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Cerebral malakoplakia

PC BLUMBERGS, JF HALLPIKE,* J McCLURE

*From the Division of Tissue Pathology, Institute of Medical and Veterinary Science, Frome Road, Adelaide and the *Department of Neurology, The Royal Adelaide Hospital, Adelaide, South Australia*

SUMMARY A case of cerebral malakoplakia is described in an 18-year-old woman who died as the consequence of a postpartum stroke. The malakoplakic lesion occurred in areas of cerebral infarction. The features of this unique case are compared with the small number of previously reported cases of cerebral malakoplakia which occurred in much younger patients and against a background of herpes simplex infection.

Malakoplakia is an uncommon chronic inflammatory lesion described originally by Michaelis and Gutmann.[1] The condition is characterised morphologically by the appearance, within macrophages, of inclusions, the Michaelis-Gutmann (MG) bodies (2-10 μm in diameter) exhibiting basophilia with haematoxylin and eosin (HE), concentric targetoid laminations, and which contain calcium, phosphate, and sometimes iron. Malakoplakia usually affects the urinary bladder[2] but its occurrence in extravesical sites is being reported with increasing frequency.[3,4] Nevertheless, cerebral malakoplakia is an extreme rarity previously being described in only five instances in neonates or very young children, usually in association with neonatal herpes simplex virus infections.[5-8] We report and assess the finding of malakoplakia in cerebral infarcts in a young woman who died as a consequence of postpartum stroke.

Case report

Mrs JW, a previously healthy 18-year-old caucasian woman who had never taken the oral contraceptive pill was admitted in May 1980 in severe pre-eclamptic toxaemia (PET) and underwent emergency caesarean section in the 34th week of her pregnancy. On the fourth postoperative day, she had an episode of confusion with right hemiparesis associated with raised blood pressure (200/130 mm Hg), recovering after some 10 min. She was given heparin, 5000 IU subcutaneously every eight hours. On the seventh postoperative day, a further episode occurred of dysphasia with right facial weakness which improved after some hours, blood pressure 140/46 mm Hg. On the tenth day she deteriorated and was transferred to the Royal Adelaide Hospital. Examination showed a severe dysphasia, mild right hemiparesis, a left hemiplegia and bilateral extensor plantar responses. The clinical impression was of ischaemic cerebral infarction in both internal carotid artery territories. The heart and other systems appeared normal. Haemoglobin 12·7 g/dl, white cell count 12·5 $\times$ 10^9/l (12 500/mm^3), normal platelets, ESR 109 mm/h. Coagulation studies were normal (NR = normal range): prothrombin ratio 1·15 (NR 0·8-1·2); partial thromboplastin time 25·0 s (NR 28-39); plasma fibrinogen 2·2 g/l (NR 1·5-4·0); serum FDP (latex screen) $<$ 10 mg/l (NR $\leqslant$ 10); thrombin clotting time 19·5 s (NR 14-20); and euglobulin clot lysis 3 h (NR $\geqslant$ 2). Renal function on admission to the Royal Adelaide Hospital was normal (creatinine 70 μmol/l (0·79 mg/100 ml)). Echocardiogram was normal. Autoimmune profile (antinuclear factors, mitochondrial, smooth muscle, and gastrin parietal cell antibodies) negative. Computerised axial tomography (CAT) showed changes of infarction in both middle cerebral artery territories, the larger lesion being on the left. Bilateral carotid angiography showed occlusion of the right middle cerebral artery 10 mm distal to its origin and occlusion of the main parietal branch of the left middle cerebral artery, there being no radiological evidence of arteritis. She became pyrexial and a small amount of retained products (culture negative) was evacuated from the uterus. Blood and vaginal cultures were negative. Initially urine cultures were negative. Renal failure supervened and was treated with haemodialysis. Eleven days before she died, a *Streptococcus faecalis* urinary tract infection was documented. Her fever persisted and there was no alteration in her neurological state. She died 37 days after the operation.

NECROPSY FINDINGS

The relevant abnormal general necropsy findings

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were bilateral bronchopneumonia, polyposis coli affecting rectum, descending colon and to a lesser degree caecum and ascending colon, splenic infarction and marantic endocarditis of the posterior mitral valve cusp. The kidneys were swollen but otherwise macroscopically normal and histological examination showed that the glomeruli were enlarged and hypercellular with mesangial hypertrophy, patchy interposition and prominent longitudinal capillary collapse. No segmental lesions were seen and immunofluorescent studies were negative. The tubules could not be properly assessed because of severe autolysis but there was no interstitial scarring or inflammation. The blood vessels were normal. The liver was normal apart from autolysis.

Neuropathological examination of the brain revealed bilateral infarction of the basal ganglia and the adjacent pyramidal tracts in the vascular territory of the middle cerebral arteries (Fig. 1). The right middle cerebral artery and the parietal branch of the left middle cerebral artery were completely occluded by organising thrombus. There was no evidence of any underlying vasculitis or atheroma in the cerebral blood vessels.

MICROSCOPIC AND ULTRASTRUCTURAL FINDINGS

The cerebral infarcts were the sites of accumulation of numerous macrophage and macrophage polykaryon cells. These often had eccentrically disposed vesicular nuclei and foamy cytoplasm and were typical of cells seen in areas of cerebral infarction. Substantial numbers of cells, however, had numerous small basophilic intracytoplasmic granules and there were many typical intra- and extra-cellular targetoid MG bodies (Fig. 2). These latter were 8-10 μm in diameter and about ten times larger than the small basophilic granules. Occasional MG bodies had a duplex or budded structure. Both smaller granules and MG bodies were observed in the extracellular space. Both structures gave positive staining reaction with the von Kossa (VK), chloranilic acid, alizarin red S, PAS and alcian blue (pH 2·5) techniques. The application of the Perl's Prussian blue stain showed positive reactions in all of the MG bodies. The smaller granules also reacted with this stain. The Gram stain did not reveal any evidence of micro-organisms.

Ultrastructurally, the presence of MG bodies was

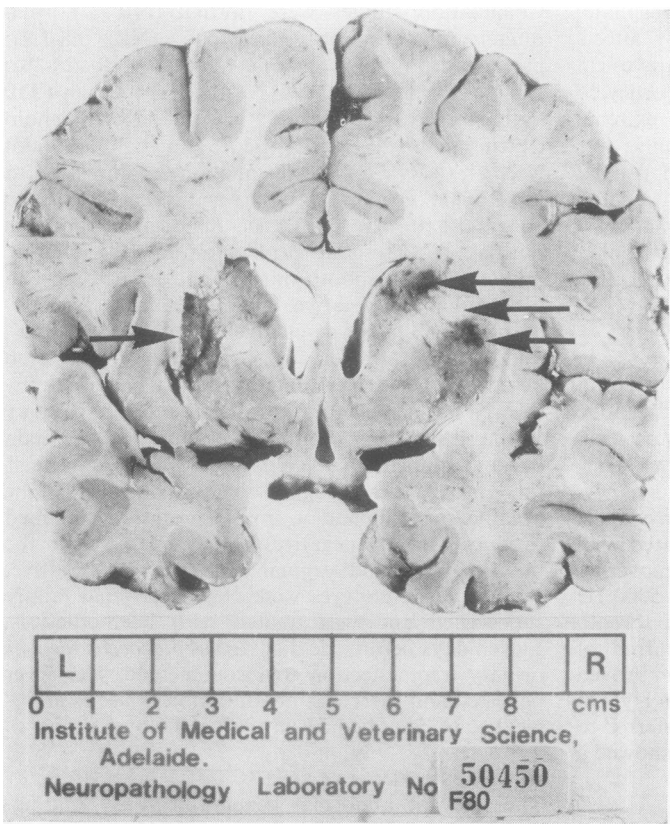

Fig. 1 *Areas of infarction are indicated by arrows.*

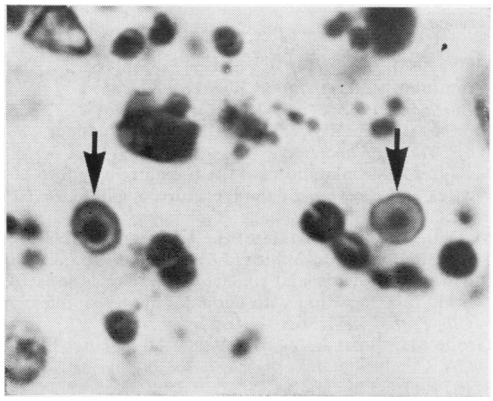

Fig. 2 *MG bodies found in the areas of infarction are indicated by arrows. Haematoxylin and eosin × 400.*

confirmed. Some of these showed a central area of rarefaction surrounded by a ring of fairly densely packed needle-shaped crystals and outside this there was a thin non-crystallised matrical zone, whilst others demonstrated a dense central core of mineralisation (Fig. 3). An *x*-ray microanalysis of the MG bodies revealed the presence of calcium, phosphorus, and iron. The peaks of calcium and phosphorus in the *x*-ray spectrograph were similar to those obtained for pure hydroxyapatite.

Discussion

There have been four previous publications reporting the presence of cerebral malakoplakia in five patients.[5–8] Among these cases, there were two boys and three girls. Four were aged less than one year and the eldest was $2\frac{3}{4}$ years. All cases had a background of herpes simplex infection (shown by rising serial serum antibody titres) but the virus was not isolated from the cerebral malakoplakic tissue in any of the cases. Therefore a causal relation between herpes virus infection and cerebral malakoplakia was not established. In all cases, the lesion consisted of an aggregation of macrophages and occasional macrophage polykaryons. In four cases, typical laminated MG bodies were observed and demonstrated. In one of the cases described by Chandra and Kapur,[7] MG bodies were not observed. This was the eldest child ($2\frac{3}{4}$ years) in the group. There were aggregations of macrophages in tissue taken by biopsy of the right frontal lobe and although serial antibody titres to herpes simplex rose significantly, it is difficult, with the absence of MG bodies, to sustain a diagnosis of malakoplakia in this case.

In our adult case, the MG bodies were found in areas of cerebral ischaemic necrosis. The cause of the arterial occlusion in this case was not established. Coagulation studies were normal. Most postpartum

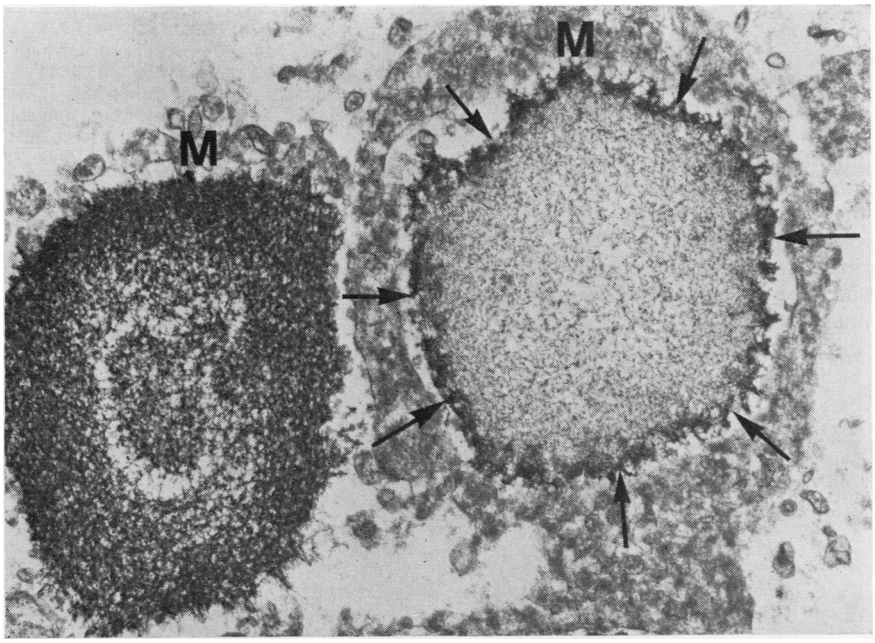

Fig. 3 *Two MG bodies in contiguity. One (on the left) shows a dense crystalline core and the other a light central zone with a crystalline periphery (arrowed). Each structure has an outer non-crystalline matrical ring (M). × 10 000.*

strokes are arterial in origin.[9] In general, the aetiology is not understood and most cases do not appear to be related to premature atherosclerosis, hyperlipidaemia or vasculitis.[10]

Malakoplakic lesions of the urinary bladder are frequently associated with urinary infection by coliform micro-organisms.[11] Although bacilliform organisms have been demonstrated by electron microscopic studies in malakoplakic macrophages,[12] this is an infrequent occurrence. Terner and Lattes[13] in a case of colonic malakoplakia claimed that their histochemical studies showed that the matrix of the MG body was composed of a non-mammalian glycolipid (by implication a derivative of *Escherichia coli*) but against this Kerr *et al.*[14] were unable to demonstrate non-human substances in their chemical analysis of material from a case of prostatic malakoplakia. Csapo *et al.*[15] produced experimental malakoplakic lesions in rat kidney and testis by the injection of Boivin antigen. This is a lipopolysaccharide-polypeptide-lipoid substance which had not been chemically completely characterised and is an extract of *E coli* cell wall.

It has been suggested[16] that malakoplakia may be the consequence of impairment of microfilamental/microtubular function of macrophages. This suggestion is based on the report by Abdou *et al.*[17] of low concentrations of cyclic GMP and poor lysosomal enzyme release after phagocytosis in and by blood monocytes of a patient with disseminated malakoplakia. These defects were reversed by in vitro incubation of monocytes with cholinergic agonists.

Microtubule formation or activity or both, is reduced in conditions of low cGMP and high cAMP concentration. We can only speculate as to what special circumstances set in train the unusual sequence of events leading to intracellualr malakoplakia in these cerebral infarcts. Perhaps the absence of a blood brain barrier at these sites of infarction allowed the selective seeding with bacterial derivatives (from the urinary tract infection), and because of an altered chemical milieu caused an impairment of macrophage microfilamental or microtubular functions and thus the formation of MG bodies.

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Requests for reprints to: J McClure, Division of Tissue Pathology, Institute of Medical and Veterinary Science, Box 14 Rundle Street Post Office, Adelaide, South Australia 5000.