Poster P509 – "Autoimmune bullous dermatoses in cancer patients treated by immunotherapy: a literature review and Italian multicentric experience"

Martina Merli*, Martina Accorinti, Maurizio Romagnuolo, Angelo Marzano, Giovanni Di Zenzo, Francesco Moro, Emiliano Antiga, Roberto Maglie, Emanuele Cozzani, Aurora Parodi, Giulia Gasparini, Pietro Sollena, Clara De Simone, Marzia Caproni, Luigi Pisano, Davide Fattore, Riccardo Balestri, Paolo Sena, Pamela Vezzoli, Miriam Teoli, Marco Ardigò, Camilla Vassallo, Andrea Michelerio, Rosanna Rita Satta, Emi Dika, Barbara Melotti, Simone Ribero and Pietro Quaglino (*corresponding author: email merlimartina93@gmail.com; affiliation Dermatology Clinic, Department of Medical Sciences, University of Turin, Turin, Italy)

Background. Immune checkpoint inhibitors (ICIs) have introduced a significant innovation in the treatment of various malignancies, including melanoma, as their mechanism of action enhances the immune system's response against cancer. However, this immune activation is not specific and can impact numerous organ systems, leading to the so-called immune-related adverse events (irAEs) in up to 70% of treated patients. The skin is the most involved organ and, among cutaneous irAEs, immunobullous eruptions have been increasingly reported in the literature. The estimated overall incidence varies from 1% to 5% and bullous pemphigoid(BP)-like eruption is the predominant phenotype.

Bullous irAEs represent a therapeutic challenge for clinicians because they might result in significant morbidity and mortality if untreated. Moreover, immunosuppressive systemic therapies and/or ICI interruption are often required to reach adequate control of the cutaneous involvement resulting in a worsening of the cancer prognosis.

Methods. We conducted a case series based on a national multicentre, retrospective, observational cohort including all patients treated with ICIs and who developed an immunobullous cirAE during treatment. Furthermore, we compared our data with the English-language medical literature concerning immunobullous cirAEs.

Results. The multicentre cohort included 45 patients who developed an ICI-induced immunobollous eruption during treatment (Table). In all cases, they developed a BP-like eruption. Forty-one patients (91%) were male, and the median age was 74 years. Nivolumab was identified as the causative drug in 62% of cases and, among these patients, immunotherapy was administered for the treatment of melanoma in 27% of cases. The median time to onset of cutaneous symptoms after ICI initiation was 35 weeks, while the median time to BP diagnosis was 48 weeks. In 19 patients (42%) pruritus without any cutaneous eruption was the first clinical manifestation, while bullous lesions appeared since the beginning in 9 patients (20%). According to CTCAE grading for bullous dermatitis, BP affected more than 30% of the body surface in 40% of patients. The first-line therapy of the cutaneous toxicity was topical steroids in 4 patients (9%), topical and systemic steroids in 41 (91%). In 18% of cases a second-line therapy was needed such as doxycycline and dapsone. Immunotherapy was permanently discontinued for 17 patients (38%), while it was temporarily held for 16 patients (36%) of which about 50% experienced a relapse after rechallenging with the same ICI.

Characteristics	All patients (N=45)
Demographics	
Sex, No. (%) male / female	41 (91) / 4 (9)
Age (years), median (range)	74 (46 - 90)
Tumour type	**No. (%)**
NSCLC	18 (40)
Melanoma	12 (27)
Colorectal adenocarcinoma	5 (11)
Renal clear cell carcinoma	5 (11)
HNSCC	4 (9)
Urothelial carcinoma	1 (2)
Tumour stage	**No. (%)**
Stage IV	33 (73)
Stage III	9 (20)
Other or NR	3 (7)
Immunotherapy	**No. (%)**
Nivolumab	28 (62)
Pembrolizumab	11 (24)
Nivolumab + ipilimumab	2 (5)
Cemiplimab	2 (5)
Spartalizumab	1 (2)
Atezolizumab	1 (2)
ICI-BP features	**Median (range)**
Time to symptoms onset after ICI initiation (weeks)	35 (4 - 260)
Time to BP diagnosis after ICI initiation (weeks)	48 (5 - 286)
First manifestations	**No. (%)**
Pruritus without other manifestations	19 (42)
Eczematous eruption	11 (24)
Bullous lesions	9 (20)
Urticarial eruption	7 (16)
Mucositis	3 (7)
Papular lesions	1 (2)
Mucosal membrane involvement	**No. (%)**
No	37 (82)
Yes	8 (18)
CTCAE grade	**No. (%)**
1	12 (27)
2	15 (33)
3	17 (38)
4	1 (2)

Characteristics	All patients (N=45)
ICI-BP diagnosis	
Histopathologic examination	**No. (%)**
Yes	28 (62)
No	17 (38)
DIF	**No. (%)**
Yes	31 (69)
No	14 (31)
IIF	**No. (%)**
Yes	26 (58)
No	19 (42)
BP180 autoantibodies	**No. (%)**
Positive	30 (66)
Negative	12 (27)
Not performed	3 (7)
BP230 autoantibodies	**No. (%)**
Positive	15 (33)
Negative	26 (58)
Not performed	4 (9)
ICI management	No. (%)
ICI temporarily held	16 (36)
BP flare after rechallenged with the same ICI	7 (16)
ICI permanently discontinued	17 (38)
ICI-BP management	
First line therapy	**No. (%)**
Topical costicosteroid	4 (9)
Topical corticosteroid + systemic corticosteroid	41 (91)
Second line therapy	**No. (%)**
Doxycycline	5 (11)
Dapsone	3 (7)
Third line therapy	**No. (%)**
Dupilumab	1 (2)
ICI-BP response	**No. (%)**
Partial to complete resolution	38 (84)
Refractory symptoms	7 (16)
Tumour response	**No. (%)**
CR or PR	9 (20)
SD	16 (36)
PD	11 (24)
NR	9 (20)

TABLE. Abbreviations: ICI, immune checkpoint inhibitor; BP, bullous pemphigoid; NSCLC, non-small-cell lung cancer; HNSCC, head and neck squamous cell carcinoma; NR, not reported; CTCAE, Common Terminology Criteria for Adverse Events; DIF, direct immunofluorescence; IIF, indirect immunofluorescence; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease.

Discussion and conclusion. Bullous autoimmune dermatoses are uncommon cirAEs and, in the literature, the BP-like eruption is the predominant phenotype reported. BP is characterized by the formation of large, tense blisters on the skin and mucous membranes, accompanied by intense itching and redness. Data collected in our case series confirm what has already been described in the literature regarding ICI-induced BP. Unlike classic BP (not ICI-induced), there is a male predominance, which has been attributed to potential gender-specific effects on immunotherapy activity. Moreover, ICI-BP tends to manifest at a younger age compared to the classic type. BP-like eruptions have been most frequently reported in patients receiving anti-PD-1/PD-L1 antibodies for melanoma and lung cancers, and it typically appears later than other cirAEs. It is often preceded by a long prodromal phase characterized by persistent pruritus and/or non-specific dermatitis. In fact, there is a significantly longer delay from symptom onset to diagnosis in ICI-BP compared to the classic form, despite similar delays from symptom onset to dermatology referral. Due to its moderate-to-severe clinical presentation and delayed diagnosis, it often necessitates discontinuation of immunotherapy and treatment with oral/intravenous corticosteroids to manage the cutaneous toxicity. Although several studies have suggested an association between the development of ICI-BP and improved cancer outcomes, it is not possible to confirm this theory based on the heterogeneous information collected. In published literature, other bullous cirAEs like pemphigus are mentioned only anecdotally, but this could further diversify the clinical manifestations of these cirAEs, representing a challenge for the clinician. Therefore, the dermatological referral is necessary to establish as soon as possible an appropriate therapy to control the cutaneous toxicity avoiding a negative impact on cancer outcome.

Main references:
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