Acute Generalized Exanthematous Pustulosis Induced by Hydroxychloroquine

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Key Words

PEAG

Adverse drug reaction

Hydroxychloroquine

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Antimalarial drugs may induce numerous cutaneous adverse drug reactions (ADR): pruritus, lichenoid and urticarial skin eruptions, mucocutaneous hyperpigmentation, as well as exacerbation of psoriasis. We report here a case of hydroxychloroquine-induced acute generalized exanthematous pustulosis (AGEP), a infrequently reported ADR with this drug. A 36-year-old woman with seronegative polyarthritis presented with an acute febrile eruption of 6 days' duration. Hydroxychloroquine (HCQ), 200 mg/day was started 12 days before the onset of the eruption because her arthralgias did not respond to prednisone (10 mg/day). She has received no other treatment for the last 2 months and denied any previous ADR. There was neither personal nor familial history of psoriasis. The eruption consisted of generalized, non-follicular pustules on erythematous base with some target-like lesions (fig. 1). Significant edema and purpuric lesions of the legs were also noticed. Besides conjunctival erythema and cheilitis, there was no other mucosal involvement. Physical examination was normal except for fever (38.5 °C) and intense general malaise. The erythrocyte sedimentation rate was 30 mm in the first hour and the leukocytosis 26,700/mm³ with a polymorphonuclear count of 24,100/mm³. Chest radiographs, liver function tests, serum mercury concentration and blood creatinine were normal. Cultures from pustule contents were negative for bacterial and fungal organisms. Skin biopsy revealed spongiform subcorneal pustules and a diffuse dermal lymphocytic infiltrate. Repeated serologic tests for cytomegalovirus, Epstein-Barr virus, Parvovirus B19, echo- and coxsackievirus were negative. Desquamation began a few days after hospitalization and a spontaneous complete resolution was obtained 1 week later. Nineteen months later there was no sign of psoriasis.

The main clinical and biological criteria of AGEP were described by Roujeau et al. [1] based on the analysis of 63 cases [1]. This entity is characterized by a sudden and simultaneous onset of high fever and widespread edematous scarlatiniform rash, soon covered by hundreds of nonfollicular, small, superficial pustules. The disease is rapidly self-limiting, fever and pustules

lasting 7-40 days, followed by desquamation for a few days [1]. A frank hyperleukocytosis is nearly constant [1]. Purpura, target erythema-multiforme-like lesions and edema are possible [1]. This entity seems distinct from acute pustular psoriasis although some cases have occurred in patients with a personal or familial background of psoriasis [1,2]. About 70% of the 63 cases of AGEP were induced by antibacterial drugs [2]. In these cases the lag-time between the introduction of the drug and the AGEP was usually short (mean: 2.5 ± 3.2 days). When nonantibiotic drugs were responsible (nonsteroidal anti-inflammatory drugs, nifedipine, acetaminophen, quinidine, carbamazepine) the lag-time was longer (mean, 18 ± 7.9 days) [1]. Although most cases were drug-induced, AGEP could also be caused by hypersensitivity to mercury or by enterovirus infection (coxsackievirus A9, echoviruses 11 or 30) [1-3].

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Fig. 1. Multiple smé on erythema.
nonfollicular pustules

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Antimalarials have been described to induce exacerbation of psoriasis [4,5]. However we do not think that our patient had acute pustular psoriasis because she had neither personal nor familial history of psoriasis, the disease was rapidly self-limiting without treatment and there was no relapse of the eruption after 19 months. We believe that our patient developed HCQ-induced AGEP because she had no feature for the other associated pustular dermatoses and fulfilled the criteria of AGEP.

Among the previously published cases of HCQ-induced erythro-dermas, some cases may be redefined as AGEP. A woman without personal history of psoriasis developed a generalized pustular eruption 3 weeks after initiation of HCQ [6]. Edema, ecchymotic lesions, high fever (39.5°C), spontaneous resolution, massive eosinophilic infiltrate of the dermis and hypocalcemia were noted, very suggestive of PEAG. Another patient without previous psoriasis developed, 2 weeks after HCQ initiation, a febrile generalized pustular rash of rapid spontaneous resolution [7]. A generalized pustular eruption has been reported in a 3rd patient without a history of psoriasis which has been diagnosed pustular psoriasis because of 2 nail dystrophy [8]. We have reported a 4th case of generalized pustulosis, with high fever, edema, purpura, and eosinophilia, occurring 3 weeks after HCQ initiation in a woman without previous psoriasis [9].

We believe that hydroxychloroquine may induce AGEP 2-3 weeks after initiation of the drug even in patients without background of psoriasis.

References

- Roujeau JC, Bioulac-Sage P, Bourseau C, et al: Acute generalized exan-thematous pustulosis. Analysis of 63 cases. *Arch Dermatol* 1991; 127: 1333-1338.
- Beylot C, Bioulac P, Doutre MS: Pustuloses exanthématiques aiguës généralisées. A propos de 4 cas. *Ann Dermatol Vénéréol* 1980;107:37-48.
- Rouchouse B, Bonnefoy M, Pallot B, Jacquelin L, Dimoux-Dime G, Glaudy AL: Acute generalized exanthematous pustular dermatitis and viral infection. *Dermatologica* 1986;173:180-184.
- Slagel GA, James WD: Plaquenil-induced erythroderma. *J Am Acad Dermatol* 1985;12:857-862.
- Luzar MJ: Hydroxychloroquine in psoriatic arthropathy: Exacerbation of psoriatic skin lesions. *J Rheumatol* 1982;9:462-463.
- Degos R, Touraine R, Civarre J, Belaich S: Erythrodermie avec aspect de psoriasis pustuleux au cours d'une maladie de Durhing traitée par l'hydroxychloroquine. *Bull Soc Fr Dermatol Syphylol* 1963;70:129-134.
- Lotern M, Ingber A, Segal R, Sandbank M: Generalized pustular drug rash induced by hydroxychloroquine. *Acta Derm Venereol* 1990;70:250-251.
- Friedman SJ: Pustular psoriasis associated with hydroxychloroquine. *J Am Acad Dermatol* 1987;16:1256-1257.
- Assier H, Auffret N, Beltzer-Garely E, Faures-Quenet B, Binet O: Pustulo-exanthématique aiguë généralisée à l'hydroxychloroquine. *Ann Dermatol Vénéréol* 1993;120:848-850.

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Pemphigus vulgaris in

Two MHC-Haploidentical Brothers

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Key Words

Pemphigus vulgaris · Major histocompatibility complex ■

Familial pemphigus vulgaris

Pemphigus vulgaris (PV) is an autoimmune bullous dermatosis caused by antibodies to desmoglein 3, a keratinocyte membrane protein [1]. Although PV etiology remains elusive, it is well known that some alleles of the major histocompatibility complex (MHC) confer a stronger susceptibility to this condition [2]. Nevertheless PV affects members of the same family with a low frequency [3]. We report two brothers with PV who shared identical MHC haplotypes. A 43-year-old white Spanish male presented with bullae and erosions of his mouth, trunk and members. A skin biopsy showed suprabasal acantholysis, and direct immunofluorescence (DIF) of per-ilesional skin revealed IgG and C3 deposition in epithelial intercellular spaces. Circulating epithelial intercellular substance antibodies (EICSA) were detected at a titer of 1/160 by indirect immunofluorescence (IIF) with monkey esophagus as substrate. Three months later, a 40-year-old brother of this patient was seen in another department of dermatology for widespread bullae and erosions. A skin biopsy and DIF confirmed the diagnosis of PV. IIF on monkey esophagus revealed EICSA at a titer of 1/160.

MHC typing of both brothers and the rest of their living relatives (mother, sister, brother, sons, daughters, nieces and nephews) was done (fig. 1). Using monkey esophagus as substrate, we

examined the presence of EICSA in the whole family and only found it in the two members clinically affected by PV.

PV is an autoimmune disease with a strong association with some MHC alleles. In Jewish patients, the alleles more commonly found are DR4 and DQ8, and in non-Jewish the former as well as DR6 and DQ5 are found [4, 5].

The relation of PV to the MHC has been well demonstrated but only a few cases of familial PV have been reported. Beutner and Chorzelski [6] found only one case of familial PV in their series of 234 cases. Reohr et al. [3] studied the MHC of two siblings with PV by restriction fragment polymorphism methods and found that they shared the DR4 and DQw 3.2 alleles.

Although familial occurrence of PV is rare, some authors have found the presence of antibodies to PV antigen at a low level in almost 50% of healthy relatives of PV patients [7, 8]. They studied sera by immunoblot, which has a better sensitivity than IIF. Ahmed et al. [7] found that the inheritance of these low antibody levels in asymptomatic relatives of PV patients was linked to DR4 or DR6 haplotypes. He postulated that some MHC alleles would confer a predisposition to PV and that a second trigger would be necessary to develop this disease. Bhol et al. [9] demonstrated that sera from patients with active PV contained antibodies to pemphigus antigen of the IgG1 and IgG4 subclasses, while sera from healthy relatives and patients in remission only had antibodies of the IgG1 subclass. Brenner et al. [10] also suggested that some drugs could act as trigger factors in some cases of familial PV.