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ORIGINAL ARTICLE

Nivolumab-induced immune-mediated colitis: an ulcerative colitis look-alike—report of new cases and review of the literature

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Abstract

Purpose Nivolumab, a monoclonal antibody-targeting programmed cell death protein-1, is being increasingly used for the treatment of some advanced neoplasms. Several of its adverse effects are a result of the upregulation of T cells, with colitis as one of the most severe, and a challenging differential diagnosis with ulcerative colitis. However, few real-life clinical practice cases have been reported beyond trials. Our aim was to report a series of new cases, reviewing previously communicated endoscopic-proven nivolumab-induced colitis.

Method All patients treated with nivolumab in three university centers were identified and those who developed immune-mediated colitis (defined as the presence of diarrhea and evidence of colitis demonstrated by colonoscopy) were described. Additionally, a review of case reports of nivolumab-induced colitis reported in the literature up to March 2018 was performed.

Results Six new cases of nivolumab-induced colitis and 13 previously reported cases out of randomized clinical trials are described. Colonoscopy showed a mucosal pattern mimicking ulcerative colitis in a large proportion of patients. Clostridium difficile superinfection was observed in two out of 19 cases. All but three patients definitively discontinued nivolumab therapy. Most patients were initially managed with oral or intravenous corticosteroids, but five of them required rescue therapy with infliximab.

Conclusions Nivolumab-induced colitis may mimic ulcerative colitis. Steroid therapy (oral or intravenously) is often efficient, but one-fourth of patients need rescue therapy with anti-TNF. Intestinal superinfection with *Clostridium difficile* or cytomegalovirus should be ruled out before starting immunosuppressive therapy.

Keywords Immune-mediated colitis · Nivolumab · Corticosteroids · Colonoscopy · Pathology

Introduction

Immune checkpoint inhibitors are monoclonal antibodies against regulatory molecules that inhibit T cell activation, consequently releasing cytotoxic T cells to target cancer cells [1, 2]. This new class of therapies is increasingly used in advanced cancers. However, they upregulate T cell function and thereby, result in misdirected stimulation of the immune system in non-cancerous tissue [3]. Therefore, they can induce a sort of adverse effects collectively known as immune-related adverse events that include colitis, hepatitis, pneumonitis, and hypothyroidism [4]. Among the immune checkpoint inhibitors, nivolumab is a fully human IgG4 monoclonal antibody targeting programmed cell death protein 1 (PD-1), approved for advanced melanoma, non-small cell lung cancer, Hodgkin's lymphoma, and bladder urothelial cancer [3, 5]. Anti-PD-1 drugs are overall less toxic than standard chemotherapy and other immune checkpoint inhibitors (i.e., ipilimumab) [6, 7]. Moreover, it has been recently described that immuno-histopathological characteristics of immune checkpoint inhibitor-induced colitis

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are distinct regarding the causative agent (anti-PD1 or anti-CTLA-4) [8], although mainly described in patients treated with anti-CTLA4.

Nivolumab-induced immune-mediated colitis (NV-IMC) has been described from randomized clinical trials (RCT) [6, 9], but scarcely reported in clinical practice. In a systematic review of case reports of adverse events associated with immune checkpoint blockade published in 2016 [10], no cases of NV-IMC were found. Our aim was to describe the prevalence in clinical practice and detailed features of NV-IMC in our cohort, as well as to review all reported cases in the literature outside RCT.

Methods

Description of new cases

All patients treated with nivolumab from June 2014 to July 2016 in three referral centers were identified from the Oncology Departments and Hospital Pharmacy databases at each hospital. Nivolumab was administered by intravenous infusion every 2 weeks at a dose of 3 mg/kg of body weight. Drug-induced diarrhea is usually classified in Oncology as diarrhea, colitis, or enterocolitis, by means of the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE) [11]. However, this grading system fails to distinguish between inflammatory and non-inflammatory origin, as well as to define the location of the involved gastrointestinal segment. Therefore, for the study purposes, we only included patients with diarrhea or bloody diarrhea with or without abdominal pain, and evidence of colitis demonstrated by endoscopic inflammation (NV-IMC).

Severity of diarrhea was graded based on the CTCAE criteria into grade 1 (increase of < 4 stools/day over baseline), grade 2 (increase of 4–6 stools/day over baseline, blood in stool, and abdominal pain), grade 3 (increase of > 6 stools/day over baseline, fever, severe abdominal pain, and peritoneal signs), and grade 4 (life-threatening consequences and urgent intervention indicated) [11]. The study was approved by the local Ethics Committee of the coordinating center (Hospital Universitari Germans Trias I Pujol).

Literature review

We searched PubMed for case reports about NV-IMC by the combination of medical subject heading terms "nivolumab," "colitis," or "diarrhea." Only those cases published as full articles out of RCT and available endoscopic evidence of colitis were included in the review.

Results

Description of new cases

In all, six patients developed endoscopy-proven NV-IMC among 122 patients treated with nivolumab (5%). A case-by-case detailed description of the main demographic, clinical, endoscopic, and histological characteristics is shown in Tables 1 and 2. Globally, most patients were male with advanced lung cancer. Only one patient was treated concomitantly with ipilimumab in addition to nivolumab (case 5). Diarrhea developed after a minimum of 1 and a maximum of 19 nivolumab infusions. All patients had marked increase of C-reactive protein (CRP) levels (median 62 mg/L, range 13–192 mg/L), and five required hospital admission. Three patients showed extensive colonic involvement (beyond the splenic flexure) at colonoscopy. Mucosal alterations were mainly continuous (5 out of 6), including edema and erythema in all cases, and mucosal ulcerations in half of them.

All patients were initially treated with systemic corticosteroids (prednisolone 1 mg/kg daily or equivalent), four of them by oral route and 2 intravenously. One patient relapsed and was switched from oral to intravenous corticosteroids. Two additional patients required a second course of corticosteroids because of refractoriness, one of them finally being treated with infliximab (three infusions). Of note, two patients had intestinal superinfections at the time of NV-IMC diagnosis (one *Clostridium difficile* and one colic reactivation of cytomegalovirus as seen by immunohistochemistry); they were both treated with corticosteroids after unsuccessful specific treatment with metronidazole and valganciclovir (cases 4 and 3, respectively). Moreover, a case of extensive NV-IMC developed in a patient with a quiescent long-standing ulcerative proctitis (case 4). Nivolumab was reintroduced in only two patients (cases 2 and 5), with mild diarrhea reappearing in one of them, but easily controlled with loperamide. No endoscopic assessment was performed after achieving clinical response in none of the patients.

Description of previously reported cases in the literature

Thirteen cases of NV-IMC [12–19] with endoscopy-proven colonic inflammation have been previously reported and are summarized also in Tables 1 and 2. Two patients were treated with ipilimumab in addition to nivolumab (cases 12 and 13). Diarrhea developed mostly after 6 to 18 nivolumab infusions (range, 2–70). CRP levels were not available in most of these case reports. Endoscopic description was not fully available in some of the cases. Extensive colitis was the most frequent phenotype, although segmentary colitis was also observed. All cases but two (treated with mesalazine and loperamide) were treated with corticosteroids. Three patients relapsed

Table 1 Detailed description of clinical and demographical characteristics of patients with nivolumab-related immune-mediated colitis

Reference	Case	Gender/age	Cancer	Nivolumab infusions until diarrhea	Grade of diarrhea	Hospital admission	C. difficile	CRP levels (mg/L)
Current series	1	M/65	Lung	4	3	Yes	Negative	13.3
	2	M/60	Lung	6	2	No	Negative	18.9
	3	M/64	Lung	1	2	Yes	Negative	62.0
	4	M/65	Lung	5	3	Yes	Positive	191.8
	5	F/50	Melanoma	4	3	Yes	Negative	106.9
	6	M/59	Lung	19	3	Yes	Negative	113
Bergqvist et al. [12]	7	M/55	Lung	18	3	NA	Negative	NA
Gondal et al. [13]	8	F/42	Melanoma	3	NA	Yes	Positive	NA
Fujii et al. [14]	9	F/82	Melanoma	6	3	Yes	NA	230
González et al. [15]	10	F/75	Lung	17	NA	NA	NA	NA
	11	M/78	Urothelial	17	NA	NA	NA	NA
	12	M/47	Melanoma	3	NA	NA	NA	NA
	13	F/66	Melanoma	2	NA	NA	NA	NA
	14	M/58	Oral squamous	7	NA	NA	NA	NA
	15	M/67	Lung	7	NA	NA	NA	NA
Kubo et al. [16]	16	M/82	Lung	7	3	NA	NA	NA
Yanai et al. [17]	17	M/51	Melanoma	4	3	Yes	NA	3.3
Iyoda et al. [18]	18	M/62	Lung	18	3	Yes	NA	NA
Yasuda et al. [19]	19	M/62	Lung	70	3	Yes	Negative	NA

M, male; *F*, female; *CRP*, C-reactive protein; *NA*, not available

while steroid tapering or discontinuation, two of them successfully retreated with IV corticosteroids. Five patients were steroid-refractory; one of them initially treated with oral corticosteroids responded to the IV route and two patients to infliximab therapy. Two additional patients were also refractory to infliximab and finally responded one to vedolizumab and the other one to the addition of oral cyclosporine. As in our own series, one superinfection by *C. difficile* occurred concomitantly to NV-IMC. Additionally, one patient had a history of Crohn's disease that was in endoscopic remission at the time nivolumab was started (case 7).

Nivolumab was reintroduced in two patients (cases 9 and 18), one of them with NV-IMC relapse (case 18).

Discussion

Immune-mediated colitis is a well-known adverse effect induced by immune checkpoint inhibitors. However, it has been scarcely described in nivolumab-treated patients, in whom a lower incidence is suspected after meta-analysis of randomized clinical trials (1–1.3%) [6, 9, 20]. In our small cohort of patients in clinical practice, and despite our requirement for a strict, endoscopy-proven case definition, we observed a significant prevalence, reaching 5%. Recently, Wang et al. reported all the immune checkpoint inhibitor-related colitis from the University of Texas MD Anderson Cancer Center until March 2017; of note, none of the 53 reported cases was related to nivolumab alone, and only 9 out of 53 received nivolumab in combination to ipilimumab, suggesting that the prevalence of NV-IMC is lower than with other immune checkpoints [21]. The real prevalence may be higher, because we chose to exclude cases with mild diarrhea (in whom colonoscopy was probably avoided), and those with diarrhea and a normal colonoscopy. We find it useful to differentiate diarrhea (mere passage of loose, frequent stools) from colitis (inflammation of the colon leading to diarrhea, abdominal pain, rectal bleeding with endoscopic findings of colonic inflammation or when imaging findings confirm large bowel inflammation) in these patients, since their management is usually different [22, 23].

Our study was not designed to assess risk factors of development of NV-IMC, and many potential epidemiologic risk factors were missed. Given the high proportion of patients with lung cancers, most of the patients developing NV-IMC were male as expected. It is noteworthy that two out of 19 patients had a past history of inflammatory bowel disease. Larger series would be needed to ascertain if inflammatory bowel disease represents a risk factor for NV-IMC.

Table 2 Detailed description of endoscopic and histological features, and treatment outcomes of patients with nivolumab-related immune-mediated colitis

Reference	Case	Endoscopic findings			Histopathological findings		Treatment	Outcome
		Extent	Type of involvement	Ulcers	LP infiltrate	Cryptic abscesses		
Current series	1	Left-sided	Patchy	No	Yes	No	OC	Resolution but relapse (resolution with IVC)
	2	Left-sided	Continuous	No	Yes	Yes	OC	Resolution
	3	Left-sided	Continuous	Yes	Yes	No	OC	Resolution
	4	Extensive	Continuous	No	Yes	No	OC	Refractoriness (resolution with IVC)
	5	Extensive	Continuous	Yes	Yes	No	IVC	Resolution
	6	Extensive	Continuous	Yes	Yes	Yes	IVC	Refractoriness (resolution with IFX)
Bergqvist et al. [12]	7	NA	NA (moderate)	NA	Yes	NA	C	Refractoriness (do not response to IFX, but resolution with vedolizumab)
Gondal et al. [13]	8	Left-sided	Continuous	Yes	Yes	NA (apoptotic bodies)	IVC	Resolution
Fujii et al. [14]	9	Extensive	Continuous	No	Yes	NA	IVC	Resolution but relapse (resolution with IVC)
González et al. [15]	10	Left-sided	Continuous	No	NA	NA	C	Resolution
	11	Extensive	Continuous	Yes	NA	NA	C	Resolution
	12	Extensive	Continuous	No	NA	NA	C	Resolution
	13	Right colon	Patchy	No	NA	NA	C	Resolution
	14	NA	Continuous	No	NA	NA	C	Resolution and relapse
	15	Sigmoid	NA	NA	NA	NA	Loperamide	Death
Kubo et al. [16]	16	Left-sided	Continuous	No	Yes	Yes	Mesalazine	Resolution
Yanai et al. [17]	17	Extensive	Continuous	No	Yes	Yes (apoptotic bodies)	IVC	Refractoriness (resolution with IFX)
Iyoda et al. [18]	18	Extensive	Continuous	No	NA	NA	IVC	Refractoriness (no response to IFX, but resolution with cyclosporine + IFX)
Yasuda et al. [19]	19	Sigmoid	NA	No	Yes	Yes	IVC	Resolution

LP, lymphoplasmocytic; *C*, corticosteroids; *OC*, oral corticosteroids; *IVC*, intravenous corticosteroids; *IFX*, infliximab

In relation to endoscopic findings, lesions were distributed continuously, as described in ulcerative colitis (UC). The most frequent were erythema, edema, loss of vascular pattern, erosions, and ulcerations. This might be of interest for differential diagnosis, especially in patients with a past history of UC. As it has been recently described, the detection of apoptotic bodies in the colonic biopsies could suggest the diagnosis of immune-mediated colitis [24]. Moreover, it should be reminded that intestinal superinfections might be present in patients with NV-IMC, leading to initial underdiagnosis.

According to algorithms developed for immune-mediated colitis [24, 25], most of the patients were initially treated with oral or intravenous corticosteroids. Up to one-fourth of them did not respond and were treated with rescue therapy, mainly infliximab. Only one patient received vedolizumab as a third-line therapy, a drug that has been theoretically supposed to be more appropriate for immune-mediated colitis by some authors [26]. However, it has been described that patients who develop corticosteroid resistance have higher mucosal TNFα, suggesting that anti-TNF agents should be a suitable drug [8]. The small sample size of our global series does not allow finding predictive factors of response to corticosteroids; however, all refractory patients had extensive colic involvement. Again, it seems to be important to rule out intestinal superinfections in these patients before escalating therapy. Finally, nivolumab was discontinued in all patients at the time of NV-IMC diagnosis, and only reintroduced in three cases, which does not allow drawing conclusions.

In summary, we describe the clinical course, endoscopic and histological features, and outcome of NV-IMC. Given the increasing use of immune-based therapies, it is expected that the occurrence of immune-mediated gastrointestinal adverse effects will become more frequent. Therefore, gastroenterologists should be aware of the growing burden and diagnostic difficulties of this condition, particularly in the most severe forms of colitis, in order to optimize treatment and rule out the most common associated complications.

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Compliance with ethical standards

The study was approved by the local Ethics Committee of the coordinating center (Hospital Universitari Germans Trias I Pujol).

Conflict of interest The authors declare that they have no conflict of interest.

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