Casos Clínicos

Hemorrhagic bullous pemphigoid: an infrequent presentation of acquired hemophilia secondary to Dipeptidyl-dipeptidase-4 inhibitors

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Resumen

La hemofilia adquirida es una enfermedad infrecuente causada por autoanticuerpos neutralizantes contra el factor VIII, que se ha asociado con enfermedades ampollares autoinmunes como el penfigoide ampolloso. Caso: Paciente de 82 años con antecedente de penfigoide ampolloso secundario al uso de inhibidores de dipeptidil-dipeptidasa-4 (vidagliptina). Consulta por hematuria macroscópica y múltiples hematomas violáceos en cara y extremidades superiores. Tras el estudio, se diagnosticó hemofilia adquirida asociada a penfigoide ampolloso inducido por inhibidores de dipeptidil-dipeptidasa-4. Discusión: La hemofilia adquirida es una complicación rara del penfigoide ampolloso. La principal hipótesis que explica esta asociación es el desarrollo de reactividad cruzada de autoanticuerpos entre epítopos homólogos presentes en el factor VIII y BP-180. Los inhibidores de dipeptidil-dipeptidasa-4 inducirían la formación de anticuerpos IgG4 contra BP-180, que también reconocen al factor VIII. El tratamiento de la hemofilia adquirida se basa en reportes o series de casos y se enfoca en el control de la enfermedad mediante inmunosupresores como corticoides, ciclosporina o rituximab.

Palabras claves: Inhibidores de dipetidil-peptidasa-4; Penfigoide buloso; Hemofilia adquirida; inhibidor de FVIII, Rituximab.

Abstract

Acquired hemophilia is a rare disease caused by neutralizing autoantibodies against factor VIII that has been associated with autoimmune blistering diseases such as bullous pemphigoid. Case: We present an 82-year-old patient with a history of bullous pemphigoid secondary to the use of dipeptidyl-dipeptidase-4 inhibitors (vildagliptin) who presented with macroscopic hematuria, multiple violaceous hematomas on the face and upper extremities. After the study, it was diagnosed as acquired hemophilia associated with bullous pemphigoid due to dipeptidyl-dipeptidase-4 inhibitors. Discussion: Acquired hemophilia is a rare complication of bullous pemphigoid. The main hypothesis explaining this association is the development of autoantibody cross-reactivity between homologous epitopes on factor VIII and BP-180. Dipeptidyl-dipeptidase-4 inhibitors would cause the formation of IgG4 antibodies against BP-180, and these antibodies also recognize factor VIII. Treatment of acquired hemophilia is based on case reports or case series. It is focused on eradicating autoantibodies with immunosuppressive drugs such as corticosteroids, cyclosporine or target therapies such as rituximab.

Key words: Dipeptidyl-dipeptidase-4 inhibitors; Bullous pemphigoid; Acquired hemophilia; FVIII-inhibitor; Rituximab.

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Trabajo no recibió financiamiento.
Los autores declaran no tener conflictos de interés.

Received:
October 17th, 2024
Accepted:
March 07th, 2025

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Acquired hemophilia (AHA) is a rare disease caused by neutralizing autoantibodies against factor VIII (FVIII).[1] In half of the cases, no etiology is found; autoimmune blistering diseases have been associated.[1,2] Bullous pemphigoid (BP) is an autoimmune subepidermal blistering disorder.[3] The medication more strongly associated is the dipeptidyl-peptidase-4 inhibitors (DPP-4is), increasing the risk of developing the disease by up to three times.[4,5] Oral DPP-4is (e.g., vildagliptin, sitagliptin, and saxagliptin) are drugs for treating type-2-diabetes-mellitus (T2DM).[3] We describe a case of AHA associated with BP secondary to the use of DDP-4is. Only two additional cases of this triple association have been reported.

Case

An 82-year-old man presented with a three-day history of multiple hematomas on the face and upper extremities, small, tense bullae on the forearms (Figure 1 a, b), and macroscopic hematuria. The patient had type 2 diabetes mellitus (T2DM) and was under treatment with metformin and insulin. Three years ago, the patient initiated vidagliptin for glycemic control and 6 months later developed bullous pemphigoid (BP), confirmed through histology (Figure 2 a, b) and direct immunofluorescence showing deposition of IgG and C3 (Figure 3), ELISA for BP-180 and BP-230 (Euroimmun®) was negative. The development of BP was attributed to the use of vidagliptin. The patient received treatment with both topical and systemic corticosteroids, and suspension of vidagliptin. The patient never achieved complete remission of bullous lesions and was managed during the following years with intermittent courses of prednisone and clobetasol cream. Laboratory workup revealed a prolonged aPTT (96 seconds; normal 25-37). Treatment with fresh frozen plasma was performed without improvement. A 1:1 plasma-dilution-test was requested, and the non-correction of the aPTT indicated the presence of an inhibitor. Further investigations revealed an FVIII activity of 2.2% (50-150) and FVIII-inhibitor 12 BU/mL. AHA associated with BP was diagnosed. An ELISA test was once again performed to evaluate BP activity, which turned out negative.

The patient was managed with prednisone 1mg/kg, with no clinical or laboratory improvement after one week. Due to treatment failure, rituximab 375mg/m2 was started on days 1-14, associated with prednisone 0.5mg/kg, achieving remission of the hematuria and normalization of his coagulation parameters after eight days. The patient cleared the FVIII-inhibitor in two months and restored normal FVIII (>100%) and aPTT levels.

Discussion

AHA is a rare complication of BP. The main hypothesis explaining their association is the development of autoantibody cross-reactivity between homologous epitopes at FVIII and the BP-180. Epidemiological evidence supports the correlation between DPP-4is and BP based on data from European-and-French-pharmacovigilance-databases.[6]

DPP-4 is a cell surface plasminogen receptor that converts plasminogen to plasmin, a major serine protease that cleaves the NC16A domain of BP-180.[4] By altering the metabolism of BP-180, gliptins may

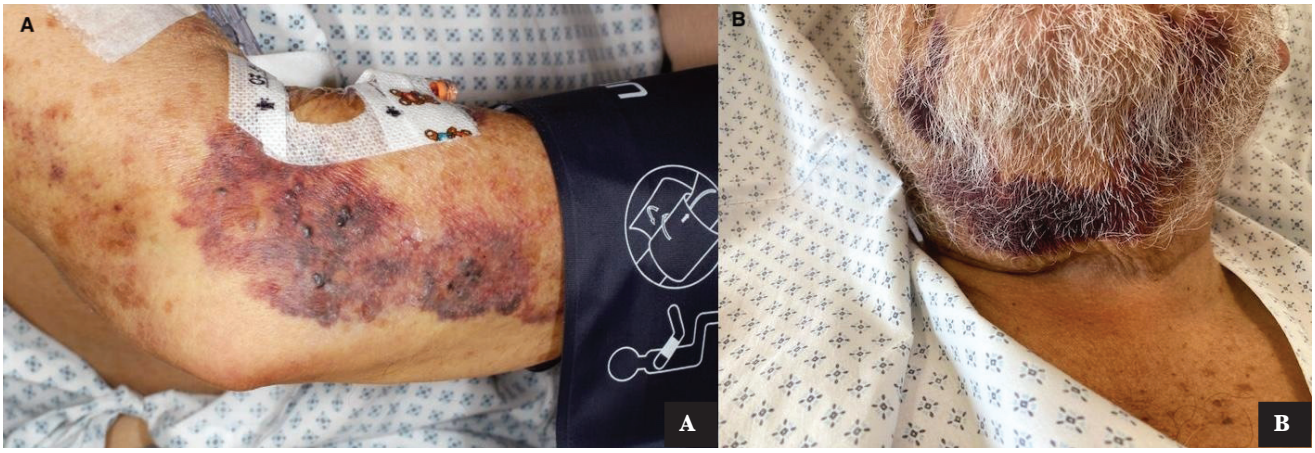

Figure 1
A. Right forearm and elbow during patient's stay in intensive care unit, revealing a significant purpuric ecchymosis. Additionally, multiple small hemorrhagic vesicles, representative of bullous pemphigoid.
B. Submental region of the patient while interned in an intensive care unit. A large purpuric ecchymosis is seen in the area.

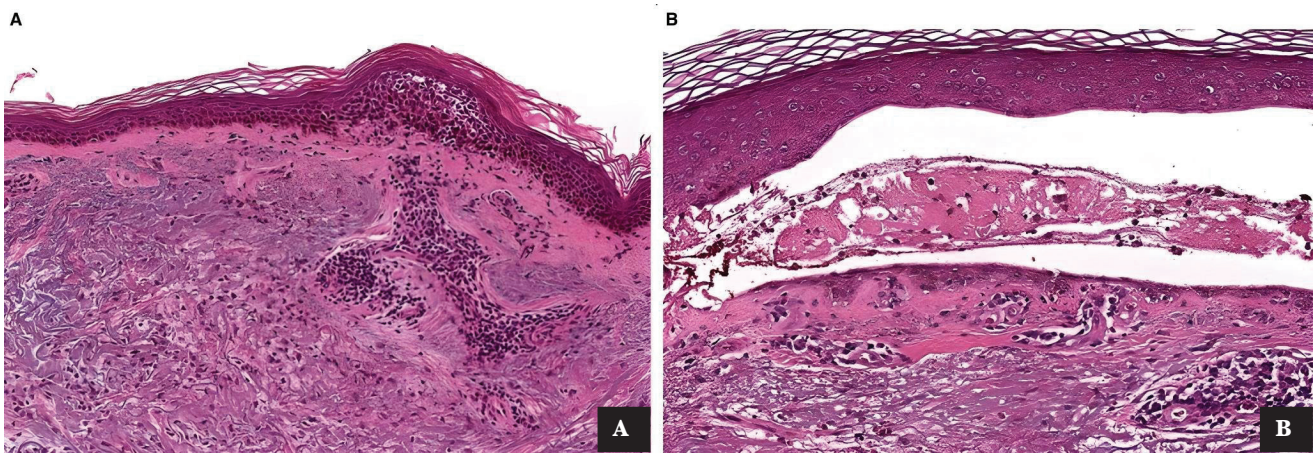

Figure 2
A subepidermal blister.
A. The epidermis shows spongiosis, vacuolar degeneration of the basal layer. (H and E 100x)
B. Exocytosis of lymphocytes and eosinophils. In the dermis, perivascular and interstitial lymphocytic infiltrate with eosinophils. (H and E 400x)

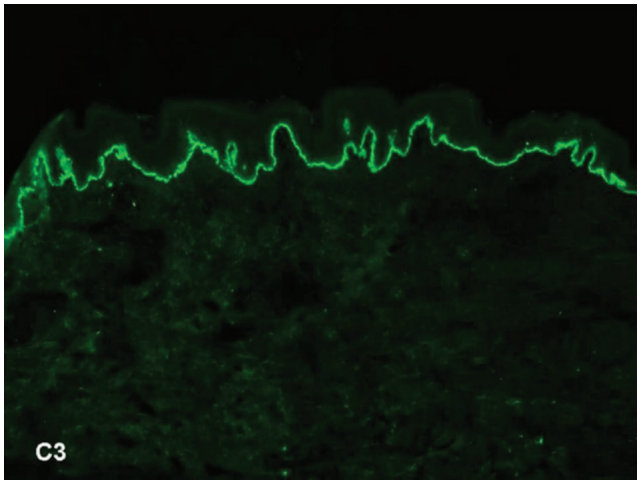

Figure 3
Direct immunofluorescence showing linear deposition of complement in the basement membrane.

trigger the formation of IgG4 antibodies against the LAD-1 region of BP-180, as opposed to the classic NC16-A region.[3] 80-90% of BP sera reacts with NC16-A region in ELISA-tests; however, conventional ELISA does not detect autoantibodies against the LAD-1 region, which explains the negative result in our patient.[9] Few case reports demonstrate the activity of IgG4 and IgG1 against the 44 kDa (A2-domain) of FVIII using immunoblotting.[2] Prud'homme et al.[7] identified the binding of anti-FVIII antibodies at the dermal-epidermal junction in skin biopsies in two cases of BP with anti-BP-180 antibodies, which would confirm a sequence homology between FVIII and BP-180.[6]

There are 41 documented cases of AHA associated with BP[2,4,6,7-36] (Table 1). Among these cases, the age distribution was 24 to 88 years. The mean time from the start of BP to the beginning of AHA was five months and varied between coinciding and three years. None of the AHA cases developed before the appearance of BP. In these cases, remission of both conditions is observed with the treatment.

With the exponential increase in metabolic diseases such as T2DM and the use of new antidiabetic drugs, these cases are expected to become more frequent. This association should be suspected in patients who develop tense blisters or have a history of BP presenting with purpura. This condition can be life-threatening; therefore, early diagnosis is essential for timely and effective treatment.

Table 1
Clinical characteristics of published cases of acquired hemophilia associated with bullous pemphigoid.

Case No.	First author [ref	Gender /age	Autoimmune disease	Associated drug	Onset before AHA	Evolution of BP under treatment	Inhibitor titer BU/mL	Treatment of AHA	Response to treatment-of AHA
1	Ikegami[8]	M65	No	No	2-3Mo	Resolved	2	Prednisolone	Resolved
2	Ikegami[8]	F67	No	No	Concurrently	Resolved	76	methylprednisolon, with relapse FVIII, prednisolone, CSA	Resolved
3	Ly[9]	M68	No	No	6Mo	Resolved	>2	CS	Resolved
4	Patel[10]	M78	Rheumatoid arthritis and vitiligo	No	4Mo	Resolved	839	FEIBA, CSA, prednisolone, hydrocortisone	Resolved
5	Zhang[11]	F49	No	No	7Mo	Resolved	147	Prednisolone, plasma exchange, CSA	Resolved
6	Gupta[12]	F84	No	No	2Mo	ND	29	Dexamethasone, CSA rFVIII, FEIBA	Resolved
7	Caudron[13]	F68	No	No	Concurrently	ND	1,4	FEIBA, Topical CS	Resolved
8	Chen[14]	M24	No	No	2Y	Resolved	256	rFVIII, plasmapheresis, methylprednisolo n, rituximab, prednisolone + CSA	Partial response
9	Qiu[15]	F60	No	No	Concurrently	ND	(+)	rFVIII, methylprednisolo n, CSA, IVIg	Remission
10	Zhang[16]	M88	No	No	4Mo	No improvement	7	Methylprednisolo ne, rituximab	Remission
11	Makita[17]	F80	No	No	12M	Resolved	20	Prednisolone	Resolved
12	Lightburn[18]	M74	No	No	Concurrently	ND	110	CSA, cyclosporine, CS, AZA, IVIg	Remission
13	Maczek[19]	F47	No	No	3M	Remission	2	CS, CSA, plasmapheresis	Remission
14	Vissink[20]	M88	No	No	Days before	Improved	(+)	CS	Died shortly after diagnosis
15	Abderrazak[21]	F71	No	No	ND	ND	(+)	CS	Died
16	Rodprasert[22]	M71	No	No	Concurrently	ND	219	CS, IVIg, cryoprecipitate, rFVIII	ND; patient transfered another hospital
17	Soria[23]	F83	No	No	3Y	Resolved	17	CS	Died of severe hemorrhage
18	Antic[24]	F38	No	No	Before	ND	2	CS	ND
19	Gouverneur[25]	M64	No	No	1M	Improved	(+)	CS, rituximab	Remission
20	Kluger[26]	M72	No	No	9M	Resolved	(+)	CS, CSA, plasmapheresis, IVIg	Remission

Case No.	First author [ref	Gender /age	Autoimmune disease	Associated drug	Onset before AHA	Evolution of BP under treatment	Inhibitor titer BU/mL	Treatment of AHA	Response to treatment-of AHA
21	Nguyen[27]	F49	No	No	4M	Minimal response	17	CS, CSA, FVIII, FEIBA	Remission
22	AlJasser[28]	M73	No	No	Concurrently	ND	(+)	CS, CSA, rituximab, IVIg, FEIBA	Remission
23	Prud'homme[7]	M61	No	No	1Mo	ND	32	CS	Improvement
24	Binet[8]	M75	No	No	21Mo	Remission	25	CS, rituximab	Remission
25	Ammannagari[29]	M69	No	No	1Mo	Resolved	34	CS, rituximab, rFVIII	Remission
26	Fakprapai[2]	F68	No	No	11Mo	Resolved	28	CS, CSA, FEIBA	Remission
27	Sugiyama[30]	F78	No	DDP-4is (Alogliptin)	6W	Resolved	8	Prednisolone	Remission
28	Chijiwa[31]	M76	No	No	4Mo	No improvement	320	FVII and prednisolone	Remission
29	Fu[32]	M77	No	SARS-CoV-2 mRNA vaccine (Moderna)	3W	ND	71	Prednisolone, FEIBA, CSA	Improvement
30	Bragança[33]	M74	No	No	Concurrently	ND	(+)	CS, FEIBA	Remission
31	Ma[34]	M63	No	No	7Mo	Remission	ND	Dexamethasone, CSA, rFVIII, rFVIIa, rituximab	Resolved
32	Matsumoto[35]	M72	No	DDP-4is	3Mo	Resolved	(+)	Prednisolone, CSA, rituximab	Remission
33	Sordeau[36]	M78	No	No	3Mo	Resolved	19	Dexamethasone and CSA, FVIII, rFVII	Remission
34	Barranca[6]	ND85	No	No	ND	Remission	ND	Rituximab and CS	Remission
35	Barranca[6]	ND55	No	No	ND	Remission	ND	Rituximab and CS	Remission
36	Barranca[6]	ND64	No	No	ND	Remission	ND	MMF	Remission
37	Barranca[6]	ND93	No	No	ND	None: flare up on topical CS	ND	None: death 48 h due to AHA	Remission
38	Barranca[6]	ND88	No	No	ND	Remission	ND	MMF and CS	Remission
39	Barranca[6]	ND83	No	No	ND	Remission	ND	Rituximab and CS	Remission
40	Barranca[6]	ND63	No	No	ND	Remission	ND	Rituximab and CS	Remission
41	Barranca[6]	ND64	No	No	ND	Remission	ND	Rituximab and CS	Remission

M, male; F, female; Mo, months; Y, years; W, weeks, DDP-4is, dipeptidyl-dipeptidase inhibitors, ND, no described, FVIII, factor VIII, CS, corticosteroids; CSA, cyclophosphamide, FEIBA, Factor VIII Anti-Inhibitor, rFVIII, recombinant factor VIII, IVIg, intravenous immunoglobulin; FVII, factor VII, rFVII, recombinant factor VII, AZA, azathioprine; MMF, mycophenolate mofetil

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