Evolving mucocutaneous eruptions following chemotherapy

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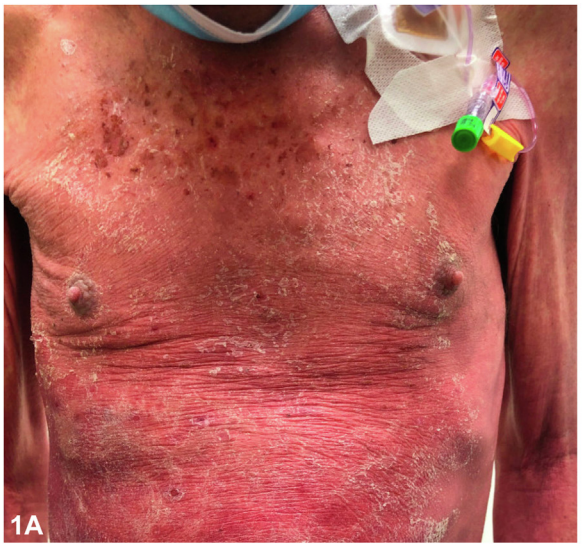

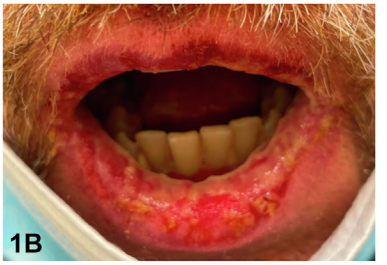

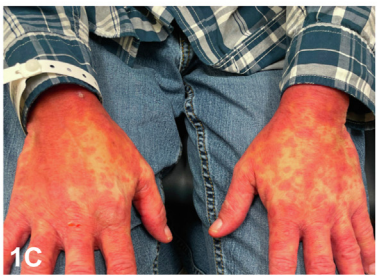

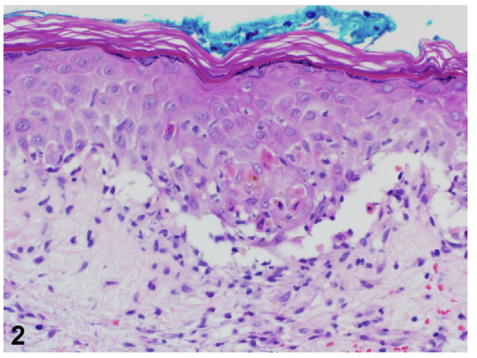

A 62-year-old male with follicular lymphoma presented with a 3-week history of worsening erythematous, coalescing papules and plaques with desquamative scale, and oral mucosa erosions starting 4 days after receiving rituximab, bendamustine, trimethoprim/sulfamethoxazole, and allopurinol (Fig 1, *A-C*). There was

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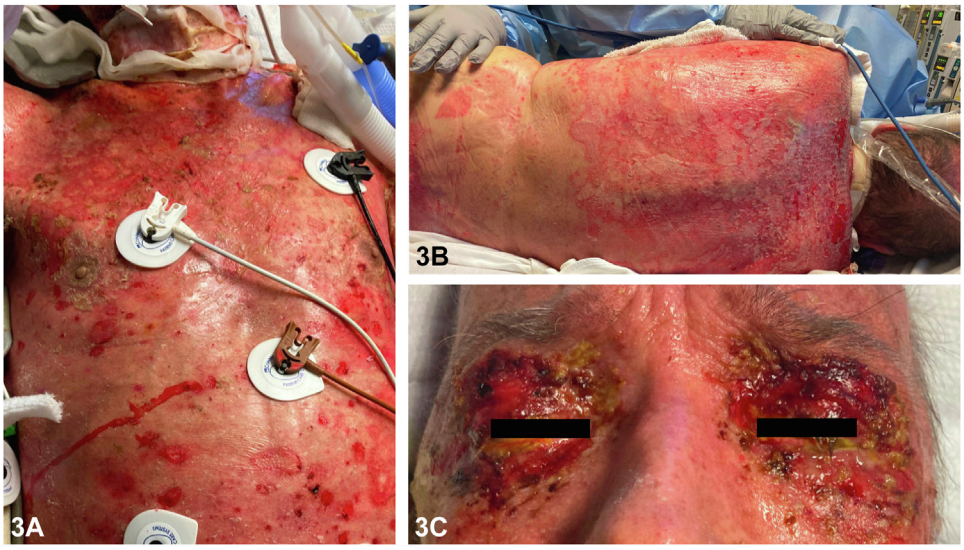

no improvement after holding medications, oral prednisone, and topical steroids. Biopsy of the dorsal hand was performed (Fig 2). Within 2 weeks, the rash progressed to erythroderma with erosions and hemorrhagic crusting of mucosal sites and diffusely on the body (Fig 3, *A-C*). Serum ELISA was positive for Bullous pemphigoid antigen I (BP230), desmoglein 3, and envoplakin, with positive indirect immunofluorescence (IF) to rat bladder epithelium.

Question 1: What is the most likely diagnosis?

A. Lichenoid dermatitis secondary to bendamustine

B. Toxic epidermal necrolysis

C. Paraneoplastic pemphigus (PNP)

D. Drug rash with eosinophilia and systemic symptoms syndrome

E. Erosive lichen planus

Answer:

A. Lichenoid dermatitis secondary to bendamustine — Incorrect. Lichenoid drug eruption is characterized by a rash resembling lichen planus with lichenoid interface dermatitis on histology. While bendamustine is a possible offending agent, the condition generally does not progress to erythroderma but resolves spontaneously following discontinuation of the drug.[1]

B. Toxic epidermal necrolysis — Incorrect. Toxic epidermal necrolysis is a severe mucocutaneous reaction characterized by coalescing macules and painful blistering progressing to widespread epidermal attachment. While trimethoprim/sulfamethoxazole, allopurinol, and biologic agents are possible inducing agents, stopping the offending drug is crucial to management, and indirect IF is negative for epithelial protein autoantibodies.[2]

C. PNP — Correct. PNP is an autoimmune blistering disease characterized by mucosal ulcerations and polymorphous skin eruptions associated with an underlying neoplasm. Histopathologic patterns on skin biopsy include epidermal acantholysis, keratinocyte necrosis, and lichenoid interface dermatitis. IgG/C3 deposits may be seen on keratinocytes and basement membrane on direct IF. Presence of PNP-associated autoantibodies and/or positive indirect IF to rat bladder epithelium helps establish the diagnosis.[3]

D. Drug rash with eosinophilia and systemic symptoms syndrome — Incorrect. Drug rash with eosinophilia and systemic symptoms syndrome is a severe drug reaction that typically occurs 2-8 weeks after drug exposure and can exhibit features including maculopapular eruptions, facial edema, fever, lymphadenopathy, blood abnormalities, and internal organ involvement.[2] Serum envoplakin antibodies are highly specific for PNP and would be negative in drug rash with eosinophilia and systemic symptoms.[3]

E. Erosive lichen planus — Incorrect. Erosive lichen planus is a variant of lichen planus characterized by painful, chronic ulcers involving the oral and

genital mucosa. Shaggy fibrin, IgM deposits at the dermoepidermal junction, and cytoid bodies on direct IF distinguish erosive lichen planus from autoimmune-bullous disorders.[4] Serum envoplakin antibodies are highly specific for PNP and would be negative in erosive lichen planus.[3]

Question 2: What is the most common underlying condition associated with PNP in adults?

A. Castleman disease

B. Non-Hodgkin lymphoma

C. Chronic lymphocytic leukemia (CLL)

D. Thymoma

E. Hodgkin lymphoma

Answer:

A. Castleman disease — Incorrect. Castleman disease is the most common underlying neoplasm for PNP in the pediatric population. Most adult PNP cases are associated with lymphoproliferative disorders, with non-Hodgkin lymphoma being the most frequent (42%), followed by CLL (29%) and Castleman disease (10%).[5]

B. Non-Hodgkin lymphoma — Correct. Most adult PNP cases are associated with lymphoproliferative disorders, with non-Hodgkin lymphoma being the most frequent (42%), followed by CLL (29%) and Castleman disease (10%). For pediatric cases, Castleman disease is the most common underlying neoplasm.[5]

C. CLL — Incorrect. While most adult PNP cases are associated with lymphoproliferative disorders, non-Hodgkin lymphoma (42%) is more frequent than CLL (29%). This is followed by Castleman disease (10%) and thymoma (6%). For pediatric cases, Castleman disease is the most common underlying neoplasm.[5]

D. Thymoma — Incorrect. Thymoma is estimated to underlie approximately 6% of PNP cases in adults. Most adult PNP cases are associated with lymphoproliferative disorders, with non-Hodgkin lymphoma being the most frequent (42%), followed by CLL (29%) and Castleman disease (10%) in adults. For pediatric cases, Castleman disease is the most common underlying neoplasm.[5]

E. Hodgkin lymphoma — Incorrect. While most adult PNP cases are associated with lymphoproliferative disorders, Hodgkin lymphoma is less common than non-Hodgkin lymphoma (42%) or CLL (29%). For pediatric cases, Castleman disease is the most common underlying neoplasm.[5]

Question 3: Which of the following autoantibody target proteins is most specific for PNP?

A. Envoplakin

B. Alpha-2-macroglobulin-like-1 antigen

C. Desmoglein 1

D. BP230

E. Desmoglein 3

Answer:

A. Envoplakin — Correct. Autoantibodies against periplakin and envoplakin are highly sensitive (82% to 86%) and specific (83% to 100%) for PNP. Autoantibodies against desmoglein 1, desmoglein 3, BP230, and alpha-2-macroglobulin-like-1 antigen have all been reported among patients with PNP with less sensitivity and specificity.[3]

B. Alpha-2-macroglobulin-like-1 antigen — Incorrect. While alpha-2-macroglobulin-like-1 antigen (protease inhibitor) autoantibodies have been detected in PNP patients, antibodies against desmosome plakin proteins are more sensitive and specific.[3]

C. Desmoglein 1 — Incorrect. While autoantibodies against desmoglein 1 have been detected in PNP patients, it is much less likely to be associated with the condition compared to the other antigens listed.[3]

D. BP230 — Incorrect. Autoantibodies against BP230 (component of hemidesmosomes) are commonly detected in the sera of PNP patients. BP230 is a member of the plakin family but it is not as specific marker for PNP as periplakin and envoplakin. It is also more commonly associated with bullous pemphigoid.[3]

E. Desmoglein 3 — Incorrect. Desmoglein 3 autoantibodies may be detected in PNP patients. However, it is not specific for PNP and more frequently associated with pemphigus vulgaris. Autoantibodies against desmosome plakin proteins are more specific for PNP.[3]

Abbreviations used:

BP230: Bullous pemphigoid antigen I
CLL: chronic lymphocytic leukemia
IF: indirect immunofluorescence
PNP: paraneoplastic pemphigus

Conflicts of interest

None disclosed.

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