Papilloedema and lymphocytic meningitis in a 68 year old man

Chris Allen, Jeanne Bell, Harry McNaughton, Charles Warlow

Case presentation
This 68 year old man presented in late February 1992 with a one month history of intermittent blurring of vision, lasting seconds, in the right eye. He also had mild intermittent occipital headache, mostly at night, with some nausea in the morning. He had noticed some hearing loss in the left ear with tinnitus for about a year, and his wife thought he was a little unsteady on his feet. He was a diabetic controlled on diet, and there had been some recent weight loss. In earlier years he had been a heavy drinker, but no longer. He had never smoked. He was known to be in atrial fibrillation and had previously had a myocardial infarction. Many years ago there had been a “shadow on the lung”, possibly tuberculosis.

On examination he was in atrial fibrillation but there were no other general medical abnormalities; his chest and abdomen were normal; there was no lymphadenopathy. There was bilateral papilloedema much more on the right than the left but he had normal visual acuities. There was mild sensorineural deafness, more on the left than the right. There were some slight cerebellar signs on the left, his reflexes were brisk but symmetric, and the plantar responses were flexor.

Computed tomography (fig 1) was reported as normal, although there was concern about aqueduct stenosis. He was polycythemic (haemoglobin 180 g/l and packed cell volume 54%). The other blood indices were normal, and the erythrocyte sedimentation rate was 2 mm/h. Numerous other investigations were done at that point and over the next few weeks and were normal. These included urea, electrolytes, liver function, proteins and protein electrophoresis, calcium, alkaline phosphatase, B12, folate, serum iron, coagulation screen, antinuclear factor, rheumatoid factor, anticardiolipin antibodies, lupus anticoagulant, creatine kinase, calcium, and chest radiograph. His ECG showed atrial fibrillation.

Because of the possibility of aqueduct stenosis a right parietal access device was inserted and the intracranial pressure peaked at 30–40 cm H2O. The protein concentration in the CSF was normal (0.3 g/l), but there were 46 white blood cells/μl (90% lymphocytes). The CSF glucose concentration was 7.1 mmol/l with a blood glucose concentration of 12.4 mmol/l. No organisms were seen on Gram stain, no acid fast bacilli were seen,

Figure 1  Contrast enhanced axial CT scans of the head showing dilated lateral ventricles with normal basal cisterns without midline shift.
and nothing was grown either then or eventually in the way of bacteria, fungi, or mycobacteria from this specimen. Oligoclonal bands were absent.

No further investigations were done at this time and it was decided to insert a ventriculoperitoneal shunt on 9 March to control the raised CSF pressure. By 16 March the pressure was less than zero, but there were still 95 white blood cells/µl in the ventricular CSF (60% lymphocytes and 40% neutrophils). The protein concentration was raised at 1.84 g/l and Gram positive cocci were seen. A shunt infection was diagnosed and he was treated with intrathecal vancomycin and oral flucloxacillin. Some scanty coagulase negative staphylococci were grown from the CSF. The patient's symptoms were not changing much, but by 21 March his ventricular CSF white count was normal, even though the protein concentration was still raised at 1.38 g/l. He was discharged on 27 March.

He was readmitted on 1 April complaining of headache, although on this occasion it occurred when lying flat. The ventricular CSF was under negative pressure but it was still lymphocytic, with a white cell count of 60 white blood cells/µl, and a raised protein of 2.67 g/l. The shunt was thought to be infected, and it was changed on 14 April. He continued to lose weight, although the papilloedema was resolving. The ventricular CSF white blood cell count went down to 3 cells/µl by 21 April, there was no growth, and he was discharged home on the 29 April.

He was readmitted to hospital on 12 May complaining of increasing unsteadiness on his feet, tiredness, nausea, and sometimes vomiting. The papilloedema was much less obvious but nothing else was found. He was again discharged home.

He was readmitted on 20 May complaining of confusion and increasing ataxia of gait, weight loss, and anorexia. On this occasion the ventricular CSF contained 51 white blood cells/µl, with a glucose concentration of 6.6 mmol/l, and a blood glucose concentration of 9.7 mmol/l; the protein concentration was still raised at 1.76 g/l. No organisms were seen in or grown from the CSF. At around this time CSF cytology was requested and no malignant cells were found, although the specimen was contaminated with blood. It was thought that he had a low grade shunt infection and he was treated with antibiotics. On 17 June the ventricular CSF was much the same, and CT (fig 2) showed bilateral but small subdural collections with possibly some enhancement of the basal cisterns, suggesting a meningeal process. On 8 July he had a barium meal, which showed some ulceration, but endoscopy was negative. On 14 July the shunt was revised. By 21 July he was deteriorating and was thought to have bilateral lower motor neuron facial weakness and bilateral ptosis. He had a period of left ventricular failure probably due to fast atrial fibrillation, and a urine infection, which was treated with gentamicin. His white blood cell count went up for the first time to 14.7 × 10⁹/l, his haemoglobin was a little lower at 149 g/l, and his erythrocyte sedimentation rate was 4 mm/h. On 29 July his alkaline phosphatase was 229 IU/l.

On 1 August a new registrar rotated to the neurology ward and performed a diagnostic examination—a procedure not requiring any instruments—which was well within his capabilities. The patient died four days later.

DR CHRIS ALLEN

We have a man who presented at the age of 68 with a one month history of blurring of vision. It lasted seconds and was in the right eye. This sort of intermittent blurring of vision does not sound like amaurosis fugax, it is not a sudden blackout of vision, and it does not seem to be optic neuritis (a less sudden subacute white-out of vision), but suggests the transient visual obscurations of someone with raised intracranial pressure, or at least papilloedema. The mild intermittent occipital

Figure 2 Contrast enhanced axial CT scans of the head showing ventricular drainage devices, less definition than before of the basal cisterns, and a peripheral hyperdense region in the left cerebral hemisphere.
headache, mostly at night with nausea in the morning, is suspicious and raises the possibility that he has a mass lesion causing papilloedema or hydrocephalus, or some other cause of raised intracranial pressure such as one of the syndromes which I like to call pseudotumour cerebri, itself sometimes caused by cerebral venous sinus thrombosis. The hearing loss is most likely to be incidental presbycusis because it has been present for about a year, with tinnitus. Diabetes suggests odd vascular complications or local infections such as mucormycosis. Weight loss and the fact that he died within six months of onset makes me think of malignancy, chronic systemic infection, or inflammation. The rest of the medical background raises other possibilities: cirrhosis or hepatoma in a previously heavy drinker, atrial myxoma or other heart disease with atrial fibrillation, and tuberculosis, sarcoidosis, or aspergillosis with the old lung shadowing.

Examination showed atrial fibrillation and no other general medical abnormalities. His chest and abdomen were normal and there was no lymphadenopathy. I was taught as a medical student, by the surgeons of course, that a rectal examination was part of the abdominal examination so I hope that a rectal examination was performed here. There was bilateral papilloedema and normal visual acuities. The normal visual acuities more or less rule out the other causes of swollen looking discs. The history and examination strongly suggest raised intracranial pressure. Raised intracranial pressure without focal signs makes one think of hydrocephalus or a lesion in a silent part of one hemisphere. He could have had raised intracranial pressure from a pseudotumour syndrome due to meningeal disease or cerebral venous sinus thrombosis. Papilloedema with normal CSF pressure can occur in the presence of a serum paraprotein. For example, a recent patient in Cambridge presented with an odd vasculitic disease of the brain demonstrated at biopsy and associated with a serum paraprotein, and one of the features she had on admission was papilloedema with normal intracranial pressure at lumbar puncture. Other possibilities are leukaemic infiltration or sarcoidosis. Posterior fossa structural or meningeal disease could explain the ataxia and cerebellar signs. The hearing loss could be due to meningeal disease as well.

The contrast enhanced CT (fig 1) shows slightly dilated ventricles but the sylvian fissures and the cisterns around the brainstem are visible. I cannot see any mass lesions in the posterior fossa and what I can see of his fourth ventricle is central and not dilated. The cerebral sulci are visible and there is no midline shift, so this man had mild hydrocephalus with a normal fourth ventricle. I do not think that the hydrocephalus caused his papilloedema.

The only abnormal tests were a raised haemoglobin, packed cell volume, and ECG evidence of atrial fibrillation. Not available, perhaps by simple omission, were measure-
Papilloedema and lymphocytic meningitis in a 68 year old man

...ments of acid phosphatase or prostate specific antigen. The polycythaemia, in a non-smoker without obvious lung disease (apart from old tuberculous shadowing), suggests the possibility of cerebellar hemangioblastoma which we would have liked to have seen in the posterior fossa on CT or a renal tumour, particularly adenocarcinoma. Other renal disease, even mild hydronephrosis, can cause polycythaemia. Twenty per cent of one series of polycythaemia induced by tumours were due to hepatomas, with testicular tumours less common.1 One of the investigations this man did not have was an ultrasound of his abdomen. To clarify the diagnosis, I think that he should probably have had an MR angiogram, to make sure there was no cerebro venous sinus thrombosis, and an ultrasound or CT of his abdomen. He should have had some CSF cytology from his lumbar CSF and tests for acid phosphatase and prostate specific antigen.

I think that he must have been under the neurosurgeons to begin with because they obviously disagreed with me about the aqeduct stenosis or perhaps were nervous about obtaining CSF, which would be the next necessary investigation. So he had a right parietal access device inserted and his intracranial pressure was raised. The CSF protein was 0-3 g/l. This CSF was presumably taken from his ventricle. Ventricular CSF should have a protein concentration about half that of lumbar CSF so this is abnormal.2 He has a low grade lymphocytic meningitis with a normal CSF glucose. Although CSF cultures were negative, no blood cultures were done. Listeria, in particular, is found more readily in the blood than in the CSF.3 Nevertheless, I think that it is unlikely that infection explains the CSF findings and this includes Lyme disease.

He continued to have a headache. This could be due to carcinomatous meningitis, which commonly presents with a headache and is the commonest single symptom in a series from the Sloane Kettering Institute of malignant meningitis,4 and he was unsteady on his feet, which is another common symptom of malignant meningitis. If he did have malignant meningitis, I think that he was most likely, based on the information we have, to have had an abdominal malignancy, gastric or other adenocarcinoma or lymphoma. Alternatively, a paraneoplastic syndrome with cerebellar atrophy could cause unsteadiness and an abnormal CSF. Papilloedema from raised intracranial pressure would be unusual in this situation although papilloedema without raised pressure is described in the paraneoplastic syndrome with optic neuritis.5

Eventually CSF was sent for cytology. The CSF was probably obtained from the ventricle but should preferably come from both ventricular and lumbar sites. There are well recorded series in which malignant cells have been consistently absent from one of the two sites, ventricular or lumbar, and present in the other.6 In malignant meningitis the CSF is positive for malignant cells in about 50% on the first sample, and in the Sloane Kettering Institute series eventually 85% were positive.1 On 17 June the ventricular CSF was much the same and CT was again performed.

This CT (fig 2) is different from the previous one. We were having a difficult time to make out a sphenoids clearly and his third ventricle is not visible although he has had more than one shunt. There is loss of definition of the central structures and it looks to me as though his brain is generally rather swollen. The CT report comments on possible meningeal enhancement, which is always difficult to judge. He has small subdural collections. I am not sure what the superficial cord-like high density in the left hemisphere is. This could be the "cord sign" of cerebral venous sinus thrombosis although I have never seen it.7 I thought that it might be enhancing meningeal infiltration. The barium meal and endoscopy help to rule out gastric cancer. By 21 July he was becoming worse and was thought to have bilateral lower motor neuron facial weakness and bilateral ptosis. Suddenly one wonders if he has any myasthenic syndrome but I think that in the current context meningeal infiltration is much more likely.

Now we come to the nice bit at the end of every clinicopathological conference when they half tell you something to try and tease you. On 1 August a new registrar rotates on to the neurology ward and performs "a diagnostic examination, not a procedure requiring any instruments, which was well within his capabilities". The patient died four days later. What on earth could he have done?

To get the final diagnosis right it is necessary to guess what the registrar did. So, did he do a rectal examination and find a malignant prostate, or a rectal carcinoma? Or did he examine the abdomen, which we are told was previously normal? Had the patient Stauffer's syndrome, a syndrome of paraneoplastic enlargement of the liver without metastasis associated with renal adenocarcinoma?8 Or did the registrar find a "great craggy lump of a hepatoma? Or did he have melanomatosis and a metastasis from this? Did the new registrar go even further and examine the testicles? Did he find a peritoneal mass from the spread of his meningal melanomatosis via his shunt into his peritoneum? This is unlikely. Did he open the patient's mouth and look at his genitals again and find ulcers suggesting Behçet's disease? Did he look at the skin and find lupus pernio, suggesting sarcoidosis, or a melanoma? Or did he find a lymph node enlarged by lymphoma?

In summary, I think that this patient had malignant meningitis from an adenocarcinoma. My best guess is a prostatic carcinoma but it may be another intra-abdominal adenocarcinoma. Forced to provide a differential diagnosis, I would suggest a paraneoplastic encephalopathy with one of the previously mentioned cancers or a cerebral venous sinus thrombosis with one of those cancers. I think that if he had cerebral venous sinus thrombosis it is unlikely that he would have died from...
this without one of the complications, such as a venous infarction or a major stroke-like event.

**DR JEANNE BELL**

We received two CSF specimens for cytology during this man’s illness. The initial specimen was negative for malignant cells. He had a further CSF sample analysed a few days before he died, which showed malignant cells that were thought to be adenocarcinoma cells. It was, however, negative for epithelial markers. We were thinking of further tests that we might do on additional specimens when he died.

At necropsy his brain was unremarkable. He had a bronchopneumonia and no sign of any tumour in his lungs. He had heavy lungs and a very large heart with an old myocardial infarction. There was a 2 cm white nodule in the cortex of the left kidney. The prostate was greatly enlarged by malignant tumour, which was also adherent to the base of the bladder and posteriorly to the rectum. I checked the spare cytopins of the CSF that we had had a few days before death to look for prostatic acid phosphatase. This was negative. Nevertheless the presumptive diagnosis was adenocarcinoma of the prostate metastatic to the subarachnoid space.

Examination of the fixed brain showed some atheroma in his vessels, the tracks of the shunt and access devices, a small aqueduct, and mildly swollen brain parenchyma. The ventricles were of normal size. Microscopic examination of the prostate showed a non-Hodgkin’s B cell malignant lymphoma (fig 3). The nodule noted in the kidney was a lymphoma with lymphoma cells also in the periadrenal fat. Pneumonia was confirmed in the lung and the brain showed wide subarachnoid spread of lymphoma involving the cranial nerve roots (fig 4). He had terminal hypoxic changes in his brain.

Immunocytochemical staining showed positivity for L26 (a B cell marker) and negativity for MT1 (a T cell marker), so this was a high grade non-follicular B cell non-Hodgkin’s lymphoma. The subarachnoid space was filled with tumour cells that had spread into the parenchyma of the brain with a related glial response. Nearly all the roots examined were infiltrated diffusely by tumour.

I need to comment on the differential diagnosis of the CSF cytology. Looking back on this case I think that I should have placed more reliance on our immunocytochemical tests. The CSF that came to us with malignant cells was assumed to show carcinoma cells and when the cells were negative for the epithelial markers it was not checked for lymphoma with T and B cell markers. If the cells are clearly malignant cytologically and they turn out to be B cells this is a strong indicator of B cell lymphoma in the CSF pathway. Nevertheless, CSF specimens are often limited in volume and we can only make a graded list of what we would choose to do with the specimen. Carcinoma is more common than lymphoma and in the presence of malignant cells we would certainly go for epithelial markers first.

**Conclusions**

*Dr Chris Allen’s diagnosis: Prostatic adenocarcinoma with malignant meningitis.*

**Pathological diagnosis:** Prostatic lymphoma metastatic to the subarachnoid space and nerve roots and metastatic to the kidney and periadrenal fat.

**Comment**

Lymphoma affecting the prostate gland, either as primary extranodal disease or as secondary spread, is very rare. By 1985 only 95 cases had been reported. Of the 13 patients studied by Bostwick and Mann (collected from 1935 to 1983), seven had primary extranodal disease. In none of the 13 patients had this spread to the CNS. The subarachnoid space is the CNS compartment most commonly involved by non-Hodgkin’s lymphoma. In 60% of cases with subarachnoid spread of the non-Hodgkin’s lymphoma there is focal parenchymal infiltration and more than 80% show cranial nerve root invasion.

The investigation performed by the new registrar was a rectal examination, which showed a hard craggy prostate gland.

This clinicopathological conference was presented at the Edinburgh advanced clinical neurology course, April 1994. We thank Judi Clarke for her help with transcription of the original.