A CASE OF ERYTHEMA MULTIFORME MAJOR (STEVENS-JOHNSON'S SYNDROME)

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It is considered that this case of the so-called Stevens-Johnson's syndrome is of interest because of the allergic background; the history of chronic nasal infection in earlier life, with the revelation of recent antral infection; the generalized lymph-gland enlargement; the exhibition of sulphonamides during the illness; and the response to treatment with cortisone.

H.A., a schoolboy, aged 14 years 8 months, was admitted to St. James's Hospital, Leeds, under the care of Dr. E. W. Jackson on January 6, 1955.

History

Largely from the mother. Prodromal symptoms had begun three weeks previously; he was feverish for one day and continued weak and anorexic for nine days. He then developed a sore throat and dry cough, and in the next three days, successively, soreness of the mouth, eyes and penile tip with scalding pain on micturition (but no frequency). His cough became productive of yellow sputum, and large amounts of yellow mucus were produced in his nose and mouth. On the 12th day (nine days before admission) he was put on to two tablets of sulphadimidine four times daily, and lozenges and eyedrops of penicillin. The eyes and mouth improved greatly on this regime, which continued until entry into hospital. In the last two days micturition had been painless. On the day before admission his temperature, which had probably been raised slightly from the onset rose much higher. The boy appeared flushed, and a rash 'like measles' was noticed on the right arm. This steadily became generalized. Systematic enquiry revealed that ten days before admission his fingers felt stiff for one day, and that a few days later he complained of transient numbness in the left thigh. He had been taking no drugs previously.

When aged 3 months, he was seen by a paediatrician because of frequent vomiting since birth; he benefited from three weeks in hospital, but the mother remembers no information about diagnosis or treatment, and the hospital records have been destroyed. However, his spleen was

said to be enlarged, and since then his mother has thought the left side of his abdomen to be full. From the age of 9 months he has had almost yearly attacks of urticaria, mainly in the summer, but without other recognized provoking factors. Until aged 8 or 9 he had constant nasal catarrh. Otherwise his health had been good, and he had a liking for physical pursuits, notably weight-lifting.

He is an only child, his twin having died at birth. His parents are well. His maternal grandmother is said to have had eczema of the forearms whenever pregnant.

Physical examination showed a poorly-looking fair-haired boy of good average physique; of adenoid facies, flushed particularly under the eyes and on the upper lids. There was an intense injection of the conjunctivae, especially the palpebral portion, and possibly some episcleritis. The lips were thickly blood-scabbed with a suggestion of old bullae at the periphery of some lesions. The mouth showed an intense stomatitis and pharyngitis, with purulent ulceration near to the lips and under the tongue, and along the tongue margins; apart from involvement in this affection the tonsils were normal. The urethral meatus was red, pouting and ulcerated and there was low grade balanitis. The skin itself showed a ham-coloured erythematopapular rash on the trunk and arms, confluent on the upper trunk and extensor aspects of the arms, scanty on the hands, neck and round the pelvis; absent on the face, head and legs apart from a trace above the patellae.

There were non-tender discrete firm glands, medium to large in both anterior triangles of neck and groins; and smaller ones in the axillae and posterior triangles of the neck; the right epitrochlear gland was felt. Palpation of the abdomen revealed, on inspiration, a firm spleen descending below the costal margin; the liver was not palpable. Examination of the heart, lungs and nervous system revealed no abnormalities. There was no tenderness over the paranasal sinuses. Blood pressure, 120/80; pulse rate, 92/min.; respiratory rate, 20/min.; temperature, 97.8°F.

The following investigations were done:

Haemoglobin: 17.1 g. %.

White Blood count: 10,600/c.mm. (neutrophils 65%, eosinophils 6% (636/c.mm.), lymphocytes 25%, monocytes 3%, Turck 1%).

Blood sedimentation rate: 21 mm. in one hour (Westgren).

Paul-Bunnell: negative.

Wassermann reaction: negative (August 9, 1955).

Swabs: From eye: negative.

From throat: negative for haemolytic streptococci and *Staphylococcus aureus*.

From urethra: direct, no pus cells or gonococci seen; culture, scanty growth of *Staphylococcus albus*, coagulase negative.

X-ray of chest and sinuses (reported on by Dr. J. Wall): 'Chronic sinus infection in both antra. Fluid level in right antrum. No pulmonary lesion noted.'

Treatment was as follows: Cortisone acetate (oral) 50 mg. 6-hourly for two days, then 25 mg. 6-hourly for three days, and finally tapered off over four days. Potassium chloride 1 g. t.d.s. Erythromycin 300 mg., 6-hourly. Streptomycin 0.5 g. b.d. Guttæ argyrol t.d.s. Benzocaine and Bradosol lozenges. Light diet and plentiful fluids. Complete bed rest.

Progress was rapid. By next day he was feeling better, and the signs were less intense. A day later the eyes were distinctly less red, and the stomatitis and rash fading. By the fourth day of treatment the mouth, throat and urethral meatus were clear, the conjunctivæ only slightly injected, and the skin showed only residual staining. The glands were smaller. The temperature remained normal apart from evening spikes of 100°, 99.4°, and 101°F. on the 10th, 11th and 12th days; cortisone was stopped on the 9th day. On the 15th day, Mr. O. C. Lord kindly did a bilateral antral washout, in view of the X-ray findings. He reported the left antrum to be clear but from the right one were obtained strings of muco-pus, typical of the end of an infection; 100,000 u. penicillin were instilled. At discharge on the 19th day, resolution was complete. Because of the question of sulphonamide hypersensitivity, the patient attended as an outpatient for patch testing to 5% sulphadimidine and 5% sulphadiazine, separately, in Paraff. Moll. Flav; these were negative after 24, 48 and 72 hours. When seen on April 15, 1955, he was fit and well, and physical examination revealed no abnormality apart from a pulse rate of 100/min., and the firm spleen which still emerged under the costal margin on deep inspiration. When last seen on August 9, 1955, he had remained well and had gained weight

and broadened. The pulse rate was 80/min. The spleen was still palpable on inspiration. There has been no relapse since.

Discussion

Hebra (1866) is credited with first recognizing the unity of the polymorphous erythemata so carefully differentiated by earlier physicians. He gave to the group, the now-established name *Erythema Exudativum Multiforme*. He declared his ignorance of the cause of the eruptions, but was aware of rare febrile cases with extensive, even confluent rashes, and recorded one case with fatal pneumonia. By the end of the century cases had been described with oral lesions and constitutional symptoms, and in 1876 Fuchs reported a case with pseudomembranous conjunctivitis. At the beginning of this century other writers, such as Barkan (1913) and Stark (1918), described cases of generalized erythema multiforme with constitutional symptoms and lesions of the membranes of conjunctivæ, mouth and genitals; but it was not until Stevens and Johnson (1922) published the histories of two children with resultant blindness, that the dramatic entity now often termed Stevens-Johnson's Syndrome, became well known. Bronchitis or pneumonia have since been shown to be associated fairly commonly. Thomas (1950) suggested that the condition be called *Erythema Exudativum Multiforme Major* to point the relation to and difference from Hebra's *Erythema Exudativum Multiforme*, to be suffixed Minor. The terms are good but clumsy; and as the condition described by Hebra is well known as *Erythema Multiforme*, the shorter forms, *Erythema Multiforme Major* (Stevens-Johnson) and *Erythema Multiforme Minor* (Hebra) would be easier to use. The relationship of so-called Stevens-Johnson's Syndrome to Behcet's disease, Reiter's disease and Ectodermosis Erosiva Pluriorificialis has been boldly discussed and classified by Robinson (1951). He considers them part of the same entity, the Ocular-Mucous Membrane Syndrome. However, Behcet's and Reiter's diseases are both *clinically* distinct from Stevens-Johnson's Syndrome; Behcet's disease on account of its absence of constitutional symptoms, the high incidence of hypopyon, and the infrequency of skin eruptions other than erythema nodosum; Reiter's disease because of its emphasis on arthritis and urethritis, the longer course, and the relative infrequency of cutaneous manifestations, prominent amongst which is keratosis blenorrhagica. Ectodermosis Erosiva Pluriorificialis, first introduced into English literature by Klauder (1937), having had its origins in French reports in the First World War, does not seem to differ significantly from the condition under discussion. However, as Soll (1947)

pointed out, the cases that Klauder originally used the term for, were midway in severity between Hebra's Erythema Exudativum Multiforme and the full Stevens-Johnson Syndrome, the ocular lesions never progressing beyond purulent conjunctivitis and the rash usually remaining peripheral. Now that we have the pituitary and adrenal hormones for treatment, we should be able to protect the eyes and make the differentiation between the groups of Klauder and Stevens-Johnson unnecessary. Although Klauder's term has the merit of drawing attention to the body orifices, it is clumsier and less euphonious than Erythema Multiforme Major.

The diagnosis in our case seems firmly based, with involvement of the skin, conjunctivae, and oral and genital mucosae, and constitutional upset. In their analysis of 81 cases, Ashby and Lazar (1951) showed the disease to affect mainly males in the first three decades of life, to be commoner in the winter months, and to have commonly a prodromal period of 1 to 13 days. (Erythema Multiforme Minor appears to have its main incidence in spring and autumn.) When the skin is involved, as is usual, it generally shows some vesicles or bullae. In our patient, although the rash was purely maculopapular with confluence, as in Stevens and Johnson's two children, it will have been noted that the appearances of the lip lesions suggested a bullous phase in their development. In the cases reviewed by Ashby and Lazar, none had lymph gland enlargement elsewhere than in the neck. However, Soll (1947) who presented 20 cases of his own, none of which had any enlargement, reviewed 22 cases from the literature; three had cervical lymphadenopathy, and one had generalized lymph gland enlargement. It may be noteworthy that he grouped all his own cases, with Klauder's cases of Ectodermosis Erosiva Pluriorificialis, intermediate between Erythema Exudativum Multiforme and Stevens-Johnson's Syndrome; 16 had no rash, and in the remainder it was confined to the hands and feet. In our case the rash was more central in distribution. It is unlikely that the chronic splenomegaly, first noted when the patient was aged 3 months, is of direct relevance to the condition being discussed. Sternal marrow and splenic puncture were therefore not considered advisable, and the cause of the enlarged spleen must remain in doubt. As there has been no personal or family history of anaemia, there is the possibility that it is due to a mutation causing a subclinical form of Gaucher's disease.

Like Hebra we do not know the cause of the condition, although infective, toxic, and allergic bases have been postulated. However, erythema multiforme lesions are known to occur rarely as a complication of treatment with drugs—sulphona-

mides, barbiturates, salicylates, bromides, cinchophen, phenolphthalein—and at times with acute rheumatism, chorea, endocarditis, tonsillitis, and arthritis. Hebra believed the roseola of cholera to be Erythema Papulatum. The major form has been seen in association with an epidemic of primary atypical pneumonia with antibody reactions (Finland *et al.*, 1948), and with Sonne dysentery and Vincent's angina (Thomas, 1950); with the exhibition of drugs, notably sulphonamides (Fletcher and Harris, 1945; Thomas, 1950; Caldwell, 1953); after vaccination and in circumstances suggesting an allergic basis (Schwartz and Brainerd, 1946). The evidence for the condition being a primary infection, of virus type, are the reporting of epidemics by a few writers, e.g., Leipner (1935), the demonstration of cytoplasmic inclusion bodies in the cells of a rabbit cornea scarified with vesicular fluid from a patient by Anderson *et al.* (1949), the isolation of herpes simplex virus from a fatal case by Womack and Randell (1953), and the good results of treatment with chlortetracycline.

Our patient's history of urticaria, and his grandmother's of pregnancy eczema, are notable in view of the allergive hypothesis of causation. The mild eosinophilia, absolute and relative, is said to be usual (Whitby and Britton, 1953). The relationship to the disease of the antral infection is problematical; it may have developed as part of the infected exudation in the respiratory tract, or it may have been present before the onset of the disease, and played a provoking part as a source of bacterial allergens. The history of chronic nasal catarrh up to the age of 8 or 9, and the adenoid facies, may therefore be significant.

Again, the relationship of the sulphadimidine to the development of the disease is not clear. It is likely that it played no part at all, for all the symptoms had developed before the drug was started, with the exception of the rash. However, the patient took it for eight days before he developed the eruption, which could have passed for a sulphonamide rash, and was not peripheral in distribution and contained no vesicular or iris lesions. The negative patch tests do not, of course, exclude hypersensitivity, which is probably vascular rather than epidermal. I think the factors of atopy and upper respiratory infection are more likely to be of significance.

Recent treatment has chiefly consisted in the new broad spectrum antibiotics, particularly chlortetracycline, and adrenocorticotropin (ACTH). Since Wammock *et al.* (1951) treated a case with adrenocorticotropin, several others have used it. Ereaux (1952) stated that 'a panel on therapeutics at the meeting of the American Academy of Dermatology and Syphilology in

Chicago in December 1951, was of the opinion that ACTH and cortisone are indicated in the treatment of erythema multiforme, especially of the Stevens-Johnson type.' Caldwell (1953) quotes three previous cases treated with ACTH in addition to that of Wammock *et al.*, and one case of his own. Bleier and Schwartz (1951) started treating a 24-year old male with cortisone on the 8th day of the disease with excellent results, but the only other cases reported as being successfully treated with cortisone that I can find in the literature are one of Ferloni and Giordano (1954), which was complicated by the excretion of urinary porphyrins, and an interesting case described by Agostas and his colleagues (1952). In the last case, the patient was a 14-year-old boy who was started on ACTH on the 8th day and responded dramatically in 12 hours; two months later, in a relapse of the condition, ACTH failed to produce a response after four days, but when he was changed on to cortisone, the therapeutic response was excellent within 48 hours. Further, Lozano (1955) treated the second and third relapses in a 31-year old man, with ACTH and cortisone respectively. Only the last episode seemed significantly shorter than the first two attacks, treated with antibiotics, the lesions receding after five days. Finally, Mauriello (1954), describing his experience with 14 cases in a U.S. Army hospital, concluded that the ACTH used in six patients and cortisone used in two patients did not materially alter or shorten the course of the disease, and in one patient in each group, new skin lesions appeared while they were on treatment with the hormones; in all cases the mouth lesions took 7 to 21 days to heal.

The variability of the effects of the hormones in different reports are probably in part due to different modes of administration and dosages, and it would appear that an inadequate response may be rectified by an increased dose, or a change of hormone. In our case the effect of the cortisone, although late in the course of the disease seemed dramatic in alleviating symptoms. However, the condition did not appear completely inactive for almost two weeks after the start of treatment, and one wonders whether in fact the duration of the disease was shortened. All in all,

the summation of evidence points to the need for controlled trials in this sphere of therapeutics.

Summary

A case of so-called Stevens-Johnson's Syndrome is presented, with a past history of recurrent urticaria, maxillary antral infection, and a history of the exhibition of Sulphadimidine during the development of the disease. Treatment with Cortisone and antibiotics was rapidly ameliorative. Patch tests to Sulphonamides were negative. Attention is drawn to the generalized lymphadenopathy, and the fact that the patient had had a chronic splenomegaly since infancy. Causation and treatment are discussed, with special reference to the steroids, and the need for controlled trials.

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