Toxic pustuloderma – a new entity?

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A schizophrenic patient, being treated with carbamazepine, developed an erythroderma which was so intense that it resulted in toxic pustulation (toxic pustuloderma). It was associated with a glandular fever-like syndrome consisting of fever, lymphadenopathy and hepatosplenomegaly with intense circulating eosinophilia. A pustular drug eruption caused by carbamazepine has not previously been reported in the literature.

Case report

In August 1981 a 22-year-old Pakistani, who was a known hebephrenic schizophrenic, began treatment with carbamazepine, flupenthixol, procyclidine and temazepam. Symptoms improved greatly: he no longer felt himself on the 'alpha-plus, plus plane', which he would previously attain 'by getting in time with a particular musical tape played through a Sony Walkman headset' and he felt he had lost the power to read other peoples' minds. In late September he returned to Karachi. Shortly afterwards he developed a cough and sore throat with fever, eruption and lymphadenopathy. Liver function tests became abnormal. He was treated with short periods of erythromycin and ampicillin with cloxacillin (Ampiclox). On his return to London he had a glandular fever-like syndrome with pyrexia, generalized lymphadenopathy, tender hepatomegaly and splenomegaly associated with generalized erythema and palatal purpura. Medication was discontinued. The Paul-Bunnell test was negative and over the next three days the patient became intensely erythrodermic.

The eruption occupied the whole integument and was associated with much dermal oedema, especially affecting the face and ears. In places the eruption was purpuric. The scalp was covered by an adherent silvery cradle cap. Over the convexities of his swollen erythematous face there were myriads of pinhead sized pustules (Figure 1) which, nevertheless, spared the beard area.

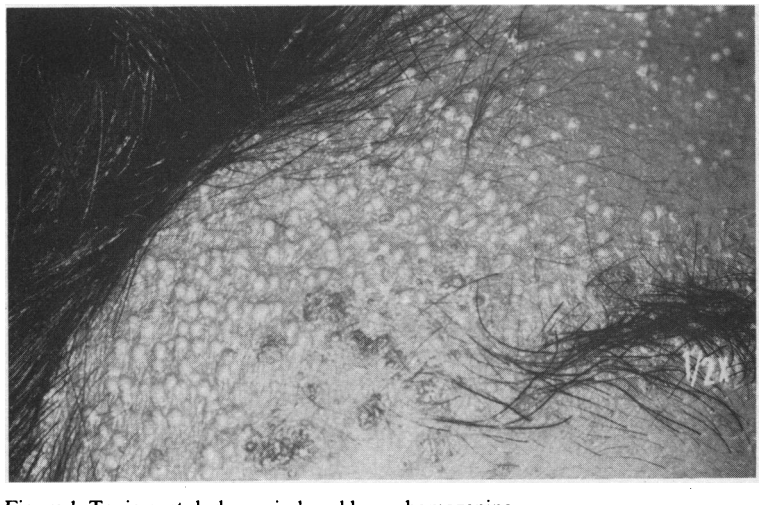

Figure 1. Toxic pustuloderma induced by carbamazepine

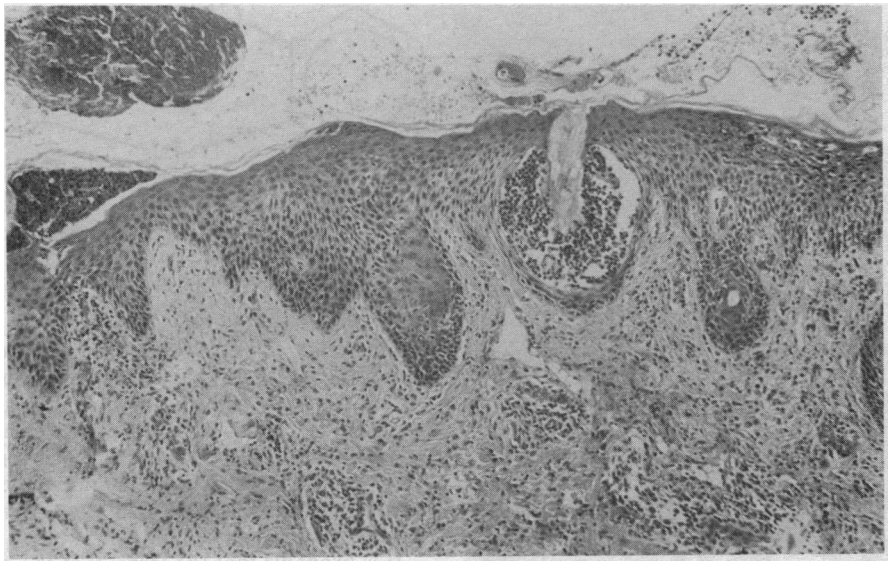

Figure 2. Toxic pustuloderma. In the superficial dermis there is an intense perivascular inflammatory infiltrate with overlying reactive parakeratosis. A sterile neutrophilic follicular pustule is seen in the epidermis. (H & E × 40)

Swabs of pustular lesions were repeatedly sterile. During the three days since stopping medication the fever had fluctuated between 37.5 and 39°C and the white cell count had risen to 23.0×10^9/l, of which 7.59×10^9/l were eosinophils. Liver function tests worsened with alkaline phosphatase 754 U/l (normal range up to 279), alanine transaminase 49 U/l (normal up to 40), and gamma-glutamyl transpeptidase 194 U/l (normal up to 50). Skin biopsy (Figure 2) showed, in the superficial dermis, an intense perivascular infiltrate with a strong lymphocytic component. Some lymphocytes were seen in the epidermis and there was overlying reactive parakeratosis. In places, superficial neutrophilic follicular pustules were present. At one site (Figure 3) a superficial dermal blood vessel appeared stuffed with eosinophils – a vivid record of the intense blood eosinophilia.

With attentive nursing and withdrawal of carbamazepine the patient recovered over the next week. Systemic steroids were not administered.

Discussion

Carbamazepine (Tegretol) (Figure 4) is chemically related to the tricyclic antidepressants and its stereochemistry is similar to that of phenytoin. Carbamazepine is used for the control of trigeminal neuralgia, epilepsy, alcohol-withdrawal symptoms and, most recently, schizophrenia (Hakola & Laulumaa 1982).

Our patient received several drugs before falling ill: carbamazepine, flupenthixol, procyclidine, temazepam, erythromycin, ampicillin and cloxacillin. Of these a glandular fever-like syndrome has previously been seen only with carbamazepine (Reynolds 1982, Lewis & Rosenbloom 1982). The most prominent feature of this patient's glandular fever-like illness was his eruption. Common adverse effects of carbamazepine are usually minor neurological and gastrointestinal symptoms and are principally dose-dependent. Generalized erythematous eruptions are also common: they occur in 3% of patients and often necessitate withdrawal of treatment (Taylor *et al.* 1981). The Committee on Safety of Medicines (personal communication 1983) has received reports of many eruptions occurring with carbamazepine, including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. Roberts & Marks (1981) reported exfoliative dermatitis.

There seem to be three ways of inducing pustulation in the skin, firstly by infection, secondly by provoking a pustular dermatosis such as acne or pustular psoriasis, and thirdly as a result of a very intense erythema (Macmillan 1973). Our patient's eruption could be interpreted as a severe drug-induced toxic erythema which had progressed to erythroderma, the inflammation of the skin being so intense that toxic

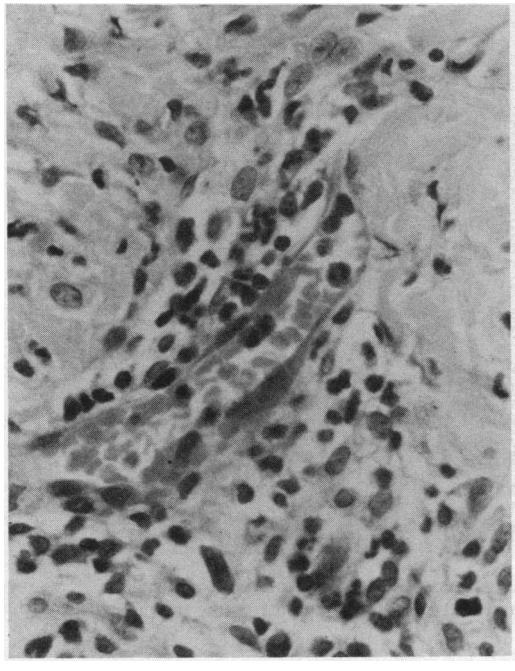

Figure 3. Eosinophilia. Many eosinophils are seen in this superficial dermal vessel which has been cut across. (H & E × 100)

pustulation had occurred. Comparable cases have been reported with chloramphenicol, piperazine, pyrimethamine and frusemide (Macmillan 1973). In three of these cases the eruption was accompanied by fever and eosinophilia.

A number of well recognized erythemas merge with the severest forms of toxic erythema. These include *erythema multiforme*, with its pathognomonic target lesions, and its variants: *Stevens-Johnson syndrome*, with mucosal erosions or bullae, and *Lyell's syndrome* (toxic epidermal necrolysis), with its scalded skin appearance. We suggest that *toxic pustuloderma* is another variant of severe toxic erythema that is characterized by a generalized erythroderma with sterile miliary pustulation, often associated with fever and

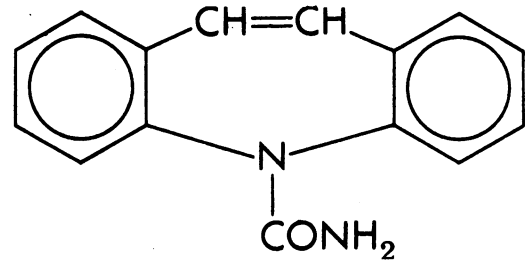

Figure 4. Carbamazepine

eosinophilia. Toxic pustuloderma should be distinguished from acneiform drug eruptions, such as occur with hormones, halogens and isoniazid, in which the principal element is an erythematous follicular papule which progresses to a pustule rather than an intense erythema which becomes complicated by sterile toxic miliary pustulation.

It is probable that the ferocity of the glandular fever-like illness in this patient and the consequent toxic pustuloderma were related both to the large doses of carbamazepine needed for the control of his schizophrenia and to its continued use for almost two weeks after the onset of the illness.

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