Confusion and middle age with four diagnoses

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THE CLINICAL STORY
In April 2000, a lady in her early fifties presented with a two-week history of gradually increasing confusion, poor memory, an unsteady gait, and intermittent nausea and vomiting. On the day of consultation, she also developed a mild occipital headache. In 1980, she had been diagnosed with breast cancer (T1N0M0) for which she had had a right mastectomy and radiotherapy. She had been intermittently treated for depression and pain in the right arm since then. She was taking regular paroxetine and amitriptyline, bendrofluazide for lymphoedema, and hormone replacement therapy. She was an ex-smoker of 10 years, and drank four units of alcohol a day. She lived with her husband. Family history was unremarkable. She was admitted to a local hospital, and transferred to the neurology department in Edinburgh four days later on the 28 April 2000.

EXAMINATION
She was agitated and confused, being orientated in time only. She could obey simple verbal and written commands. Registration was normal, but she scored zero for recall and attention. Her mini-mental state examination score was 10/30. Cranial nerve examination was unremarkable. Tone, power and reflexes in the limbs were normal. The plantars were flexor. Joint position sense appeared normal. However, she had marked truncal and gait ataxia. She had a scar from her right mastectomy, mild right arm lymphoedema, but no breast lumps or palpable lymph nodes. She was afebrile. Otherwise, general examination was normal.

INVESTIGATIONS
The full blood count showed a haemoglobin of 109 g/L, MCV 83 fl (80–99 fl), MCH 27 pg (27–37 pg). Her ESR was 30 mm/h. The follow-
ataxia in a woman: discussed at the Edinburgh Course in 2001

ing blood tests were normal or negative: white blood cell count (6.3 × 10⁹/L), platelets, coagulation, C-reactive protein, urea and electrolytes, glucose, liver function, thyroid function, calcium, phosphate, immunoglobulins, ANF, rheumatoid factor, ANCA, VDRL, serum ACE, the tumour marker CA125, alpha-fetoprotein, toxoplasma dye test, and IgM for Toxoplasma gondii. A chest X-ray was normal except for evidence of previous breast surgery. Computed tomography (CT) of the brain, performed at the referring hospital, was reported as showing ‘extensive patchy low density in both temporoparietal areas, but worse on the right. There is white matter change, cortical low density and patchy cortical enhancement with contrast on the margins. To the right of the midline is a small area of ring enhancement’ (Fig. 1). CT scans of chest, abdomen and pelvis were normal, as was bone scintigraphy. After admission to the neurology

Figure 1. Enhanced CT brain scan 2 weeks into the illness showing a ring enhancing lesion in the right cerebral hemisphere.
department, a magnetic resonance (MR) brain scan was performed, but only a post contrast T1 sagittal image was obtained, because the patient was very restless. This showed ‘innumerable cerebral metastases throughout the cerebrum with probable leptomeningeal deposits as well’ (Fig. 2).

**MANAGEMENT**

A first diagnosis was made, resulting in the syncopal collapse of her husband when he was told. A lumbar puncture was then performed, with normal CSF opening pressure, a protein of 0.81 g/L, glucose of 3.3 mmol/L (serum glucose 5.0 mmol/L), 6 white cells/mm³ and 46 red cells/mm³. No organisms were grown. Cytology showed a chronic inflammatory cell infiltrate, mainly consisting of lymphocytes. Toxoplasma dye test and IgM for *Toxoplasma gondii* showed no evidence of past or present infection. Oligoclonal bands were not requested. A right temporal brain biopsy was carried out on 12 May. Polymerase chain reaction (PCR) and long-term culture of the biopsy material showed no evidence of infection with *Mycobacterium tuberculosis*. In situ hybridization for the papova virus JC was negative. However, on the day of the brain biopsy, initial smear results from pathology suggested the presence of granulomata. Therefore, a second diagnosis was made, and treatment started. Later on the same day, further pathological analysis suggested a possible third diagnosis and another treatment was started. A week later, following the full pathological report, a final diagnosis was made, and more appropriate treatment was started. On 19 May, a second MR brain scan was done with gadolinium, under general anaesthetic, with dual echo acquisition in the axial phase. This showed scattered areas of marked enhancement in the cerebral and posterior fossa white matter (Fig. 3).

**CLINICAL DISCUSSION**

Dr Geraint Fuller

First, I should remind you that the world of the clinicopathological conference is different. It is an educational vehicle, not least for the person who actually does it. It is also entertainment. In Edinburgh it is a blood sport, and you know what happens to the fox! This lady presented with a subacute onset of confusion with ataxia, nausea and mild headache, without long tract signs, and she was otherwise reasonably well – a subacute diffuse or multifocal encephalopathy. A CT scan was performed on day 14 (Fig. 1), and she was transferred to Edinburgh, where an MR scan was done but her restlessness limited the study to a post-contrast T1 sagittal view (Fig. 2). There were deep white matter, subcortical, including corpus callosum, brain stem and cerebellar lesions, ependymal and periventricular white matter changes, which were
enhancing, and one was cystic. The report was remarkably confident, ‘disseminated cerebral metastases’. I think this is the first diagnosis that led to her husband’s faint (why was he standing up when given the news?). Investigations were carried out to look for the source of the metastases. The blood results were all unremarkable, although some would only have been available much later. A chest X-ray, bone scan, and CT of chest, abdomen and pelvis, were all normal. Cerebrospinal fluid (CSF) examination showed only a chronic inflammatory cell infiltrate on cytology, with a slightly elevated CSF protein and normal glucose. The differential diagnosis of multiple ring-enhancing lesions includes primary and metastatic brain tumours, abscesses, granulomata, resolving haematomas, infarcts and demyelinating disease. We can exclude resolving haematoma and infarct, because of the large number of lesions. The scan findings allow us to exclude paraneoplastic, metabolic, nutritional and vascular causes of diffuse and multifocal encephalopathies so we can concentrate on neoplastic, inflammatory and infective aetiologies as listed in Table 1.

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Neoplasia
In malignant meningitis I would expect the CSF to be consuming more glucose, but the scan results would be consistent with breast carcinoma metastases, other metastases and lymphoma. The CSF results may put multicentric glioma slightly ahead of the others.

Inflammatory
Sarcoidosis would fit the clinical picture, but the blood results are less convincing, and I would like to see more basal meningitic change on the scan, with a 'consumptive' CSF. Clinically, primary angiitis is a possibility, though the bloods, the CSF and the scans are strongly against it. Clinically, it does not fit with multiple sclerosis (MS), with the absence of long tract signs. The ependymal enhancement is not favourable for either MS or acute disseminated encephalomyelitis (ADEM).

Infection
The ring enhancing lesions do not fit viral encephalitis and progressive multifocal leukoencephalopathy (PML) at all, and so I will not discuss them further. The patient would be more unwell with a pyogenic abscess, with pyrexia, abnormal bloods and CSF, even though the scan would do well. The other infections are very unlikely even if the scans are compatible, unless she was immunocompromised, but there is no suggestion of this. We have no travel history, and I am sure I would have been told about this, as there is nothing like a good foreign travel red herring!

At this stage, the differential diagnosis consists of multicentric glioma, metastases, lymphoma, TB, ADEM, and abscesses. The correct investigation to do next was a biopsy and on day 28 a biopsy was taken of the right temporal lobe, which they tell us was TB and JC virus negative. However, I have to remember that this was not known immediately. The biopsy results were not straightforward. We have a smear, which suggested the presence of granulomata and therefore multinucleated giant cells were probably seen as well as swollen macrophages and lymphocytes. Reconsidering my differential diagnosis before the biopsy, the only one that has granulomata is TB. So, I think that the second diagnosis that was given was TB, and the second treatment was anti-TB treatment. Later that day, after further pathological analysis, a third diagnosis was made, which was enough for her doctors to start a different treatment. A week later, a full pathology report was issued which led to a final diagnosis, which I think was probably a surprise. It led to more appropriate treatment. The final MR scan was done on day...
35 (Fig. 3). It showed multifocal brain pathology affecting the deep white matter, subcortical areas including the corpus callosum, brainstem and cerebellum.

Sarcoidosis
If we rely on the presence of granulomata, sarcoidosis remains a possibility. In sarcoidosis, central nervous system involvement occurs in 5% of cases, commonly involving the optic nerve (38%) and other cranial nerves (33%), but only 10% have cognitive decline. Blood tests are usually not helpful as angiotensin converting enzyme is normal in 75% and the ESR is only abnormal in 6%. The CSF is also usually unhelpful because in 55% of cases a pleocytosis is seen, and 90% have a normal glucose. On the MR scan, 44% show white matter lesions, which are not ring enhancing. Dramatic meningeal enhancement is seen in 37% with less ependymal enhancement (Zajicek et al. 1999).

Granulomatous angiitis
This is a difficult diagnosis, with a protean presentation. Headaches, multifocal neurological deficits and encephalopathy occur, with a subacute onset. The CSF is again very variable, sometimes with a pleocytosis and a normal glucose. The MR scan is not usually dramatic, with white and grey matter lesions, which may enhance, and which include the leptomeninges. On histopathology, small arteries (200–500 µ) are inflamed with giant cells, but these are often difficult to find, so finding them in a smear would be odd.

Acute disseminated encephalomyelitis (ADEM)
I will mention ADEM, even though granulomata are not found, as I liked the scan for ADEM, but clinically it fits less well.

Another incorrect solution?
The frozen section showed a non-caseating granuloma with no organisms, suggesting a diagnosis of sarcoid. The patient was started on steroids. The full histology described granulomata associated with blood vessels giving us granulomatous angiitis for diagnosis four and again the treatment was steroids. However, in this scenario the treatment would not have been changed and so this diagnosis cannot be correct. I am eliminating pyogenic infection as discussed earlier. The later results exclude TB but other possibilities include nocardia, Whipple's disease, cryptococcosis, histoplasmosis, blastomycosis, amoebiasis, toxoplasmosis and oysteriasis. However, I rejected the last six of these earlier as they are usually found in immunosuppressed patients. We will review them.

Neurocysticercosis
This is unlikely. There tend to be more cystic lesions around the ventricles on the scan. Anyway there have been no reports of Taenia solium in UK pigs for many years (Ministry of Agriculture and Fisheries 1998). British neurocysticercosis cases were recently reviewed and all eight of them were acquired abroad (Wadley 2000).

Amebic meningoencephalitis
This is very rare and usually rapidly fatal.

Cryptococcosis
Cryptococcus neoformans causes infections worldwide. We think of it causing meningitis in AIDS patients, with occasional cryptococcomas. Occasionally, cryptococcomas can occur without meningitis (Selby Lopes 1973). Pathology shows an inflammatory response consisting of lymphocytes, plasma cells, and multinucleated giant cells. However, cryptococci are frequently seen.

Histoplasmosis
This is extremely rare in the UK, is more common in males, and starts as a respiratory infection. The central nervous system is involved but invariably in the context of a multisystem disease.

Blastomycosis
This can cause opportunistic or pathogenic infections, almost invariably associated with lung disease and does not usually occur in this country. So again, I will eliminate this diagnosis.

Another incorrect solution?
The frozen section showed a granuloma and possible cryptococcus or histoplasma. Diagnosis three was a fungal infection and the treatment was amphotericin. Diagnosis four was the exact fungus, and the treatment remained amphotericin. Therefore, there would have been no change of treatment, so again this scenario cannot be correct.

Nocardia
Nocardia asteroides is a Gram positive acid-fast bacterium, which can cause opportunistic and
I would like to describe a completely new condition - Whippophilia Neurologica! Its main feature is that it occurs in neurologists and is characterized by an overwhelming desire to diagnose Whipple’s disease in meetings. This diagnosis is usually wrong.

Toxoplasmosis
This is caused by the coccidian parasite Toxoplasma gondii. In most immunocompetent people it only causes a mild febrile illness. But there are rare cases of cerebral toxoplasmosis in immunocompetent adults. The pathology consists of areas of necrosis associated with polymorphonuclear cells, mononuclear cells and microglia with leptomeningeal involvement. Multinucleated giant cells have been seen (Bobowski & Reed 1958).

Whipple’s disease
This is a rare multisystem infection caused by Tropheryma whippelii. The pathology shows small ‘chalky’ granulomata scattered in the grey matter of cerebral and cerebellar cortex, and subependymal grey matter around the ventricles, which may spread to the white matter and into the subarachnoid space. The macrophages stain periodic acid-Schiff (PAS) positive. Occasionally multinucleated giant cells are seen. The diagnosis is made by electron microscopy, identifying the bacillus in PAS positive debris, or by polymerase chain reaction (PCR). Clinically, 5% of patients have only neurological disease, but 5–40% have some neurology involved in their disease (Anderson 2000). Higher function changes are very common. Eye movement disorders, myoclonus, epilepsy and aseptic meningitis are all seen. About 80% of neurological patients have systemic features. However, usually the onset is slower than in this lady. The imaging is variable, with atrophy, white matter change, mass lesions with contrast enhancement, and ring enhancing lesions. The CSF shows nonspecific changes of pleocytosis and a normal glucose.

The final solution?
The frozen section showed necrotic granulomata, lipid-laden macrophages, and some silver impregnation of foamy macrophages giving a third diagnosis of toxoplasmosis. The serology and CSF antibody tests were requested. The patient was started on sulfadiazine and pyrimethamine with folinic acid. Further histology showed widespread PAS positive cells and no evidence of tachyzoites on immunostaining. Electron microscopy or PCR confirmed T. whippelii, and the treatment was switched to ceftriaxone. Alternatively, the formal report arrived finding nocardia with methenamine silver stain, and culture confirmed nocardia later. The treatment was then changed to cotrimoxazole.

Therefore, for my diagnoses, diagnosis one is metastatic carcinoma, after the scan. Diagnosis two is tuberculosis, following the smear report. Diagnosis three is cerebral toxoplasmosis, and diagnosis four is either Whipple’s disease or nocardia infection. I am not sure which. This is where I would like to describe a completely new condition - Whippophilia Neurologica! Its main feature is that it occurs in neurologists and is characterized by an overwhelming desire to diagnose Whipple’s disease in meetings. This diagnosis is usually wrong. However, if the diagnosis has ever been right in the past, the neurologist’s desire to diagnose Whipple’s again becomes incurable. As a young doctor, and much to everyone’s surprise, including my own, I correctly diagnosed a case of Whipple’s disease, and so, as a result of my own affliction with Whippophilia Neurologica, I will go for Whipple’s disease as my final answer in this case.
**PATHOLOGY**

**Professor Jeanne Bell**

We were limited to a CSF sample and biopsy material. The CSF request form suggested the possibility of metastatic disease. However, the CSF showed lymphocytes indicating chronic inflammatory changes, with no malignant cells. The biopsy was performed due to the suspicion of infection. Intraoperatively a smear was performed, but not a frozen section because of the clinical suspicion of tuberculosis, which is considered high risk. The smear showed inflammatory changes only, with macrophages with foamy cytoplasm, giant cells and lymphocytes but no granulomata (Fig. 4), notwithstanding the impression picked up by the clinicians. The written pathology report was issued 6 days after operation. The paraffin section confirmed grossly abnormal hypercellular brain tissue, containing blood vessels surrounded by inflammatory cuffs of lymphocytes (Fig. 5), and foamy macrophages (Fig. 6) similar to those seen in the smear. The foamy macrophages suggested the third diagnosis of Whipple’s disease. However, subsequent staining with PAS, which stains Whipple organisms brightly, was negative. There was an active chronic inflammatory infiltrate related to blood vessels. This was confirmed as mixed lymphocytic in type by staining with CD3 showing T cells (Fig. 7) and CD20 showing B cells (Fig. 8). The white matter was gliotic (Fig. 9). We did a reticulin stain to see whether the infiltrate around the blood vessels was permeating and stretching the reticulin framework as found in a malignant infiltrate such as lymphoma, but instead the reticulin was fragmented. A stain for the CD68 macrophage marker showed many microglia and macrophages within the infiltrate around the blood vessels and in the damaged parenchyma. This was a lymphocytic and macrophage infiltrate.

The main pathology in the biopsy was in the white matter. The grey matter was relatively normal, and at the junction of the grey and white matter there was only reactive gliosis. There were no areas of necrosis or infarction, but instead there was gross demyelination, shown by the lack of staining with Luxol fast blue. In the meninges, there was a low-grade inflammatory infiltrate, which was reflected in the CSF results. The blood vessels looked normal so this was not a vasculitic condition. There were no well-formed granulomata. The Ziehl–Nelson stain and the culture were negative, so cerebral TB was excluded. The negative PAS stain ruled out Whipple’s disease. In situ hybridization was negative for the JC virus. There was little oedema in this biopsy, often found in acute multiple sclerosis, and anyway the clinical setting made this unlikely. Hence, the specialist stains were all negative. We asked for other specialist opinions and our final consensus diagnosis was ‘an inflammatory demyelinating condition.’ There was no classical perivascular demyelination, instead it was a pan-demyelinating condition. The final diagnosis therefore was acute inflammatory demyelination, with our favourite being acute disseminated encephalomyelitis.

**Dr Anna Williams**

The first diagnosis made was indeed metastatic carcinoma, presumed to be from the previous breast carcinoma nearly 20 years before. However, because of this long time interval, the diagnosis was sufficiently uncertain for us to seek a pathological diagnosis. The CSF results were unhelpful, and so we went on to brain biopsy. The first pathology report was preliminary and given by telephone, on the day of the biopsy. The transcript written in the notes clearly states that granulomata were seen in the biopsy. This information suggested the second diagnosis of tuberculosis, and the patient was immediately started on antituberculosis treatment. However, as you have heard, there were actually no granulomata seen and none reported in the final pathology report. Further pathological investigation showed the presence of foamy macrophages and so the third suggested diagnosis was Whipple’s disease. This diagnosis was revoked with a negative PAS stain. The final pathological diagnosis was acute inflammatory demyelination, so the final clinical diagnosis was acute disseminated encephalomyelitis and the patient was treated with steroids.

This patient survived and improved significantly with steroid treatment. Her mini mental-state examination rose seven points to 17/30 in one week, however, she became emotionally labile and inappropriate. She required treatment with antipsychotics for an organic psychosis of a manic type. She went to a local rehabilitation hospital 5 weeks after admission, and for the next 8 months she was reasonably well at home. However, her symptoms of ataxia and emotional lability began to deteriorate again. She had another MR brain scan which showed a general improvement in lesion load and there were no obvious new lesions. Her symptoms deteriorated further and she was started on citalo-
Figure 4 Smear preparation of biopsy material, showing blood vessels with a mix of different cells including some with rather vacuolated cytoplasm and a few larger multinucleate cells. The smear appears inflammatory with no evidence of tumour cells. Periodic acid Schiff reagent, original magnification × 100.

Figure 5 Paraffin section of biopsy material showing abnormal white matter containing a central vessel surrounded by lymphocytes. The white matter is pale, consistent with demyelination, and shows large reactive astrocytes with pink cytoplasm scattered diffusely. Haematoxylin and eosin, original magnification × 100.

Figure 6 Abnormal white matter showing numerous collections of pale macrophages. Haematoxylin and eosin, original magnification × 100.

Figure 7 Immunocytochemical staining of abnormal white matter to show T lymphocytes (CD3 positive) concentrated around a vessel and scattered through the parenchyma. Original magnification × 100.

Figure 8 White matter stained for B lymphocytes (CD20 positive) showing that these are confined to the perivascular lymphocytic cuffs and not present in the parenchyma. Original magnification × 100.

Figure 9 Abnormal gliotic white matter (immunocytochemistry for the astrocyte marker, glial fibrillary acidic protein) showing relationship to perivascular cuff of lymphocytes and macrophages within the white matter. Original magnification × 100.
pram. Therefore, clinically, there is no evidence of another event or a distinct relapse. Radiologically, there was no good evidence of new lesions, so the problem is likely to be a fluctuation in the symptoms from her original disease, along with a prolonged psychological reaction. However, we still must bear in mind that she could have had a first episode of multiple sclerosis.

Clinical diagnoses suggested by those looking after the patient
1. Metastatic carcinoma.
2. Cerebral tuberculosis.
4. Acute disseminated encephalomyelitis.

Dr Geraint Fuller’s diagnoses
1. Metastatic carcinoma.
2. Cerebral tuberculosis.
3. Cerebral toxoplasmosis.

Final Pathological Diagnosis
Acute inflammatory demyelination, consistent with acute disseminated encephalomyelitis.

REFERENCES
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