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FIFTEEN CASES OF TOXIC EPIDERMAL NECROLYSIS (LYELL)

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Abstract. Fifteen patients with toxic epidermal necrolysis (Lyell) are described. Ten had acute infections and 4 non-infectious diseases at the onset of the necrolysis. All were on drugs (sulfonamides in 5, penicillin in 3, thiazides in 4). Treatment with steroids in high doses stopped the progress immediately. All 11 patients on steroids together with antibiotics survived, but 2 of 3 patients on steroids alone died from infections.

Since the first description of toxic epidermal necrolysis in 1956 by Lyell and by von Lang & Walker an increasing number of cases have been reported. In 1970 a monograph edited by Braun-Falco & Bandmann appeared, with several contributors (3). As a collection of data of further cases may contribute to an understanding of this typical, dangerous and interesting syndrome, 15 new cases will be presented.

All patients, 6 males and 9 females, were treated at the Department of Dermatology, Sahlgrenska sjukhuset, Gothenburg, Sweden, during the years 1963–1970. One case, number 1, has been published before, because of complications of the eyes leading to perforation of the cornea and blindness (1). The ages were respectively: 43, 59, 60, 66, 71 and 79 years in males, and 1, 20, 24, 39, 48, 51, 61, 61 and 74 years in females.

DISEASES AT THE TIME OF ONSET

Only one patient, the child, was patently healthy at the onset of the toxic epidermal necrolysis. Of the remaining 14 patients, 10 had acute infections during the period just preceding the eruption (acute cystitis in 6, inflammation of the female adnexa in 1, tonsillitis in 2, and secondary infection after an operation for fracture of the femur in 1 patient). One of these patients, moreover, had hypertension; 1 arteriosclerotic changes from heart and brain; 1, rheumatoid arthritis; and 1, subacute lupus erythematosus. The 4 patients without acute infections had infarctus myocardi, heart insufficiency, ulcus cruris and epileptic seizures (alcoholismus chronicus) respectively.

DRUGS AT THE TIME OF ONSET

The drugs taken by the patients during 1 week prior to the development of the skin symptoms are shown in Table I.

It will be noticed that 5 patients were on sulfonamides (Sulfapral®), 3 on penicillin, 4 on thiazides, 3 on barbiturics, 1 on phenolphthalein and 1 on phenylbutazon. The polypharmacy is evident.

CLINICAL PICTURE

Prodromal symptoms occurred in all patients during the next few days prior to skin eruption (tiredness, headache, pains in the muscles and joints, feeling of sickness). Some complained of the intense tenderness of their skin. Fever of a high degree was present in all but three cases on admission to hospital. (In one patient no information is available in this respect.) In the skin the lesions were of two kinds which, however, could be mixed. In one type there was only a slight diffuse erythema with loosening of the epidermis, either with or without collection of fluid in large flaccid bullae—in these cases the description "scalding syndrome" seems to be highly appropriate. In the other type the picture was erythema multiforme-like and epidermolysis developed initially in the middle of the cocards. Later the lesions became confluent and larger

Table I

Patient no.	Drugs taken for 1 week or less before onset of toxic epidermal necrolysis
1	Phenolphthalein
	Chlordiazepoxide (Librium®)
2	Phenylbutazone (Butazolidin®)
	Tetracyclinehexamethaphosphate (Tetradecin®)
3	Sulphamethizole + sulphamethoxypyridazine (Sulfapral®)
4	AD-Vitamins
5	Sulphamethizole + sulphamethoxypyridazine (Sulfapral®)
	Bendroflumethiazide (Salures®)
6	Insulin
	Penicillin (Cetacillin®)
	Chlortetracycline (Aureomycin®)
	Phenatone + paracethamol + prothipendyl. chloride + caffeine + codeine phosphate (Lunedon®)
7	Digoxin (Lanacrist®)
	Benzylpenicillin
	Sulphamethizole + sulphamethoxypyridazine (Sulfapral®)
	Chlorothiazide (Chlotride®)
	Vitamins
8	Digitalis
	7-(2-hydroxipropyl)-theophylline (Theon®)
	Ephedrine
	Trichlormethiazide (Flutra®)
	Promethazine chloride (Lergigan®)
	Acetylglycinamidechloride hydr. (Ansopal®)
	Meballymal sod. + allyl (-2 bromallyl) mallonylcarbamide calcium + hydroxizine dichloride (Vesparax®)
9	Ethyl (3,3-diphenyl-1-methyl-propyl (dimethyl-ammon. bromide + promethazine chloride (Cetiproman®)
	Phenytoin (Difhydan®)
	Phenemal
10	Levotyroxine sod. (Levaxin®)
	Chloroquine phosphate (Klorokin®)
	Penicillin
	Enhexymal
11	Sulphamethizole + sulphamethoxypyridazine (Sulfapral®)
	Atropin. sulph. + theobromia + phenemal (Hypertonal®)
	Polythiazide (Renese®)
	Potassium chloride
12	Potassium chloride
	Acid. *N*-(2-furylmethyl)-4-chloro-5-sulphamoyl-antranile (Lasix®)
	Digoxin
	Chinidine sulphate
	Diaxepam. (Valium®)
13	Sulphamethizole + sulphamethoxypyridazine (Sulfapral®)
14	Prednisolone (15 mg)
	Penicillin
	Salicylates
	Extr. fl. rh. pursh. examar. (Cas-Evac®)
15	Potassium chloride
	3-hydroxi-3-(4-chloro-3-sulphamoyl-phenyl)-1-oxoisoindoline (Hygroton®)
	Acid. acetylsalicyl. + (2-diethyl-aminoethyl)-fenthiazinecarboxyl-(10)-chloride-dextropropoxi-phenechloride + caffeine + phenazone (Doleron®)

areas of typical necrolysis developed. In 6 patients the necrolysis was almost total; in 9, parts of the skin remained macroscopically normal. In 2 patients the main skin lesions were localized to the face and upper part of the body, in 2 the main distribution was on the lower back, hips and gluteal regions. In 2 patients the face was remarkably spared in spite of a very severe eruption on the rest of the body. The observations on the distribution of the skin lesions were obtained on admission to hospital. With intense steroid therapy the progress usually stopped immediately. In 2 cases where full effect of the steroids was not obtained at once, further severe progress occurred with involvement of new areas of the skin, until the dosage was increased. The bleeding tendency from the surfaces was often pronounced, leaving black crusts.

Mucosal changes were seen in all but 5 patients, the mouth, conjunctivae, trachea, bronchi and genitals being involved. One patient coughed up casts of the bronchial tree. The coadhesion-tendency of the mucosae was a prominent feature. The mouth, eyes and genitals had to be closely observed and the adhesions were, in some patients, forcibly loosened each day to prevent complete adhesions. Hairloss was observed as also was a loss of the nails. Signs of secondary infection in the skin rarely occurred during the treatment.

LABORATORY INVESTIGATIONS

On admission to hospital, i.e. usually within a few days after the debut of the disease and before starting the treatment, the following laboratory values were noted: Haemoglobin: 8.2 g% 1/12, 9.3 g% 1/12, normal 10/12. White cell count: below 9 000 5/12; above 9 000 7/12. Differential count: 28% red cells 1/12, 18% 1/12, normal 10/12. Platelet count (5 patients): 94 000, 393 000, 336 000, 536 000, 476 000. Bleeding time: normal 4/4. Clotting time: normal 4/4. Sedimentation rate: below 20 mm 5/9, above 20 mm 4/9. Serum creatinine: normal 11/11. Proteinuria: 2/12. Pyuria: 3/12. Haematuria: 1/12. Electrolytes in serum: sodium: low 3/10, normal 7/10; potassium: low 1/10, normal 9/10; chlorides: low 1/10, normal 9/10; carbon dioxide: low 1/10, normal 9/10; protein: low 3/10, normal 7/10. Prothrombin index: normal 4/4. Serum proteins: albumin: low 8/8; alfa-globulin: high 8/8; alfa-2-globulin: high 6/8, normal 2/8; beta-globulin: high 6/8, normal 2/8; gammaglobulin: high 6/8 (in 3 cases marked increase), normal 2/8. Thymol reaction: high value 2/6, normal 4/6. *GOT:* normal 4/4. *GPT:* normal 2/2. Antistreptolysin-titre: normal 1/1. Antistaphylosin-titre: normal 1/1. Wassermann reaction: normal 6/6. Meinicke reac-

tion: normal 7/7. Kline reaction: normal 7/7. Blood sugar: normal 5/5. LE-cells: negative 1/1. Blood in stool: negative 4/4. Coombs' test: negative 1/1. IgG, IgA, IgM normal 1/1. Antinuclear factors were studied in one patient with indirect fluorescence antibody technique: negative in dilution 1/15 against homologous nuclear substance (leucocytes) and negative in 1/25 against heterologous nuclear substance (erythrocytes from chicken).

MICROSCOPIC PICTURE

A microscopic examination was performed in all but 2 of the patients—the child and the acutely ill man with myocardial infarction. In 9 the classical picture of epidermal toxic necrolysis was found with a complete necrolysis of the epidermis and slight changes in the corium with discrete infiltrates of lymphocytes around the vessels. In one patient signs of acantholysis were also observed and in one patient the acantholysis was severe with intraepidermal bullae. In 2 the microscopic picture was unspecific.

TREATMENT

1. *Steroids.* All patients except the man with the myocardial infarction who died before any treatment was given, were initially treated with high dosages of steroids equivalent to 200–600 mg cortisone. The patient with erythematodes received 100 mg. In all but two there was a prompt control of the eruption. In one patient a therapeutic effect was gained with 60 mg prednisolone, but not with 40 mg and in one other an effect was gained with 150 mg prednisolone, but not with 60 mg. In only one patient did a relapse occur when the steroid dose was lowered. The initial morbidostatic dose in this case was 120 mg prednisolone. When the dose was gradually reduced to 25 mg the skin lesions reappeared. With 60 mg a clinical effect was again achieved and the dose could thereafter be brought down to 5 mg, with which the patient left the hospital.

2. *Antibiotics.* The patient with myocardial infarction died before any treatment was given. All the other patients except 3 received antibiotics from the beginning; 2, penicillin, and 9, tetracycline. Of those who did not receive antibiotics, one died from staphylococcal sepsis and one of bronchopneumonia together with internal bleeding.

3. *Other.* In some cases narcotics had to be given to relieve the pain from the skin. Therapy by infusion was given as in extensive burns. Topically, vioform- and tetracycline powders proved effective to control secondary infections. Nonadherent compresses proved very helpful. The patients were isolated under sterile conditions.

PROGNOSIS

After 2 weeks to 3 months, 7 patients were discharged healthy from the hospital, without any steroids. Four patients were referred to other hospitals, still with a low dose of steroids. One patient with a history of coronary thrombosis died from a new myocardial infarction on the day of admission, one patient died after 3 weeks from a staphylococcal sepsis, and one after 3 weeks from bronchopneumonia and internal bleeding. In one patient with a healed skin, steroid treatment had to be reinstituted subsequently because of later developing eye lesions; she suddenly died after 4 months.

COMMENTS

All patients, except the child, had other diseases at the time of the outbreak of the necrolysis, mostly acute infections. In all, likewise with the exception of the child, a number of drugs were taken just prior to the outbreak. The children do not seem to react to provoking factors in the same way as do the adults (4). In the child no bacteriae were grown from the skin lesions, and no clinical signs of staphylococcal infections were found. Of the drugs taken by these patients, some may be noticed which have previously been associated with the development of epidermal necrolysis (2): sulfonamides (Sulfapral®), penicillin, thiazides, phenylbutazone, phenolphthalein, barbiturates.

In one patient there were signs of acantholysis besides of the necrolysis and in another the acantholysis was severe, corresponding to the picture of pemphigus. In both cases the clinical picture was a classical example of toxic epidermal necrolysis, and in both patients the steroids could soon be withdrawn yet with continuing healing of the skin. This speaks against the occurrence of true pemphigus but raises the question as to

whether acantholysis may occur in toxic necrolysis in addition to the classical microscopic picture of this syndrome.

Very high doses of steroids brought about an immediate stop to the progress of the disease. Eleven patients treated with steroids in combination with antibiotics survived, while 2 of the 3 patients who received steroids but not antibiotics, died from infections.

Our experiences support the opinion that initial intense steroid treatment is indicated in toxic epidermal necrolysis.

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