

Drug-Induced Hypersensitivity Syndrome

Clinical and Biologic Disease Patterns in 24 Patients

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Abstract: Drug-induced hypersensitivity syndrome (DIHS), also called drug rash with eosinophilia and systemic symptoms (DRESS), is a severe reaction usually characterized by fever, rash, and multiorgan failure, occurring 1–8 weeks after drug introduction. It is an immune-mediated reaction involving macrophage and T-lymphocyte activation and cytokine release, although no consensus has been reached as to its etiology. The skin, hematopoietic system, and liver are frequently involved. DIHS can mimic severe sepsis, viral infection, adult-onset Still disease (AOSD), or lymphoproliferation.

We describe 24 consecutive patients with DIHS who were hospitalized between September 2004 and March 2008. Criteria for inclusion in this observational study were suspected drug reaction, eosinophilia $\geq 500/\mu\text{L}$ and/or atypical lymphocytes, involvement of at least 2 organs (skin being 1 of them), with suggestive chronology and exclusion of other diagnoses. Our cohort of 12 women and 12 men had a median age of 49 years (range, 22–82 yr), and 11 had skin phototype V or VI. Patients with mild or no rash were immunocompromised (7/24)—defined as treatment with prednisone (≥ 10 mg/d) and another immunosuppressant drug, or human immunodeficiency virus infection. All patients were febrile (>38 °C), 14 had localized or generalized edema, 7 had pharyngitis, 8 had lymphadenopathy, 22 had hepatitis, 4 had nephritis, 2 had noninfectious and nonlithiasic angiocholitis or cholecystitis. Ten patients were hypotensive, 5 of whom had associated laboratory signs and/or imaging findings suggestive of acute myocardial dysfunction. Half of the patients had hemogram abnormalities, including eosinophilia. Nine DIHS patients fulfilled the Fautrel criteria for AOSD diagnosis, including glycosylated ferritin $<20\%$ in 4/11, with or without laboratory characteristics of hemophagocytosis. Twenty DIHS episodes occurred during the less sunny months of October to March.

We determined 25-hydroxyvitamin D₃ (25[OH]D₃) levels in 18 patients and found that 9 patients had vitamin D deficiency (<25 nmol/L or <10 $\mu\text{g/L}$) and 5 had vitamin D insufficiency (25–50 nmol/L). Moreover, 25(OH)D₃ levels were inversely correlated with ferritin values. After culprit-drug withdrawal, outcomes were favorable for all

patients, including those with cardiac abnormalities under slow tapering of glucocorticoids.

We recommend looking for the frequent but underdiagnosed hypersensitivity myocarditis with noninvasive diagnostic tools, such as N-terminal probrain natriuretic peptide, and promptly withdrawing the culprit drug and starting glucocorticoids. Vitamin D deficiency might be a DIHS risk or severity factor, especially for patients with high skin phototype and during the winter. Because DIHS clinical and laboratory patterns share similarities with AOSD and hemophagocytosis, DIHS should be included in their differential diagnoses.

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Abbreviations: 25(OH)D₃ = 25-hydroxyvitamin D₃, AOSD = adult-onset Still disease, CRP = C-reactive protein, DIHS = drug-induced hypersensitivity syndrome, DRESS = drug rash with eosinophilia and systemic symptoms, EBV = Epstein-Barr virus, HHV6 = human herpesvirus 6, HIV = human immunodeficiency virus, IL = interleukin, LDH = lactate dehydrogenase, MRI = magnetic resonance imaging, N = upper limit of normal, NT-proBNP = N-terminal-probrain natriuretic peptide, SMX-TMP = sulfamethoxazole-trimethoprim, Th1-type = T-helper type 1.

INTRODUCTION

Drug-induced hypersensitivity syndrome (DIHS) was described in 1950 by Chaiken et al,¹⁵ as the triad of fever, rash, and multiorgan failure occurring 1–8 weeks after an aromatic anticonvulsant drug had been started. Roujeau and colleagues^{4,7,71} renamed the syndrome DRESS: drug rash with eosinophilia and systemic symptoms. Organ failure differentiates DIHS from other drug-associated eruptions.^{4,7,71} The most frequently imputed drugs are antiepileptics^{4,7,44,48,71,90} (phenobarbital, phenytoin, carbamazepine, lamotrigine); antimicrobials (minocycline,^{5,47,48} β -lactams,⁹⁰ sulfonamides,^{4,7,29,31,63,68,71} abacavir,⁵⁶ nevirapine⁵⁶); and allopurinol,⁹⁰ dapsone,^{7,71} sulfasalazine,⁷ neomecazole,⁷ and fludione.⁷ The biologically reactive metabolites,⁴⁹ for example, hydroxylamine for sulfamethoxazole^{26,63} and arene oxide for aromatic antiepileptics,^{48,61} are thought to play a central role in DIHS.⁶⁴ These metabolites are responsible for a delayed immunologically mediated reaction, with macrophage and T-lymphocyte activation and cytokine release, although no consensus has been reached concerning its etiology.^{7,18,26,48,49,61–64,87,88} The incidence of DIHS is unknown (1/1000–1/10,000 for antiepileptic drugs)^{4,7,44,48,71,90} but is paradoxically higher for immunocompromised patients, such as those with human immunodeficiency virus (HIV) infection.^{19,24} The clinical heterogeneity of DIHS symptoms makes diagnosis difficult. Usual differential diagnoses include severe bacterial or viral infections, malignancies, and autoimmune diseases.^{71–90}

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Systemic glucocorticoids are usually recommended for patients with life-threatening visceral manifestations, such as severe hepatitis, interstitial pneumonia, and nephritis.^{4,7,34,71,72,90} Viral reactivation, mostly human herpesvirus 6 (HHV6), reported by several authors,^{78,85,86} occurring after the onset of symptoms does not change the decision to start glucocorticoids.^{4,7,71,85,86}

The literature on DIHS consists of case reports and retrospective series.^{7,15,71} The outcome can be fatal, mainly attributable to liver failure,^{71,90} when the causative agent is not withdrawn in time. A recent description of fatal DIHS with myocarditis suggested that the clinical and therapeutic management can be improved.⁷²

Before constituting our cohort, we observed patients with established DIHS who had clinical and laboratory manifestations evoking adult-onset Still disease (AOSD). AOSD is a systemic inflammatory condition of unknown etiology and heterogeneous symptoms. Patients typically have high spiking fever, arthralgia or arthritis, transient maculopapular rash, lymphadenopathy, hepatosplenomegaly, serositis, and/or pharyngitis.^{20,28} Marked neutrophilic leukocytosis and high C-reactive protein (CRP) levels are generally present, as are mildly elevated liver enzymes.^{20,28} Hemophagocytic syndrome, due to excessive macrophage activation and cytokine storm, can be associated with AOSD.^{2,22,25,41} Thus, whenever possible, we looked for laboratory signs suggestive of AOSD and/or hemophagocytosis in our patients, paying particular attention to levels of ferritin and its glycosylated form,²⁷ lactate dehydrogenase (LDH), and triglycerides. Indeed, dramatically decreased glycosylated ferritin has been proposed as a diagnostic marker of AOSD.^{27,28}

Some authors have indicated a role of genetic factors in DIHS because its overall incidence is reported to be higher in black people.^{76,77,88,90} Vitamin D insufficiency is more prevalent among people with dark skin.³⁹ Pertinently, vitamin D protects against inflammatory and autoimmune conditions.^{9-13,81} Therefore, we looked for 25-hydroxyvitamin D₃ (25[OH]D₃) insufficiency, which might also play a role in DIHS, in addition to genetic factors. We conducted the current study to identify new informative laboratory parameters and to propose better adapted management based on our series of 24 consecutive DIHS patients followed in a single center.

PATIENTS AND METHODS

Patients

We describe 24 consecutive patients diagnosed with DIHS between September 2004 and March 2008, in a single, 940-bed, university hospital. The patients were hospitalized in internal medicine, dermatology, endocrinology, rheumatology, or hepatogastroenterology departments. All cases included in this observational study were reported to the regional pharmacovigilance center responsible for reviewing patients' medical records with the attending physician to establish a diagnosis of DIHS.

Diagnostic Criteria

DIHS was diagnosed based on the criteria proposed by Bocquet et al⁷ in 1996, and modified in 2004 by Bégon et al⁴ and in 2005 by Roujeau⁷¹ because a cutaneous reaction was inconstant: suspicion of a drug reaction; eosinophilia $\geq 1500/\mu\text{L}$ and/or atypical lymphocytes; and failure of at least 2 organs (skin being 1 of them). However, no consensus has been reached in the literature about DIHS diagnostic criteria, which are still based on consensus by experienced teams.^{4,7,14,44,71,90} The term

"syndrome" denotes that a constellation of signs and symptoms is present. A patient may lack 1 of the features but still satisfy diagnostic criteria. We did not consider severe drug-related cutaneous eruptions without involvement of other organ systems. In our patients, eosinophilia was defined as $>500/\mu\text{L}$, which was our laboratory's upper limit of normal (N). HHV6 infection or reactivation was not systematically sought. Although it was recently proposed as a diagnostic criterion,⁷⁸ it becomes serologically detectable only after DIHS onset, and its presence does not change patient management. Infectious diseases, also responsible for fever and rash, including cytomegalovirus; HIV; Epstein-Barr virus (EBV); and hepatitis A, B, and C viruses, were excluded.

Clinical characteristics and laboratory parameters were recorded for each patient, that is, the clinical manifestations and laboratory findings present at disease onset, the time until diagnosis and until complete recovery, and the highest recorded temperature.

Skin Phototype

Skin phototype was established for each patient, according to Fitzpatrick.³⁰ Patients were classified as phototype I–VI according to the color of their skin and its reaction to moderate sun exposure.

Search for Putative Drugs

We established a list of drugs used within the 8 weeks preceding the onset of symptoms, including self-medications and herbal drugs, after questioning the patient, his/her general practitioner, and pharmacist. This interval was chosen based on previous reports on DIHS.^{7,58,71,78,90} The drugs incriminated were retained after chronology, signs, and symptoms had been analyzed according to the methodology described by Bégaud et al.³ For each patient, 1 or 2 drugs were finally considered at least possibly (positive response to its/their withdrawal with no further investigation) or probably (positive rechallenge) responsible.³ Other diagnoses were excluded after extensive laboratory and imaging investigations. Patient outcomes were compatible with a drug-induced reaction when clinical and laboratory characteristics normalized and no relapse occurred once the drug had been discontinued, sometimes associated with glucocorticoid treatment.³

Laboratory Studies

Standard laboratory tests (hemogram, prothrombin time, liver enzymes, creatine phosphokinase, bilirubin, creatinine, CRP) were available for all patients. For most patients, LDH, triglycerides, and whenever possible, 25(OH)D₃ levels, were measured.

In accordance with recent literature data, we defined vitamin D insufficiency as 25(OH)D₃ values between 25 and 50 nmol/L (10–20 $\mu\text{g/L}$), and vitamin D deficiency as values <25 nmol/L (<10 $\mu\text{g/L}$).⁶ For comparison, we used the median 25(OH)D₃ values determined for 681 patients aged 16–91 years (median, 52 yr) seen in our hospital from October 2006 to March 2007 as the control. This period was chosen because it was during the 6 months of the year with the least sun.⁶

Serum N-terminal-probrain natriuretic peptide (NT-proBNP) was assessed when heart dysfunction was suspected.⁴³ Serum NT-proBNP concentrations <300 ng/L excluded heart failure. Abnormal levels were considered to be 450 (1.5N), 900 (3N), and 1800 ng/L (6N) for patients aged <50 , 50–75, and >75 years, respectively.⁴³

We paid particular attention to laboratory parameters known to be associated with AOSD and/or hemophagocytosis: leukocytosis, CRP, LDH, triglycerides, and ferritin and its

TABLE 1. Demographic Data and Clinical Involvement for 24 Patients With Drug-Induced Hypersensitivity Syndrome

Parameter	No. of Patients (%)
Demographic features	
Sex (age in yr)	
F (46.7 ± 18.7)	12 (50)
M (54.1 ± 15.2)	12 (50)
Skin phototype	
I/II	5 (21)
III/IV	8 (33)
V/VI	11 (46)
Clinical characteristics	
Immunocompromised	11 (46)
Drug-related*	8 (33)
HIV-induced	3 (13)
Fever >38°C	24 (100)
Skin involvement	
Major (requiring hospitalization)	17 (71)
Mild or moderate	7 (29)
Edema†	14 (58)
Lymphadenopathy	8 (33)
Low blood pressure	10 (42)
Major organ dysfunction	
Liver‡	13 (54)
Kidney§	4 (17)
Heart	5 (21)
Biliary tract	2 (8)
Other organ affected	
Lung	4 (17)
Pharynx	7 (29)
Joints	4 (17)
Brain	4 (17)
Pancreas	1 (4)

*Patients were taking prednisone ≥ 10 mg/d and 1 of the following drugs at the time of DIHS onset: methotrexate, azathioprine, leflunomide, sulfasalazine, adalimumab, imatinib mesylate, hydroxyurea, cytarabine, or bortezomib.

†Facial edema, especially around the eyes, is highly suggestive of DIHS and differs from angioedema, which is an immediate anaphylactic reaction.

‡Liver involvement is defined as alanine aminotransferase ≥ 5 times the upper limit of normal value.

§Kidney involvement is defined as a doubling of the previous creatinine value.

glycosylated form. We compared these values in the current patients with those of patients who had been diagnosed with AOSD, with or without hemophagocytosis, by Arlet et al² and Fautrel et al.²⁸ Normal ferritin values were 20–250 $\mu\text{g/L}$. The normal glycosylated ferritin fraction, determined after separation from nonglycosylated ferritin by concanavalin-A affinity chromatography, ranged from 50% to 80% of total ferritin, as previously described.²⁷ We used the classification criteria proposed by Fautrel et al²⁸ for AOSD diagnosis to determine the number of DIHS patients who also met the AOSD criteria. Major criteria were spiking fever $\geq 39^\circ\text{C}$, arthralgia, transient erythema, pharyngitis, neutrophils $\geq 80\%$ of white blood cells, and glycosylated ferritin $\leq 20\%$. Minor criteria were maculopapular rash and leukocytes $\geq 10,000/\mu\text{L}$. At least 4 major criteria

or 3 major criteria + 2 minor criteria are required to diagnose AOSD with 80.6% sensitivity and 98.5% specificity.

Statistical Analysis

Results are expressed as means \pm standard deviation or numbers. For statistical analyses we used SigmaStat software (version 3.0). We used the Mann-Whitney nonparametric test to compare the 25(OH)D₃ values of the DIHS and control groups. We used the Spearman rank-order correlation test to compute the correlation coefficient between ferritin and 25(OH)D₃ levels.

RESULTS

Overall Description

Twenty-four DIHS cases were reported to the pharmacovigilance center. The 24 patients were evenly divided between the 2 sexes, and ranged in age from 22 to 84 years (46.7 \pm 18.7 yr for women and 54.1 \pm 15.2 yr for men) (Table 1). Eleven patients had skin phototypes \geq V.

At admission, all patients were febrile (38–40 °C), sometimes accompanied by chills and shivering. Eleven patients were considered to be immunocompromised: 8 were taking prednisone (≥ 10 mg/d) and another immunosuppressant (methotrexate, azathioprine, leflunomide, adalimumab, imatinib mesylate, hydroxyurea, cytarabine, or bortezomib), and 3 patients were HIV infected.

Seventeen patients had skin lesions sufficiently severe to require hospitalization (see Table 1). Fourteen patients had periorbital and facial edema, without any lingual or pharyngolaryngeal edema. Other markedly edematous areas included hands, legs, feet, penis, and scrotum. A patchy macular and papular, pruriginous rash was the most common skin lesion. The upper trunk, face, and arms became affected first, with the legs becoming involved later. In 3 of these 14 patients, erythroderma ensued. With resolution, desquamation occurred. One patient had leg petechiae associated with edema and a generalized morbilliform eruption. Mucous membrane involvement was subtle, never severe, but was observed in half of the patients: mild or moderate conjunctival redness, erythema of the oral mucosae, tonsillar plaques, pharynx erythema, intraoral petechiae, white papules and/or erosions. All patients with moderate or mild skin reactions were immunocompromised, compared to only 4 of the 17 patients with severe skin involvement.

One patient experienced acute generalized exanthematous pustulosis associated with facial edema and erythroderma; he was considered to have DIHS because of associated multiorgan failures: severe hypotension, hepatitis (elevated liver enzyme levels at 15N), acute renal failure (creatinine 470 $\mu\text{mol/L}$, compared to 130 $\mu\text{mol/L}$ before and after DIHS resolution), cervical and iliac lymphadenopathies >1 cm in diameter, and eosinophilia (7870/ μL).

No patient experienced toxic epidermal necrolysis or Stevens-Johnson syndrome. When a skin biopsy was obtained, the most common histologic finding was edema and keratinocyte necrosis in the epidermis, interface dermatitis, and, in the superficial derma, a dense, perivascular lymphocytic infiltrate with variable edema.

Eight patients had tender, localized or generalized lymphadenopathy, which disappeared after discontinuation of their culprit drug or drugs, sometimes with glucocorticoids. No biopsy was performed.

All but 2 patients had elevated alanine aminotransferase levels, >5N in 13 of them.

Two patients, including 1 with cardiac abnormalities, developed cholangitis or nonlithiasic cholecystitis, ascertained by

liver and biliary tract ultrasonography. Serology and reverse transcriptase-polymerase chain reactions were negative for HHV6, HHV8, cytomegalovirus, and EBV. One of them was HIV infected. Rapid regression, under prolonged glucocorticoids and short-term antibiotics for the former case and with neither surgery nor antibiotics for the latter case, was consistent with the diagnosis of a drug-related event. Recovery was ascertained by ultrasonography or magnetic resonance imaging (MRI).

Four patients had doubled their known basal creatinine levels; 2 of them had allopurinol-related DIHS. The other organs involved were lung, pancreas, and pharynx (see Table 1).

The outcome was favorable for all patients, with return to normality after drug withdrawal, associated with systemic glucocorticoids (0.3–1 mg/kg per day) for 11 patients, slowly tapered over 4–12 months. All patients survived without sequelae, except 1 of the 5 patients who had myocarditis suggested by cardiac MRI (see below). No relapses occurred; 1 patient became glucocorticoid dependent. Patients were hospitalized for a mean of 12.8 ± 8.7 days.

Putative Drugs

The culprit drugs were allopurinol (n = 4), sulfasalazine (n = 3), azathioprine (n = 1), other antiinflammatory drugs (n = 3), sulfamethoxazole-trimethoprim (SMX-TMP) (n = 3), other nonsulfonamide antibiotics (n = 5), proguanil with atovaquone or chloroquine (n = 2), pyrimethamine alone or combined with sulfadoxine (n = 2), carbamazepine (n = 1), neomecarazole (n = 1), hydroxyurea (n = 1), and bortezomib (n = 1). Drug rechallenge was positive in 5 patients, (SMX-TMP in 2, bortezomib, pyrimethamine, and vancomycin once each). Rechallenge was accidental or because the incorrect drug was initially imputed, except for bortezomib in 1 patient without any other therapeutic option. Median time to DIHS onset after starting the drug was 15 days (range, 1–62 d). The shortest onset intervals of 1 and 3 days were observed after drug rechallenge.

Cardiovascular Manifestations

Ten patients were hypotensive without any features of anaphylactic reaction, including 4 patients who were admitted to the intensive care unit for systolic blood pressure <100 mm Hg. Hypotension was never associated with angioedema, bronchoconstriction, or urticaria. Five of those patients experienced cardiac dysfunction, which started suddenly with the onset of DIHS, a median of 7 days after initiation of the imputed drug (Table 2). They were aged 29–64 years and had no known history of cardiovascular disease. Four of them had elevated NT-proBNP levels, 1.5–7.1N (the level was not available for 1 patient). Troponin I was normal for all 5 patients with drug-induced cardiac abnormalities. The patient who had the most severe heart insufficiency and who had cardiac MRI features highly suggestive of myocarditis also had an extremely high eosinophil count. Eosinophil counts for the others were normal or moderately elevated. Four of the 5 patients had negative T waves on electrocardiograms, which disappeared after the resolution of symptoms. Only 1 patient (with 5720 eosinophils/μL) underwent cardiac MRI, which showed several zones of hyperintensity strongly suggestive of acute myocardial inflammation, without ischemia.

Glucocorticoids (prednisone) were started at the dose of 1 mg/kg per day. Schedules varied, but the dose was progressively tapered over 4–12 months. The outcomes were favorable, without sequelae, for 4 patients. Only the most severely affected patient had persistent chronic cardiac insufficiency secondary to fibrotic scars after resolution of acute heart failure.

TABLE 2. Characteristics of the 5 Patients With Cardiac Involvement

Sex/ Age (yr)	Birth Country	SP	Immune Status	Imputed Drug	Time to Onset (d)	BP (mm Hg)	HR (beats/min)	NT- proBNP	Cardiac Symptoms		GC				
									ECG	TTE or CMRI	Other Organ Involvement	Eosinophil Count (/μL)	CRP (mg/L)	Treatment Duration (D–Mo)	Sequelae
F/29	Mali	VI	Normal	Sulfasalazine	10	92/40	116	6.3N	Negative T waves	Normal	Angiocholitis, hepatitis	1200	101	+ (D13–Mo5)	None
F/32	CI	VI	HIV+	Pyrimethamine	7	120/70	120	1.5N	Negative T waves	Normal	Lymphadenopathy, hepatitis	300	64	+ (D9–Mo12)	None
M/46	CI	VI	CML, imatinib, hydroxyurea	Hydroxyurea	4	80/48	120	NA	Negative T waves	ASA hypokinesia, LVEF 40%	Hepatitis, thrombocytopenia	450	301	+ (D1–Mo4)	None
M/64	Turkey	III	Normal	Vancomycin (rechallenge)	1	92/48	108	7.1N	Negative T waves, 1-mm ST-depression	Septal myocarditis, severe hypokinesia, LVEF 40%*	Severe skin reaction	5720	78	+ (D2–Mo10)	Cardiac insufficiency
M/31	Thailand	IV	HIV+	SMX-TMP	21	106/54	146	5N	NA	NA	Nephritis	760	31	+ (D22–Mo6)	None

Abbreviations: AGEF, acute generalized exanthematous pustulosis; ASA, anteroseptoptical; BP, blood pressure; CI, Caribbean islands; CML, chronic myeloid leukemia; CMRI, cardiac magnetic resonance imaging; D–Mo, number of days after DIHS onset that glucocorticoids were started and number of months continued; ECG, electrocardiogram; GC, glucocorticoids; HR, heart rate; LVEF, left ventricular ejection fraction; N, upper limit of the normal value; NA, not available; SP, skin phototype; TTE, transthoracic echocardiography.
*CMRI was available for only this patient.

Hematologic Parameters and Comparison With AOSD Patients

All patients had abnormal hemograms: 14 had leukocytosis (Table 3), with $\geq 80\%$ neutrophils for 9 of them; 2 patients were pancytopenic; 1 had agranulocytosis; 5 patients had transient lymphocytosis ($>4000/\mu\text{L}$) but 16 were lymphopenic ($<1100/\mu\text{L}$). Eosinophilia ($>500/\mu\text{L}$) was observed in only 12 patients and was transient; 14 had circulating atypical lymphocytes and/or band forms; only 2 were thrombocytopenic.

All patients had elevated CRP levels, exceeding 150 mg/L in 8. Plasma LDH, triglycerides, and ferritin concentrations were high in 92%, 58%, and 74% of the patients, respectively. When glycosylated ferritin was assessed (n = 11), it was $<20\%$ in 4 patients (see Table 3).

Our DIHS patients shared with AOSD, associated with hemophagocytic syndrome or not, the following laboratory abnormalities: high levels of leukocytes, neutrophils, CRP, LDH, ferritin, and triglycerides (see Table 3). Nine of our DIHS patients fulfilled the Fautrel criteria for the diagnosis of AOSD.²⁸

25(OH)D₃ Levels

Twenty DIHS episodes occurred during the winter, from October to March. The median 25(OH)D₃ concentration, determined for 18/24 patients at the time of DIHS, was 24.6 nmol/L, which is significantly lower (p = 0.003 by Mann-Whitney test)

than the median concentration of the control group (40.5 nmol/L). Fourteen (78%) of the 18 DIHS patients had vitamin D deficiency (n = 9) or insufficiency (n = 5), compared to 19% of the 681 control patients (Figure 1). Data were not stratified by patient skin color, as this information was not available for the control patients. A statistically significant negative correlation (r = -0.60; p = 0.023, Spearman rank-order correlation) was found between 25(OH)D₃ and ferritin concentrations in the 14 patients who had ferritin levels determined before the initiation of systemic glucocorticoids (data not shown).

DISCUSSION

Data from the 24 consecutive patients in the current study, to our knowledge the largest cohort with severe DIHS described to date, confirm that skin, mucosae, and liver are predominantly involved. Based on our analysis of this cohort, we have identified 3 previously unhighlighted aspects of this syndrome: the frequent occurrence of heart dysfunction, the low levels of 25(OH)D₃; and the similarities shared by DIHS, AOSD, and hemophagocytosis.

Drug-induced hypersensitivity myocarditis was described more than 60 years ago.³¹ It is probably still underdiagnosed, as demonstrated by several case reports in which the diagnosis was made postmortem^{8,29,37,46,72} or in explanted hearts of patients awaiting heart transplantation.^{36,40,80,84} Hypersensitivity

TABLE 3. Laboratory Features of Patients With DIHS and Patients With AOSD, With or Without Hemophagocytosis

Characteristic	DIHS	AOSD and Hemophagocytosis	AOSD
	(Present Report) No. (%)	(Ref. 2) No. (%)	(Ref. 28) No. (%)
No. of patients	24	6	72
Age, yr (range)*	50.4 ± 17.1 (29–84)	43.3 ± 16.6 (22–72)	35.2 ± 13.5
No. with leukocytosis ($>10,000/\mu\text{L}$)	14 (58)	2 (33)	64 (89)
Mean leukocyte count ± SD	18,514 ± 7,581/ μL	†	
No. with $\geq 80\%$ neutrophils	9	2/6 (33)	
C-reactive protein (mg/L) (nl < 5)			
Mean ± SD (range)	131 ± 111 (14–467)	236 ± 131 (39–355)	
Lactate dehydrogenase (IU/L) (nl < 200)			
No. tested	22	6	
Mean ± SD (range)	1044 ± 1084 (306–4788)	1544 ± 1398 (350–3600)	
No. with value $>2\text{N}$	13/22 (59)	4/6 (67)	
Triglycerides (mmol/L) (nl <1.5–<1.6)			
No. tested	14	6	
Mean ± SD (range)	2.3 ± 1.3 (1.27–5.7)	3.1 ± 1.0 (1.9–4.24)	
No. with value $>\text{N}$	11/14 (79)	6/6 (100)	
Ferritin ($\mu\text{g/L}$) (nl 20–250)			
No. tested	19	6	72
No. with value $>20\text{N}$	3/19‡ (16)	5/6 (83)	
No. with value $>5\text{N}$	9/19 (47)	5/6 (83)	28/72 (39)
No. with value $>\text{N}$	14/19 (74)	6/6 (100)	50/72 (69)
Glycosylated ferritin (%) (nl > 50)			
No. tested	11	5	
No. with value $<20\%$	4/11 (36)	4/5 (80)	52 (72)
No. with value $<50\%$	8/11 (73)	5/5 (100)	

Abbreviations: N, upper limit of the normal value; nl, normal value; No. tested, number of patients with level tested.

*Mean ± SD (range).

†Two patients had leukocytosis: 13,730/ μL and 27,600/ μL , respectively.

‡Excluding 1 patient who had received multiple blood transfusions.

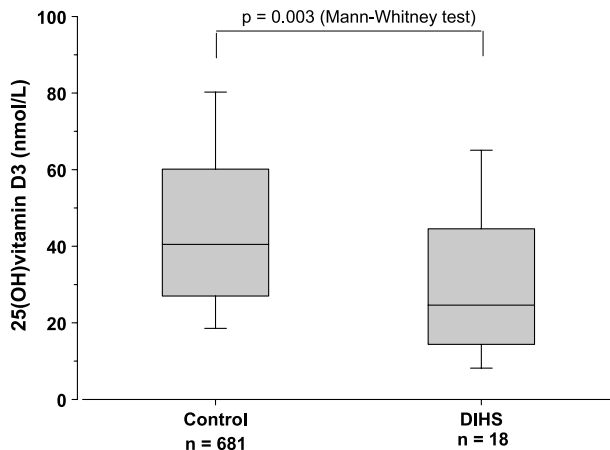


FIGURE 1. The 25(OH)D₃ concentrations of patients with drug-induced hypersensitivity syndrome and control patients. (All samples collected during the winter months, October to March.) The horizontal line inside the box is the median; the lower and upper limits of the box are the 25th and 75th percentiles, respectively; and the T-bars show the range of values.

myocarditis was diagnosed in 44 of 525 (8%) explanted hearts.^{36,40,80,84} Histopathologic examination of those explants showed patchy, mixed inflammatory infiltrates with eosinophils, histiocytes, lymphocytes, and a few neutrophils in necrotic areas; granuloma or granuloma-like lesions and non-necrotizing vasculitis in small arteries and arterioles, composed of mononuclear cells and eosinophils.^{8,29,36,40,80,84} Endomyocardial biopsy is a poorly sensitive tool^{36,84} because unaffected zones are often sampled for this disease in which inflammatory infiltrates are patchy.^{8,29,36,40,80,84} Lesions predominate in the basal region of the heart, explaining the occurrence of sudden death.^{29,37,46}

A direct role of eosinophil degranulation in myocardial damage has been advanced.^{8,29,34} Eosinophils secrete highly toxic cationic proteins,⁹³ oxygen metabolites, and potent lipid mediators. Experimental results showed that ventricular function decreased in rats with eosinophilia⁷³ or exposed to eosinophil peroxidase,⁷⁹ and that isolated rat heart cells died within a few seconds after coming into contact with concentrated eosinophil-granule proteins.⁸² These proteins increase the permeability of heart cell membranes and inhibit mitochondrial function by irreversible inactivation of α -glutarate dehydrogenase and pyruvate dehydrogenase. Eosinophilia suggests interleukin (IL)-5 production by a T-helper type 2 cell-mediated process.^{17,38,59} In our population, 1 patient with imaging findings suggestive of acute myocarditis also had high peripheral eosinophilia (5720/ μ L), but the eosinophil counts of the 4 other patients with cardiac abnormalities were normal or only moderately elevated (see Table 2).

Myocarditis may be part of DIHS involving several other organs,^{8,29,37,46,84} or the heart may be the most affected or the only organ involved. Nonspecific symptoms are variable and include tachycardia, low blood pressure, dyspnea, chest pain, malaise, and sudden cardiac death.^{29,37,46,80} Drugs classically involved in DIHS, as well as others such as clozapine or dobutamine, have been imputed.^{29,37,46,80}

Myocarditis remains rarely described in DIHS patients. Seven cardiac abnormalities were reported in the retrospective study of 216 patients entered into the French pharmacovigilance database over 15 years.⁶⁸ Our observations suggest that heart dysfunction is frequent, occurring in 5 of our 24 (21%) patients.

We suspect that 5 other hypotensive patients with no evidence of anaphylactic reaction might also have had DIHS-related cardiovascular anomalies. The authors of 2 studies^{37,46} pointed out the need for simple diagnostic tools to diagnose drug-induced hypersensitivity myocarditis. We second that suggestion and recommend the systematic determination of cardioselective biomarkers, such as NT-proBNP,⁴³ to elucidate whether symptoms experienced by a patient are cardiac or not. Theoretically, troponin I levels should not be elevated in these patients because, according to histologic studies,^{29,72} myocardial necrosis is usually rare or patchy during the course of hypersensitivity myocarditis. Sabatine et al⁷² reported a fatal case of proven hypersensitivity myocarditis with elevated troponin I corresponding to extensive and necrotizing eosinophilic myocarditis in biopsied specimens. Troponin I evaluation is also useful to exclude other diagnoses, such as myocardial infarction. In addition to electrocardiogram and echocardiography, cardiac MRI should be performed, as it is a highly sensitive and noninvasive tool to visualize focal myocarditis lesions (Ben m'rad, unpublished data) often missed by endomyocardial biopsy,^{29,84} by analogy to myocarditis and cardiomyopathy of other origins.¹

The particularly favorable outcomes of our patients, compared to the negative, even fatal, outcomes of several cases,⁷² seem attributable to the prompt withdrawal of the responsible drug, together with rapid administration of high-dose glucocorticoids,³⁴ which were then slowly tapered. Indeed, DIHS may have a prolonged relapsing course, lasting up to 18 months.^{14,58,71,72} None of our patients relapsed after discontinuation of glucocorticoids over 4–12 months.

AOSD and DIHS have several common clinical and laboratory features, such as fever, lymphadenopathy, and liver injury, that can make them hard to distinguish. In our DIHS patients, major and minor AOSD criteria were frequent: pharyngitis and arthritis, leukocytosis with >80% neutrophils, high ferritin levels with glycosylated form <20%, and elevated LDH (see Table 3); and 9 DIHS patients satisfied the Fautrel criteria for AOSD diagnosis.²⁸ Moreover, the absence of eosinophilia or only minimal skin changes in DIHS patients are frequent, especially in immunocompromised patients. The differential diagnosis for AOSD includes infections, malignancies, and autoimmune diseases. We think that DIHS should be added to this list.

Hemophagocytic syndrome²⁵ is associated with and triggered by various conditions, such as primary or acquired immunodeficiencies, infections (in particular EBV-related disorders), non-Hodgkin lymphomas (mostly T-cell and natural killer-cell types), solid tumors, drugs,⁵² or systemic diseases including AOSD.^{2,22,25,41} In the absence of consensual criteria,⁴¹ hemophagocytosis in adults is diagnosed when acute fever, hepatosplenomegaly, lymphadenopathy, and variable cytopenias are associated with elevated serum LDH, ferritin, triglycerides, and liver enzyme levels.²⁵ Bone-marrow histology was not obtained for our patients to confirm hemophagocytosis because it was not required for DIHS diagnosis^{4,7,71} and treatment. The similarities between AOSD and hemophagocytic syndrome and their coexistence suggest that common pathogenic mechanisms are involved,^{2,16,22,25,67} with excessive activation of T lymphocytes and macrophages. Clinical and laboratory characteristics of the patients in the current study, together with data from the literature, indicate that DIHS could be attributable to similar mechanisms.²⁵ The main difference would be the nature of the offending pathogen. Specific activation of T cells by drugs or their metabolites has been demonstrated for carbamazepine,⁶¹ phenytoin,⁸⁷ lamotrigine,⁶² and sulfamethoxazole.^{26,63} These

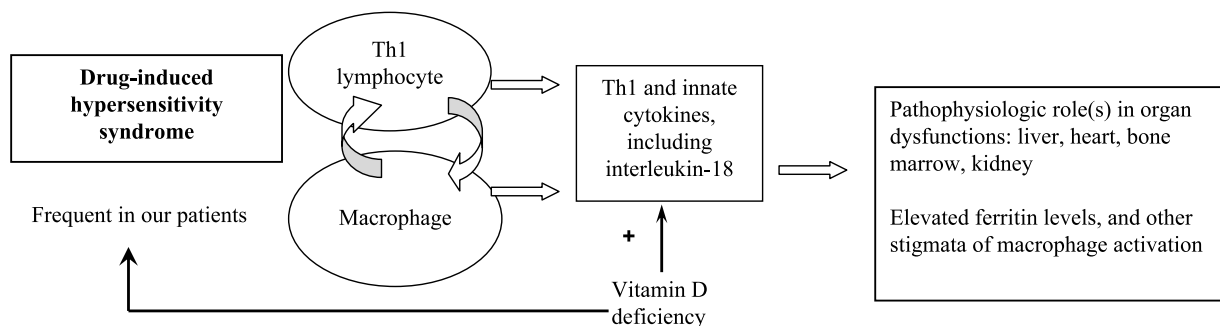


FIGURE 2. Suspected interactions between drug-induced hypersensitivity syndrome, vitamin D deficiency, and severity of the syndrome.

T-cell populations are more often of the T-helper type 1 (Th1-type),⁶⁶ with the production, by specific T-cell clones, of interferon- γ that activates macrophages.^{26,61–64,87} DIHS is also characterized by macrophage activation.^{25,52} Enhanced secretion of tumor necrosis factor may determine the severity of tissue damage.⁶⁹ Patients' high CRP levels suggest the involvement of IL-6.¹⁶ A few DIHS episodes were associated with proven hemophagocytic syndrome.^{25,52} The high ferritin levels we observed in most of our patients, associated with elevated triglycerides and LDH concentrations, suggest that hemophagocytic syndrome due to macrophage activation is frequent in DIHS.⁵¹ Therefore, DIHS should be added to the list of diseases that can lead to macrophage activation syndrome.

Black skin is considered to be a risk factor for DIHS.^{4,58,71,90} Some authors recommended avoiding drugs that can cause severe DIHS in black-skinned relatives of patients who developed DIHS, considering the DIHS attributable to a genetic predisposition.^{70,76,77,90} Evidence of such a genetic predisposition to DIHS has been shown only in rare clinical situations: a 100% association between severe cutaneous adverse reactions related to allopurinol and HLA-B*5801 in homogeneous Han Chinese population⁴² and a strong association between abacavir-related DIHS and HLA-B*5701.⁵⁶ Eleven of our 24 patients had skin phototype V or VI, regardless of their geographic origin (Asia, Africa, Caribbean islands). Twenty of the 24 episodes occurred during the winter months, and 14 of the 18 DIHS patients who had 25(OH)D₃ levels determined had profound insufficiencies or deficiencies (see Figure 1). Vitamin D has well-established antiinflammatory and antiproliferative properties, through negative regulation of cytokines (IL-2, interferon- γ , IL-12, and IL-18) and growth factors, produced by antigen-presenting cells and T lymphocytes.^{9–13,21,50,53,54,57} Experimental and clinical data suggest that vitamin D protects against inflammatory and autoimmune conditions.^{9–13,32,33,57,94} It is not possible from the current study to ascertain if low vitamin D levels either are causative or represent a risk factor for DIHS, or, less probably, are a consequence of DIHS. Nevertheless, the significant inverse correlation we observed between plasma 25(OH)D₃ and ferritin levels allows us to think that vitamin D deficiency (or insufficiency) might favor macrophage-dependent inflammatory reactions mediated by proinflammatory and Th1-type cytokines⁷⁴ and might be a risk factor for DIHS. The predisposition of black-skinned patients could, at least partly, be explained by vitamin D deficiency,³⁹ even though the role of genetic polymorphisms cannot be excluded. It is not known whether correction of vitamin D insufficiency or systematic vitamin D administration could prevent DIHS.

IL-18 is a potent proinflammatory cytokine that strongly stimulates T lymphocytes, natural killer cells, and macrophages.^{23,35,65,91,92} IL-18 is presumed to play a central role

in AOSD.⁴⁵ Several authors have established that changes in IL-18 levels were closely correlated with ferritin and LDH levels.^{16,45} IL-18 is also thought to play a role in hemophagocytic syndrome, because its levels were correlated with clinical activity, ferritin and triglycerides levels, and interferon- γ production.^{55,60,83} Taking into account the numerous clinical and laboratory similarities between AOSD, hemophagocytic syndrome, and DIHS (see Table 3), we propose as a working hypothesis that IL-18 might be involved in DIHS (Figure 2). This hypothesis is supported by recent data indicating that vitamin D, at relevant physiologic concentrations, can suppress IL-18 synthesis, and also that mice, which do not express vitamin D receptors, exhibit up-regulation of IL-18.⁵⁰

There is abundant literature on HHV6 reactivation occurring 2–4 weeks after the onset of DIHS.^{85,86} Authors recently suggested that HHV6 reactivation could be a diagnostic and even a prognostic marker of DIHS.⁷⁸ However, in cases of reactivation, clinicians administered neither antiviral drugs nor contraindicated glucocorticoids for severe forms of DIHS. Thus, despite viral reactivation in 62 of 100 patients, 50 of 62 received systemic glucocorticoids with favorable outcomes.^{85,86} We did not look for viral reactivation because it occurs too late after DIHS onset and because its presence would not have influenced our decision to initiate glucocorticoids. We mainly focused on ruling out EBV and cytomegalovirus infections, when patients were hospitalized.

Conclusion

Based on our study of the clinical, laboratory, and radiologic characteristics of the current cohort of 24 consecutive patients diagnosed with DIHS, we propose the following tools to improve the care of patients with suspected DIHS. First, we recommend an active search for cardiac dysfunction (tachycardia, hypotension, systematic determination of NT-proBNP, and, if necessary, echocardiography and possibly cardiac MRI) even in the absence of eosinophilia. The possibility of drug-induced myocarditis mandates immediate drug withdrawal and administration of glucocorticoids with a very slow tapering schedule. Second, we recommend the systematic search for vitamin D deficiency, which could be a DIHS risk or severity factor, especially in high skin-phototype patients and during the winter. Third, we propose that DIHS must be included in the differential diagnosis of AOSD, with or without reactive hemophagocytic syndrome. Fourth, we suggest that acute hypersensitivity myocarditis may be more frequent than previously thought. Hence, in the case of acute myocarditis with no evident etiology, a history of drugs administered within the preceding 2 months should be obtained, and the diagnosis of myocardial involvement related to DIHS should be considered.

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