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Letter to the Editor

Grover's disease in oncologic patients: clinicopathologic features and systematic review

Dear Editor,

The pathogenesis of Grover's disease (GD) is unclear despite recent evidence suggesting that it may involve an overexpression of interleukin 4(IL-4).[1] To date, an association between GD and malignancies, as well as between GD and systemic oncologic treatments, has been sporadically reported in the literature. However, considering that GD has been observed in association with various conditions (e.g., ultraviolet rays, heat, excessive sweating, infection), it is not always easy to associate the onset of GD with a specific trigger. Two hundred fifty-seven articles were retrieved from PubMed and 594 from Ovid (EMBASE, Scopus, and Web of Science). After removing duplicate studies (n = 564), 287 articles were selected, and a final number of 20 articles reporting a total of 31 patients were included in this systematic review, as summarized in Table 1. The median age was 65 years, with a male prevalence. All GD cases were metachronous to the

Table 1 Clinicopathologic features and baselines

	***n* (%)**
Gender	
M	23 (74)
F	8 (26)
Age	65 (–)
Anatomic area	
Back	24 (77)
Chest	20 (65)
Limbs	16 (52)
Head/neck	2 (6)
Clinical aspects	
Papules	29 (94)
Vesicles	16 (52)
Blister	1 (3)
Excoriation	10 (32)
Histology	
Eosinophils	5 (16)
Lymphocytic infiltrate	9 (29)
Necrotic keratinocytes	1 (3)
Acanthosis	3 (10)
Suprabasal acantholysis	19 (61)
Dyskeratotic keratinocytes	12 (39)
Parakeratosis	3 (10)
Comorbidities	
Internal	2* (6.5)
Dermatologic	3† (9)
TGD	8.4 ys (–)
Primary malignancy‡	
Solid tumor n = 14	50
Melanoma	6
Renal	2
Lung	2
Cutaneous SCC	1
UP adenocarcinoma	1
Breast	1
Colon	1
Hematologic n = 14	
Leukemia	9 (50)
Myeloma	3
Lymphoma	1
Unknown hematologic disease	1
Oncologic treatment	
Immunotherapy	8 (28.6)
Cytarabine	2 (7)
Cyclophosphamide	2 (7)
Hydroxyurea	2 (7)
Daunorubicin	2 (7)
Etoposide	2 (7)
Interleukin-4	3 (11)
Not specified	1 (3.6)
Radiotherapy	1 (3.6)
Other	8 (28.6)
TGDT	14.5 ds (–)
Grover therapy	
Topical steroids	12 (39)
Systemic steroids	2 (6)
Spontaneous resolution	17 (55)
Suspension of oncologic therapy	
Yes§	5 (16)
No	26 (84)

UP adenocarcinoma, adenocarcinoma of unknown primary origin; SCC, squamous cell carcinoma; TGDT, median time from the start of oncologic therapy and the onset of GD; TGD, time from the diagnosis of the malignancy to the development of Grover disease (GD).

*One patient with hypertension, one patient with a transitory ischemic attack (TIA).

†Three cases of bullous pemphigoid.

‡The site of the primary malignancy was reported in 28 cases (28/31; 90%).

§One patient suspended vemurafenib definitively; one patient stopped ipilimumab to switch to pembrolizumab, but due to the disease progression, returned to ipilimumab; however, the GD worsened, and the patient died due to the malignancy; one patient stopped anastrozole, and subsequently GD improved; finally in two patients, GD improved after the suspension of the oncologic treatment but it was no specified if after the suspension of the treatment the patient switched to another oncologic therapy.

primary tumor. Metastatic melanoma[2] (21%) and hematologic malignancies[3] (50%) were the malignancies more strongly associated with GD, while immunotherapy[2,4] (28.6%) was the most common observed oncologic treatment. Bullous pemphigoid (BP) was the most commonly associated cutaneous disease.[1] Regarding histological features, all cases showed typical histological aspects of GD. However, eosinophilic infiltration (16%), lymphocytic infiltrate (29%), and necrotic keratinocytes (3%) were also observed in some cases.[1–4] The median time between the start of the treatment for the primary malignancy and the onset of GD was 14.5 days. When reported (8/31; 26% of cases), median survival from GD diagnosis to death and/or last follow-up was 6 months (ranging between 15 days and 36 months). Only in five cases (16%) was the oncologic treatment stopped due to the onset of GD. Regarding the treatment of GD, 12 patients applied topical steroids, while two patients took systemic steroids; spontaneous resolution was observed in the remaining 17 patients. From our institution, we collected a total of 4 GD cases that arose after an oncologic diagnosis. They were all male patients, with a median age of 72 years (ranging between 68 and 75), with the main clinicopathologic features and related treatments reported in Figure 1a–f.

The median age of GD onset in oncologic patients and the gender distribution are similar to GD in healthy populations.[1] In this regard, increased sweating and bed rest in this class of patients (especially oncological) could explain this association. Among malignancies, melanoma, and hematologic malignancies were the most represented[2,3]; all cases of GD were metachronous to the primary tumor and arose after the initiation of oncologic treatment, above all, immunotherapy.[4] Most likely, immunotherapy (as well as other oncologic treatments) induces an alteration in the homeostasis of the immune system, causing the onset of GD in some patients.[1–4] Regarding dermatologic comorbidities, BP was the most common. As reported by Kahazaeli *et al.*,[1] the two

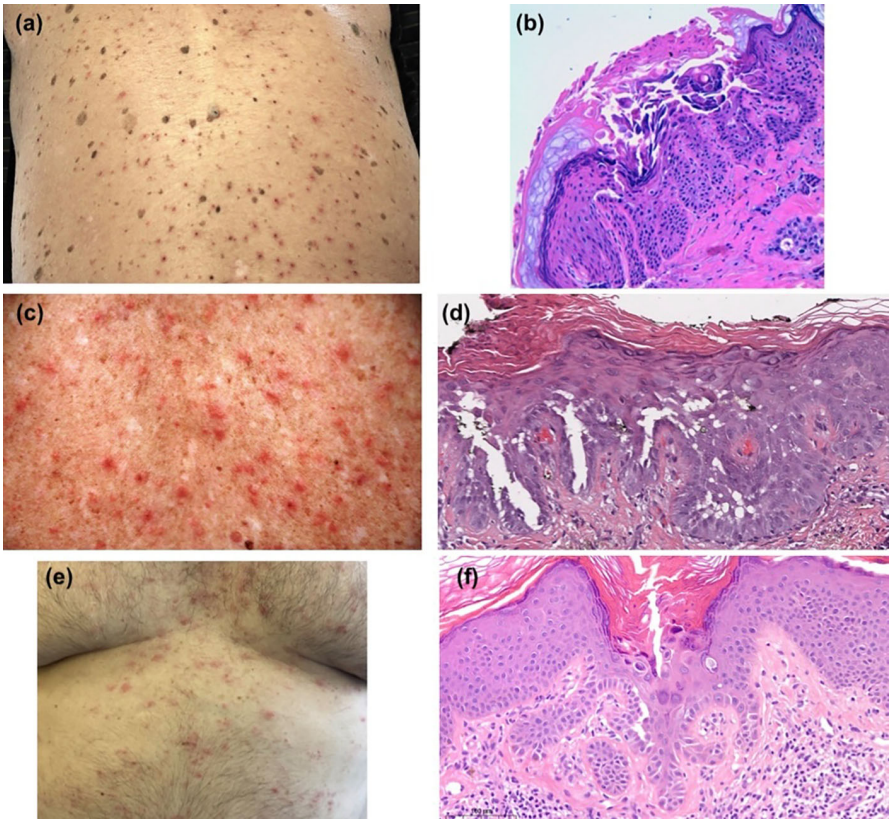

Figure 1 (a) A male patient under treatment with lenalidomide for multiple myeloma developed multiple erythematous papules, mainly on his back. (b) Histology showed focal acantholytic dyskeratosis consistent with GD. (Hematoxylin and eosin (H-E), 100×). The cutaneous manifestations partially improved with topical clobetasol. (c) A male patient with prostatic adenocarcinoma presented with erythematous papules and eroded macules across his chest and trunk. (d) Histopathology showed acanthosis and focal acantholytic dyskeratosis consistent with GD. (H-E, 200×). The patient was treated with topical steroids and systemic antihistamines, with partial improvement. (e) A male patient with a recent diagnosis of metastatic melanoma developed a synchronous cutaneous manifestation at the level of the chest and back associated with itching. (f) The histology was consistent with GD. (H-E, 300×). The patient was treated with topical steroids, which partially improved the cutaneous manifestation

diseases can coexist in the same patient, sharing the same trigger factors (e.g., ultraviolet rays, medications); at the same time, the scratching induced by GD may lead to cell destruction and the release of BP antigens, therefore activating autoimmunity. Finally, the alteration of immunological homeostasis may play a pivotal role in the induction of both GD and BP in the same patient, and this is confirmed by the fact that in all cases reported in the literature of BP associated with GD, patients underwent immunotherapy.[4] Finally, treating the underlying malignancy and reducing the time patients spend in bed certainly improve the disease. Usually, GD is self-resolving, but it can also be managed with topical or systemic steroids or with anti-IL-4/IL-13 therapies in some selected and resistant cases.[5]

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