Atypical features of cutaneous adverse drug reactions during therapy for hairy cell leukemia

Julie Castagna, Emmanuelle Amsler, Flore Kurihara, François Chasset, Annick Barbaud, Angèle Soria

Clinical Communications

Atypical features of cutaneous adverse drug reactions during therapy for hairy cell leukemia

Julie Castagna, MD[a, *]

julie.castagna@aphp.fr

Emmanuelle Amsler, MD[a]

Flore Kurihara, MD[a]

François Chasset, MD[a]

Annick Barbaud, MD, PhD[a]

Angèle Soria, MD, PhD[a, b]

[a]Service de Dermatologie et d'Allergologie, Hôpital Tenon, Paris HUEP, APHP, Paris, Sorbonne Universités, Paris, France

[b]Centre d'Immunologie et des Maladies Infectieuses – Paris (Cimi-Paris), INSERM U1135, Paris, France

*Corresponding author: Julie Castagna, MD, Service de Dermatologie-Allergologie, Hôpital Tenon, AP-HP, Sorbonne Université, 4, rue de la Chine, 75020 Paris, France.

Conflicts of interest: E. Amsler and A. Soria received fees from Sanofi-Genzyme and Novartis laboratories. F. Chasset received fees from GlaxoSmithKline and Celgene laboratories (advisory board). A. Barbaud received fees from Novartis and Genevrier laboratories. The rest of the authors declare that they have no relevant conflicts of interest.

Clinical Implications

- Cutaneous adverse drug reactions in patients with hairy cell leukemia treated with cladribine could be potentially severe with a high incidence of systemic symptoms. An extensive allergological workup is needed for cutaneous adverse drug reactions in patients with hairy cell leukemia treated with cladribine because of a high risk of cosensitization.

Hairy cell leukemia (HCL) is a rare mature B-cell leukemia. Patients classically display splenomegaly, pancytopenia, and typical hairy lymphocytes accumulated in the spleen and bone marrow. The purine analog cladribine is the first-line treatment for HCL and induces high rates of long-lasting remission. Recently, some publications have reported a high incidence of cutaneous adverse drug reactions (CADRs) in individuals with HCL treated with cladribine.[1,2] Herein, we report clinical features and drug test results related to CADRs in patients with HCL after cladribine therapy.

All patients with suspected CADRs after cladribine therapy for HCL between 2005 and September 2019 in our department were included.

We retrospectively collected clinical data and drug allergy workup data. After chronological analysis of all suspected drugs, patch tests were performed first. If results were negative, skin prick tests and intradermal skin tests (for drugs with injectable form) with delayed reading at day 2 were performed for all suspected drugs (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Finally, challenge tests were administered for drugs that tested negative. For some patients and when necessary, cross-reactivity between drugs of the same class was explored.

Twelve patients were included (Table I): 5 women and 7 men with a median age of 52 years (31-68). Eight patients had maculopapular exanthema (MPE) with systemic symptoms (MPE-SS, systemic symptoms including fever and visceral involvement appearing simultaneously or in the few days following skin rash and with a RegiSCAR score < 4) (Figure 1, *A*), 2 patients had acute generalized exanthematous pustulosis (AGEP), and 2 patients had drug rash with eosinophilia and systemic symptoms (DRESS) syndrome (RegiSCAR score ≥ 4). For all patients, skin rash occurred during the aplasia stage, with a median occurrence at 12 days (10-15) after cladribine initiation.

Table I Clinical and allergological data in 12 cladribine-treated patients with HCL with CADRs

No.	Sex/age (y)	Clinical presentation/skin	Suspected drug (duration of	Culprit drug confirmed with	Cosensitization/cross-reactivity	Recurrence

		histology	treatment in days before reaction)	positive skin test result/positive provocation test result		
1	F/43	MPE-SS/compatible with CADRs	Cotrimoxazole (10), allopurinol (10)	0/ND	No/ND	0
2	F/59	DRESS syndrome/compatible with neutrophilic dermatitis	Valaciclovir (17), atovaquone (17), allopurinol (10)	Atovaquone (PT)/0	Yes/ND	MPE with amoxicillin 8 mo later
3	M/54	AGEP/compatible with AGEP	Valaciclovir (21), cotrimoxazole (21)	Valaciclovir, cotrimoxazole (PT)/ND	Yes/yes (aciclovir)	AGEP with amoxicillin and IFN-α-2b 4 y later, DRESS syndrome with cefuroxime 8 y later
4	F/36	MPE-SS/compatible with CADRs	Piperacillin-tazobactam (9), valaciclovir (9), atovaquone (9), clarithromycin (1), amikacin (1)	Piperacillin-tazobactam, valaciclovir, atovaquone (PT)/0	Yes/yes (amoxicillin)	0
5	M/55	MPE-SS/normal	Cotrimoxazole (10), amoxicillin-clavulanic acid (4), ciprofloxacin (4)	Amoxicillin-clavulanic acid (PT)/0	No/ND	0
6	M/50	MPE-SS/compatible with CADRs	Cotrimoxazole (10), fluconazole (10)	0/cotrimoxazole	No/ND	0
7	F/64	DRESS syndrome/compatible with CADRs	Valaciclovir (10), atovaquone (10), ciprofloxacin (2), cefixime (2)	Atovaquone (PT)/0	No/ND	0
8	M/43	MPE-SS/compatible with CADRs	Metoclopramide (10), cotrimoxazole (9), lederfoline (9), amoxicillin-clavulanic acid (3), ciprofloxacin (3)	Amoxicillin-clavulanic acid (IDT)/ND	No/ND	0
9	M/47	AGEP/ND	Atovaquone (10), valaciclovir (10), ceftriaxone (1), iopromide (0)	Atovaquone, valaciclovir, iopromide (PT)/ND	Yes/no	0
10	M/54	MPE-SS/ND	Cotrimoxazole (9), amoxicillin-clavulanic acid (4), ciprofloxacin (4), piperacillin-tazobactam (0), amikacin (0)	Amoxicillin-clavulanic acid, piperacillin-tazobactam (PT)/0	No/yes	MPE with amoxicillin 5 y later
11	F/68	MPE-SS/compatible with CADRs	Cotrimoxazole (5), valaciclovir (5)	0/valaciclovir	No/ND	0
12	M/31	MPE-SS/compatible	Piperacillin	Piperacillin	Yes/yes (amoxicillin	MPE with iomeprol 6 mo later

12	M/31	MPE-SS/compatible with CADRs	Piperacillin-tazobactam (30), meropenem (8), iomeprol (6)	Piperacillin-tazobactam, iomeprol (IDT)/systemic reactivation during skin testing (Figure 1, *C*)	Yes/yes (amoxicillin-clavulanic acid, iobitridol, iodixanol, iohexol [Figure 1, *B*])	MPE with iomeprol 6 mo later

F, Female; *IDT*, intradermal test; *M*, male; *ND*, not done; *PT*, patch test.

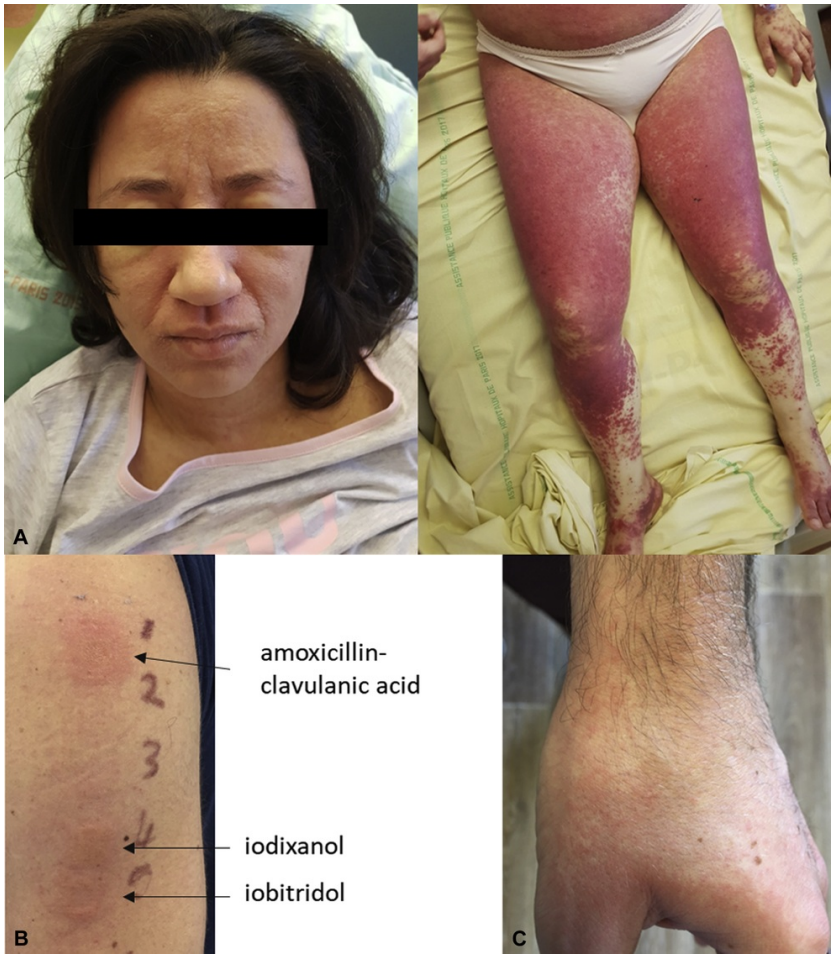

Figure 1 (**A**) MPE in patient 4. (**B**) Drug skin test results for patient 12: positive patch test results for amoxicillin-clavulanic acid and 2 iodinated contrast agents (iodixanol and iobitridol) on day 2. (**C**) Reactivation of MPE on day 2 in patient 12 during positive patch test results for amoxicillin-clavulanic acid and iodixanol and iobitridol.

Drug allergy evaluations were positive in 11 of 12 patients, and the results are presented in Table I. Antibiotics (cotrimoxazole, piperacillin-tazobactam, amoxicillin-clavulanic acid), valaciclovir, atovaquone, and iodinated contrast media were inducers in 7, 4, 4, and 2 patients, respectively. Cladribine was not implicated because of the lack of chronological imputability due to its short half-life of a few hours (5.4 hours). A cosensitization (defined by more than 1 positive drug skin test result and/or drug challenge test result) to different molecule classes was found in 5 of 12 patients. A cross-reactivity between molecules of the same

class was observed in 4 of 5 patients (Fig 1, *B*). Moreover, 4 patients had at least 1 other CADR (3 MPE, 1 DRESS, and 1 AGEP) several months/years after the first episode; the additional CADR appeared after readministration in patients 10 and 12 and after new sensitization to another drug class in patients 2 and 3, confirmed by drug allergy evaluations (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). For patient 12, reactivation of MPE, without systemic symptoms, was induced by drug skin tests (Fig 1, *C*). All patients were in the aplasia stage during CADRs, and 8 of 12 patients still had lymphopenia at least 6 months after cladribine administration, including 3 of 4 patients with CADR reoccurrence.

CADRs are skin manifestations resulting from systemic drug administration, ranging from erythema to much more severe reactions such as AGEP, DRESS syndrome, or toxic epidermal necrolysis with systemic involvement (hepatitis, interstitial nephritis, or pulmonary, cardiac, or pancreatic involvement). Moreover, overlapping features between MPE and DRESS syndrome, called MPE-SS, have been described, suggesting a continuous spectrum between both diseases, with minor forms of DRESS syndrome, also called MP/DR[3] and mini-DRESS,[4] existing.

Thirty-eight cases of CADRs have been previously reported in patients with HCL treated with cladribine. Among them, 13 patients had systemic symptoms and 2 patients had severe CADRs (1 patient had DRESS syndrome, and 1 patient had lethal toxic epidermal necrolysis). The median delay in onset after cladribine introduction was 14 days (3-187). In 3 patients, a possible cosensitization to multiple drugs was suspected[1,5,6] but was confirmed in only 1 patient.[6]

Meher-Homji et al[2] recently showed a higher prevalence of antibiotic allergy in cladribine-treated patients with HCL (26 of 43 patients [60.47%]), compared with that in cladribine-treated patients with hematological malignancies (14%) and that in fludarabine-treated patients with chronic lymphocytic leukemia or follicular lymphoma (25%). Among the 26 patients allergic to antibiotics, 3 had DRESS syndrome (RegiSCAR score = 4) and 1 had MPE-SS. Only 5 of 26 patients had allergological investigations with skin tests, results for which were positive for antibiotics in 4 patients, but cosensitization was not assessed. As in our series, cladribine was also not tested. Indeed, because of its lack of chronological imputability, having a very short elimination half-time, it is not considered as a causal agent.

We report for the first time a very high risk of cosensitization to CADRs in individuals with HCL treated with cladribine. Cosensitization is an unusual situation reported only in approximately 18% of patients with DRESS syndrome, whereas it occurs in relation to only 0.3% of other CADRs.[7] However, in cladribine-treated patients with HCL, cosensitization was frequently observed (41.7%), even in patients without DRESS syndrome criteria. We also found a risk of CADR reoccurrence after cladribine therapy.

HCL is a rare disease representing 2% of all leukemia and with an annual incidence of 1/500,000. Cladribine is always recommended; it is the first-line treatment.[1] CADRs seem to be more prevalent in HCL than in other hematological diseases treated with cladribine.[2,8]

Interestingly, in a cohort of 68 patients treated with cladribine for mastocytosis reported by Barete et al,[8] no patient declared CARD. Thus, the role of cladribine is not clear, but we hypothesize that durable immune alterations due to both cladribine therapy and the abnormal functionality of lymphocytes during HCL could be responsible for this high rate of CADRs. Indeed, a profound $CD4^+$ lymphopenia, including regulatory T cells, is induced by cladribine and could result in hypersensitivity and decrease drug tolerance in patients with HCL.[1] This could be similar to the immune alterations induced by immune checkpoint blockade in melanoma, which enhance the risk of CADRs with other subsequent therapies.[9] However, there is no study confirming this hypothesis.

Allergists, dermatologists, and hematologists should be aware of the risk of potentially severe CADRs and the high risk of cosensitization for patients with HCL treated with cladribine.

Acknowledgments

We thank Dr Hafida Gaouar, Dr Tullia De Risi-Pugliese, and Dr Aurore Hamelin for providing cases and for their help in the realization of this work. We obtained written permission to include their names in the Acknowledgments section.

References

1. C. Ganzel, M.E. Gatt, A. Maly, D. Ben-Yehuda and N. Goldschmidt, High incidence of skin rash in patients with hairy cell leukemia treated with cladribine, *Leuk Lymphoma* **53**, 2012, 1169–1173.

2. Z. Meher-Homji, C.S. Tam, J. Siderov, J.F. Seymour, N.E. Holmes, K.Y.L. Chua, et al., High prevalence of antibiotic allergies in cladribine-treated patients with hairy cell leukemia—lessons for immunopathogenesis and prescribing, *Leuk Lymphoma* **1**, 2019, 1–6.

3. M. Pinto Gouveia, A. Gameiro, I. Coutinho, N. Pereira, J.C. Cardoso and M. Gonçalo, Overlap between maculopapular exanthema and drug reaction with eosinophilia and systemic symptoms among cutaneous adverse drug reactions in a dermatology ward, *Br J Dermatol* **175**, 2016, 1274–1283.

4. C. George, A. Sears, A.-G. Selim, S. Walsh and D. Creamer, Systemic hypersensitivity reaction to Omnipaque radiocontrast medium: a case of mini-DRESS, *Clin Case Rep* **4**, 2016, 336–338.

5. M.R. Grey, N.G. Flanagan and P.R. Kelsey, Severe skin rash in two consecutive patients treated with 2-chlorodeoxyadenosine for hairy cell leukaemia at a single institution, *Clin Lab Haematol* **22**, 2000, 111–113.

6. A. Kokunai, H. Azusawa, H. Murota, C. Ohhata, I. Katayama, S. Murata, et al., Hypersensitivity reactions to multiple drugs during the course of hairy cell leukemia treated with 2-chlorodeoxyadenosine, *Arerugi* **55**, 2006, 662–666.

7. A. Barbaud, E. Collet, B. Milpied, H. Assier, D. Staumont, M. Avenel-Audran, et al., A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions: drug patch tests for SCAR, *Br J Dermatol* **168**, 2013, 555–562.

8. S. Barete, O. Lortholary, G. Damaj, I. Hirsch, M.O. Chandesris, C. Elie, et al., Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis, *Blood* **126**, 2015, 1009–1016, quiz 1050.

9. A.R. Naqash, D.M. File, C.M. Ziemer, Y.E. Whang, P. Landman, P.B. Googe, et al., Cutaneous adverse reactions in B-RAF positive metastatic melanoma following sequential treatment with B-RAF/MEK inhibitors and immune checkpoint blockade or vice versa: a single-institutional case-series, *J Immunother Cancer* **8** (7), 2019, 4.

Online Repository

Table E1 Concentrations and vehicles used for patch test and prick and intradermal tests

Drug	Patch test*	Prick test	Intradermal test
Amoxicillin	Amoxicillin trihydrate 10% petrolatum (Chemotechnique)	200	2-20
Amoxicillin/clavulanic acid	Amoxicillin trihydrate 10% petrolatum + potassium clavulanate 10% petrolatum (Chemotechnique)	200/40	2/0.4-20/4
Piperacillin-tazobactam	Piperacillin-tazobactam 10% petrolatum (lyophilysate of commercial solution)	200/25	2/0.25-20/2.5
Iomeprol	As is (150)	150	15-150
Iobitridol	As is (250)	250	25-250
Iodixanol	As is (270)	270	27-270
Iohexol	As is (180)	180	18-180

Drugs concentrations used for skin tests are in milligram per milliliter.

* Patch tests were performed with Chemotechnique supports when they were available. If not, the drugs were diluted freshly, as follows: - diluted to 30% in petrolatum for tablets, - diluted to 30% in saline for commercial solutions and/or as is for iodinated contrast media, and - diluted to 10% in petrolatum for lyophilysate of commercial solution.

Table E2 Drug allergy evaluations for CADR recurrences in patients 2 and 3

Patient no.	Sex/age (y)	Clinical presentation	Suspected drug (duration of treatment in days before reaction)	Culprit drug confirmed with positive skin test result/positive provocation test result
2	F/59	MPE 8 mo after first reaction	Amoxicillin (0)	Amoxicillin (IDT)/ND
3	M/54	AGEP 4 y after first reaction	Amoxicillin (1) and IFN-α-2b (10)	Amoxicillin (patch test and IDT), IFN-α-2b (IDT)/ND
		DRESS syndrome 10 y after first reaction	Cefuroxime (1)	Patch test result with cefuroxime negative, positive with ceftriaxone (cross-reactivity exploration)/ND

F, Female; *IDT*, intradermal test; *M*, male; *ND*, not done.

Queries and Answers

Query: If there are any drug dosages in your article, please verify them and indicate that you have done so by initialing this query
Answer: There is no drug dosages.

Query: Correctly acknowledging the primary funders and grant IDs of your research is important to ensure compliance with funder policies. We could not find any acknowledgement of funding sources in your text. Is this correct?
Answer: Yes

Query: Please confirm that the conflicts of interest statement is complete and accurate.
Answer: Yes it is.

Query: Please confirm that given names and surnames have been identified correctly and are presented in the desired order and please carefully verify the spelling of all authors’ names.
Answer: Yes