Ulcerating Stomatitis Associated with Streptomycin Therapy

This is a short report relating to the development of stomatitis in two patients undergoing streptomycin therapy for tuberculosis, an event which I had not previously encountered or found recorded by others.

CASE 1

A married woman aged 57, with no history of hypersensitivity, had had pulmonary tuberculosis diagnosed in 1947, but received no treatment until May, 1956, when she had bilateral upper-lobe disease with sputum positive for tubercle bacilli. Streptomycin, 1 g. daily, and isoniazid, 400 mg. daily, were started early in May, and in mid-June a bilateral linear stomatitis, corresponding to the line of the cutting edges of the molars, developed; and, after two to three weeks, showed patchy ulceration with heaped-up, yellow edges which were not detachable. The area was most painful. Because of fairly severe and generalized caries her teeth were gradually extracted. The stomatitis spread over the inner surfaces of the cheeks and lips, which were fiery red and very painful, with tough yellow edges on the ulcerated areas. However, antituberculous treatment was continued.

On admission on May 2, 1956, her white-cell count was 9,000 per c.mm. (neutrophils 76%, eosinophils 1%, lymphocytes 19%, monocytes 4%), and the haemoglobin, 74%. Red and white cells were normal morphologically.

On June 13 (onset of stomatitis) the white-cell count was 9,800 per c.mm. (neutrophils 60%, eosinophils 15%, lymphocytes 23%, monocytes 2%). The eosinophil count on June 15 was 940; on July 25 18% of 7,800; on September 13 26% of 7,000; and on September 17 1,320 per c.mm. Blood examination at this time showed no abnormality other than mild normochromic normocytic anaemia. Mouth swabs grew no pathogenic bacteria, and at no time were fungi or yeasts found. The Wassermann and Kahn reactions were negative.

On October 8 streptomycin and isoniazid were discontinued, as it was thought that one or other, or both, might be responsible for the mouth lesions; there being now widespread stomatitis, patchy ulceration, cheilitis, and glossitis, which caused so much pain that only fluids or pulqueous foods could be taken. Apart from sporadic fever of 99 to 100° F. (37.2 to 37.8° C.), the patient was otherwise well, if dejected. Cervical lymph nodes were slightly enlarged and tender, but all other nodes were normal. The liver and spleen were not palpable, and there was no skin rash. The mouth improved very slowly, but by October 15 the eosinophil count had fallen to 370 per c.mm., and in late October the lesions were much improved. In mid-November the mouth was normal, the eosinophil count being between 95 and 220 per c.mm.

Calcium B P.A.S., 3.5 g. four times a day, and isoniazid, 400 mg. daily, were started on November 28, and by December 20 the mouth was still normal and the patient eating well. At this date P.A.S. was replaced by streptomycin, 1 g. daily, and three days later painful cheilitis and stomatitis recurred with one or two small ulcerated areas, though the eosinophil count did not exceed 300 per c.mm. The drugs were then withdrawn and aneurine hydrochloride, 25 mg. intramuscularly twice daily, was given empirically with concentrated vitamin-B complex by mouth, but recovery took over three weeks. She has had no recurrence, and streptomycin has not been used again.

CASE 2

A man aged 54, with no history of hypersensitive illness, had had pulmonary tuberculosis diagnosed in 1917. He was admitted to hospital in January, 1956, with spinal and genito-urinary tuberculosis and sputum positive for tubercle bacilli. In February sodium P.A.S., 20 g. daily, and isoniazid, 400 mg. daily, were started. No ill effects were noted. In August P.A.S. was replaced by streptomycin, 1 g. daily. During the first week in October stomatitis similar to that in the previous patient occurred, and progressed quickly

in precisely the same way to extensive and painful involvement of the buccal surface of the cheeks and lips with generalized bright-red glossitis; patchy ulceration, which was particularly severe on the inner surface of the lips, showed the same firm yellow edges. There was sporadic fever of 99 to 101° F. (37.2 to 38.3° C.), but otherwise he felt well, apart from dysphagia due to the mouth lesions. The cervical lymph nodes were slightly enlarged and tender, but other nodes were normal. There was no skin rash, splenomegaly, or hepatomegaly.

The white-cell count on admission (January, 1956) was 9,000 per c.mm. (neutrophils 67%, eosinophils 4%, lymphocytes 24%, monocytes 5%); normal morphology. The red-cell count and morphology were normal. The white-cell count on October 17 was 12,000 per c.mm. (neutrophils 75%, eosinophils 9%, lymphocytes 13%, monocytes 3%). On October 24 the eosinophils numbered 1,525 per c.mm. (14% of 11,000), and on October 26, 1,406 per c.mm. Mouth swabs grew scanty *Staphylococcus aureus*, but no fungi or yeasts were ever seen. The Wassermann and Kahn reactions were negative, and no impairment of renal function was discovered.

The antituberculous drugs were withdrawn on October 25 and the lesions slowly cleared until, by mid-November, the mouth was normal. Four weeks after cessation of the drugs the white cell count was 7,800 per c.mm. (neutrophils 58%, eosinophils 1%, lymphocytes 36%, monocytes 5%).

On November 27 calcium B P.A.S., 14 g. daily, with isoniazid, 400 mg. daily, were started, and after three weeks there was no ill effect, the eosinophil count on December 5 being 210 per c.mm. On December 18 P.A.S. was replaced by streptomycin, 1 g. daily, and on December 21 stomatitis recurred, the eosinophil count at this date being 730 per c.mm. Drugs were continued until December 26, when they were withdrawn, as stomatitis and cheilitis, with ulceration and glossitis, were almost as severe as they had been originally. Concentrated vitamin-B complex was now given by mouth. The condition cleared slowly over three weeks, and has not recurred, P.A.S. and isoniazid being administered latterly.

DISCUSSION

The striking features of these cases are their close similarity, the eosinophilia, and the rapidity of relapse when streptomycin was recommenced. Apart from the antituberculous drugs, no other factors common to both patients could be found, and streptomycin batches varied daily or weekly.

Occurrence of the mouth lesions when streptomycin was administered, recovery when it was withdrawn, freedom while receiving P.A.S. and isoniazid, and quick recurrence when streptomycin was reintroduced, strongly suggest that the latter drug was in some way responsible. The associated eosinophilia may imply hypersensitivity, though there was no other evidence of this, and it would seem unlikely to be expressed as so local a phenomenon. Many patients, never exhibiting hypersensitivity at any time, who are receiving streptomycin for treatment of tuberculosis show mild eosinophilia, but in my experience this does not exceed 6 to 8% of the total count; should it do so, frank hypersensitivity, such as skin rash, declares itself within a few days or has already done so at the time of the count.

Deficiency of the vitamin-B complex seems an improbable cause, especially when the speed of relapse is considered, and, in any case, the evidence that parenterally administered streptomycin causes vitamin deficiency has never been persuasive. Local pathogenicity of normal mouth organisms under the influence of streptomycin therapy might have occurred, though the negative mouth-swab cultures, normal neutrophil count, and speed of relapse add little confirmation, but it is not excluded. The stomatitis was not tuberculous.

The observations on these patients remain unexplained.

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