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High frequency of cutaneous eruptions within the first year after allogeneic hematopoietic stem cell transplantation

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Abstract

Background: The diagnosis and management of eruptions after hematopoietic cell transplantation (HCT) is a challenge due to their atypical clinical presentation and the biology biased by immunosuppression and graft. The diagnosis is therefore based on multiple grounds. Few studies have focused on the occurrence of a skin rash during the first year of transplantation.

Objectives: To assess the frequency of rashes in this period, as well as their differential diagnosis and multidisciplinary management.

Methods: We performed a retrospective monocentric descriptive study in the Department of Blood Diseases of Lille University Hospital. All patients who received allogeneic HCT between January 1, 2018, and December 31, 2019, were included.

Results: We included 196 patients with allogeneic HCT. Of these, 89 (45.4%) presented a skin rash during the first year after transplantation. Among them, 78.7% were diagnosed with acute graft versus host disease (GVHD), 6.7% chemotherapy toxicity, 4.5% chronic GVH, 2.2% of infectious origin and 1.1% drug hypersensitivity. The outcome was mainly favourable (74.2% experienced resolution). A skin biopsy was performed in 9% of cases. Viral polymerase chain reactions (PCRs) were positive in 7.1% of tested patients.

Conclusions: Our study revealed a high frequency of skin rashes in stem cell transplant patients, thus justifying the multidisciplinary management of these high-risk patients, which require both dermatological and haematological early expert assessment.

KEYWORDS
cutaneous reaction, graft versus host disease, hematopoietic stem cell transplantation, skin eruption

INTRODUCTION

Hematopoietic cell transplantation (HCT) is a valuable therapeutic option for both malignant (such as acute leukaemia or multiple myeloma) and nonmalignant haematological diseases (such as aplastic anaemia).[1] The allogeneic HCT itself, the prophylactic immunosuppressive treatment and infections play a role in the development of many different conditions. Indeed, the diagnosis of cutaneous eruption is a challenge for the caring physician due to their variable presentations. Whereas skin reactions following allogeneic HCT are common (affecting 67 of 137 patients during the first 180 days after HCT in the study by Champlain et al.[2]) and may considerably impact the morbidity and the mortality of these patients, few studies have focused on their clinical presentation, epidemiology, and management. Known causes of skin conditions after HCT include the "engraftment" syndrome,[3,4] the eruption after lymphocyte recovery or after aplastic chemotherapy regimen for conditioning,[5] acute graft versus host (GVH) disease (aGVHD)[6,7] (Figure 1), and chronic GVH disease (CGVHD)[6,7] (Figure 2). Other causes are bacterial infection, viral infection or replication (Figure 3),[2] skin toxicity from chemotherapy[8] (Figure 4) and other drug-induced reactions[5] (Figure 5).

In this context of HCT, physicians are faced with atypical clinical presentations, biology biased by immunosuppression and the absence of pathognomonic elements on the histopathological analysis of biopsies.

We aimed to assess the frequency of skin rashes in a population of patients followed during the first year after transplantation in a single university centre and to describe their diagnostic and therapeutic approach.

METHODS

We conducted an observational, descriptive, retrospective study in the Department of Blood Diseases of the University Hospital of Lille, France. All adult patients who received allogeneic HCT, for any indication, from the 1 January, 2018 to the 31 December, 2019, were included. All patients were written informed of potential research using collected data in the field of healthcare research.

All patients were seen every week in haematologic consultation for clinical examination and laboratory test assessment for several months. A dermatologist was

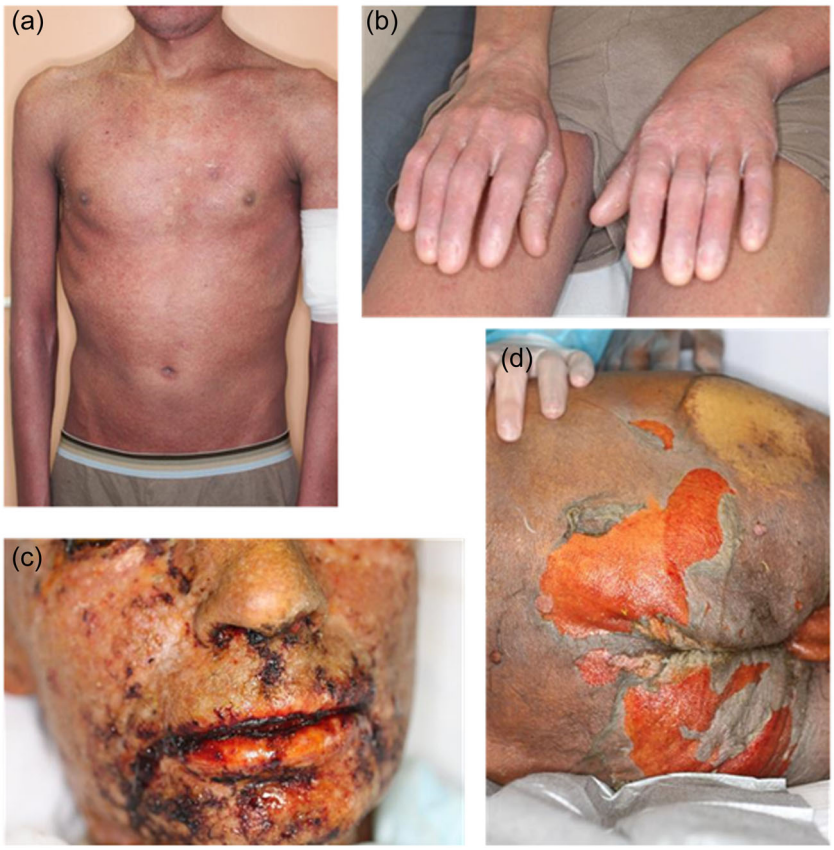

FIGURE 1 Acute graft-vs.-host disease (aGVHD) (a) and (b) maculopapular eruption. (c) and (d) Epidermal necrolysis.

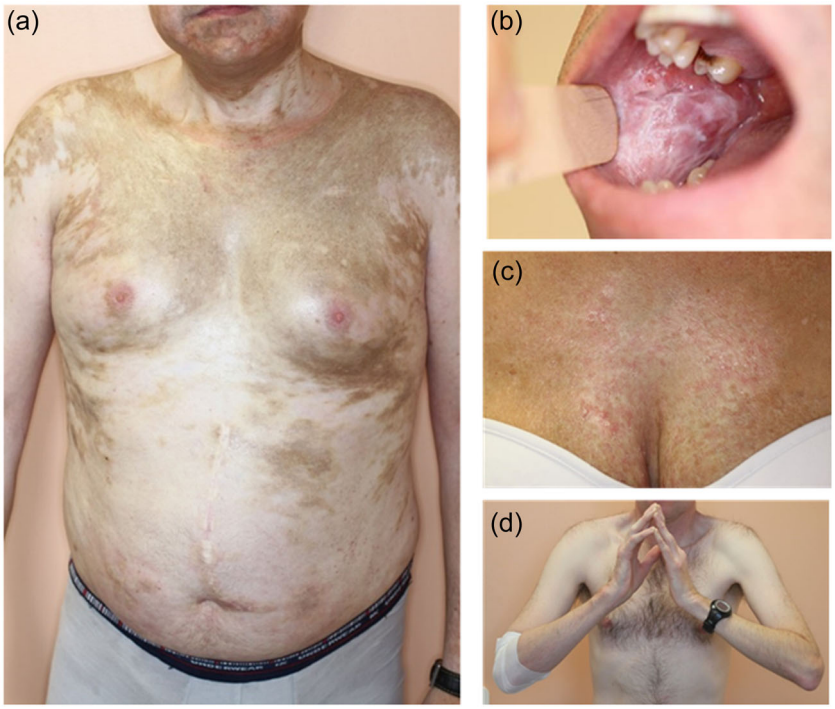

FIGURE 2 Chronic graft-versus-host disease (cGVHD) (a) Poikiloderma. (b) Mucosal lichenoid involvement. (c) Cutaneous lichenoid involvement. (d) Sclerosis.

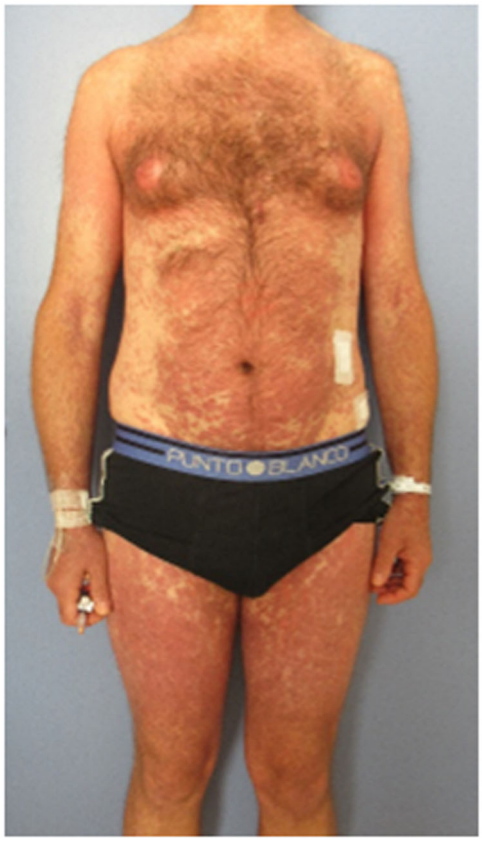

FIGURE 3 Viral eruption (EPSTEIN-Barr virus [EBV]).

consulted if there were diagnostic or management difficulties. Biopsies were then performed by the dermatologist in case of diagnostic uncertainty. Data were collected from computerized medical record.

Based on the normal or nonnormal distribution determined by the Shapiro–Wilk test, the quantitative variables were expressed as mean (standard deviation) if the distribution was normal and median (quartile 1–quartile 3) in the opposite case.

The study was approved by the French "commission nationale de l'informatique et des libertés" under the reference "DEC21-182."

RESULTS

Population

We included 196 patients who received allogeneic HCT between January 2018 and December 2019. No patients were excluded from the analysis. We recorded 78 women (39.7%) and 118 men (60.2%), with a mean age of 52.3 ± 13.0 years. Ten patients had a history of skin disease (5.1%) and 51 declared potential drug allergy that was ruled out by skin test (26%) (Table 1). Allogeneic HCT was performed for 117 acute

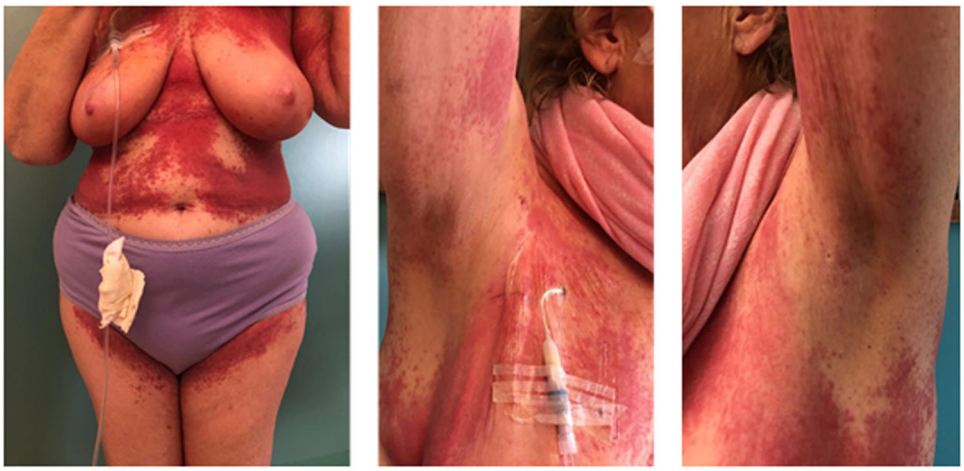

FIGURE 4 Chemotherapy toxicity 4 days after cytarabine (acute myeloblastic leukaemia).

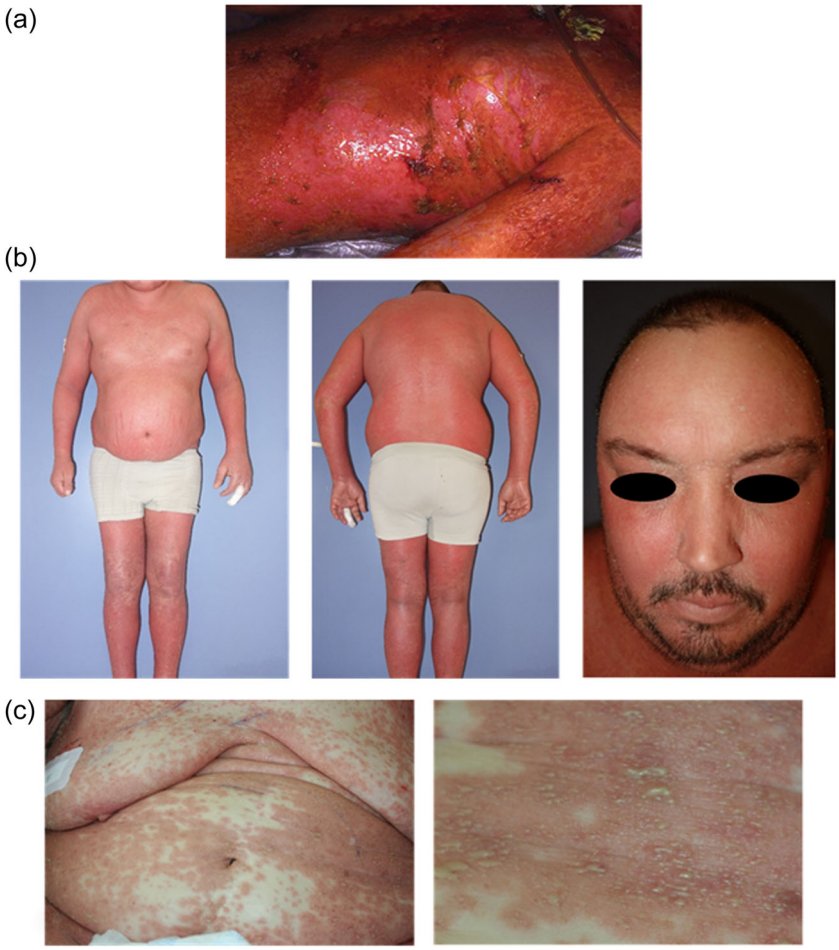

FIGURE 5 Drug hypersensitivity. (a) Toxic epidermal necrolysis. (b) Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. (c) Acute generalized exanthematous pustulosis.

leukaemias (59.7%), 29 myelodysplastic syndromes (14.8%), 25 lymphomas (12.8%), 18 myeloproliferative syndromes (9.2%), 4 bone marrow aplasias (2%) and 2 myelomas (1%). There were 99 matched-unrelated (50.5%), 41 matched-related (20.9%), 30 mismatched-unrelated (12.7%) and 25 mismatched-related (12.7%) transplants. Stem cells were mainly derived from peripheral blood ($n = 120$, 61.2%). (Table 1).

TABLE 1 Description of the study population.

Settings	Values *n* (%)
Mean age	52.3 (13.0)
Gender	78 females/118 males
Dermatologic history	10 (5.1%)
Allergic history	51 (26%)
Acute leukaemia	117 (59.7%)
Myelodysplastic syndrome	29 (14.8%)
Lymphoma	25 (12.8%)
Myeloproliferative syndrome	18 (9.2%)
Aplasia	4 (2%)
Myeloma	2 (1%)
Number of therapeutic lines	2 (1–3)
Types of transplants	
Matched related	41 (20.9%)
Matched unrelated	100 (51%)
Mismatched related	25 (12.7%)
Mismatched unrelated	30 (15.3%)
Origin of the HCT	
Peripheral blood	120 (61.2%)
Medullary	76 (38.8%)
Umbilical cord	0 (0%)

Abbreviation: HCT, hematopoietic cell transplantation.

Characteristics of the skin eruption

We observed 89 patients (45.4%) who experienced a rash during the first year after transplantation. The median time lapse from transplantation to the onset of rash was 32 (19–308) days. The retained diagnoses were acute GVH disease ($n = 70/89$, 78.7%), chemotherapy-related toxicity ($n = 6/89$, 6.7%), rash from infectious origin ($n = 2/89$, 2.2%) (1 perineal cellulitis and 1 mycosis), chronic GVH disease ($n = 4/89$, 4.5%) and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome ($n = 1/89$, 1.1%) (Figure 6). For six patients, other diagnoses were made (6.7%), including rosacea, erythema nodosum, eczema, palmoplantar erythema, erythema ab igne and urticaria. The diagnoses according to the different types of HCT are summarized in Figure 7. The clinical characteristics by diagnostics are described in Table 2. Among the 89 patients who experienced a skin rash, the final diagnoses were made in 65 cases by the haematologists alone (73.0%) whereas in 24 cases the dermatologist's expertise was required (27.0%).

Blood viral tests

During the rash, blood viral PCR (polymerase chain reaction) was performed in 85 patients (95.5%) and was positive in six patients (7.1% of the tested patients). The most frequent virus identified was HHV6 (4 positive of 81 tested). The viral testing profile is detailed in Table 3. All patients with positive viral tests had a diagnosis of aGVHD.

Biopsy results

A skin biopsy was done in eight patients (9.0%). Indications of biopsy, results of histopathological analysis and the final diagnoses are described in Table 4. The histological analysis of the skin biopsy was helpful to achieve a final diagnosis among differential diagnoses in three cases, to confirm the suspected diagnosis in one case, and to diagnose an unsuspected disease in one case. In two other cases, the retained diagnosis was not supported by the biopsy analysis.

Management

Treatment was systemic corticosteroids in 51 patients (57.3%), topical corticosteroids in 45 patients (50.6%), initiation or increase in the dosage of an immunosuppressant in 12 patients (13.5%), abstention and closed monitoring for 11 patients (12.4%), use of moisturizers in 8 patients (9.0%), discontinuation of suspected causative drug in 2 patients (2.2%) and antibiotics in 1 patient (1.1%). Another therapy was prescribed for three patients (9.0%) (one specific treatment of haematologic disease, one photopheresis and one antihistamines).

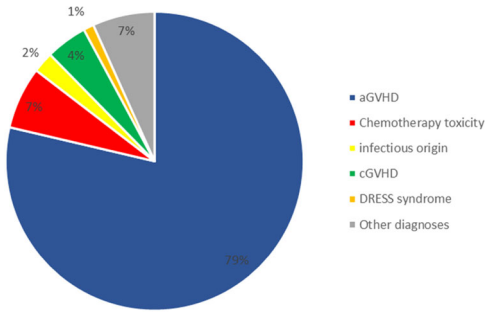

FIGURE 6 Proportion of each retained diagnosis.

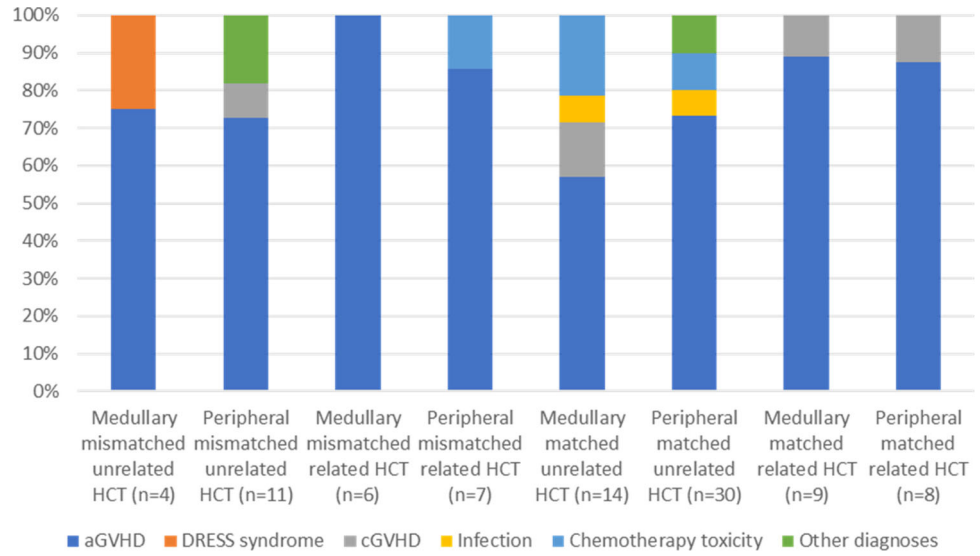

FIGURE 7 Retained diagnoses according to the type of hematopoietic cell transplantation (HCT): Medullary mismatched unrelated HCT (four patients: three acute graft versus host disease [aGVHD], 1 DRESS). Peripheral mismatched unrelated HCT (11 patients: 8 aGVHD, 1 chronic graft versus host disease [cGVHD], 2 other diagnoses [1 urticaria, 1 unknowing diagnosis]). Medullary mismatched related HCT (six patients: six aGVHD). Peripheral mismatched related HCT (seven patients: six aGVHD, one chemotherapy toxicity). Medullary matched unrelated HCT (14 patients: 1 infection, 2 cGVHD, 8 aGVHD, 3 chemotherapy toxicity). Peripheral matched unrelated HCT (30 patients: 2 infection, 22 aGVHD, 3 chemotherapy toxicity, 3 other diagnoses [1 rosacea, 1 eczema and 1 unknowing diagnosis]). Medullary matched related HCT (nine patients: one cGVHD, eight aGVHD). Peripheral matched related HCT (eight patients: one cGVHD, seven aGVHD).

Outcome

During follow-up, 66 patients (74.2%) had fully recovered, in 4 patients (4.5%), symptoms had worsened, in 7 patients (7.9%) symptoms had changed, 3 patients (3.4%) were stable and 9 (9.0%) were improved. At 12 months, 56 complete remissions (63.0%) and 21 deaths (23.6%) were recorded for patients with a rash, whereas 62 complete remissions (58.0%) and 28 deaths (26.1%) were recorded for patients without a rash.

DISCUSSION

Our study included 196 patients with allogeneic HCT between 2018 and 2019, mainly treated for acute leukaemia (59.7%). Half of the patients received a pheno-identical allogeneic HCT (50.5%) from peripheral circulating blood (61.2%). Regarding our primary endpoint, 89 patients (45.4%) developed a skin rash following allogeneic HSCT within a period of 32 (range: 19–308) days after the allogeneic HCT. Acute GVHD was the most common diagnosis (78.7%).

There are few recent studies in the literature regarding skin rashes in allogeneic HCT. Our institution is the only one performing HCT according to international guidelines in the North of France. The standardized management of patients allows for a precise phenotyping of a representative population of patients with allogeneic HCT. Patients are regularly followed up in a haematology consultation (weekly during the first months after transplantation) with a systematic clinical examination and a biological assessment. Thus, the records of dermatological manifestations are exhaustive. In case of diagnostic uncertainty or unfavourable evolution, patients are seen in a collegial consultation between haematologist and dermatologist. No patients were lost for follow-up during the study period.

Our study highlights the high frequency of rashes in allogeneic HCT patients. Almost half of the patients present a rash during the first year of follow-up. The frequency is even higher in the study of Champlain et al.,[2] with 67% out of 137 in allograft patients developing a rash within the first 180 days after transplantation. Hence, a skin rash is a common event that requires appropriate management.

Our results are concordant with the literature since the retained diagnoses were mainly aGVHD in the studies by Champlain et al. (45%)[2] and Chanprapah et al. (58%).[9] The main differential diagnosis is drug hypersensitivity. In our study, only one case of DRESS syndrome was described, and in the study of Champlain et al., 8% of rashes were consistent with drug hypersensitivity. The diagnosis of drug hypersensitivity is a

TABLE 2 Clinical characteristics by diagnosis.

Settings	aGVHD ($n = 70$)	cGVHD ($n = 4$)	DRESS ($n = 1$)	Infection ($n = 2$)	Toxicity ($n = 6$)
Type of HCT					
Matched related	21%	50%	0%	0%	0%
Matched unrelated	43%	25%	0%	100%	83%
Mismatched unrelated	19%	25%	100%	0%	17%
Mismatched related	17%	0%	0	0%	0%
Peripheral blood	61%	50%	0	50%	50%
Medullary	39%	50%	100%	50%	50%
Delay after HCT(days)	31	177	16	160	17
Localization					
Photoexposed area	4%	0%	100%	0%	17%
Face	62%	25%	100%	0%	33%
Trunk	81%	100%	100%	50%	33%
Back	49%	75%	100%	100%	50%
Arms	53%	50%	100%	50%	83%
Legs	33%	25%	100%	0%	33%
Clinical signs					
Erythema	98%	100%	100%	100%	100%
Papules	30%	50%	0%	0%	20%
Oedema	9%	0%	100%	50%	20%
Purpura	2%	0%	0%	0%	0%
Erythroderma	11%	0%	100%	0%	0%
Skin detachment	5%	50%	0%	0%	0%
Vesicles	7%	0%	0%	0%	20%
Lichenification	4%	50%	0%	0%	0%
Mucosal damage					
Oral	13%	33%	0%	0%	0%
Ophthalmic	5%	0%	0%	0%	0%
Anal	2%	0%	0%	0%	0%
Genital	3%	33%	0%	0%	0%
Associated disorders					
Hepatic	8%	0%	0%	50%	0%
Renal	11%	0%	100%	0%	0%
Pulmonary	6%	0%	100%	0%	0%
Digestive system	27%	0%	0%	0%	0%

Abbreviation: DRESS, drug rash with eosinophilia and systemic symptoms; HCT, hematopoietic cell transplantation.

challenge in the context of multiple drug therapies and immunosuppression. Dermatologic symptoms (maculopapular exanthem, mucosal involvement or bullae) and systemic damage (renal and pulmonary) can be similar in aGVHD and drug hypersensitivity. An early diagnosis is essential since both conditions are serious and potentially life-threatening. Byun et al.[10] aimed to compare the clinical features of GVHD and drug hypersensitivity. They suggested that facial involvement was more often seen in GVHD, especially when both face and palms/soles were involved; however, facial oedema is frequently described as clinical sign of DRESS syndrome. Diarrhoea and hyperbilirubinemia were more frequent in aGVHD.[10] A skin biopsy can support one or another diagnosis, but the results of histopathological analysis must be evaluated with caution and by experienced dermatopathologists.[11] The diagnosis of drug hypersensitivity is firmly based on an imputability investigation and allergy testing, which is not always possible in these patients because of concurrent immunosuppressive treatment or by obvious ethical reasons.

The viral replication or reactivation status was carried out in 85 patients and was positive in 6 (7.1%) cases; all patients with positive blood viral tests were diagnosed with aGVHD. Hence, the results of virological tests must be interpreted with caution.[5] HHV6 is considered as a risk factor of aGVHD,[12] and aGVHD can be associated with viral reactivation. Systematic screening of viral reactivation or primary infection in the context of a skin rash following an allogeneic HCT is then questioned.

Concerning outcomes, no deaths were linked to the skin eruption. In Chanprapaph's study, the mortality following aGVHD was approximately 15%.[9] However, this refers to all aGVHD-related manifestations (i.e., cutaneous, gastrointestinal and liver). Otherwise, no data about morbidity and mortality related specifically to a skin rash following transplantation are available to our knowledge.

Our study has some limitations, especially its retrospective design. The low number of drug reactions did not permit drawing any conclusion regarding clinical data that could be useful to tell drug reactions from aGVH disease.

In conclusion, our study highlights the high frequency of skin eruptions within the first year after allogeneic HCT. A multidisciplinary approach is needed, concerning haematologists and dermatologists for an

TABLE 3 Results of blood viral PCR.

Viral PCR	Number of patients
All performed PCR	85 (95.5% of patients)
All positive PCR	6 (7.1% of the tested patients)
Performed EBV PCR	80 (89.9% of patients)
Positive EBV PCR	1 (1.3% of tested patients)
Performed CMV PCR	83 (93.3% of patients)
Positive CMV PCR	1 (1.2% of tested patients)
Performed HHV6 PCR	81 (91.0% of patients)
Positive HHV6 PCR	4 (4.9% of tested patients)
Performed Parvovirus B19 PCR	10 (11.2% of patients)
Positive Parvovirus B19 PCR	0 (0% tested of patients)

Abbreviation: EBV, EPSTEIN-Barr virus; PCR, polymerase chain reaction.

TABLE 4 Description of indications, results of biopsies and final diagnosis in patients with biopsies.

#	Suspected diagnostic	Biopsy results	Final diagnosis
1	aGVHD	Drug hypersensitivity or aGVHD	aGVHD
2	Relapse of disease	aGVHD	aGVHD
3	Vasculitis or viral eruption	Drug hypersensitivity or aGVHD or viral eruption	No final diagnosis (death)
4	aGVHD or viral eruption	aGVHD > viral eruption	aGVHD
5	Drug hypersensitivity or aGVHD or viral eruption	aGVHD > Drug hypersensitivity or viral eruption	aGVHD
6	aGVHD or drug hypersensitivity	Drug hypersensitivity > aGVHD > viral eruption	aGVHD
7	aGVHD	Viral eruption or eczema> drug hypersensitivity or aGVHD	aGVHD
8	aGVHD or phototoxicity	aGVHD > drug hypersensitivity	aGVHD

Abbreviation: aGVHD, acute graft versus host disease.

appropriate diagnosis and management, especially considering the complexity of these patients and the potential severity of the skin eruption.

AUTHOR CONTRIBUTIONS

Study conception and design: Frédéric Dezoteux, Delphine Staumont-salle, Léonardo Magro, David Beauvais, Valérie Coiteux, Micha Srour. *Data collection*: Valentine Dambricourt, Adrien Bassompierre, Léonardo Magro, David Beauvais, Valérie Coiteux, Benoît Cattteau, Sarah Faiz, Claire Le Calve, Micha Srour. *Analysis and interpretation of results*: Valentine Dambricourt, Frédéric Dezoteux. *Draft manuscript preparation*: Valentine Dambricourt, Frédéric Dezoteux. All authors reviewed the results and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors. The datasets generated during the current study are available from the corresponding author on reasonable request. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Ethics approval (include appropriate approvals or waivers): The study was approved by the French "commission nationale de l'informatique et des libertés" under the reference "DEC21-182." All included patients were informed of the use of their medical data for research purposes.

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