

Systemic delayed hypersensitivity reaction to chlorambucil: a case report and literature review

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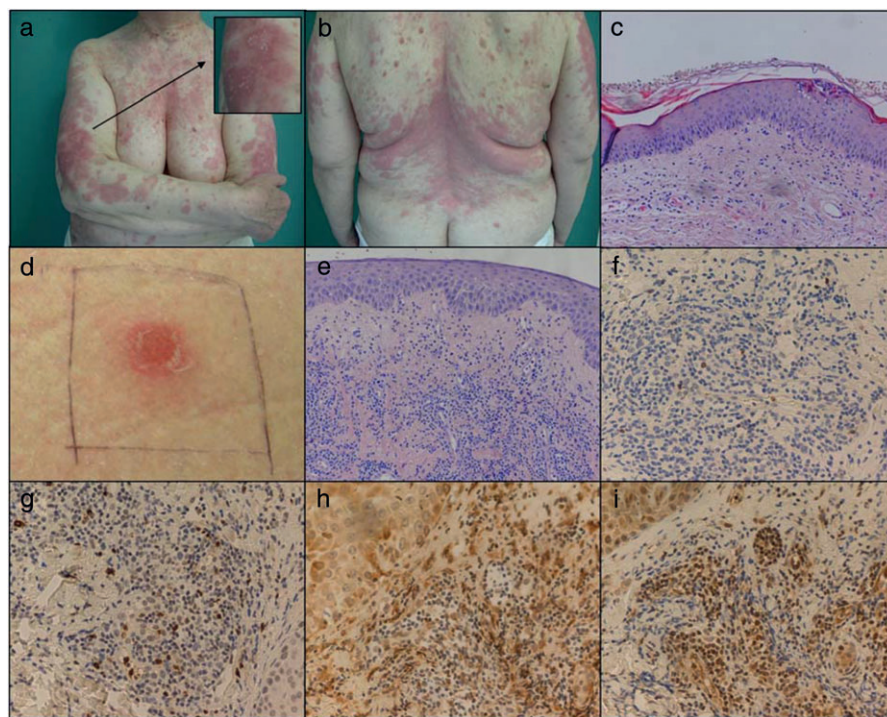
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Chlorambucil is an alkylating agent and a stable derivative of nitrogen mustard. It is primarily used for the treatment of several chronic lymphoproliferative diseases. The drug is generally well tolerated. Significant acute toxicities are dose-related bone marrow depression (leukopenia and thrombocytopenia), gastrointestinal tract symptoms (anorexia, nausea, and vomiting), and neurotoxic manifestations. Cutaneous adverse drug

Fig. 1. (a, b) Erythema multiforme-like eruption with (arrow) focal pustules. (c) Skin biopsy: spongiosis with lymphocytes and eosinophils infiltrating into the upper dermis. (d) Positive patch test reaction to chlorambucil (++) at day 4). (e) Patch test biopsy: spongiosis and lymphocytic infiltrate. (f–i) Immunohistochemical findings: (f) CD8⁺ lymphocytes, (g) high expression of perforin, (h) high expression of granzyme B, and (i) high expression of fatty acid synthase ligand.



reactions (CADRs) attributable to chlorambucil are rarely reported (1).

Case Report

A 76-year-old non-atopic woman was admitted with an itchy widespread erythema multiforme-like eruption and focal pustules on the upper limbs (Fig. 1a,b) without mucosal involvement and systemic symptoms. She had been recently diagnosed with chronic lymphocytic leukaemia and treated with oral chlorambucil (8 mg daily) and prednisone (25 mg daily) for 10 days every month. The eruption started 4 days after the end of the third therapy cycle. Testing with a full laboratory panel, including autoimmunity, inflammatory and serological (Epstein–Barr virus, cytomegalovirus, hepatitis C, and hepatitis B) markers, pustule swab, and chest X-ray, gave negative results. Skin biopsy revealed spongiosis with lymphocyte exocytosis, an upper dermal infiltrate with lymphocytes, and eosinophils (Fig. 1c). Chlorambucil was stopped, and the eruption resolved with 2 weeks of continuing oral prednisone (25 mg daily) and topical clobetasol (twice daily).

Four months later, patch testing with chlorambucil 0.1% pet. was performed, with 48 h of occlusion by the use of Haye's Test Chambers® (Haye's Service, Alphen aan den Rijn, The Netherlands) on Soffix® tape (Artsana, Grandate, Italy). The readings on day (D) 2, D4, and D7,

according to ICDRG criteria, showed a ++ reaction to chlorambucil (Fig. 1d), which yielded negative reactions in 20 control subjects. A biopsy of the positive patch test reaction confirmed the same eczematous findings as in lesional skin (Fig. 1e); the related immunohistochemical study (2) showed CD8⁺ lymphocytes, and high expression of perforin, granzyme B (GrB), and fatty acid synthase ligand (FASL) (Fig. 1f–i).

Discussion

CADRs induced by chlorambucil are rare, mainly delayed and severe, and present with variable clinical manifestations (Table S1 in File S1) (1, 3–11). Among these, pustular features have never previously been reported. Our case confirms the diagnostic value of patch testing in the setting of chlorambucil non-immediate CADRs. In fact, a literature review showed that patch tests with chlorambucil, if performed in patients with systemic delayed reactions, always gave positive results (Table S1 in File S1). Patch test concentrations varied widely from 0.01% to 10% (Table S1 in File S1); herein, we have shown that a low concentration (0.1%) is safe and able to elicit a positive result, as confirmed by the patch test biopsy. Moreover, the immunohistochemical study performed on the positive patch test allowed us to speculate on the involved pathogenic mechanism: the high expression levels of perforin, GrB, FASL and CD8⁺ lymphocytes

suggest a IVc cytotoxic mechanism, as observed in toxic epidermal necrolysis (TEN) (12). This finding underlines the high specificity of a patch test in systemic delayed reactions. When a pathogenic IVc mechanism is hypothesized, a challenge test performed without, or before, a patch test could cause not only recurrence of the same CADR (1, 6–8), but also a more severe reaction, such as TEN (2).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

File S1. Supporting information

Table S1. Cases of chlorambucil sensitivity reported in the literature.

Table 1. Cases of chlorambucil sensitivities reported in literature

Authors	Sex, age	Clinical manifestations	Patch test ^o		Challenge
			%	Result	
Vissian MM, et al (3)	M, 14	TEN		Np	Np
Knisley RE, et al (4)	F, 62	Maculo-papular eruption	Unknown	pos	Np
Millard LG, et al (5)	M, 69	UAS	0.01, 0.1, 1.0	neg	Pos
Peterman A, et al (6)	F, 61	Urticarial-like eruption		Np	Pos
Hitchins RN, et al (7)	F, 72	Bullous EM		Np	Pos
	F, 58	Maculo-papular eruption	Unknown	pos	Pos*
	M, 72	Exfoliative dermatitis	Unknown	pos	Pos*
Barone C, et al (8)	F, 57	TEN	5, 10	pos	Pos*
Zervas J, et al (9)	M, 75	Generalized itching		Np	Np
Torricelli R, et al (10)	M, 63	Erythroderma	Unknown	pos	Np
Aydogdu I, et al (11)	M, 60	TEN		Np	Np
Vaida I, et al (1)	M, 70	DRESS		Np	Pos

TEN: Toxic Epidermal Necrolysis; UAS: Urticaria-Angioedema Syndrome; EM: Erythema multiforme;
DRESS: Drug reaction with eosinophilia and systemic symptoms.

Np: Not performed; ^o: all in pet.; pos: positive; neg: negative; *performed before the patch test.