Progressive multifocal leucoencephalopathy, sclerosing cholangitis, bronchiectasis and disseminated warts in a patient with primary combined immune deficiency

S A Misbah, G P Spickett, A Zeman, M M Esiri, T B Wallington, J B Kurtz, H M Chapel

Abstract
A 24 year old man presented with an unusual primary combined immune deficiency syndrome characterised by a profound lymphopenia of CD4 cells, selective serum IgG2 subclass deficiency, poor polysaccharide antibody responses, disseminated warts, recurrent sinopulmonary infection and bronchiectasis. The developed progressive multifocal leucoencephalopathy (PML) in association with sclerosing cholangitis.

Progressive multifocal leucoencephalopathy (PML) usually occurs as an opportunistic infection in patients with secondary defects in cellular immunity. The occurrence of progressive multifocal leucoencephalopathy (PML) as an opportunistic infection in patients with defective cellular immunity secondary to human immunodeficiency virus (HIV) infection, Hodgkin's disease, chronic leukaemia and immunosuppressive treatment is well known. Its association with primary immune deficiency is less well known and reports of its development in primary immune deficiency are exceedingly rare.

Case report
A caucasian boy born to unrelated parents in 1966 was first seen at another hospital at the age of 3 years on account of flexural eczema, recurrent tonsillitis, and otitis media. By the age of 5 a hoarse voice led to the detection and removal of vocal cord polyps. Two years later generalised warts were first noted. In 1976 a right middle and lower lobe lobectomy was performed for bronchiectasis. Cystic fibrosis was excluded on the basis of a normal sweat test.

In December 1983 a dermatological opinion was sought for extensive warts which covered his neck, trunk, arms and knees. He was noted to be lymphopenic with a low T helper cell (CD4) count. Human papillomavirus type 3 was detected in a shave biopsy specimen of a wart by DNA hybridisation. He was given etretinate 20 mg daily for one year during which time there was some improvement that was not sustained. HIV serology was negative. In December 1984 Isoprinosine, a T cell stimulant was given (1 g four times a day) with no objective improvement in his warts. Isoprinosine was discontinued in July 1985. The lymphopenia of CD4 positive cells remained unchanged (fig 1). He was lost to follow up over the next five years until June 1990 when he was transferred to the neurology department at Oxford with a three month history of difficulty in walking, focal seizures, and jaundice of four weeks' duration.

On examination he was cachectic, dyspnoic, and jaundiced. Disseminated warts and bilateral digital clubbing were noted. Neurologically he was partly orientated, followed simple commands, and could perform basic arithmetic. Bilateral optic atrophy, hypertonic limbs with ankle clonus, hyperreflexia, a right extensor plantar response and bilateral cerebellar deficits were noted. A cranial computed tomogram showed a left cerebellar hemispheric cyst with numerous low density lesions in both thalamic nuclei, right caudate

nucleus, and the right parietal lobe. A magnetic resonance imaging scan demonstrated high signal areas in both cerebral hemispheres, the basal ganglia and the left cerebellar hemisphere. Cell markers in peripheral blood are shown in fig 1. Delayed type hypersensitivity skin tests were precluded by the presence of extensive warts.

There was a family history of optic atrophy affecting his maternal uncles, maternal grandmother, and three of her sisters and one brother. Analysis of his mitochondrial DNA showed a point mutation at a site different to that described by Wallace in classic Leber's optic neuropathy (Poulton et al, personal communication). Further studies are in progress.

**Laboratory investigations**

Results of immunological investigation are shown in table 1 and fig 1.

The results of chemical analyses are as follows: aspartate transaminase 99 IU/l (normal range 15–42); alkaline phosphatase 3379 IU/l (normal range 80–250); γGT 357 IU/l (normal range 15–40); bilirubin 194 μmol/l (normal range 3–17); calcium 2·09 mmol/l (normal range 2·1–2·6); plasma phosphate 1·0 mmol/l (normal range 0·8–1·45); sodium 142 mmol/l (normal range 135–145); potassium 4·3 mmol/l (normal range 3·5–5·0); urea 4·1 mmol/l (normal range 2·5–6·7); creatinine 90 mmol/l (normal range 70–150); uric acid 164 μmol/l (normal range 200–450); β2 microglobulin 2·5 mg/dl (normal range 0–3·0); caeruloplasmin 50·4 mg/dl (normal range 16–60).

The combination of a predominant defect in cellular immunity and hyponatraemia raised the question of purine nucleoside phosphorlyase (PNP) deficiency. Detailed metabolic studies of the purine and pyrimidine pathways were undertaken in conjunction with Dr Anne Simmonds, Guy's Hospital, London, which excluded PNP deficiency (table 2).

A liver biopsy specimen showed focal portal tract fibrosis with a mixed inflammatory cell infiltrate, in the absence of ductular dilatation, highly suggestive of sclerosing cholangitis.

A diagnostic cerebellar biopsy specimen showed very large, bizarre, multinucleate astrocytes (confirmed by a positive reaction for glial fibrillary acidic protein and negative reactions for leucocyte common antigen and epithelial markers). Immunofluorescence studies performed at the Virus Reference Laboratory, Colindale, showed the presence of polyoma JC virus. DNA hybridisation using probes for human papillomavirus (HPV) 1, 2, 3, 4, 5, and 6 were negative. Following the diagnosis of PML active treatment was considered inappropriate and he gradually deteriorated and died a few days later.

A limited post mortem examination confined to the head showed a swollen brain (1505 g; forebrain 1328 g) with some autolysis and obvious softening of the left cerebellar hemisphere. The large vessels looked healthy while the leptomeninges were diffusely thickened. Acute haemorrhage was noted in the softened white matter of the right parietal lobe.

**Histologically in all areas of the cerebrum there were multiple small and moderate sized lesions containing numerous enlarged oligodendrocyte nuclei with basophilic inclusion bodies typical of PML. Some lesions contained**

<table>
<thead>
<tr>
<th>Table 1 Immunology</th>
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<tbody>
<tr>
<td>IgG (normal range 6–13 g/l)</td>
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<tr>
<td>IgG1 (normal range 3·2–10·29 g/l)</td>
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<tr>
<td>IgG2 (normal range 1·2–4·6 g/l)</td>
</tr>
<tr>
<td>IgG3 (normal range 0·2–1·9 g/l)</td>
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<tr>
<td>IgG4 (normal range 0·0–1·3 g/l)</td>
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<tr>
<td>IgM (normal range 0·8–2·5 g/l)</td>
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<tr>
<td>IgG (normal range &lt;1·25 U/l)</td>
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<tr>
<td>C3 (normal range 65–180 mg/dl)</td>
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<td>C4 (normal range 15–50 mg/dl)</td>
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</table>

**Polymavirus serology**

<table>
<thead>
<tr>
<th>Serum</th>
<th>CSF</th>
<th>Ratio</th>
</tr>
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<tbody>
<tr>
<td>JC</td>
<td>1:320</td>
<td>1:32</td>
</tr>
<tr>
<td>BK</td>
<td>1:1280</td>
<td>1:5</td>
</tr>
<tr>
<td>Albumin (mg/dl)</td>
<td>3400</td>
<td>25</td>
</tr>
<tr>
<td>IgG (mg/dl)</td>
<td>890</td>
<td>73</td>
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ND = Not done

<table>
<thead>
<tr>
<th>Table 2 Red cell purine and pyrimidine studies</th>
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<tr>
<td>Nucleotide (μmol/l)</td>
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<tr>
<td>--------</td>
</tr>
<tr>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>Adenosine diphosphate</td>
</tr>
<tr>
<td>Adenosine monophosphate</td>
</tr>
<tr>
<td>Guanosine triphosphate</td>
</tr>
<tr>
<td>Guanosine diphosphate</td>
</tr>
<tr>
<td>Nicotinamide adenine dinucleotide</td>
</tr>
<tr>
<td>Nicotinamide adenine dinucleotide phosphate</td>
</tr>
<tr>
<td>Uridine diphosphate glucose</td>
</tr>
<tr>
<td>Ornithine</td>
</tr>
<tr>
<td>Enzymes (nmol/mg haemoglobin/h)</td>
</tr>
<tr>
<td>Adenine phosphoribosyl transferase</td>
</tr>
<tr>
<td>Hypoxanthine guanine phosphoribosyltransferase</td>
</tr>
<tr>
<td>Adenosine deaminase</td>
</tr>
<tr>
<td>Purine nucleoside phosphorylase</td>
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</tbody>
</table>
Figure 2  Cerebellar biopsy specimen hybridised with biotinylated JC virus specific nucleic acid probe. Dark nuclei of oligodendrocytes are those that contain virus (weak haematoxylin counterstain).

or were surrounded by astrocytes with bizarre enlarged nuclei as in the cerebellum. There was very little inflammation surrounding these areas except for increased numbers of reactive microglia. In situ DNA hybridisation for JC virus showed clear evidence of JC virus nucleic acid in many oligodendrocytes and in a minority of the bizarre astrocytes (fig 2).

Discussion
The combination of a predominant cellular immune deficiency, intractable viral infection, a low serum uric acid and a progressive neurological syndrome were suggestive of PNP deficiency. PNP is an important enzyme in the purine salvage pathway, deficiency of which leads to the accumulation of metabolites such as inosine, deoxyinosine, guanosine and deoxyguanosine which are toxic to lymphocytes (T’> B). This results in impaired cellular immunity with relatively preserved humoral immune function in the early stages. With disease progression, however, substantial humoral immune deficiency is seen. Clinically, these patients present with a history of recurrent or persistent viral infection (particularly varicella zoster or cytomegalovirus) and often develop a spastic diplegia.

PNP deficiency was, however, excluded by the demonstration of normal levels of PNP activity in erythrocytes. The demonstration of an abnormal red cell nucleotide pattern (table 2) along with three unidentified pyrimidine metabolites is intriguing and raises the question of a hitherto uncharacterised error in pyrimidine metabolism.

The predisposition of immune deficient patients to develop extensive warts is well documented. Brooks et al have recently described a kindred with an X-linked combined immunodeficiency where five living males manifested severe varicella, chronic papilloma- virus infection, and recurrent sino-pulmonary infection on a background of pronounced T cell lymphopenia, diminished lymphocyte proliferation to mitogens, decreased interleukin-2 production by mitogen stimulated lymphocytes and poor polysaccharide antibody responses, despite having normal total immunoglobulin concentrations.4 Our patient’s immune defect approximates closely to that described by Brooks. It would be interesting to see whether any of his patients go on to develop PML in the long term.

The recent description of primary combined immunodeficiency disorders due to defective expression of the T cell receptor complex (Ti-CD3) or impaired signal transduction in the presence of a normal Ti-CD3 complex has led to renewed interest in primary deficiencies of cellular immunity.5 Patients with the severe form of T cell receptor immunodeficiency present as severe combined immunodeficiency (SCID), but patients with the mild form may remain asymptomatic or manifest a moderate combined immunodeficiency.

Although our patient’s lymphocytes expressed normal amounts of CD3 on their cell surface, the possibility of defective signal transduction cannot be ruled out because Ti-CD functional studies were not carried out. To characterise these patients more completely it would be important to quantitate expression of the Ti-CD3 complex in addition to carrying out functional studies—delayed type hypersensitivity skin tests, lymphocyte transformation.

Despite clear evidence of impaired humoral immunity (low IgG2, poor polysaccharide antibody responses, bronchiectasis) in our patient it was felt that immunoglobulin replacement at this late stage would have been unlikely to influence the outcome. The benefits of immunoglobulin replacement in improving lung function have been proved in other antibody deficient patients. In contrast, immunoglobulin replacement is unlikely to have prevented or changed the clinical course of PML.

Serological surveys suggest that exposure to JC virus, the causative agent of PML, is fairly widespread. Although primary infection with the virus is not associated with an identifiable clinical syndrome, the virus may remain latent in the kidneys of some normal subjects until the onset of immunosuppression triggers reactivation. Mori et al have recently reported the detection of JC virus DNA in the brains of apparently immunocompetent elderly patients in the absence of PML, raising the possibility of viral latency in the brain as well.6 Since its initial description in 1958 PML has proved to be remarkably resistant to treatment in most patients. A recent report which documents partial therapeutic success with the use of prolonged cytarabine treatment in HIV positive patients with PML is therefore encouraging.

Glioma formation in immunosuppressed subjects with JC virus infection has been described.8 Although the bizarre, large, multinucleated astrocytes which were present in the
biopsy specimens from our patient closely resemble those described in the case reported by Castaigne et al, we are not convinced that these cells were part of a truly neoplastic lesion in our case. There was a cyst present in one affected cerebellar hemisphere but no obvious tumour mass was detectable at surgery or necropsy. We therefore regard the bizarre astrocytes, a few of which clearly contained JC virus nucleic acid, as falling at the extreme end of the well recognised spectrum of pleomorphic astrocytic change seen in PML.

The cause of our patient’s sclerosing cholangitis was unclear. Sclerosing and ascending bacterial cholangitis have been associated with campylobacter and cryptosporidial infection in patients with primary immune deficiencies. It has been suggested that bacterial overgrowth in the upper small intestine may be an important predisposing factor in these cases. Interestingly, primary sclerosing cholangitis in immunocompetent subjects has recently been associated with significantly increased titres of serum antibodies to JC and BK viruses. This raises the possibility that reactivation of polyoma virus may have been responsible for both PML and sclerosing cholangitis in our patient.

We thank Professor John Newsome-Davis FRS for permission to report this case. Drs Anne Simmonds and Paul Holloway kindly carried out the biochemical investigations. We thank Lynda Beckley for typing the manuscript.


Isolation of Legionella pneumophila serogroup 14 from a human source

M Castellani Pastoris, C Berchicci, G Pallonari

Abstract

A strain of Legionella pneumophila serogroup 14 was isolated during a retrospective study, after death from the spum of a patient who had had acute leukaemia and pneumonia. This is the third strain of that serogroup to be isolated from a human source. This event emphasises the importance of performing culture as well as serological tests, so as to detect cases of legionellosis caused by strains which rarely cause fatal clinical illness.

Since 1976, when a "new" micro-organism, Legionella pneumophila, was first isolated, 14 serogroups of this species have been described. All serogroups are potential pathogens for humans, but some seem to cause illness more frequently than others.

To our knowledge, only two human isolates of L pneumophila serogroup 14 have been described: one was isolated at the Minnesota Department of Health, Minneapolis, USA (strain 1109-MN-H); and the other was isolated at Ruchill Hospital, Glasgow, Scotland (strain 1586-SCT-H).

Case report

A 28 year old man in relapse of acute leukaemia after autologous bone marrow transplantation a year previously was admitted to hospital with a 10 day history of fever, followed by diarrhoea, epigastric pain, earache, and a white cell count of 7 × 10⁹/l. A chest x-ray picture was unhelpful. Laboratory examinations showed antibodies to hepatitis viruses A and B. The patient was initially treated with imipenem, and thereafter with teicoplanin and ceftazidime. After a positive blood culture for Candida pseudotropicalis vancomycin and amphotericin were added. He developed a scantily productive cough. Ceftazidime was replaced with piperacillin. A chest x-ray picture four days later showed the presence of confluent densities in the middle right and lower lobes and the left parahilar area. Antibiotic treatment was changed to imipenem and co-trimoxazole. Dyspnoea and peripheral cyanosis appeared the following day, and the
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Lesley Fallowfield serves as a timely reminder which should be essential reading for clinicians. Algorithms are discussed, but we would question their usefulness. The way to learn to diagnose malignant melanomas is to see them and to be taught about them in a clinical setting.

E HIGGINS
A DU VIVIER


The new Simmers volume on haematopathology is a brave attempt to encompass all you need to know about the subject in a little short of 1000 pages. The stage is set with a short introductory essay on basic immunology and this is followed by what is essentially a comprehensive textbook on the thymus. Three chapters are devoted to the normal lymph node and non-neoplastic lymphadenopathies and are followed by a chapter on the spleen which, curiously, hardly addresses lymphoma. The following chapter of some 350 pages, while entitled "neoplastic disorders of lymphoreticular tissue," deals essentially with lymph node neoplasms with only the occasional mention of extranodal lymphomas. A section on immunohistochemistry rounds off the haematopathology, but is followed by a quite irrelevant chapter on lymphatics which surely belongs elsewhere.

There is much to be commended in this book. With few exceptions, including the extranodal lymphomas referred to above, its coverage is encyclopaedic, it is comprehensively illustrated, and the index is unusually good. It is appropriately easy to use and, consequently, will be a useful bench book. The chapter on the thymus is especially valuable because there is no other comparable text on this subject. It is a pity, however, that the Müller-Hermelink classification of thymomas, although praised, is not used.

However, this book cannot be recommended to those seeking enlightenment about this difficult and sometimes controversial branch of pathology. The two short chapters at the beginning and end of the book, on basic immunology and immunohistochemistry, respectively, comprise the only gestures to "science". Molecular genetics, which has contributed so much to recent advances in our understanding of haematopathology, does not feature at all. It is, surely, inexcusable not to have mentioned immunoglobulin light chain restriction, CD10 positivity, immunoglobulin gene rearrangement and the t(14;18) translocation in the 25 pages and 42 illustrations devoted to follicular lymphoma. Pathologists are now much less exercised about the classification of non-Hodgkin's lymphomas than this book would suggest, having settled for either the working formulation or the updated Kiel classification. Developments in immunophenotyping and molecular genetics are beginning to stimulate new thoughts about lymphoma classification, but in this respect the book moves decisively backwards to the largely abandoned classification of the British National Lymphoma Investigation.

The publishers of this series have, for some reason, chosen to persist with the same dull format as that of the first (1966) edition. The illustrations are also rather flat and grey. The aim seems to be to present British pathology as a dignified, conservative descriptive discipline; this accentuates the faults of this book and masks its strengths. The authors deserve better.

P G ISAACSON

Notices

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Applicants with the MRCPath who would like to discuss and ascertain requiring a locum should contact The General Secretary, 221 Preston Road, Brighton BN1 6SA. Tel (0273) 561188. Fax: (0273) 541227.

Melanoma '93
A joint meeting of the Royal College of Pathologists and the Melanoma Study Group, sponsored by the South East Thames Regional Health Authority Quality Initiative.

6 and 7 May 1993,
Brighton Conference Centre

This two day consensus conference will address problems in the biopsy diagnosis of melanocytic disorders. As well as formal presentations by Bernard Ackerman (New York) and David Elder (Philadelphia), the programme will include presentations and discussions of professed cases and papers. Hotel accommodation and car parking will be available at discount rates. The conference takes place during the Brighton International Festival. A spouse programme will be available.

Further details are available from Dr N Kirkham, Dept of Histopathology, Royal Sussex County Hospital, Brighton BN2 5BE, UK. Fax: 0273-600182.

Corrections

An author's name was accidentally omitted from the list on a piece of correspondence: Current views on cervical neoplasia (J Clin Pathol 1992;45:643). We apologise to Dr R A Burnett.

In the same issue the legend of the following figure was incomplete (Misbah et al, J Clin Pathol 1992;45:624-7). The correct version is reproduced below:

Figure 1 Serial lymphocyte counts. Normal ranges: total lymphocytes (2.0-4.0) × 10⁹/l, CD3 (0.6-1.5), CD4 (0.4-1.0), CD8 (0.2-0.7), B cells (0.1-0.5).