

Diffuse dermal mucinosis secondary to colony stimulating factor-1 receptor monoclonal antibody treatment: a novel and peculiar drug-induced diffuse cutaneous mucinosis

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ABSTRACT

Colony-stimulating factor-1 receptor (CSF1R) inhibitors represent a new class of immune-modulatory drugs, mostly investigated in clinical trials in different malignant neoplasms. Four patients, diagnosed with recurrent or advanced malignant neoplasm and treated with a combination of anti-PD-L1 and anti-CSF1R monoclonal antibodies, developed an asymptomatic cutaneous eruption characterized by an ill-defined pseudoedematous to waxy diffuse infiltration with a reticular cobblestone-like pattern. Histopathological examination revealed diffuse mucin deposition involving the superficial and mid dermis with fragmented and scattered elastic fibers.

The exact pathogenic mechanisms implicated in the development of mucin deposits in patients treated with CSF1R inhibitors remain to be elucidated. A reduced degradation and clearance of components of the extracellular matrix by macrophages secondary to CSF1 pathway inhibition may be hypothesized. Shredding and fragmentation of elastic fibers may result of the increased accumulation of mucopolysaccharides.

This observation illustrates the new spectrum of skin-related toxicities secondary to new targeting therapies. This may contribute to a better understanding of the underlying pathogenic mechanisms in skin diseases characterized by a persistent dermal glycosaminoglycan deposition.

KEY WORDS

Drug reaction, anti-CSF1r, anti-PD-L1, colony-stimulating factor-1 receptor inhibitor, dermal mucinosis, skin toxicity

INTRODUCTION

A better understanding of the pathogenic mechanisms implicated in neoplastic and inflammatory disorders enabled the development of novel drugs, targeting specific molecules involved in cell growth and immune system modulation. The emergence of molecular-targeting agents with novel mechanisms of action has been associated with the appearance of a new spectrum of skin-related toxicities.

Colony-stimulating factor-1 receptor (CSF1R) inhibitors represent a new class of immune-modulatory drugs mostly investigated in clinical trials in different malignant neoplasms. Treatment with humanized anti-CSF1R monoclonal antibodies (mAb) leads to a CSF-1 pathway blockade, inhibiting the production of inflammatory mediators by macrophages. By decreasing the activity of CSF1R-dependent tumor-associated macrophages (TAMs) and the recruitment of TAMs to the tumor microenvironment, CSF1R blockade enhances T-cell infiltration and antitumor T-cell immune responses¹. Reported side-effects of CSF1R inhibitors include fatigue, elevated liver enzymes, facial and peripheral edema, rash, nausea or vomiting².

Here, a series of patients treated with an anti-CSF1R are reported, presenting a generalized pebbled cutaneous eruption secondary to diffuse dermal mucin deposition. This peculiar “drug-induced cutaneous mucinosis” represents a new and characteristic clinicopathological entity to be included within the spectrum of cutaneous mucinosis.

Our local ethics committee, CEIC Parc de Salut Mar (2016/7038), approved this study. Consent was obtained for publication from the clinical trial sponsor.

PATIENT REPORTS

Four patients (3 males, 1 female) with ages ranging from 52 to 72 years, all of them diagnosed with recurrent or advanced malignant neoplasms (lung adenocarcinoma [Patient 1], small cell lung carcinoma [Patient 2], melanoma [Patients 3 and 4]), were included in a clinical trial consisting of a combined treatment with anti-PD-L1 and anti-CSF1R mAbs (Table 1).

Long after the treatment onset (from 14 to 26 weeks), all patients developed an asymptomatic cutaneous eruption characterized by a diffuse pebbly appearance in the chest, back and proximal aspects of upper and lower extremities.

That the first two patients previously developed a pruritic eruption must be highlighted. Patient 1 presented an eczematous eruption on extremities one month before the development of the characteristic cutaneous lesions and after 16 weeks of treatment onset. Patient 2 manifested multiple erythematoviolaceous papules, some arranged in a linear distribution, on the trunk and proximal regions of all limbs three weeks before (after 13 weeks of treatment onset). The latter dermatosis was interpreted as a lichenoid eruption due to anti-PD-L1 mAb, resolved with topical corticosteroids.

Patients 3 and 4 presented persistent facial and palpebral edema and discrete edema on the trunk and extremities, overlapping with new skin lesions.

A complete hematological and biochemical survey disclosed no significant abnormalities. No peripheral eosinophilia, thyroid abnormalities or circulating paraproteins were detected.

Physical examination revealed a pseudoedematous-to-waxy diffuse infiltration of the chest and back, with a reticular cobblestone-like pattern, resulting from the confluence of leathery skin-colored to yellowish slightly raised areas. A close-up examination disclosed an apparently ill-defined edematous background, leaving depressed small oval to round islands mimicking clinically either boxcar or rolling acne scars (Figure 1).

Histopathological features

Several biopsies from raised and depressed areas were obtained in each patient. Histopathological examination disclosed a slightly atrophic epidermis and widely spaced dermal collagen fibers, most prominent in the papillary and upper reticular dermis but also extending into the deep dermis. A fine basophilic fibrillar material was observed between separated collagen bundles. A discrete lymphoid perivascular inflammatory infiltrate was also noted in the papillary dermis. Neither fibroblast proliferation nor sclerosis were observed (Figure 2a-b). Alcian blue pH 2,5 and aldehyde fuchsin (orcein) stains demonstrated a diffuse mucin deposition involving the superficial and mid dermis, and fragmented and scattered elastic fibers (Figure 2c-d). These changes were less pronounced in apparently non-lesional areas (Figure 2e-f).

Electronic microscopy showed an increased number of proteoglycans dissecting collagen bundles, that appeared broken, compacted and disaggregated instead of well packed (Figure 2g). These changes were accompanied by fragmented, porous and ragged-looking elastic fibers impregnated with proteoglycans (Figure 2h).

Follow-up

Patients 1 and 2 presented tumor progression after 7 and 5 months of treatment, respectively, and combined immunotherapy was switched to platin-based chemotherapy. In Patient 1 complete regression of the cutaneous lesions was noted after 10 months of withdrawal, whereas Patient 2 died 6 months later without clinical clearance of the lesions.

Combined treatment was also withdrawn in Patient 3 due to tumor progression, with clear-cut improvement 8 months later. She received subsequent treatment with an anti-CD25 mAb in a clinical trial. Unfortunately, no post-treatment data is available for Patient 4 due to loss of follow-up.

DISCUSSION

Cutaneous mucinoses are a heterogeneous group of conditions characterized by the accumulation of glycosaminoglycans (hyaluronic acid, sulfate, and heparin) in the dermis and/or hair follicles. This process may occur as a primary idiopathic disorder or secondary to connective tissue (lupus erythematosus, scleroderma, dermatomyositis), inflammatory (graft-versus-host disease) and granulomatous (granuloma annulare) disorders, among others³.

Development of drug-induced or toxic dermal mucinous deposits is an exceedingly unusual event, occasionally reported either as a localized phenomenon secondary to interferon injections⁴ or anti-TNF treatments⁵; or in a subset of distinctive disorders, including toxic oil syndrome or eosinophilia-myalgia syndrome⁶.

We report a novel and clinically characteristic form of “drug-induced cutaneous mucinosis” secondary to anti-CSF1R mAb. This new class of immune-modulatory drugs has been recently incorporated in the treatment armamentarium of advanced malignant neoplasms, but also in several inflammatory conditions in which aberrant CSF1 signaling has been proved⁷. Despite all patients received the combination of anti-CSF1R and anti-PD-L1 mAbs, we consider the CSF1 pathway blockade as the cause of the observed effects, since cutaneous mucin deposits have been observed in monkeys treated with anti-CSF1R⁸, and conversely no cases of dermal mucinosis had been published insofar with anti-PD1 or PD-L1 therapies⁹. Notably, one of our patients presented a distinct mild lichenoid cutaneous eruption secondary to anti-PD-L1 treatment, previous to cutaneous mucinosis.

The observed clinical picture showed some similarities with the symmetrical skin pebbling eruption reported in patients with Hunter syndrome, or mucopolysaccharidosis type II, a rare lysosomal storage disease caused by a deficiency of iduronate-2-sulfatase, which breaks down glycosaminoglycan giving rise to mucin dermal accumulation¹⁰. In Hunter syndrome, the lesions tend to arrange bilaterally involving the area between the scapulae and axillae, although more widespread lesions have also been reported¹¹. Histologically,

irregularly and separated collagen bundles by interfibrillar mucin deposition were also observed¹⁰.

Several adverse events secondary to anti-CSF1R treatment have been reported (fatigue, elevated liver enzymes, facial and peripheral edema, rash, nausea or vomiting)² but no cases of cutaneous dermal mucinosis secondary to CSF1R blockade had been reported to our knowledge. In a phase 1 study with the anti-CSF1R emactuzumab in locally advanced diffuse-type tenosynovial giant cell tumors of the soft tissue, periorbital edema was observed in 64% of subjects (n=16), followed by rash (n=10), subacute cutaneous lupus erythematosus (n=1) and dermatohypodermatitis (n=1). All adverse cutaneous side effects reversed after stopping the treatment¹².

Pognan et al⁸. studied the periorbital swelling by the administration of lacnotuzumab, another anti-CSF1R mAb, on cynomolgus monkeys. Histologically, periorbital edema corresponded to dermal and subcutaneous accumulation of a basophilic material that stained with Alcian blue, corresponding to mucin. Asymptomatic mucin accumulation was also noted in other organs. After drug withdrawal, periorbital swelling slowly resolved in all subjects.

The exact pathogenic mechanisms implicated in the development of mucin deposits in patients treated with CSF1R inhibitors remain to be elucidated. A reduced degradation and clearance of the components of extracellular matrix by macrophages secondary to CSF1 pathway inhibition may be hypothesized. Shredding and fragmentation of elastic fibers may result of the increased accumulation of mucopolysaccharides.

In conclusion, a novel subset of drug-induced diffuse cutaneous mucinosis secondary to anti-CSF1R treatment is reported. This observation illustrates the new spectrum of skin-related toxicities secondary to new molecular-targeting therapies, and it may be helpful for a better understanding of the underlying involved pathogenic mechanisms in skin diseases characterized by a persistent dermal glycosaminoglycan deposition.

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LEGENDS

Figure 1. Clinical pictures of Patient 1 (a,b) Patient 2 (c), Patient 3 (d,e) and Patient 4 (f). Multiple skin-colored to whitish papules in a cobblestone pattern and apparently unaffected skin mimicking clinically either boxcar or rolling acne scars can be observed in all patients.

Figure 2. Histopathological changes seen in optical (a-f) and electronic microscopy (g-h). a-b) Slightly atrophic epidermis and separated collagen bundles due to an accumulation of basophilic material, predominantly on the upper dermis (H&E, 5x/10x). c) Mucin deposition in the upper and mid dermis between collagen fibers (Alcian blue pH 2.5 10x). d) Fragmented and scattered elastic fibers in dermis (aldehyde fuchsin 10x). e-f) Less pronounced changes seen in normal skin, with scarce mucin deposition and preserved elastic fibers (Alcian blue pH 2.5/Aldehyde fuchsin 10x). g) Ultrastructural examination showing filamentous structures resembling spider webs, corresponding to proteoglycans, dissecting collagen bundles appearing broken, compacted and disaggregated (x25K). h) Electron microscopic image showing porous, gelatinous and frayed-looking elastic fibers, impregnated with proteoglycans (x25K).

TABLES

Table 1. Clinical characteristics of patients

Patient	Age/Sex	Malignant neoplasm (year of diagnosis)	Previous treatments	Treatment Onset [†] (weeks)	Involved area	Associated cutaneous lesions	Follow-up [‡]
1	63/M	Lung adenocarcinoma (2013)	Surgery, RDT, vinorelbine	20	Trunk	Previous eczematous eruption on extremities (4 weeks before)	Complete regression after 10 months of withdrawal
2	72/M	Small-cell lung carcinoma (2015)	Surgery, several courses of polychemotherapy, nivolumab	16	Trunk	Previous lichenoid rash on trunk and extremities (3 weeks before)	Died 6 months later without clear-cut improvement
3	60/F	Melanoma (2015)	Surgery, pembrolizumab, anti LAG-3 + nivolumab	14	Trunk and proximal upper extremities	Facial and palpebral edema Discrete edema on trunk and extremities	Complete regression after 8 months of withdrawal
4	52/M	Melanoma (1997)	Surgery, interferon, vemurafenib, nivolumab, anti LAG-3 + nivolumab	26	Trunk and proximal upper extremities	Facial and palpebral edema Discrete edema on trunk and extremities	Unknown (lost of follow-up)

[†]Period of time from the onset of treatment and the development of skin lesions

[‡]Since the initiation of the treatment

M: Male, F: Female, w: weeks, RDT: radiotherapy, anti LAG-3: anti lymphocyte activation gene-3