab, and fecal transplantation showed efficacy for three patients. Treatment by fecal transplantation results in a 91% cure rate after 1 month in the general population [35]. When CDI and CIC occur concurrently, treatment is more difficult and requires several lines of therapy (Table 7).

### Review of the literature

The first reported case of CDI with immunotherapy was published in 2015 by Gupta *et al* [22]. The patient was 72 years of age and received ipilimumab and nivolumab for high-grade non-Hodgkin's lymphoma. A second case was published in 2015 [23]. The patient was 65 years of age and received ipilimumab for stage III unresectable melanoma. A third observation was published in 2019 [24]. The patient was 59 years of age and received pembrolizumab, pemetrexed, and carboplatin for metastatic nonsmall-cell lung cancer. All three patients had diarrhea with a positive test for *Clostridium difficile*. Antibiotic therapy had no effect. The patients recovered with the introduction of corticosteroids.

Del Castillo *et al.* [36] published a study in 2016 on 740 patients treated with immunotherapy for metastatic

melanoma, reporting the incidence of severe infections. Ten patients presented with severe CDIs.

In December 2019, Babacan and Tanvetyanon [25] published a five-case series of superimposed CDI during CIC. The patients had carcinoma of the lung (large cell neuroendocrine and adenocarcinoma). The reported immunotherapy was tremelimumab and durvalumab, nivolumab, durvalumab, and tremelimumab monotherapies. Four patients had CIC complicated by CDI and one patient had CDI followed by CIC, then recurrent CDI. For this patient, as for patient 12 in our study, CDI may reveal CIC. Most patients had no antibiotic therapy before CDI, strengthening the hypothesis that CIC may be a contributing factor to CDI.

As mentioned in the introduction, CIC shares clinical, endoscopic, histological, biological, and therapeutic similarities with IBD [14,37,38]. Intestinal inflammation and significant alterations in the gut microbiota, as observed in both IBD and CIC, are associated with increased colonization and infection with opportunistic microorganisms such as *Clostridium difficile*. Among patients with IBD, the incidence of CDI is higher than in the general population [21,39]. In our cohort, the incidence of CDI among patients with CIC was also higher than that of the general population. Our results show that endoscopic and histological features were nonspecific for the differentiation of CIC from CDI. Only two patients with CDI had pseudomembranes on endoscopy, as for IBD.

In the IBD population, patients with CDI show a more severe disease course than in the general population: long hospitalization, colectomy, and death [39]. CDI is recognized as a surrogate marker of disease severity. In our population, we had a large proportion of hospitalizations but no colectomies or death.

Our observation suggests that CDI may complicate or reveal CIC. Active IBD predisposes patients to CDI due to alterations in the gut microbiome. *Clostridium difficile* is a toxin-producing bacterium that leads to worsening of the underlying IBD [40]. The exact pathogenic role of *Clostridium difficile* is not yet known in IBD. *Clostridium difficile* may cause isolated infectious colitis superimposed on IBD, or conversely, may precipitate an IBD flare-up, leading to two separate but

**Table 7 Outcome of patients**

Patient number	Continuation or discontinuation of immunotherapy	Reason of discontinuation	Response to immunotherapy
1	Discontinuation	Digestive toxicity	Complete response
2	Discontinuation	Progression	Progression
3	Discontinuation	Progression	Progression
4	Discontinuation	Progression	Progression
5	Discontinuation	Digestive toxicity and progression	Progression
6	Discontinuation	Digestive toxicity	Partial response
7	Continuation		Progression
8	Continuation		Partial response
9	Discontinuation	Digestive toxicity	Partial response
10	Discontinuation	Digestive toxicity	Lack of data
11	Discontinuation	Digestive toxicity	Partial response
12	Discontinuation	Digestive toxicity	Partial response
13	Discontinuation	Digestive toxicity	Complete response
14	Continuation		Partial response
15	Discontinuation	Digestive toxicity	Complete response
16	Continuation		Progression
17	Continuation		Progression
18	Discontinuation	Complete response	Complete response
	Discontinuation	Complete response	Complete response

simultaneous inflammatory processes. A third mechanistic possibility may be that IBD flare-ups occur independently of *Clostridium difficile*, which is merely a colonizer [41]. Conversely, IBD is a risk factor for the development of CDI [40] and this may also be true for CIC.

There are currently no guidelines for the treatment of CDI in IBD. A number of authors have proposed the initiation or resumption of immunosuppressive therapy within 48–72 h of starting antibiotic therapy [29,40]. The same management of CDI complicating CIC could be reasonably proposed.

**Strengths and limitations of the study**

Despite its population of only 18 patients, this is the largest cohort study of CDI with immunotherapy in patients with melanoma. The cohort consisted of patients from multiple centers. The other limitation was the absence of a control group. This study was also subject to a recall bias and a center effect.

**Conclusion**

Among patients treated with immunotherapy, CDI can occur alone or in association with CIC. CDI appears to reveal CIC, and CIC appears to predispose patients to CDI.

Testing for *Clostridium difficile* should always be performed for patients treated with immunotherapy who present with diarrhea. CDI in patients receiving immunotherapy can be severe, with three fulminant cases in this study. The treatment of concurrent CDI and CIC is challenging but can rely on the results of studies performed on IBD populations that support the initiation or resumption of immunomodulators within 48–72 h of starting antibiotic therapy.

With the increasing use of immunotherapy and the increasing frequency of CDI, further studies are needed to understand the link between CDI and CIC.

**Acknowledgements**

**Conflicts of interest**

There are no conflicts of interest.

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