Progressive multifocal leucoencephalopathy: remission with cytarabine

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SYNOPSIS A patient with a 14 year history of sarcoidosis developed a progressive left cerebral hemisphere lesion. The clinical diagnosis of progressive multifocal leucoencephalopathy was confirmed by brain biopsy and remission occurred after treatment with cytosine arabinoside.

Progressive multifocal leucoencephalopathy (PML) is a rare demyelinating disease which was first described by Åström et al. (1958) and viruses have since been found in the cerebral lesions (Zu Rhein, 1969). Two virus types have been identified, Polyoma JC (Weiner et al., 1973) and SV 40 (Padgett et al., 1971; Weiner et al., 1972). The disease usually occurs in patients already suffering from a condition in which the immunological system is in some way compromised. Richardson's review (1970) of 85 cases included 45 with lymphoproliferative disorders, 10 with myeloproliferative disorders, and 14 with granulomatous disorders. The prognosis is poor with a progressive deterioration over less than six months and spontaneous remissions are rare (Åström et al., 1958; Hedley-Whyte et al., 1966). Recently, the nucleic acid base analogues idoxuridine and cytarabine have been used in the treatment of some virus diseases, but remission has been reported in only one treated case of PML (Bauer et al., 1973).

CASE REPORT

This 52 year old nursing tutor was known to have had pulmonary sarcoidosis for 14 years which had been treated with a constant dose of prednisolone 7.5 mg daily for the last seven years. She first noticed weakness of the movements of the right thumb in October 1972 and this was associated with some clumsiness in writing. She was first admitted to hospital in March 1973 with increasing difficulty in the use of her right hand. There was minimal spasticity at the right wrist and elbow and there was slight wasting and moderately severe weakness of the small muscles of the hand associated with considerable difficulty in fine manipulation. There was minimal weakness of elbow extension and shoulder abduction; the supinator and finger reflexes on the right were pathologically brisk. The neurological examination was otherwise normal.

Radiographs of the skull and cervical spine were normal. Electroencephalography (EEG) showed brief bursts of irregular 2–4 Hz activity with more continuous underlying theta activity in the left frontotemporal region (Fig. 1a). A technetium-99m brain scan and a left carotid angiogram were normal.

After a few weeks back at work she noticed drooping of the right side of the mouth and slight difficulty with speech. She found increasing difficulty in doing the Daily Telegraph crossword, her right arm became progressively weaker, and she noticed some tendency to drag the right leg. She was therefore readmitted in July 1973 and was then found to have marked dysphasia with perseveration. Her concentration was impaired and even the most simple conversation was limited to no more than three or four words at a time. Visual fields were full. She had an upper motor neurone type right facial weakness and severe cortical weakness of the right hand and forearm associated with wasting of these muscles. There was moderately severe weakness of elbow extension and shoulder abduction on the right. There was some weakness of the right leg of pyramidal distribution, the right arm and leg were spastic with pathologically brisk reflexes, clonus at the wrist and ankle, and the right planter response was extensor.

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Investigations showed a blood haemoglobin level of 12 g/dl and a white cell count of 4700/mm³, neutrophils 85%; lymphocytes 7%; monocytes 4%; eosinophils 3%; ESR was 10 mm in the first hour. Serum protein level was 59 g/l; albumin 40 g; globulin 19 g/l with normal electrophoretic pattern; immunoelectrophoresis showed IgG 750 mg/dl, IgA 160 mg and IgM 36 mg/dl (all slightly reduced). Lymphocyte transformation to phytohaemagglutinin showed marked depression. Serum antibody titres to mumps S and V were both less than 1/8; Herpes 1/16; Mantoux test was negative at 1/100; serological tests for syphilis were negative. Cerebrospinal fluid was at normal pressure and contained 0.3 g/l protein with no excess of globulin and no cells. Radiographs of the chest showed changes consistent with sarcoidosis and apical tomography confirmed bilateral upper zone fibrosis without cavitation.

**FIG. 1** (a, top left) EEG during first admission (2 April 1973). (b, top right) EEG before treatment (27 June 1973). (c, left) EEG after treatment for nine months (31 May 1974). See text for description.

**FIG. 2** Pale focal and confluent demyelinating lesions in the cerebral white matter and deep cortex. Luxol fast blue/Nissl, ×15.
The third repeat dilatation minimal region (Fig. 1b). 4 Hz slight displacement bursts intermittent grossly asymmetrical (bottom); the cytoplasmic network (top). The centre lacked myelin and oligodendrocytes, while axons and nerve cells were relatively preserved. The oligodendrocytes in the border of the lesions were abnormal with rounded nuclei enlarged up to 15 μm containing acidophilic inclusions. In the centre of the lesions there were large astrocytes with multiple nuclei and ample cytoplasm with foamy macrophages containing neutral lipid. The white matter and the cerebral cortex away from the lesions were normal apart from some perivascular cuffs of lymphocytes and macrophages. Brain smears, which were available within 10 minutes of the biopsy, showed the same cytological features as the sections. Electron microscopy showed masses of rounded virus particles about 40 nm in diameter and viral filaments about 28 nm in diameter in many of the abnormal oligodendrocyte nuclei. In a few cells the rounded virus particles were found to extend from under the outer nuclear membrane into a membrane lined cytoplasmic network (Fig. 3) and some were seen in the extracellular space.

Biopsy material in liquid nitrogen was sent to the Virus Reference Laboratory, Colindale, for identification of the virus. A 10% suspension of the brain tissue was prepared and inoculated into human fetal brain cells. After an incubation period of seven weeks a virus belonging to the Polyomavirus genus was isolated. This strain was designated COL 2.

A portion of the 10% brain suspension was diluted in tissue culture medium and centrifuged at 18 000 rpm/h and examined by electron microscopy for negatively stained virus particles. Spherical particles with typical polyomavirus morphology were observed. Using the technique of immune electron microscopy (Field et al., 1974) the virus was identified as being antigenetically similar to Polyomavirus JC. It was not related to Polyomavirus BK or simian 40, two other viruses belonging to this genus which have been recently isolated from man.

She has been treated with intermittent five day courses of cytarabine in a daily dosage of 2 mg per kilogram body weight. The treatment was started in

![FIG. 3 Virions and viral filaments in a nucleus (bottom); the virions extend into a membrane bound cytoplasmic network (top). Epon, uranyl acetate/lead citrate, \( \times 75 \, 000 \).](image-url)
the middle of August 1973 and she has now had 13
courses separated by successive intervals of seven,
seven, 14, 21, 28, 35, 35, and 14 days; the last four
courses have been at intervals of three weeks. The
only side-effect has been slight nausea during the
days of administration which has been controlled with
prochlorperazine. Throughout this time her
haemoglobin, white cell count, and platelet count
have been measured repeatedly and have remained
within the normal range.

A slight but definite improvement was first
noticed soon after finishing the first course of treat-
ment. She was discharged from hospital at the end of
the second course and at that time her dysphasia had
improved considerably allowing conversation at a 10
to 12 word level. Some power had returned to her
right shoulder and right hip flexion was stronger. Six
weeks after starting treatment she was able to finish
about half the Daily Telegraph crossword. In con-
versation there was occasional perseveration and
she would correct herself by association. The facial
weakness had improved and she no longer dribbled.
After three months she had taught herself to write
left-handed, she was reading two novels a week and
usually finishing the Daily Telegraph crossword.
Movements of the right hand remained severely im-
paired and the arm moderately spastic. There was
only minimal weakness of right hip flexion and her
gait was normal.

Since returning to work at the beginning of
November 1973, just over a year after the onset of
her symptoms and about three months after the
start of treatment, she has managed her job as a
nursing tutor satisfactorily. She has found her
recent memory slightly impaired but has been able to
give her lectures. The EEG has been recorded at
the onset of each course of treatment and first showed
a definite improvement about a month after the start
of treatment, since when it has shown further im-
provement (Fig. 1c). The interval between treat-
ments has now been fixed at three weeks because she
found that she did not feel very well with longer
intervals, although this was not accompanied by any
change in her physical signs.

**DISCUSSION**

This patient has been shown by brain biopsy to
fulfil the criteria of PML associated with
Polyomavirus JC. The association of a pro-
gressive focal neurological disease with localized
EEG changes and only minimal evidence of
cerebral atrophy in a patient with sarcoidosis and
depressed cellular and humoral immunity led to
the diagnosis. The history of mumps in the
autumn of 1972 may be relevant. Live mumps
vaccine may temporarily depress tuberculin
sensitivity (Kupers et al., 1970) and this attack
may have compromised her immune state to the
extent that PML could develop.

More than 100 cases of PML have been
reported. These include only four or five cases
with spontaneous remission (Hedley-Whyte et
al., 1966; Richardson, 1970). Narayan et al.,
(1973) have correlated the type of virus with the
progress of the disease in 13 cases of PML. The
prognosis of those patients with the JC virus was
worse (mean survival less than six months) than
those with SV 40 (mean survival 20 months).

This patient's improvement began within 10 to
14 days of starting treatment and within three
months she was well enough to return to work.
In the only other case of PML treated with
cytarabine, improvement also occurred shortly
after treatment was started. This patient also had
sarcoidosis (Bauer et al., 1973). It will be neces-
sary to treat many more patients before improve-
ment can be ascribed to the treatment with an
adequate degree of certainty. Brain biopsy is necessary to
confirm the diagnosis and identify the virus. In
view of the continued underlying immune de-
pression and the doubtful ability of the treatment
to eliminate the virus from the brain com-
pletely, it may be necessary to continue inter-
mittent chemotherapy indefinitely.

**ADDENDUM** (February 1975)

Treatment has continued with five day courses
of cytarabine (2 mg/kg) separated by intervals of
three weeks. No complications from this treat-
ment have arisen. She has continued to improve
throughout this time and there is now no
evidence of aphasia, minimal facial weakness,
moderate spastic weakness of the right arm,
function of her hand remains severely impaired,
there is no weakness in the right leg. As the
spastic weakness improved, so an obvious cere-
bellar ataxia became apparent in the right arm,
preumably due to involvement of crossed rubro-
thalamocortical cerebellar pathways.

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REFERENCES


