Clinicopathological conference

Dizziness and confusion after bone marrow transplantation

A 44 year old woman presented to the Hammersmith Hospital with dizziness and cognitive impairment five months after receiving a bone marrow transplant. Despite intensive treatment her condition deteriorated and she died two months later. A stereotactic biopsy of the brain and postmortem findings were diagnostic. We presented a summary of her case, minus the final diagnosis, to Professor Christopher Kennard, professor of clinical neurology at Charing Cross and Westminster Medical School, and asked him to reach a diagnosis.

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Case history

DOS: A 44 year old woman, who had received a bone marrow transplant, presented in October 1991 with a two week history of cognitive impairment noted by her husband. Eight years previously she had had Philadelphia positive chronic myeloid leukaemia diagnosed while she was pregnant. After delivery she was treated with hydroxyurea and busulphan, and in May 1991 she received bone marrow from a volunteer unrelated donor after conditioning with cyclophosphamide and total body irradiation. Her prophylaxis against graft versus host disease comprised T cell antibodies (Campath 1G), cyclosporin A, and methotrexate. The transplant was complicated by grade II graft versus host disease of the skin and upper gastrointestinal tract and candidiasis, which responded to high dose steroids and fluconazole.

Five months later, she presented with dizziness and severe oral herpes simplex ulcers. Despite treatment with acyclovir the dizziness persisted, and she was also found to have behavioural changes, poor concentration, and reading and writing difficulties and she was unable to count money in the shops. On examination she had no fever impaired short term memory, severe dyscalculia, mild constructional apraxia, and left visual inattention. She scored 25 out of 30 on the Folstein mini-mental state questionnaire.

CK: Before considering any investigations we should try to localise the lesions that are giving rise to the symptoms and signs. This patient presented initially with non-specific symptoms of dizziness and poor concentration. Two weeks later she had impaired short term memory, which is a much more specific symptom that implies impairment of the bilateral temporal lobe. This leads us to consider herpes simplex encephalitis, which predominantly affects the temporal lobes, although it is unusual for this to occur in association with activated oral herpes simplex.

The next sign, left visual inattention, localises the lesion to the posterior right cerebral hemisphere, probably the right parietal lobe. Then we come to her dyscalculia: without more detailed neuropsychometry we cannot be certain of the type (aphasic, visuospatial, or true arithmetic) and hence which hemisphere is affected, although dyscalculia usually localises to the left.

True apraxia of construction is associated with a dominant left hemisphere lesion, though it may be due to visuospacial disturbances resulting from a parietal lesion on the right. Reading and writing difficulties may be localised specifically to a left angular gyrus lesion. So, in addition to evidence of a definite right parietal lesion and a probable left angular gyrus lesion, we also have evidence of bilateral disturbances of the cerebral hemisphere, which are more difficult to localise.

DOS: Investigations showed a normal full blood count, with no evidence of a relapse of her leukaemia. Biochemical tests, a test for C reactive protein, blood cultures, and echocardiography all gave normal results. Cerebrospinal fluid was under normal pressure with a white cell count of 2×10^6/l. Her protein and glucose concentrations were normal, no organisms were detected, and India ink stain showed no cryptococcus.

MR: Computed tomography on admission showed three non-enhancing low attenuation lesions in the right temporal lobe and adjacent to the left frontal and posterior horns, without mass effect. A second scan showed a slight increase in the size of these lesions. The magnetic resonance imaging scan showed high signal lesions matching these, plus several others in both hemispheres (fig 1).

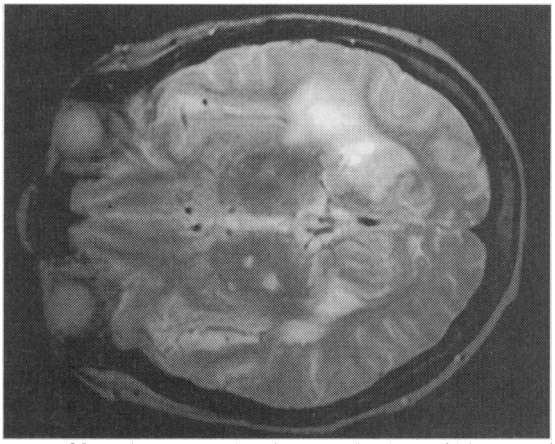

FIG 1—*Magnetic resonance imaging scan showing multiple areas of increased signal in white matter in T2 weighted image*

Differential diagnosis

CK: We have to consider whether the patient's neurological condition is due to a recurrence of her original disease or a direct effect of treatment, either cyclosporin or total body irradiation plus methotrexate. Or could it be related to graft versus host disease? Finally, is it somehow related to immunosuppression, either infection or malignancy?

The imaging shows multiple central nervous system lesions, predominantly in the white matter. If we assume a low CD4 count the patient would be in a similar situation to that of AIDS patients. We therefore should consider the following differential diagnoses.

Viral infections—Herpes simplex encephalitis in immunocompromised patients is rare, tends to be acute, and is not normally associated with oral vesicles. Varicella zoster commonly causes cerebral vasculitis, although myelopathy or multifocal leucoencephalopathy can occur months after the rash has subsided, affecting white matter.[1] Cytomegalovirus can be

excluded because it affects the cortex and subcortical grey matter.

Bacterial infections—A normal cerebrospinal fluid cannot exclude tuberculomas. Patients with low attenuation on computed tomography in the cerebral hemispheres can turn out to have tuberculosis. Although meningitis is the common presentation of infection with *Listeria monocytogenes*, multiple abcesses may occur, particularly in the lower brain stem.[2]

Fungal infections—Cryptococcus gives rise to mass lesions on computed tomography. Aspergillosis causes multiple hypodense lesions and fever. Candida causes either basal meningitis or thrombosis with infarction secondary to invasion of blood vessels. Coccidiomycosis gives rise to chronic meningitis. All of these can, therefore, be excluded.

Toxoplasmosis—This can present with subacute onset of cerebral dysfunction but tends to occur more in grey than white matter, predominantly in basal ganglia. It is rare after bone marrow transplantation, with only 31 reported cases.[3] Cerebral lesions in toxoplasmosis also tend to enhance with contrast, which was not present in this case.

Vascular causes—There is nothing from the systemic examination to suggest vasculitis, and there was no stepwise deterioration.

Lymphoma—Examination failed to show enlarged lymph nodes, liver, or spleen, making metastatic lymphoma less likely. Primary cerebral lymphoma, a B cell lymphoma localised to the brain, is, however, seen in systemic lupus erythematosus, congenital immunodeficiency, and AIDS and after organ transplantation.[4] Lymphoma presents with confusion and memory loss and progresses subacutely. The median time from onset to death would also fit (nine months, range 5·5 months-4 years). The cerebrospinal fluid is often normal. Computed tomography usually shows diffuse, nodular, or patchy contrast enhancement.

Progressive multifocal leucoencephalopathy—This is a rare viral infection due to Jakob Creutzfeldt polyoma virus that is well documented in immunocompromised patients, such as those with lymphoma, chronic leukaemia, AIDS, sarcoidosis, and organ transplantation. The condition presents from six months to five years after the onset of the original disease, with unifocal motor or visual symptoms, or both, progressing to multifocal cerebral disease.[5] Patients usually deteriorate rapidly, with a median survival of four months, although there are occasional remissions. Non-enhancing lesions occur in the white matter on computed tomography and magnetic resonance imaging.

Post-bone marrow transplant leucoencephalopathy—This is a rare white matter degeneration occurring particularly in patients who have central nervous system irradiation before bone marrow transplantation. Computed tomography shows multifocal white matter lesions, producing focal signs, lethargy, confusion, and progressive deterioration.[6] This would be unlikely in this case as the patient had total body irradiation but no additional irradiation to the brain.

Drugs—Cyclosporin is toxic to the central nervous system and can cause seizures, tremors, parkinsonian-type syndromes, and visual disturbances as a result of damage to the occipital lobe, which is usually associated with hypomagnesaemia and microangiopathic haemolytic anaemia.[7] Computed tomography shows hypodense lesions, mainly in the occipital lobe (grey and white matter). These normally recede when the drug is discontinued (which did not occur in this case).

Progress of patient

DOS: Initially this woman was treated for toxoplasmosis (sulphadiazine and pyrimethamine). Steroids and cyclosporin A were discontinued. She remained alert but deteriorated intellectually, with receptive dysphasia, worsening dyscalculia, spatial disorientation, and impaired short term memory. She scored 8/30 on her Folstein questionnaire. She had a left homonymous hemianopia and a left hemiparesis. She therefore had a stereotactic brain biopsy at the National Hospital for Neurology and Neurosurgery, and was given intravenous and intrathecal cytosine arabinoside. She became mute and tetraparetic and eventually died.

Clinical diagnosis

CK: The patient had a brain biopsy, deteriorated rapidly, and died over four months. Herpes simplex would be a possibility. Do we have an electroencephalogram?

DOS: It was non-diagnostic.

CK: Was there any preceding varicella zoster infection?

DOS: No.

CK: So I think I will have to reject that. We have already dismissed the cytomegalovirus. The neurological investigations preclude tuberculosis and it would have been unusual for a patient to die so rapidly. We have already excluded listeria. Had the patient been abroad?

DOS: No.

CK: She was given the correct treatment for toxoplasmosis, but the lesions got bigger and she died. Although not all patients respond to appropriate treatment, I think that this was not the diagnosis in this woman. We have excluded vascular causes. While we can rule out lymphoma elsewhere, primary cerebral lymphoma is still a possibility, although the fact that she had several lesions discourages this possibility. Were there any abnormalities in the blood film to suggest cyclosporin toxicity?

DOS: No.

CK: We can rule this out. Were T cells removed before transplantation?

DOS: Campath 1G is an in vivo T cell depletor, and although a CD4 cell count was not done in this patient, other patients with bone marrow transplants have low CD4 cell counts.

CK: In that case I am left with three possible diagnoses: progressive multifocal leucoencephalopathy, primary cerebral lymphoma, or a very unusual case of herpes simplex encephalitis. I would rule out herpes simplex and primary cerebral lymphoma for radiological reasons and therefore I am left with progressive multifocal leucoencephalopathy.

Discussion of pathology

JS: Stereotactic brain biopsy of the right parietal lobe gave four 2 mm fragments of abnormal tissue with marked demyelination of white matter together with accumulation of lipid-laden microglia. Few enlarged astrocytes were identified, which suggests progressive multifocal leucoencephalopathy, although hyperchromatic oligodendroglia were not seen and in situ hybridisation for Jakob Creutzfeldt virus gave negative results.

The necropsy was done three days after death. Serial transverse sections of the brain showed numerous areas with softening of white matter (fig 2). Lesions were identified in the left parietal, temporal, and frontal lobes, the corpus callosum, the right parietal lobe, and bilaterally in brain stem and cerebellar white matter. The ill defined nature of the lesions is useful in distinguishing progressive multifocal leucoencephalopathy from other focal demyelinating diseases such as

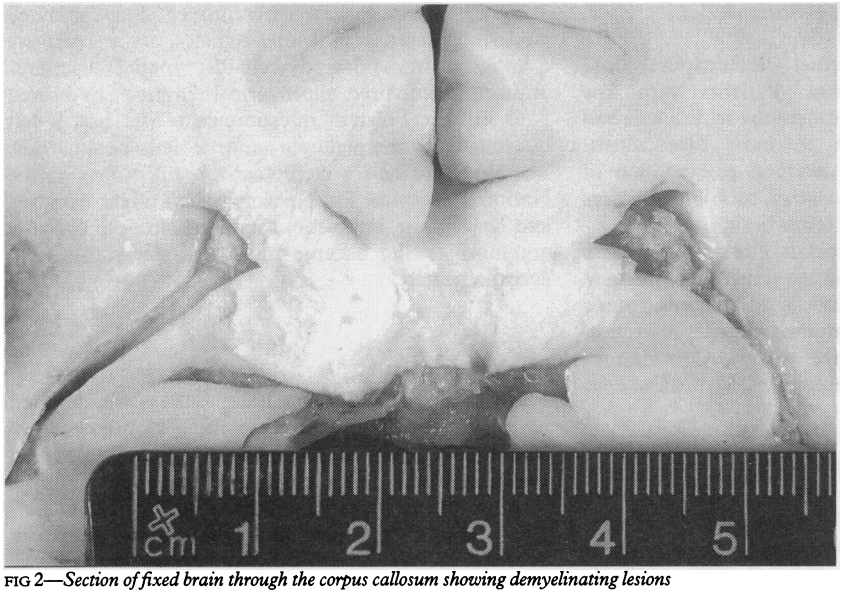

FIG 2—*Section of fixed brain through the corpus callosum showing demyelinating lesions*

multiple sclerosis, in which the lesions are sharply circumscribed.

Sections from affected areas showed the typical morphological features of progressive multifocal leucoencephalopathy. In well developed lesions there are clear zones. Centrally the degenerate foci are composed predominantly of microglial cells (immunohistochemically reactive with HAM 56) containing ingested myelin (fig 3), with a scattering of reactive enlarged astrocytes. Peripherally the white matter contains moderate numbers of enlarged hyperchromatic oligodendroglial cells with a homogeneous nuclear staining pattern. The oligodendroglia produce and support myelin in the central nervous system and infection impairs their function, resulting in demyelination. We were able to confirm infection by in situ hybridisation with a biotinylated probe to Jakob Creutzfeldt virus (provided by Professor Scaravilli; fig 3). The distribution of infected cells at the edge of the lesions may explain the negative results of in situ studies on the original biopsy specimen.

The possible differential diagnoses of primary cerebral lymphoma and of other infections have been mentioned. A small cuff of lymphoid cells was present around a few cerebral vessels, but these had normal morphology and T cell immunophenotype. There was no evidence of toxoplasmosis, and immunostains for cytomegalovirus and herpes simplex viruses I and II gave negative results. The bone marrow was normocellular with good engraftment and no evidence of residual or recurrent disease. The pathological diagnosis was thus progressive multifocal leucoencephalopathy after bone marrow transplant for chronic myeloid leukaemia.

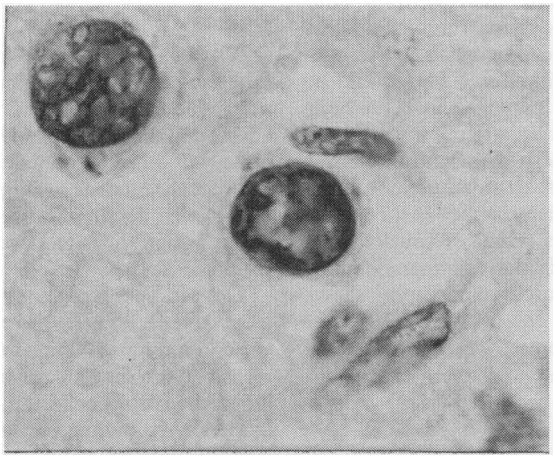

FIG 3—*Two infected oligodendrocytes from periphery of demyelinated lesion, labelled by in situ hybridisation for Jakob Creutzfeldt viral DNA with biotinylated probe*

Discussion

JMG: Why did you not think HIV infection was a possibility?

CK: To die within five months would be unusual.

JMG: We have two bone marrow transplant patients who possibly acquired HIV infection after a blood transfusion in 1982-3. One of them died within six months of the transplant with a clinical picture similar to AIDS, although we cannot be certain.[8] The other is alive and asymptomatic 10 years after transplantation.

JS: Dr Brooks, you looked after the neurological side, do you have any further comments?

DB: When we see an isolated white matter lesion in an immunosuppressed patient, even without enhancement on computed tomography, we always suspect toxoplasmosis and treat it. After two to three weeks we do a biopsy if we are not getting a satisfactory response. We suspected lymphoma or progressive multifocal leucoencephalopathy in this patient.

PL: I think that the gross anatomy of the lesions favoured progressive multifocal leucoencephalopathy, which is a centrifugal white matter disease, rather than lymphoma, which is centripetal. This raises all sorts of questions about the differential response of the oligodendroglial-myelin complex to different disease processes. The other interesting feature is how the same virus causes death of oligodendroglia and transformation of astrocytes.

FS: The biopsy specimen was examined in our laboratory. Although by definition progressive multifocal leucoencephalopathy is a white matter disease, the grey matter is often affected, leading to cortical thinning.

Antibody titres for polyoma viruses in donor and recipient of bone marrow transplant

	Serum		Cerebrospinal fluid	
	BK	Jakob Creutzfeldt	BK	Jakob Creutzfeldt
Donor	80	320		
Recipient:				
Before bone marrow transplantation	10	2560		
After bone marrow transplantation (October)	5	320	<5*	40†
After bone marrow transplantation (November)	5	640	<5*	10†

*Negative results on polymerase chain reaction.
†Positive results on polymerase chain reaction.

KW: We had a good indication that she had progressive multifocal leucoencephalopathy even before the brain biopsy as serum antibody levels to Jakob Creutzfeldt virus were raised six months before her illness, and during her illness there was evidence of intrathecal antibody synthesis (the normal ratio of serum to cerebrospinal fluid antibodies being 256:1). The polymerase chain reaction test recently developed by the Virus Reference Division of the Central Public Health Laboratory confirmed the presence of Jakob Creutzfeldt viral DNA in the cerebrospinal fluid and absence of BK polyoma viral DNA (table). In conclusion progressive multifocal leucoencephalopathy may be diagnosed after death without the need for brain biopsy.[9]

The BMJ welcomes grand rounds from other hospitals.

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Lesson of the Week

Spontaneous fractures in children and adolescents with cerebral palsy

S Lingam, Jane Joester

Children and adolescents with cerebral palsy have a tendency to sustain spontaneous fractures

Children and adolescents with cerebral palsy, in addition to the motor disability, have other, associated disabilities: hearing and visual impairment, learning disabilities, failure to thrive in infancy and poor growth in childhood, and scoliosis. They are prone to dislocations, particularly dislocation of the hips. They also develop other contractures and deformities, which may need surgery.

We report on five children and adolescents who developed spontaneous fractures of long bones, an association which, as far as we are aware, is not recognised.

Subjects

The five subjects, aged 10 to 19 years (four male and one female) with various types of cerebral palsy, were resident pupils at Meldreth Manor School, run by the Spastics Society. All the subjects received regular physiotherapy at school and were looked after by trained and experienced care staff. The overall management is multidisciplinary. The subjects were all severely disabled, with little or no voluntary movement, and the four boys were severely hypertonic.

The care staff, nurses, and physiotherapists observed a change in the behaviour of these subjects, and during examination fracture was suspected. The fractures were confirmed radiologically in each case. The table shows the details of the subjects and the sites of the fractures. None of the subjects had a spiral fracture.

All the subjects were managed with plastering and immobilisation. The fractures healed rather quickly. Radiographs of other long bones did not show any other fractures in any of the subjects; they showed generalised demineralisation and thinning of the bones and did not show rickets. Rickets due to a biochemical imbalance was ruled out in three subjects in whom concentrations of calcium, phosphorus, and alkaline phosphatase were determined.

Details of five subjects with cerebral palsy who sustained spontaneous fracture; site of fracture; and time taken for fracture to heal*

Subject No	Age at fracture (years)	Type of cerebral palsy and associated disability	Site of fracture	Time taken for fracture to heal (weeks)
1	15	Athetoid dystonia	Femur, tibia, fibula	3
2	17	Spastic tetraplegia; visual impairment	Femur	3
3	16	Spastic tetraplegia, scoliosis, athetosis, dystonia	Femur	4
4	10	Spastic tetraplegia	Femur	4
5	19	Spastic tetraplegia	Femur	Not known

*All male except subject 1.

Discussion

Spontaneous fractures are seen in children and adolescents with osteogenesis imperfecta, which is a disorder of bone formation, but are not common in those with Marfan's syndrome or other collagen disorders. Fractures are associated with osteoporosis because of fragile bones and with rickets and osteomalacia because of softening of the bones. We do not understand the mechanism of the fracture and quick healing of bones in children and adolescents with cerebral palsy. In our five subjects the bone matrix showed demineralisation in the *x* ray films, indicating osteoporosis. Osteoporosis is possibly due to the lack of strain on the bones because of the lack of physical activity. It is also interesting that children and adolescents with osteogenesis imperfecta do not fracture the long bone of their arms as they have some useful hand movements and are generally able to ride their own wheelchair and use computer switches.

In addition, children and adolescents with cerebral palsy have deficient muscle bulk and tend to develop contractures. They are also fairly immobile. Some have increased tone in some groups of muscles, and some have involuntary extensor spasms, which can also cause excessive muscle pull to some bones. We believe that spontaneous fractures are perhaps due to poor muscle support to the long bones and to the stresses on these bones. Bone requires appropriate strain for optimal maintenance of strength (strain is the slight deformation of a solid material in response to applied force).[1]

It is important to recognise that children and adolescents with cerebral palsy have a tendency to sustain spontaneous fractures, particularly as such fractures may be confused with non-accidental injury or traumatic fractures. Particularly because failure to thrive is also common in children and adolescents with cerebral palsy the cause of a fracture should not always be attributed to injury.

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