Short report

Idiopathic granulomatous meningitis

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SUMMARY A 69 year old female presented with eight discrete episodes of paraparesis over a period of six weeks. Each episode lasted between 10 and 30 minutes and resolved spontaneously. The cause of her symptoms was not established during life and at necropsy she was found to have granulomatous meningitis of the cerebral convexites. The clinical and pathological aspects of this rare condition are discussed.

A granulomatous meningeal reaction characterised by the proliferation of granulation and fibrous tissue, lymphocytic and giant cell infiltration and reactive endarteritis may be found in syphilis, tuberculosis, certain CNS fungal infections and neurosarcoidosis. To our knowledge only two cases which were not due to any of these causes have been reported. We describe a third case of granulomatous meningitis of unknown cause. We suggest that this is a separate entity clinically distinguishable from the other forms of granulomatous meningitis. We use the term idiopathic granulomatous meningitis for this condition.

Case report

A 69 year old right-handed widow was well until six weeks before admission to the Institute of Neurological Sciences, Glasgow. She started to drag her legs when she walked and this also happened after a hot bath. The right leg was affected more than the left. She also had difficulty when climbing stairs and in getting up from a low chair. She described eight discrete identical episodes of acute paraparesis each lasting 10 to 30 minutes. These episodes were always preceded by paraesthesiae in the legs. The upper limbs and face were spared. With the first episode there was definite slurring of speech, but this had not recurred subsequently. She had no bladder, bowel or ocular symptoms, but complained of slight backache. Her appetite was poor and she had lost approximately two stones in weight in the past two years. She also had recurrent, moderately severe occipital headaches which readily responded to simple analgesics. On systemic enquiry she denied any gastrointestinal, respiratory, cardiovascular or urinary symptoms.

There was no relevant past medical history. She had smoked 20–40 cigarettes per day for many years and did not drink alcohol. There was no relevant drug history.

On physical examination she looked well and was well-nourished. Her pulse was 72 per minute and regular. Blood pressure was 150/80 mm Hg. There were no cardiac, carotid or spinal bruits. Her peripheral pulses were present. Examination of the chest and abdomen was normal. On neurological examination her gait was slow, but otherwise normal. Examination of the cranial nerves and upper limbs was entirely normal. There was bilateral lower limb spasticity more marked on the right than the left, slight bilateral weakness of hip flexion and moderate pyramidal weakness in the right leg. Reflexes were increased in the lower limbs, the right plantar response was equivocal and the left flexor. There was non-sustained clonus at both ankles. On sensory examination there appeared to be considerable diminution of sensation to pain and light touch up to the level of T7 on the right. Joint position sense was reduced at the right hallux and vibration sense was impaired to the right costal margin.

Investigations revealed a haemoglobin of 12.7 g/dl, the ESR was 60 mm in the first hour. The following investigations were normal: blood urea and electrolytes, liver function tests, random blood glucose, B12 and folate. Antinuclear factor was weakly positive. Serological tests for syphilis were negative. Two temporal artery biopsies were normal. Visual evoked responses were normal. A computerised tomographic (CT) brain scan showed symmetrical dilatation of the lateral and third ventricles and generalised enlargement of cortical sulci. These appearances would be consistent with mild brain atrophy. Full-length myelography was normal. CSF protein
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was 0·58 gm/l with less than five nucleated cells per mm$^2$ and there were no CSF oligoclonal bands detected. However, CSF percentage IgG of total protein was 19·0% and the IgG/albumin index was 1·09 (normal values in our laboratory are less than 10% and 0·26–0·66 respectively). These results indicated a possible breakdown in the blood-brain barrier.

The patient was considered to have ischaemic vascular disease of the spinal cord and was discharged. In view of the unexplained high ESR and weight loss, arrangements were made for her to attend the follow-up clinic with a view to possible steroid therapy, but she died a few weeks later.

Pathological findings

At necropsy the principal abnormalities were an enlarged heart (495 g) due to left ventricular hypertrophy, extensive calcific atheromatous stenosis of the coronary arteries, an atheromatous aneurysmal dilatation of the arch and proximal part of the thoracic aorta, bilateral pulmonary oedema (L Lung 690 g; R lung 925 g) and a chronic duodenal ulcer. Death was attributed to acute left ventricular failure secondary to coronary artery insufficiency and hypertensive heart disease.

Neuropathological Findings

The fixed brain weighed 1360 g. The meninges overlying the parasagittal cortex of each cerebral hemisphere were thickened and yellow-green in colour. In contrast the meninges over the lateral convexities and at the base of the brain were normal. Serial coronal slices confirmed that the abnormalities were limited to superior medial quadrants of the convexities: additional features included foci of necrosis and adhesion to underlying brain tissue. The hind brain and spinal cord were normal. There was no evidence that the intracranial pressure had been high during life and the ventricles were normal.

Microscopy of multiple sections embedded in paraffin wax showed that the abnormal meninges were focally necrotic and infiltrated by a granulomatous process characterised by numerous macrophages, lymphocytes, plasma cells and multinucleated giant cells (figure). There was involvement of both veins and small arteries in the form of endarteritis obliterans but no evidence of a primary arteritis. There was an increased amount of perivascular reticulin but fibrosis was not a prominent feature. There was extension of the process into sulci and superficial layers of the cortex. An astrocytosis was seen around the infiltrate. There were no infarcts. These abnormalities were limited to the parasagittal regions of the cerebral hemispheres. The only other abnormality was mild infiltration by lymphocytes of the meninges of the dorsal segments of the spinal cord. Gram stain for bacteria, Ziehl Neelsen for tuberculosis, Levaditi’s silver stain for treponema, Grocott’s methenamine silver method for fungi, PAS and Leishman stain failed to demonstrate any organisms. Microbiological examination of fresh material was not done.

Discussion

Granulomatous inflammation is characterised by the formation of inflammatory masses which are largely composed of granulation and fibrous tissue and aggregation of giant cells with or without areas of necrosis. These changes may be found in the meninges in neurosyphilis, tuberculosis, some fungal CNS infections and in sarcoidosis. We have found only two cases of granulomatous meningitis in the English medical literature in which exhaustive investigations have excluded these known causes. This latter group probably represents a separate clinical entity of idiopathic granulomatous meningitis which is aetiologically and prognostically distinct.

At the turn of the century Gower$^1$ referred to a form of chronic meningitis occurring in alcoholics and affecting mainly the cerebral convexities and this was pathologically similar to granulomatous meningitis. He attributed this form of meningitis to the direct toxic effect of alcohol and suggested that it is rarely diagnosed during life because it is usually over-shadowed by the other features of alcoholism. However, subsequent observations failed to confirm chronic alcohol toxicity as a cause of granulomatous meningitis, and it is highly unlikely that alcoholic granulomatous meningitis is a separate clinical entity.

Despite their similarities, the various forms of granulomatous meningitis differ in their clinical presentations, treatment and prognosis. There are also subtle histopathological features which can be useful in the differential diagnosis of these conditions. The first documented case of granulomatous meningitis of unknown aetiology was reported in a patient with chronic renal failure who presented with optic atrophy due to granulomatous thickening of the leptomeninges leading to constriction of the optic nerve at the optic foramina. Silent granulomas were found at the base of the skull and also the cerebral convexities.$^2$ Chalif et al$^3$ described another patient with intermittent right hemispheric syndrome, features of raised intracranial pressure and a left parietal lobe lesion on CT scanning.

Fig Granulomatous meningitis. In addition to the chronic inflammatory cell infiltrate comprising lymphocytes, plasma cells and macrophages, there are a number of multi-nucleate giant cells (arrow). H & E × 530.
Histological examination (following craniotomy) revealed generalised granulomatous meningitis. Although fibrosis predominated in this case, it is histologically different from other lesions which cause proliferation of fibroblastic elements, for example, fibromatosis, reactive fibrosis due to radiotherapy and inflammatory fibrosis following subarachnoid haemorrhage.\(^4\)

The necropsy findings in our patient were typical of granulomatous meningitis. However, the presentation simulated ischaemic vascular disease. Although we cannot explain the sensory level, we think that the clinical picture was probably due to recurrent thrombotic occlusion of cortical blood vessels in the vicinity of the inflamed meninges. It is remarkable that our patient had no significant systemic symptoms (apart from weight loss) and there were no changes in her CSF, although her ESR was consistently raised.

The typical histopathological feature of syphilitic granulomatous meningitis is perivascular infiltration of lymphocytes and plasma cells with a fibroblastic reaction.\(^5\) Endarteritis is always a prominent feature and is usually complicated by thrombosis leading to cerebral infarcts. In longstanding cases proliferation of subependymal glia is a prominent feature. The condition has a predilection for the basal meninges leading to obstructive hydrocephalus and interstitial neuritis of the cranial nerves.\(^6\) Vascular syndromes are the commonest presentation of all forms of neurosyphilis. Diffuse encephalitic symptoms with superimposed focal signs are also common in this condition.\(^7\) In the spinal cord syphilitic meningial hypertrophy usually affects the cervical enlargement and causes root symptoms and, in the later stages, spinal cord compression.

Similarly, the proliferative meningitis of tuberculosis usually affects the basal meninges,\(^9\) commonly causing cranial nerve palsies and hydrocephalus due to exudates and adhesions.\(^10\) Hydrocephalus may also result from impaired CSF absorption at the arachnoid villi. Endarteritis of the circle of Willis is a common pathological finding and accounts for the syndromes of vascular occlusion in this condition. A meningeal granulomatous hypertrophy may co-exist with any of the other forms of tuberculosis of the CNS.\(^11\) Signs of meningeal irritation are usually present at some stage, but may be inconspicuous.\(^12\)

Diffuse or localised granulomatous meningitis is the commonest complication of intracranial fungal disease. Characteristically the meninges are thickened and the Virchow-Robin spaces are dilated by gelatinous material. Microscopically there is minimal cell response with perivascular aggregation of lymphocytes, occasional giant cells and macrophages. Fungi are usually found in the granuloma in aggregates. Cryptococcosis is the commonest fungal infection affecting the CNS and is usually associated with Hodgkin’s disease, other reticuloses\(^13\) and more recently AIDS.\(^14\) The onset is usually insidious and systemic symptoms may be slight. The CSF glucose is characteristically less than 2 mmol/l,\(^15\) the protein is elevated and there is a monocytic pleocytosis of variable degree. However, the CSF may be normal.\(^16\)

A late feature and by far the commonest CNS lesion in sarcoidosis is granulomatous meningitis (incidence 5–16%).\(^16\)–\(^18\) Characteristically the giant cell granuloma of sarcoidosis is non-caseating, has an affinity for blood vessels and usually affects the basal meninges. In contrast to idiopathic granulomatous meningitis, neurosarcoidosis is characterised by increased CSF protein, pleocytosis and normal glucose.\(^19\) However, the latter may occasionally be reduced.\(^16\)

To summarise, idiopathic granulomatous meningitis is distinguished from other conditions which cause a granulomatous meningeal reaction by its predilection for the cerebral convexities, the lack of significant systemic features, the absence of CSF changes and its comparatively benign course. Exclusion of sarcoidosis, syphilis, tuberculosis and fungal CNS infection is essential since these conditions respond to specific treatment.

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