Recalcitrant course of Bullous pemphigoid indicating the coexistence with Hypereosinophilic syndrome. A case report and literature review.

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Abstract

Bullous pemphigoid is an autoimmune disorder characterized by blister formation. Hypereosinophilic syndrome is a myeloproliferative disorder that presents with papules, nodules, urticarial lesions, and blisters. The coexistence of these disorders may highlight common molecular and cellular factors. We describe a 16-years-old patient with coexistence of hypereosinophilic syndrome and bullous pemphigoid.

Introduction:

Bullous pemphigoid is one of the most common blistering dermatosis which is characterized by autoantibodies against hemidesmosomal proteins mucosa including the oral cavity, nose, eyes and genital area in addition to skin (1). Hypereosinophilic syndrome (HES) is a myeloproliferative disorder characterized by persistent hypereosinophilia leading to possible organ damage with cutaneous manifestations or systematic ones (2). Several cases of BP with coexisting HES have been reported in the literature. Peripheral eosinophilia which are reported in both BP and HES are not only important in indicating the severity of both diseases, but also play a role as a pathogenic factor in these diseases (3). We describe a female patient who was initially diagnosed with bullous pemphigoid. Later because of the unresponsiveness for usual treatment to BP and because of persistent eosinophilia, the diagnosis of idiopathic hypereosinophilic syndrome associated with BP was made.

Case presentation:

A 16-years-old female patient presented to our hospital with a generalized bullous eruption. History goes back for five years before when she started complaining from scattered bullae on her trunk and she was treated successfully with prednisolone 15 mg daily that was tapered gradually. One year before she was referred to our center, she started complaining from bullous lesions again. Unfortunately, there was no response to dapsone, IVIG, rituximab and even the previous dose of prednisolone. Later, she was referred to our hospital with generalized bullae. Her physical examination showed multiple tense bullae on both lower and upper extremities, trunk (figures 1, 2, 3), and neck in addition to oral lesions. Skin biopsy was done and the histological findings showed sub-epidermal blisters with eosinophilic perivascular infiltrates. Direct immunofluorescence (DIF) study showed linear C3 and IgG deposits at the dermoepidermal junction. Laboratory findings included hyper eosinophilia (44% in peripheral smear with an absolute eosinophil count). According to internal medicine consult, bone marrow biopsy and aspiration was performed. The results revealed hypercellular bone marrow with 75% eosinophils and blasts. The final diagnosis was bullous pemphigoid associated with hypereosinophilic syndrome. Genetic testing for FIP1L1-PDGFRA fusion gene was negative. So high dose prednisolone 40 mg was initiated. There was complete resolution for her skin lesions. Later prednisolone was tapered gradually.

Discussion :

The skin is the most frequent organ involved in HES affecting more than half of the patients and ranging from urticarial lesions, pruritic papules or nodules, and mucosal ulcers (4). Histopathological studies of papular or nodular lesions usually show abundant eosinophilic perivascular infiltrates in addition to neutrophilic and mononuclear ones, whereas mucosal ulcers histology includes nonspecific mixed cellular infiltrates with no vasculitis (4).

Bullous pemphigoid is the most blistering autoimmune disease with prevalence in elderly population (5). Histopathological studies show subepidermal blister formation rich with eosinophils, whereas direct or indirect immunofluorescence assays demonstrate the presence of IgG and/or C3 deposition along the basement membrane zone (5). The cornerstone in treatment of BP is corticosteroids including topical or oral ones, in addition to treatment with other medications like doxycycline, dapsone and immunosuppressants drugs (5). Recent studies showed a role of eosinophils and IgE autoantibodies in addition to anti-BP180 and BP230 IgG autoantibodies as a pathogenic causative factor in BP (6).

HES is one of the heterogeneous entities characterized by eosinophilic infiltrates especially bone marrow and heart followed by lungs, liver and spleen (7). One of HES cutaneous manifestations is blister formation usually in the epidermis or dermal-epidermal junction making it one of the differential diagnosis of BP (7). Till now, about 9 cases of BP with coexisting HES have been reported in literature (table 1). The coexistence of these two disorders may highlight similar molecular and cellular background (7).

Treatment of HES is based on the presence or absence of the FIP1L1-PDGFRA fusion gene. When the genetic test is positive the best treatment is imatinib, whereas when the test is negative corticosteroids is considered as a first line of treatment (8).

This case report shows the important role of dermatologists in diagnosing every skin manifestation even when cutaneous lesions are limited because it can highlight a life-threatening condition (9). BP is a very common blistering disorder that can be associated with HES (9). HES must be considered especially in patients with atypical response to corticosteroids with blood eosinophilia (9). Our patient presented first with limited bullous lesions that resolved with corticosteroid treatment, but later recurred with a more generalized aggressive course with no response for low dose of corticosteroids. After diagnosing the coexistence with HES, prednisolone 1 mg/kg/day (treatment dose for HES), there was complete resolution and relief for symptoms and skin manifestations.

This report shows the importance of skin manifestations even though when there is localized limited lesions since it may highlight a life-threatening condition where early diagnosis and treatment can improve the prognosis (10).

Author/year	Sex age	Region	Location	Physical Examination	FIP1L1-PDGFRA gene	treatment
G.M.Palleschi/1996	Man/77	Italy	Trunk/Limb	Erythematous papule	unknown	corticosteroid
F.Belganaoui /2002	Man/56	France	generalized	pruriginous/ bullous dermatose	unknown	corticosteroid
A.Muller/2006	Man/71	Germany		pruriginous, Bullous-pemphigoid	Negative	First: corticosteroid then Imatinib
V.Felbert/2006	Women	Germany	Generalized	prurigo-like lesion	unknown	corticosteroid

Author/year	Sex age	Region	Location	Physical Examination	FIP1L1-PDGFRA gene	treatment
Sike.Hofmann/2006	Man/70	Germany	Feet, buttock, leg	Tense bullae, papule, excoriation	Negative	Dexamethasone(3 days), Imatinib
Hassam BE	31/woman	Iran	generalized	bullae	negative	Corticosteroid, Interferon-Alfa is foreseen
Maniyan KM/2019	55/woman	India	Forearm, Leg, Trunk, Face	Papule, Vesicles, Tense bullae	unknown	Prednisolone, Dapsone, Diethylcarbamazi
Khallaayoune M/2021	74 years old	Iran	unknown	bullous rash	unknown	unknown
Abdollahimajd F/2021	16/woman	Iran	Generalized skin lesion, Oral mucosa	Tense bullae	negative	Prednisolone

Table 1: Review of literature of Bullous pemphigoid cases associated with Hypereosinophilic syndrome in chronological order. The table includes patients' age and gender/ clinical presentation/ FIP1L1- PDGFRA gene/ and treatment

Key Clinical Message: As dermatologists, we must be careful in diagnosing every skin manifestation even when cutaneous lesions are limited because it can highlight a life-threatening condition. Early diagnosis and treatment can improve the prognosis.

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Figure legend:

Figure 1.

Multiple tense and flaccid bullae on trunk and abdomen varying in size in addition to erosions.

Figure 2.

Tense and flaccid bullae on back.

Figure 3.

Tense and flaccid bullae and erosions on upper extremities.