DEATH FROM DERMATITIS AND STOMATITIS DURING STREPTOMYCIN THERAPY

BY

R. A. PALLISTER, O.B.E., M.D., M.R.C.P.

(From the General Hospital, Penang, Federation of Malaya)

Dermatitis is a complication that may occur during the administration of streptomycin, but usually it is relatively mild and unimportant. Stomatitis is a less common complication. It is therefore desirable to report the following two fatal cases in which fever and lesions of the skin and mucous membranes occurred during the treatment of pulmonary tuberculosis with this drug.

Case 1

The patient, a Chinese man aged 25, was admitted to the General Hospital, Penang, on November 26, 1948, complaining of cough, blood-stained sputum, and loss of weight. The duration of his illness was about one year. Radiological examination of the lungs showed bilateral fibro-caseous disease, and the sputum contained acid-fast bacilli. He also had bilateral epididymitis with sinuses, and the prostate was rather enlarged, hard, and fixed. His temperature rose daily to about 101° F. (38.3° C.). Because of the fever he was given 2 g. of streptomycin daily from November 29. After four days the temperature became normal and remained so for a further week, but it then began to rise again to a daily maximum of 101° F. On December 18 he had a sudden further rise of temperature up to 104° F. (40° C.) associated with the symptoms described below. He continued to have an irregular high temperature until the 21st, when he died.

This terminal illness consisted of fever, stomatitis, and dermatitis. On being questioned on December 18, the day the severe fever started, he stated that he had not been feeling well for the previous 24 hours. There had been a burning sensation of the lips and throat, irritation of the eyes, and itchiness of the chest and abdomen. He had also noticed some reduction in the amount of urine passed and a slight burning sensation on micturition.

On examination a generalized punctate erythematous rash was seen. This was especially marked on the trunk, but the face, palms, and soles were clear. The lips were red and sore, and inside the mouth there were dirty white ulcerated areas on the mucous membrane of both cheeks, on the lower gums, and on the right tonsil. He had a watery discharge from the eyes and the conjunctivae were injected. There was no urethral discharge. The streptomycin was stopped on the 18th and penicillin substituted. "Pentnucleotide" injections were also given. On the morning of the 21st he vomited and his pulse was rapid and weak. He died the same afternoon. The leucocyte counts during this time showed a severe leucopenia. The figures were:—December 19: total leucocytes, 2,000 (polymorphs 10%, lymphocytes 78%, mononuclears 10%, eosinophils 2%); December 20: total leucocytes, 3,200 (polymorphs 21%, lymphocytes 69%, mononuclears 8%, eosinophils 2%). Bacteriological examination of material from the mouth lesions showed a few fusiform bacilli in a smear, and *Streptococcus viridans* was grown on culture.

Case 2

This patient, a Chinese man aged 28, was admitted to hospital on March 13, 1949, following a haemoptysis. The history of his illness went back eight or nine months, when he had been seen with a fairly early tuberculous lesion of one lung. He refused treatment at that time, but remained fairly well until a month before his admission, when he began to lose weight and suffer from extreme lassitude. He was found to be febrile on admission to hospital, but his general nutrition was fairly good. The sputum contained acid-fast bacilli, and an x-ray

film of the chest showed widespread bilateral disease. This consisted of a recent spread from a more chronic lesion in the left upper lobe.

Streptomycin was started on March 24 with a dosage of 1 g. daily. Until this date the temperature had remained high, the daily maxima being between 101 and 103° F. (38.3 and 39.4° C.), but with streptomycin the temperature fell to a much lower level within three days. For about a week the temperature was below 100° F. (37.8° C.), but it then began to rise again, and for the next two weeks the patient suffered from an irregular fever rising to a maximum of 104° F. (40° C.). On April 18 he refused his daily streptomycin injection because it was causing pain, but was persuaded to have it the following day. On April 20—that is, after receiving 26 g. of streptomycin—a rash was noticed and the drug was stopped. The symptoms described below then developed. The temperature remained high for a further ten days and then gradually settled to normal. During this complication the patient grew rapidly worse, and he died on May 26.

The first signs of the rash were a redness and swelling of the skin which suggested an urticaria to the doctor seeing it. By the third day, however, patches of superficial ulceration appeared on the palate, and in a further day or two the symptoms had grown very severe. The skin of the face was red but showed some desquamation. Over the trunk the skin was bright red; on the limbs it was a purplish red, with some vesicles on the legs. The lips were sore, the mucous membrane of the cheeks, tongue, and palate was covered with an almost confluent purulent membrane, and there was a mucopurulent discharge from the mouth. The taking of fluids by mouth was almost impossible at this time. The eyelids were puffy and could scarcely be opened. There was some pus in the conjunctival sac, but conjunctivitis was not very severe.

The white cell count on April 26 was 18,000 per c.mm. (polymorphs 75%, lymphocytes 12%, mononuclears 1%, eosinophils 12%). In two weeks from the onset of this complication the rash showed some improvement, the skin being less inflamed and beginning to scale. The patient had, however, lost much weight and was in a very poor state. The mouth lesions improved very slowly and haemorrhagic crusts persisted on the lips. When he died, five weeks from the onset, the lesions had not completely healed.

Apart from symptomatic treatment he had "anthisan," penicillin, and calcium injections. Before the onset of the rash the only drug received which could have caused symptoms was phenobarbitone.

Comment

The two cases described have a considerable resemblance to severe erythema multiforme, a disease which occurs in Malaya. With Dr. C. T. Hu I have described elsewhere (Pallister and Hu, 1949) a patient under general treatment for pulmonary tuberculosis who developed this disease. Should, however, this name be attached to the condition affecting the two patients it is still possible that streptomycin is an aetiological factor. This is more probable than assuming a coincidence as an explanation, for lesions of this type are uncommon and it would be rather surprising to find two patients with them in a comparatively small group of streptomycin-treated patients unless the drug played some part in their causation. Furthermore, Beham and Perr (1948) have described three cases of stomatitis and Thevathasan (1949) a single case in patients under streptomycin therapy. In both these reports the stomatitis was shown to be the result of sensitivity to the drug. Sumner (1949) has described three patients who developed lesions of the mouth and skin. These lesions were, however, attributed to food deficiency due to the bacteriostatic action of streptomycin on vitamin synthesis by intestinal organisms, and the clinical picture was not quite the same as in the two fatal cases described above. Nevertheless, poor nutrition, which is not rare in Malaya, may play some part in skin and mucous membrane damage.

It is reasonable to suggest, therefore, that abnormal sensitivity to streptomycin or a direct poisoning by the drug is the most probable cause of the symptoms.

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UNUSUAL MANIFESTATIONS OF MALARIA

BY

A. K. NANDI, B.Sc., M.B.Cal., M.R.C.P.Ed.

Additional Physician, Medical College Hospitals, Department of Medicine, Calcutta

Malaria is an arch-simulator and a great mimic of all diseases. The multiplicity and duplicity of the disease cannot be overemphasized. In spite of the classical division of pernicious malaria into types—cerebral, a'gid, gastro-intestinal, cardiac, renal, purpuric, etc.—a practitioner is sometimes faced with very peculiar symptom-complexes, and becomes bewildered regarding the probable diagnosis. During my practice in malarious districts for more than sixteen years I came across many such puzzling cases, some of which are worth recording.

Case Reports

Case 1.—In 1939, at Jalpaiguri, North Bengal, a healthy robust boy aged about 12 suddenly became unconscious and fell down while taking his meal before going to school. I saw him within an hour of the attack. He was then having epileptiform fits. His temperature and blood pressure were normal, the liver and spleen were not palpable, and no abnormality was detected in the heart and lungs. The pupils were moderately dilated and reacted sluggishly to light. The question was whether it was a case of epilepsy—although he had never had such an attack before—or of cerebral malaria, Jalpaiguri being a highly malarious district. Blood was immediately taken and a few M.T. rings were found in the blood slides. Quinine was given parenterally and the boy recovered after being unconscious for about 48 hours. The interesting feature in this case is that no rise of temperature occurred at the time of examination, nor was there a history of malaria within six months of the attack. The temperature rose, however, to 100° F. (37.8° C.) about four to five hours after the attack.

Case 2.—In 1941, also at Jalpaiguri, a postal clerk aged about 40 complained of a severe burning sensation and pain in both hands, including the fingers, for about one week. The pain was so excruciating that he had sleepless nights. On examination there was an erythematous flush of both palms and the fingers were slightly swollen, the tips being extremely tender. His temperature varied from 100 to 103° F. (37.8 to 39.4° C.). There was a history of recurrent attacks of malaria. He consulted local doctors, who prescribed sedatives, sulphonamides, and hot boric compresses, but without the slightest relief. When I saw him he appeared to have acute lymphangitis, and thinking it might be of filarial origin I sent the blood for examination for eosinophilia and microfilaria. I was extremely surprised to hear that the blood slides revealed M.T. rings. With hesitancy I gave quinine, and the result was spectacular. The temperature dropped to normal, and the redness and swelling of the palms and fingers, the pain, and the burning sensation all diminished considerably after one injection of 10 gr. (0.65 g.) of quinine bihydrochloride. The patient was fully cured after three injections.

I have never found any mention in the literature that malaria parasites can give rise to lymphangitis or lymphatic obstruction.

It may be that the syndrome was due to obstruction of the capillaries by the parasites.

Case 3.—In 1945 at Burdwan, West Bengal, a boy aged about 14 had an attack of fever on returning from school; this was accompanied by a chill but no definite rigor. The next morning he was seen by a local doctor, who gave him quinine. That afternoon, however, his temperature shot up to 104° F. (40° C.). He had great difficulty in swallowing food, his voice was nasal, and liquid food regurgitated through the nose. The doctor thought it was a case of diphtheria, and I was called in. On examination there was no patch in the throat; the boy was fully conscious, and had a high temperature, slight enlargement of the spleen, and paralysis of the soft palate; no other abnormality was detected. His blood was examined and M.T. rings were found. The boy made an uneventful recovery after one week's course of quinine.

Case 4.—In 1947, at Dacca, Eastern Pakistan, a man of about 30 returned home with severe headache after a morning walk. A little later he became unconscious and had severe convulsions—twitchings of face and arms were particularly severe. His pulse was very slow, varying from 30 to 35 a minute, and was irregular. The blood pressure was 120/78 mm. Hg. His pupils were slightly contracted and equal, and feebly reacted to light. Jerks were rather brisk, Babinski's reflex was flexor, and abdominal reflexes were sluggish. The axillary temperature was 98° F. (36.7° C.). The liver and spleen were not enlarged. The lungs were normal and there was partial heart-block. Adams-Stokes syndrome was diagnosed by a local doctor, who called me in for an opinion. On inquiry it was learnt that the patient had had two or three attacks of malaria about six months before. A specimen of blood was at once sent for examination, and the report came back that the slides contained many M.T. rings. Quinine was first administered intravenously with glucose, then intramuscularly, and the patient recovered after being unconscious for seven days. During this time he was fed by intragastric drip, and atropine, adrenaline, and nikethamide were given. The interesting feature of this case was heart-block giving rise to an unduly slow irregular pulse. There was a rather small rise of temperature throughout the whole course; on the first day it rose to 99° F. (37.2° C.) towards the evening, and on subsequent days it varied from 97 to 101° F. (36.1 to 38.3° C.).

Case 5.—A man aged about 24 was brought to the emergency room of the Medical College Hospitals, Calcutta, in January, 1949, with a history of severe pain in the abdomen and vomiting for about 48 hours. He was very dehydrated, the tongue was coated and dry, the pulse rapid and feeble, and the abdomen greatly distended, with marked tenderness and rigidity over the epigastrium. There was bilious vomiting and absolute constipation for two days. His temperature was only 99° F. (37.2° C.). The spleen and liver could not be palpated owing to pronounced distension of the abdomen. He was admitted to a surgical ward as a case of "acute abdomen" requiring immediate operation. While the house-surgeon was giving pre-operative treatment the patient had a severe rigor and the temperature shot up to 105° F. (40.6° C.). The blood was immediately examined and Q.T. parasites (band forms) were found. He was at once transferred to my ward and given 10 gr. (0.65 g.) of quinine bihydrochloride with normal saline and glucose intravenously. Quinine was given intravenously at intervals of six hours for two more doses and the patient made a dramatic recovery. The occurrence of a rigor immediately before the operation was providential; otherwise the result might have been disastrous. The presence of Q.T. parasites in such a case is extremely unusual.

Summary

Five cases presenting rare manifestations of malaria are recorded, each of which was confirmed by positive blood findings; in four cases the causative organism was *Plasmodium falciparum*, but in the fifth case it was *Plasmodium malariae*, which is extremely unusual. The peculiar symptom-complex in each case may be explained by the fact that sporulation of the malignant parasite generally takes place in the internal