Medical Memoranda

Prolonged Generalized Vaccinia Complicating Acute Leukaemia

Prolonged generalized vaccinia or vaccinia gangrenosa is a rare complication of vaccination which has been reported in patients with congenital and acquired hypogammaglobulinaemia (Kempe, 1960), lymphosarcoma Öberg *et al.*, 1958), chronic myeloid leukaemia (Vladimirovskaya, 1961), and chronic lymphatic leukaemia (Beerman and McGuire, 1944; Bousser *et al.*, 1955; Olansky *et al.*, 1956; Blumenthal, 1957; Mendansky *et al.*, 1960; Erichson and McNamara, 1961; Vladimirovskaya, 1961; Fekety *et al.*, 1962). An isolated case is recorded in acute leukaemia (Kozłowska and Sztymela, 1961). We now present details of the course and treatment of a patient briefly reported previously (Davidson and Hayhoe, 1962).

CASE HISTORY

A farm labourer aged 21 was admitted to Addenbrooke's Hospital on September 28, 1961. He had been ill for three

months with asthenia and loss of weight. For three weeks prior to admission he had suffered from severe flitting pains in the joints. He had previously been healthy and had not been vaccinated. His temperature was 101° F. (38.3° C.) and he sweated profusely. The lower end of the femur was tender to palpation, light pressure on the sternum produced pain, there were scattered purpuric spots on the skin of the legs, but there were no other abnormal physical signs.

Examination of the blood showed: Hb. 11.7 g./100 ml.; P.C.V. 36.5%; reticulocytes 2.5%; W.B.C. 6,600/c.mm., with 15% blast cells; platelets 447,000/c.mm. Bone-marrow, 95% blast cells. X-ray examination of the chest and skeleton revealed no abnormality.

The course and treatment are summarized in the Chart. During the first week in hospital fever persisted despite tetracycline 250 mg. six-hourly. The severe bone pains required repeated injections of pethidine, 100 mg., for relief. The introduction of prednisone 40 mg./day on October 3 was followed by a dramatic remission in the fever and bone pain. He was discharged from hospital on continued prednisone. The general condition improved, the weight increased to 98 kg., and the Hb rose to 16 g. The peripheral leucocyte and platelet counts remained within normal limits, but a second bone-marrow aspiration still showed 50% blast cells.

On January 29, 1962, he was readmitted as a surgical emergency with severe central abdominal pain and vomiting.

Summary of course and treatment.

His temperature was 101° F. (38.3° C.) and he sweated profusely. Examination of the urine for cells and organisms was negative, and x-ray films of the chest and abdomen revealed no abnormality. The severe bone pains recurred and he required pethidine 100 mg. four-hourly and occasional morphine 16 mg. intramuscularly for relief. Examination of the blood and bone-marrow confirmed a relapse of the leukaemic state.

While in the surgical ward the patient was vaccinated against smallpox because of indirect contact with a suspected case. A single small area of skin over the right deltoid muscle was vaccinated using the multiple pressure technique (Harries and Mitman, 1951). On February 3 therapy with 6-mercaptopurine 150 mg./day was started in an attempt to control the leukaemia. A reduction in the dose of prednisone was associated with a severe exacerbation of the bone pains which were finally controlled when the dose of prednisone was raised to 60 mg./day.

The lesion of the primary vaccination increased slowly and progressively, and on February 15 was 10 cm. in diameter. The surrounding skin was red and indurated with scattered satellite vesicles. The regional lymph nodes in the right axilla were enlarged and tender. On February 19 there was evidence of generalized vaccinia with scattered vesicles on the trunk. The 6-mercaptopurine therapy was discontinued and the dose of prednisone was reduced. Examination of the serum proteins showed a total of 5.7 g. and an electrophoretic pattern with normal γ -globulins, an increase in α_1 - and α_2 -globulins, and a slight reduction in albumin. The antivaccinal neutralizing titre was 1:100 and remained unchanged after 2 g. of human antivaccinal γ -globulin. A transfusion raised the Hb from 7.9 to 10.6 g. The lesion of the primary vaccination increased in size to about 15 cm. in diameter (Davidson and Hayhoe, 1962, illustration). Further generalized lesions appeared on the scalp, tongue, buccal mucosa, trunk, and scrotum. There were scattered vaccinal lesions on the limbs, including the site of a cut-down over the right ankle. The generalized lesions increased in size to about 2-3 cm. in diameter and were covered by a black eschar similar to that seen in the primary lesion. Cultures taken from these lesions were positive for vaccinia virus.

N-methylisatin β -thiosemicarbazone (33T57) (Bauer and Sadler, 1960) 5 g. daily was given for seven days and the patient was transferred to Brookfields Hospital for isolation. By March 5 there was no further extension of the lesions, and during the following 10 days the scabs separated leaving a large granulating lesion at the site of primary vaccination. The patient's general condition improved, the Hb increased from 7.8 to 11 g., the platelet count rose to 140,000, but the W.B.C. of 7,000 still contained 4% blast cells. The antivaccinal titre at this stage was 1:200.

Recurrence of bone pains on March 10 heralded relapse of the leukaemia, and pethidine and morphine were administered frequently. The platelet count fell to 35,000, and he developed generalized purpura with bleeding from the granulating ulcer. The blast cells in the peripheral blood increased to 25%. A blood transfusion raised the Hb to 10 g., the dose of prednisone was increased to 60 mg./day, and 6-mercaptopurine therapy was restarted at a dose of 100 mg./day, but remission could not be induced and the patient died on April 1.

Summary of Necropsy Report.—The histology of the organs was that of acute leukaemia. The ulcer over the right deltoid muscle showed evidence of healing with an excess of granulation tissue.

DISCUSSION

Prolonged generalized vaccinia in leukaemia might reflect the general predisposition to virus infections resulting from defective antibody formation (Silver *et al.*, 1958; Barr and Fairley, 1961). This mechanism cannot be invoked in our patient in view of the adequate

antivaccinal neutralizing titre (Conolly *et al.*, 1962). Alternatively, the cellular defence mechanisms may have been at fault (Kempe, 1960; Turk *et al.*, 1962). The problem is complicated by possible adverse effects of therapy. Experimental (Bugbee *et al.*, 1960) and clinical experience (Olansky *et al.*, 1956) suggest that steroids impair the immune response to vaccinia. Anti-metabolites may have a similar detrimental effect (Schwartz *et al.*, 1958; Goh *et al.*, 1961). Thus an important aspect of the treatment of virus complications of leukaemia is withdrawal of chemotherapy (Pinkel, 1961).

As to the use of 33T57, benefit is reported in the treatment of eczema vaccinatum (Turner *et al.*, 1962; Mainwaring, 1962), but a single reported case of prolonged generalized vaccinia treated with this drug failed to respond (Conolly *et al.*, 1962). Our patient improved while on 33T57 and no toxic manifestations were observed, but withdrawal of steroids and anti-metabolite may have facilitated the response. Death was finally due to a relapse of the acute leukaemia.

In view of the severe reactions reported, it is important to avoid vaccination of patients suffering from leukaemia or lymphoma as well as any patients on steroid or anti-metabolite therapy. If travel regulations cannot be evaded (Dixon, 1962) the possibility of using killed vaccine should be considered (Kempe, 1960).

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