Intracranial Leukaemia and the Cerebrospinal Fluid

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With the prolongation of survival in patients with acute leukaemia the incidence of central nervous system involvement has shown a coincidental increase (Evans *et al.*, 1970). Its actual frequency, however, remains difficult to estimate, for symptoms and signs may be minimal and meningeal leukaemia often occurs during bone marrow remission. Reports on patients with acute leukaemia and signs of raised intracranial pressure in whom examination of the cerebrospinal fluid has shown no increase in white cell count are few. The cases of two patients with acute myeloblastic leukaemia, both of whom were in relapse and had signs of raised intracranial pressure without cells in the cerebrospinal fluid, are described here. Both responded to therapy with systemic and intrathecal cytotoxic agents.

Case 1

A 22-year-old woman presented with a four-week history of fever, severe frontal headaches, giddiness, nausea, and vomiting which had failed to respond to antibiotic therapy. Five days before admission she had noted spontaneous bruising followed by the sudden onset of diplopia. On admission to hospital she had superficial bruising and sternal tenderness. Examination of the central nervous system showed a right sixth cranial nerve palsy and bilateral papilloedema with retinal haemorrhages. Her haemoglobin was 13.0 g/100 ml, platelets were 26,000/mm³, and total leucocyte count was 11,000/mm³ (17% blasts, 12% premyelocytes, 8% myelocytes, 1% metamyelocytes, 32% neutrophils, and 30% lymphocytes). Bone marrow aspiration confirmed acute myeloblastic leukaemia. The cerebrospinal fluid pressure was greater than 300 mm, and the fluid contained no cells and proved sterile on culture. The protein content was 55 mg/100 ml and glucose 54 mg/100 ml.

During the initial two weeks she was treated systemically with two five-day treatment courses consisting of intravenous daunorubicin 1.5 mg/kg on the first day and intravenous cytosine arabinoside 1.0 mg/kg 12-hourly for five days. Her peripheral leucocyte count was 4,600/mm³ with 42% blasts on completion of this course and there was no improvement in her neurological signs. The therapy was repeated with the addition of mercaptopurine 2.5 mg/kg by mouth, and during the next three weeks six lumbar punctures were performed with cytosine arabinoside instilled intrathecally in doses of 25 mg/m² on each occasion. In no specimen were cells found. Throughout this period the cerebrospinal fluid pressure fell steadily to 130 mm and the papilloedema and retinal haemorrhages resolved. The right abducent nerve function returned to normal. Despite further intensive systemic therapy she failed to achieve a bone marrow remission and died six weeks later. Necropsy was not performed.

Case 2

A 29-year-old woman was admitted to hospital with a three-month history of malaise and recurrent upper respiratory tract and oral infections. She had a pyrexia of 38.4°C, gingival hypertrophy, oral

ulceration, sternal tenderness, and generalized superficial bruising. Her haemoglobin was 9.6 g/100 ml, platelets were 43,000/mm³, and total leucocyte count was 26,800/mm³ (81% blasts, 3% neutrophils, and 16% lymphocytes). Bone marrow aspiration confirmed acute myeloblastic leukaemia. She was treated with blood transfusions, antibiotics, and five seven-day courses of intravenous daunorubicin 1.0 mg/kg on the first day, intravenous cytosine arabinoside 3.0 mg/kg daily for three days, mercaptopurine 2.5 mg/kg by mouth for five days, and prednisolone 40 mg daily for seven days, with an interval of seven days in between each course. She achieved a complete bone marrow remission (less than 5% blasts).

Four weeks later, when she returned for a further course of therapy, clinical examination showed no abnormality but bone marrow aspirate contained 35% blasts. Ten days later she complained of headaches and vomiting, and on examination she had bilateral papilloedema and haemorrhages in the right fundus. The cerebrospinal fluid pressure was greater than 300 mm, and the fluid contained no cells and proved sterile on culture. The protein content was 30 mg/100 ml and glucose 52 mg/100 ml. Systemic therapy was started with two-day courses of thioguanine 75 mg/m² by mouth 12-hourly and intravenous cytosine arabinoside 100 mg/m² 12-hourly. Eight lumbar punctures were performed during the subsequent four weeks and cytosine arabinoside was instilled intrathecally in doses of 25 mg/m² on each occasion. The pressure fell to 140 mm and in no specimen were cells found. Her headaches and vomiting ceased and the retinal haemorrhages and papilloedema resolved. Despite further systemic therapy she died 10 weeks later. Necropsy was not performed.

Comment

Infiltration of the arachnoid mater accounts for most cases of central nervous system leukaemia (Nies *et al.*, 1965) and is associated with the presence of blast cells in the cerebrospinal fluid. Intracranial haemorrhage from leukaemic deposits or secondary to thrombocytopenia, infiltrations of the dura mater, and diffuse intracerebral infiltration are less often seen (Moore *et al.*, 1960). Non-metastatic neurological syndromes have also been reported (Currie *et al.*, 1970). Clinically, leukaemic involvement of the central nervous system may be manifest as signs of meningeal irritation, increased intracranial pressure, seizures, or cranial nerve palsies (Cramblett, 1959).

Both the present patients developed signs of raised intracranial pressure without localizing signs or symptoms, and cells were not found in the cerebrospinal fluid. This presentation in the absence of cells in the cerebrospinal fluid has been described in a 5-year-old child with acute lymphoblastic leukaemia by Yatziv *et al.* (1971). As these patients did not have blast cells in the cerebrospinal fluid it is unlikely that the arachnoid mater was involved by the leukaemic process, but it is probable that central nervous system leukaemia was responsible for the clinical features although a self-limiting cause such as benign intracranial hypertension cannot be excluded. Cerebrospinal fluid pressure became normal and symptoms disappeared after systemic and intrathecal administration of cytotoxic chemotherapy, and it seems reasonable to conclude that treatment was associated with a lowering of intracranial pressure perhaps with some regression of leukaemic deposits.

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