Acute Generalized Exanthematous Pustulosis Due to the Combination of Chloroquine and Proguanil

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Key Words
Acute generalized exanthematous pustulosis (AGEP) · Skin drug eruption · Chloroquine · Proguanil

The association of chloroquine and proguanil is widely used for antimalarial prophylaxis in Plasmodium falciparum – endemic countries with limited to moderate chloroquine resistance [1]. We report the 1st case of acute generalized exanthematous pustulosis (AGEP) due to this drug combination.

A 34-year-old woman with a previous history of maculopapular skin rash induced by mefloquine in 1995 was referred to our department in February 1996 because of the rapid onset of a generalized eruption of 2 days’ duration. The eruption began on the face and trunk and subsequently spread to the limbs. It consisted of a diffuse erythema with multiple superficial nonfollicular pustules. A few target lesions were present on the limbs. The rash was highly pruritic. There was no mucosal involvement. She was slightly pyrexial (38°C). She had been taking chloroquine (100 mg/day) and proguanil (200 mg/day) for 10 days as an antimalarial prophylaxis during a travel across Togo (West Africa). She had not been given other medication in the past 3 months and had no history of psoriasis.

Laboratory investigations disclosed hyperleukocytosis (22.7 × 10⁹/l) with polynucleosis (20 × 10⁹/l) and eosinophilia (1 × 10⁹/l). Histopathologic examination of a skin biopsy specimen showed multilocular spongiform subcorneal pustules containing polymorphonuclears and eosinophils.

Chloroquine and proguanil were stopped. The eruption resolved after 8 days with no further recurrence. Epicutaneous tests performed 6 months later with chloroquine, proguanil and mefloquine were negative.

AGEP is a recently described entity [2] mostly related to drugs, principally antibiotics (beta-lactams and macrolides). Four cases of AGEP due to hydroxychloroquine have been previously reported, the last in 1995 [3] but no case of AGEP induced by chloroquine or proguanil has ever been published.

Chloroquine, an amino-4 quinoleine has a few cutaneous side effects apart from pruritus (which may occur in up to 75% of patients) and exacerbation of psoriasis [4, 5].

Proguanil and cycloguanil, two biguanide derivatives, may induce mouth ulcers [6] without any particular skin side effects. They are seldom used alone and mostly given in combination with chloroquine.

Finally, mefloquine, an amino-alcohol, can produce life-threatening adverse cutaneous reactions [7] but has no known cross-hypersensitivity with chloroquine.

In our case, it was not possible to distinguish between chloroquine and proguanil as the culprit of the AGEP and future antimalarial prophylaxis was further complicated by skin reaction to mefloquine.

Reports of severe cutaneous toxicity in patients taking antimalarials and possible cross-reactions are highly warranted.

References

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Conjugal Leprosy among Libyan Patients

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Key Words
Leprosy · Consanguinity

Leprosy has been known to occur among many members of the same family indicating the possibility of genetic predisposition [1, 2]. The presence of genetic factors in leprosy has long been debated and work in this field has indeed implicated genetic susceptibility to leprosy in humans [3–7]. However, conjugal infection of leprosy seems to be uncommon as it is reported very rarely in the literature [8, 9]. As consanguineous marriages are very common among the Libyan population, we tried to analyse the prevalence of leprosy among consanguineous couples and compared it with the occurrence of leprosy among couples without any history of consanguinity.

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Letters to Dermatology

The patients data were obtained from the Leprosy Register of the Clinic at Jamahiriya Hospital, Benghazi. A total of 269 such couples were included in the present study. Most of our patients had a low socio-economic background and came from the rural areas of Eastern Libya. Of 269 married patients registered, 25 gave a positive history of consanguinity. They had married either their first cousins or very close blood relatives. The remaining 244 patients did not give any history of consanguinity.

Out of 25 consanguineous couples, both partners were affected in 8 cases (32%) and only 1 partner was affected in the remaining 17 couples. Out of 244 patients without any history of consanguinity, both partners were affected in 7 cases (2.87%) and only 1 partner was involved in the remaining 237 cases.

The statistical analysis by $\chi^2$ test is shown in table 1, which revealed a significant difference among the groups studied ($p<0.01$).

Clustering of leprosy patients within families has been interpreted by many authors as a reflection of genetic influence of susceptibility to the disease [4, 7, 10, 11]. However, the rate of conjugal infection has been stated to be between 0.33 and 9.7% in the literature [9]. Kaur et al. [12] did not observe any significant difference between the general population and married partners of leprosy patients at risk of getting the disease either.

In our study, leprosy occurred in 32% of couples with a positive history of consanguinity, whereas it occurred only in 2.87% of cases with no history of consanguinity. This was highly significant and may point to a probable genetic predisposition to the disease, indicating that people with the same genetic background are more prone to develop the disease than people with different genetic backgrounds.

As most of the patients were not sure of the duration of the disease, it could not be definitively determined whether these patients developed the disease after or before marriage.

The patient had widely distributed spider-like telangiectases on her back and front of the trunk (fig. 1B). The liver function tests and basic red cell indices were normal. Drug-induced autoimmunity causing telangiectases was ruled out by autoantibody testings (antinuclear antibodies and extractable nuclear antibodies) which were negative. Anti-scl-70 antibodies were negative as well. Drug-induced telangiectases were suspected, and subsequently the patient received only enalapril with a satisfactory effect on hypertension.

A 70-year-old woman had her hypertension treated with enalapril and felodipine for several years, without any additional medications. Approximately a year before admission the dose of felodipine had been doubled from 5 to 10 mg daily. Within 2 weeks telangiectatic skin lesions appeared.

$\chi^2=3.51; d.f.=1; p<0.01.$

Acknowledgment

We wish to thank Mr. Gener R. Ronquillo for typing the manuscript.

References


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Truncal Telangiectases Coinciding with Felodipine

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Skin reactions caused by calcium antagonists include urticaria, pruritus, alopecia, erythema multiforme and exfoliative dermatitis [1]. Nifedipine- and amlodipine-induced facial telangiectases have been described [2–5]. We report a patient who developed truncal telangiectases while taking felodipine.

A 70-year-old woman had her hypertension treated with enalapril and felodipine for several years, without any additional medications. Approximately a year before admission the dose of felodipine had been doubled from 5 to 10 mg daily. Within 2 weeks telangiectatic skin lesions appeared.

The patient had widely distributed spider-like telangiectases on her back and front of the trunk (fig. 1B). The liver function tests and basic red cell indices were normal. Drug-induced autoimmunity causing telangiectases was ruled out by autoantibody testings (antinuclear antibodies and extractable nuclear antibodies) which were negative. Anti-scl-70 antibodies were negative as well. Drug-induced telangiectases were suspected, and subsequently the patient received only enalapril with a satisfactory effect on hypertension.

Histological examination presented enlarged capillaries parallel to the skin surface clearly indicative of telangiectases. Mast cell staining was negative excluding telangiectasia maculopapularis eruptiva perstans.

Two months later the telangiectases had slightly faded, and 29 months after the onset they were still clearly detectable (fig. 1D) and, according to the patient, more prominent during sweating.

Table 1. $\chi^2$ analysis of patients of consanguineous and non-consanguineous couples

<table>
<thead>
<tr>
<th>History of consanguinity</th>
<th>Both partners affected</th>
<th>One partner affected</th>
<th>Total</th>
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<tbody>
<tr>
<td>Yes</td>
<td>8 (32.0%)</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>No</td>
<td>7 (2.87%)</td>
<td>237</td>
<td>244</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>254</td>
<td>269</td>
</tr>
</tbody>
</table>

$\chi^2=3.51; d.f.=1; p<0.01.$
In the cases of nifedipine- and amlodipine-induced telangiectases [2–5], the telangiectases were distributed on photoexposed areas and the mechanisms of the reactions considered phototoxic.

Felodipine-induced telangiectases have not been described before. The manufacturers (Astra, Sweden) were not aware of any other similar cases. Our patient presented the telangiectatic lesions on light-protected areas. To our knowledge the current patient had not been exposed to sunlight in conjunction with the development of the symptoms. The mechanism remains unknown, most likely being the vasodilatatory effect of felodipine leading to chronic vasodilatation.

Greater awareness of these side effects of calcium antagonists might be needed by physicians, as complete resolution on stopping the drug is not always seen.

References

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Multiple Actinic Keratosis and Skin Tumors Secondary to Hydroxyurea Treatment

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Key Words
Hydroxyurea · Skin Cancers

Hydroxyurea is an antimetabolite used in the treatment of chronic myelogenous leukemia, polycythemia vera, and essential thrombocytosis. It inhibits the enzyme ribonucleotide reductase which prevents the conversion of ribonucleotides to deoxyribonucleotides. It can cause cutaneous side effects that are usually not severe enough to warrant discontinuation of therapy. Partial alopecia, increased pigmentation, scalings, atrophy of the skin and subcutaneous tissues, dryness, nail changes, erythema of the face and hands, ulcerations, and plantar keratoderma have been described. In 1992, Stasi et al. [1] suggested that patients who are on long-term hydroxyurea therapy may develop multiple actinic keratoses and skin tumors, both squamous cell carcinomas and basaliomas. Since their first report, only a second case has been described [2].

A 73-year-old male patient, retired veterinary, phototype 2, was seen with multiple actinic keratoses on the face, the balding scalp, and the ears. He also had a squamous cell carcinoma of the left ear, that was surgically excised. He denied strong sun exposure. He had a 10-year history of polycythemia vera, well controlled with hydroxyurea. Because of the unusually rapid development of the cutaneous lesions, this treatment was discontinued, and changed to busulfan. No relapse was noted during the 14 following months.

We would like to underline the predisposition to the development of multiple actinic keratoses of patients on long-term hydroxyurea therapy. In this case of associated skin carcinoma, we suggest that an alternative treatment should be used.

References

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Not All Black Follicular Plugs Are Comedones!
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The recent case report ‘Peculiar distribution of comedones: A report of three cases’ [1], more particularly the second case, deserves some critical comments.

The small black plugs, located along the creases of the forehead or in the criss-crossed grooves of the cutis rhomboidalis nuchae in old men with sun-damaged skin, do not usually disclose the histopathological aspect of comedones.

Comedones are plugs of infundibular keratin; in acne patients, sebum and corynebacteria are often entrapped in the greasy keratin plugs and sometimes some tiny hair shafts are visible among the keratin layers. The black plugs with this striking alignment along the bot-
tom of the skin grooves in sun-damaged skin (fig. 1) show a quite different histopathological aspect. They are constituted by a keratin coat filled with numerous telogen vellus hair shafts and dust particles evidenced in polarized light (fig. 2). At their surface these plugs look like minute brooms. Therefore they cannot be considered as comedones: They are the clinico-pathological hallmark of trichostasis spinulosa [2].

References

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Reply
Dermatology 1998;196:275

Pityriasis Rosea and Human Herpesvirus 7, a True Association?

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Key Words
Pityriasis rosea · Human herpesvirus 7

We reply to a study by Drago et al. [1] which stresses the difficulties to prove that an infectious agent can be a causal or at least an associated factor in a pathologic state. This has been well illustrated by recent advances in the pathogenesis of Kaposi’s sarcoma in which an infectious origin had been suggested by several epidemiological studies [2]. Thus, numerous candidates were proposed such as cyto-megalovirus, human herpesvirus (HSV) 6, human papillomavirus 16 and 18, human T lymphotropic retrovirus 1 or Mycoplasma penetrans until a true association with a new γ-herpesvirus named HHV-8 could be demonstrated, using representational differential analysis [3]. Even now, the causal role of this virus remains debated.

In the same way, various clinical arguments favor the role of an infectious agent in the pathogenesis of pityriasis rosea (PR), such as an occasional association with prodromal symptoms or recent upper respiratory tract symptoms, an increased incidence during the fall, winter and spring, reports of cases in families or communities and even the possibility of occupational contamination of dermatologists [4, 5]. Earlier observations showed evidence of picornavirus-like intranuclear inclusion bodies in African green monkey kidney cells incubated with suspensions of PR scales or skin [6] or virus-like particles directly in PR lesions [7–9]. Nevertheless, a recent PCR study, using only one set of primers, failed to disclose any picornavirus sequence in PR lesions from 8 patients [10]. Serologic studies showed no association with common infectious agents such as influenza A and B, parainfluenza type I, II or III and mycoplasma [11].

Drago et al. [1] evaluated 12 patients with acute PR in comparison with 12 patients with other noninfectious dermatoses and 25 healthy controls. The authors were able to demonstrate first the presence of HHV-7 DNA sequences not only in peripheral blood mononuclear cells (PBMC) but also in plasma and skin from PR patients. It is noteworthy that while the plasma of control patients was negative, HHV-7 sequences could be observed in PBMC from 44% of controls. Secondly, cultured mononuclear cells from all patients disclosed a cytopathic effect consisting in ballooning cells and syncitia. Virions with structural features were observed in the supernatant of these cultures while none of these morphologic aspects could be observed in the samples from control patients and from 5 patients retested 1 year after PR.

HHV-7 is a β-herpesvirus isolated in 1990 from CD4+ T lymphocytes from PBMC from a healthy patient [12]. Latent virus can be detected in the PBMC from most healthy individuals while HHV-7 is persistently present in cell-free saliva [13]. At present, infection with HHV-7 is not known to be associated with any disease [13]. The clinical features of the primary infection are unknown although a few cases of exanthema subitum with HHV-7 seroconversion have recently been published [13, 14]. Whether PR is associated either with a specific or nonspecific reactivation of HHV-7 infection remains to be demonstrated. Additional studies such as serial serum sample analysis showing a significant increase in HHV-7 antibody levels and electron immunomicroscopy are needed.

References

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