The clinical diagnosis and treatment of microgliomatosis: report of a case

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Microgliomatosis (Russell, Marshall, and Smith, 1948) or primary reticulosis of the brain (Miller and Ramsden, 1963) is usually considered a pathological curiosity and the diagnosis has almost invariably been made on necropsy material. Yet the structure of the tumour suggests that it may be radiosensitive and every effort should therefore be made to reach a diagnosis during life. In reporting a case in which the condition has been treated by radiotherapy with some success we wish to discuss the diagnostic criteria and the therapeutic measures adopted.

CASE REPORT

G.R. (L.H. no. 367692), was a company director, aged 66, who was well until three months before admission when he developed polyuria and polydipsia. Diabetes mellitus, of maturity onset type, was diagnosed. In spite of adequate control with oral hypoglycaemic drugs he became increasingly drowsy, confused, and disorientated.

On admission in November 1967 he was demented, with a dysphasia mainly of receptive type. There was papilloedema on the left side with haemorrhages and exudates and the right disc was pink without being swollen. His visual fields were full and his pupils normal. There was a right hemiparesis, affecting mainly the face and upper limb, accompanied by a right grasp reflex and a right extensor plantar response. There were no abnormal physical signs outside his nervous system, and his blood pressure was 130/85 mm Hg.

Investigations showed a normal blood count, a blood sugar of 120 mg/100 ml., a blood urea of 36 mg/100 ml., and normal electrolytes. The erythrocyte sedimentation rate was 68 mm in one hour. The cerebrospinal fluid was clear and colourless, contained less than 20 mg protein/100 ml. and less than 1 cell/cu. mm. A radiograph of the skull showed a slight shift of the calcified pineal gland to the left. A right carotid angiogram suggested some increase in space between the anterior and middle cerebral arteries and an apparent shift of the midline structures to the left. A gamma encephalogram showed evidence of a deep lesion to the left of the midline in the anteroposterior scan. The lateral scans showed a diffuse increase of activity over the left side without definite localization. An air ventriculogram showed a small shift of the midline structures to the right, with poor filling

of the inferior parts of the frontal horns and an irregularity in the roof of the right anterior horn.

A tentative diagnosis of a bifrontal cerebral tumour was made and three needle biopsies were carried out in an attempt to establish a definite histological diagnosis. On 5 December 1967 wet films and paraffin sections were prepared (S.D. 8240/67). The former showed small foci of abnormal cellularity and some lymphocytic cuffing of blood vessels, suggestive of an inflammatory rather than a neoplastic lesion. No tumour was seen in the section. A week later the procedure was repeated (S.D. 8363/67). Wet films showed a few vessels surrounded by tightly packed sheets of oval or elongated, homogeneous tumour cells with oval, vesicular nuclei (Fig. 1). Several vessels were heavily cuffed with small mononuclear cells, predominantly lymphocytes (Fig. 2). Some parts of the brain tissue were infiltrated by small, irregular, darkly staining cells, interpreted as atypical microglia (Fig. 3). Other fields showed normal brain tissue, which also formed the entire content of the minute fragment kept for paraffin sections. The appearances of the films strongly suggested microgliomatosis. A further attempt to confirm the diagnosis in paraffin sections was made on 9 January 1968 (S.D. 169/68). The material obtained on this occasion showed perivascular cuffing with lymphocytes and microglial cells, also patchy infiltration of the parenchyma with typical and atypical microglia. In conjunction with the previous wet films we concluded that sufficient support had been obtained for a diagnosis of microgliomatosis and that treatment by irradiation was justified.

Radiotherapy was given using the Picker telecobalt unit at 80 cm S.S.D. Parallel opposed lateral fields 20×10 cm were used to include the whole brain, curvature of the skull being allowed for by wax compensators. The midline dose was 3,000 r. and the incident dose 2,200 r., given in 15 equal fractions from Monday to Friday over 18 days. Treatment was completed uneventfully. There was no evidence of any increase in intracranial pressure during irradiation—in fact, the patient's condition improved rapidly during the course of treatment. He became progressively more alert and his orientation in time and space returned almost to normal. All focal signs, including hemiparesis and dysphasia, disappeared and his plantar responses became flexor. The appearances of the optic discs returned to normal. The only residual disability was a mild, cheerful dementia with occasional outbursts of temper when provoked by

FIG. 1. *Edge of sheet of tumour cells with fairly uniform, large, oval nuclei. Wet film. Morris's methylene blue and eosin, $\times 330$.*

FIG. 2. *Blood vessels cuffed with small mononuclear cells. Wet film. Morris's methylene blue and eosin, $\times 170$.*

problems or people. He was capable of leading a normal life with his family, though he did not return to work. He stayed at home leading a relatively normal life for 14 months and was then again admitted with increasing dementia and signs of a right hemiparesis. No papilloedema was noted. Further pneumoencephalographic studies, brain biopsy or puncture seemed inadvisable. He received a further course of irradiation which was similar in all respects to the first. He again showed a good clinical response to treatment, losing all his focal signs and symptoms, but retaining a fair degree of dementia. He was later transferred to a hospital for chronic sick

where he died suddenly two months later. No necropsy was performed.

DISCUSSION

In an attempt to establish the diagnostic criteria of microgliomatosis we have reviewed 56 cases reported in the literature in which sufficient clinical data are available and the diagnosis had been adequately confirmed histologically (Yuile, 1938; Kinney and Adams, 1943; Russell *et al.*, 1948; Losli, 1956;

FIG. 3. *Brain tissue infiltrated with small, darkly staining, atypical microglial cells. Wet film. Morris's methylene blue and eosin, $\times 330$.*

Cervos Navarro, 1957; Fisher, Davis, and Lemmen, 1959; Kernohan and Uihlein, 1962; Miller and Ramsden, 1963; Rubinstein, 1964; Adams and Jackson, 1966; Barnard, 1968; Miller, 1968; personal communication).

Of the 56 patients, 19 were female and 37 were male. The age of presentation varied between 15 and 82 years. The average age was 50 years. Twenty-one out of 37 patients who had either lumbar or ventricular punctures were shown to have raised intracranial pressure. Twenty-nine cases presented with pyramidal tract signs and 36 with ocular signs, such as diplopia, homonymous hemianopia, or loss of conjugate eye movements. Glycosuria or a raised blood sugar was reported in five cases. Polydipsia and polyuria for which no pituitary cause was found at necropsy was reported in one other; no information about the urine or blood sugar is available.

The clinical picture which emerges provides few clues to the diagnosis. In most cases a diagnosis of intracranial tumour was made and in 21 cases craniotomy or burr holes were performed. Of these, 14 died suddenly within two weeks of the operation. Otherwise the disease usually runs a subacute course, the average interval between the onset of symptoms and death in the untreated patients being 3.3 months with a longest survival of 23 months. Another untreated case appears to have had a spontaneous remission and lived five and a half years before terminal recurrence of the condition (Barnard, 1968).

Our own patient presented with a rapidly progressive dementia, focal signs in the dominant left hemisphere, and papilloedema. The significance of

the diabetes mellitus discovered shortly before the onset of cerebral illness in this and other cases remains uncertain. The clinical history and physical signs suggested a rapidly growing cerebral tumour and further investigations were directed towards accurate localization and histological identification of the tumour.

Radiographic studies proved to be somewhat confusing and contradictory. Straight views of the skull and carotid angiograms suggested a right-sided tumour with a slight shift of midline structures to the left. Air studies, on the other hand, suggested abnormalities in both frontal lobes with a small shift to the right. Electroencephalograms were not particularly helpful, but a gamma scan produced an unusual picture suggesting both a localized and a diffuse lesion in the left hemisphere. Perhaps the clinical picture of a cerebral tumour unlocalized by special techniques should have suggested microgliomatosis among other possibilities such as diffuse or multifocal tumours. In the reviewed cases, EEGs, carotid angiograms, and ventriculography were often carried out with conflicting results.

Examination of the CSF did not contribute any information in our case, though in the literature reviewed five cases showed microglial cells and a further eight showed lymphocytes in the fluid. In these cases it was suggested retrospectively that the cells could well have been microglial rather than lymphocytes (Miller and Ramsden, 1963). The ultimate diagnosis must rest on histological identification of the tumour in a biopsy specimen. In view of the dismal record of past attempts at surgery, any major procedure ought to be avoided, but it

appears that a needle biopsy through a burr hole is well tolerated. The histological diagnosis of a scattered, multifocal condition with the variegated appearances presented by microgliomatosis is bound to cause difficulty in a small specimen, but this cannot be avoided. In our case, wet films turned out to be more informative than paraffin sections, probably because they survey a larger amount of tissue and thus reduce the random sampling error. Even so, useful preparations were obtained only on the second attempt. In view of our lack of past experience in the diagnosis of microgliomatosis in wet film preparations, it was considered essential to obtain confirmation on paraffin sections, which necessitated a third biopsy. To summarize the findings: the juxtaposition of normal brain tissue, tissue infiltrated by typical or atypical microglia, vessels cuffed by lymphocytes and microglial cells, and vessels surrounded by tumour consisting of primitive reticulum cells was considered characteristic of microgliomatosis.

The decision to treat the patient with deep x-ray therapy was based on the theoretical assumption that microgliomatosis, being a local form of malignant reticulosis, ought to be radiosensitive. Support for this view was obtained from past experience of two cases treated with radiotherapy. One (Fisher *et al.*, 1959) was treated for an unspecified cerebral tumour, subsequently shown to be microgliomatosis at necropsy. The patient survived for four years and was able to return to work for a period of three years. The other patient (Barnard, 1968) was diagnosed as a case of microgliomatosis after a craniotomy and biopsy. He received a post-operative course of radiotherapy and rapidly lost all symptoms and signs. When seen two years later he was symptom free.

The planning of irradiation of our patient also presented a problem in that microgliomatosis is known to involve widespread and widely scattered areas of the central nervous system and accurate localization is impossible. The spinal cord may be involved in some cases (Miller and Ramsden, 1963). It was obvious that treatment of the whole brain was essential; it was, however, debatable whether to include the cord in this field. In view of the complete absence of cord symptoms, we decided not to treat it until definite evidence of spinal involvement became apparent.

The results of radiotherapy must be considered as satisfactory in that a striking regression of symptoms and signs occurred on two occasions. On the first occasion the patient's mental condition improved from that of profound disorientation to a relatively mild intellectual defect. After the second treatment the results were less gratifying but his mental state

improved enough for him to be able to care for himself in hospital. His first remission lasted for 14 months and a further remission was again obtained with irradiation. His survival well exceeded the expectation of life in the untreated condition. It is possible that better results might have been obtained had the patient been treated earlier and with a higher dose of radiation. Owing to the delay in diagnosis, treatment was started nearly five months after the onset of symptoms by which time the disease was in an advanced stage. The first course of radiotherapy of 3,000 r obviously failed to eradicate the tumour. A dose to the limit of brain tolerance—for example, 4,000 r—would be more likely to sterilize a deposit of reticulosarcoma than the smaller dose administered.

SUMMARY

A case of microgliomatosis in a 66-year-old man is reported. A selective review of the literature indicates the usual presentation and the rapidly progressive course of the untreated disease leading to death within a few months. We suggest that the clinical picture of a cerebral tumour without true localization after sophisticated investigation should raise the possibility of a diffuse process such as microgliomatosis.

Two reported cases which received radiotherapy obtained satisfactory remissions, and we report a third in whom the diagnosis was confirmed by cerebral biopsy—largely with the aid of wet film preparations—and who lived for 16 months after his first course of treatment. On this, and on one other subsequent occasion, he showed a marked clinical improvement after radiotherapy. We conclude that radiotherapy has a definite place in the treatment of microgliomatosis.

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