

Lymphocytic Meningitis Following Insertion of a Porcine Dermis Dural Graft

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We describe a case of lymphocytic meningitis following insertion of a porcine dermis implant to repair an operative dural defect. Histology of the excised implant revealed local abscess formation with a granulomatous reaction. Oligoclonal Immunoglobulin G, part of which could be removed by absorption with the porcine dermis, was present in the patient's cerebrospinal fluid, and, to a less marked degree, in his serum. The cerebrospinal fluid glucose was markedly depressed. An unusual hypersensitivity reaction to the porcine implant was considered the most likely explanation for this meningitic illness. The patient went on to make a full recovery following excision of the implant.

KEY WORDS: Dura mater; Lymphocytic meningitis; Cerebrospinal fluid; Oligoclonal bands

A wide variety of materials have been used to repair spontaneous and operative defects in dura mater. These include pure gold (2), rubber (1), polythene (3), freeze-dried cadaveric dura mater (4), and pretreated porcine dermis (11). The last has been widely used with few reported complications. We describe an unusual case in which local abscess formation and a granulomatous reaction to a porcine dermis implant was associated with a subacute lymphocytic meningitis and an oligoclonal humoral immune response.

Case Report

A 33-year-old man, who was otherwise fit without any stigmata of neurofibromatosis, had a history of progres-

sive disturbance of his cervical spinal cord first beginning 10 years previously. A magnetic resonance imaging (MRI) scan showed a tumor compressing the cervical spinal cord (Figure 1 *a*): at cervical laminectomy this was found to be an intramedullary Schwannoma of segments C4-C6, which was extending outside the cord as a large polypoid mass. The extramedullary part of the tumor was excised leaving approximately one-third of the tumor within the cord. To provide a local decompression, we left the dura open widely and the defect was covered with a free Zenoderm Corium implant (supplied by Ethicon Ltd), approximately 10 × 3 cm in area. The patient made an uncomplicated initial recovery, with considerable improvement in his neurological signs, and was discharged home on postoperative day 10. Two weeks after surgery, when the postoperative steroids were discontinued, he developed some headache which cleared when the steroids were reinstituted for a further fortnight. He then remained well until 1 month later when he first complained of malaise, headache, night sweats, and fever, with brief visual obscurations and episodes of clouding and loss of consciousness. He had marked bilateral papilloedema. An MRI scan showed only the residual intramedullary tumor (Figure 1 *b*). The ESR was 10 mm/h, and there was a mild peripheral neutrophilia with normal total white cell count. At lumbar puncture, the cerebrospinal fluid (CSF) opening pressure was 36 cm with a lymphocytic pleocytosis, moderately elevated protein concentration, and reduced glucose concentration (Table 1). Gram and Ziehl-Neelsen stains of the CSF were repeatedly negative, and no bacterial or fungal organism could be cultured. CSF cytology on each occasion revealed a predominance of small lymphocytes, with occasional erythrocytes, monocytes, polymorphs, eosinophils, and plasma cells. There were no malignant cells. Blood cultures were negative on several occasions. Serological tests for syphilis, brucella, staphylococci, toxoplasma, histoplasma, coccidioides, mycoplasma, chlamydia, rickettsia, and a range of viruses were negative. Results of immunochemical analysis of CSF are detailed below.

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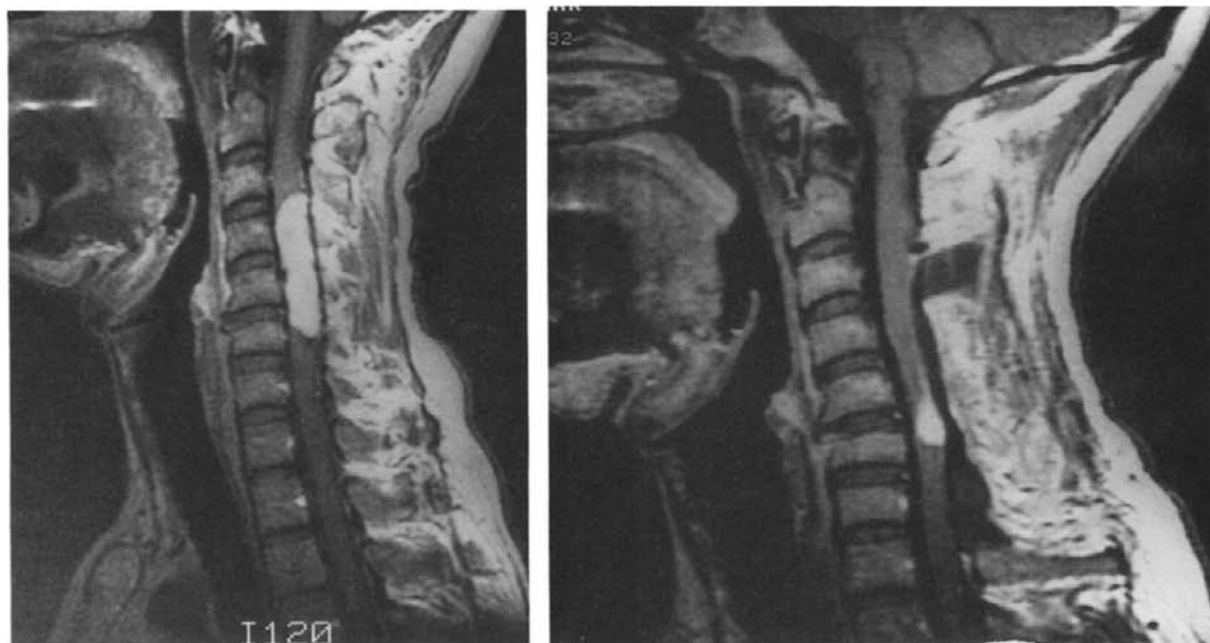


Figure 1. T1-weighted magnetic resonance images with gadolinium enhancement, sagittal views. (a) Before surgery, showing a large intramedullary tumor of the cervical spinal cord extending over segments C4-C6. (b) At 2 months after surgery, a small patch of residual tumor at C5-C6 level is evident. There is no extraaxial mass.

An allergic reaction to the porcine dural graft was suspected but as a precaution antituberculous therapy was instituted in combination with dexamethasone. The patient's symptoms, however, persisted. As the CSF pressure remained high a ventriculoperitoneal shunt was inserted 4 months following the initial surgery. At 2 weeks later, in view of a persistent swinging fever with head and neck pain, and lymphocytic CSF, his original wound was reexplored. At the level of the dura, in the vicinity of the dural graft, we encountered a cavity filled with yellow pus and lined with fragmented xenoderm. There was no engorgement or vascularity of the adjacent tissue of the kind usually associated with infection. The pus and Xenoderm were removed, and the cavity was

irrigated with antibiotics and hydrogen peroxide. The pus proved sterile on culture.

The patient's condition improved immediately following surgery. During the following 4 weeks, he was treated with broad-spectrum antibiotics as his fever recurred intermittently with persistence of a lymphocytic CSF. Thereafter his condition steadily improved. He left hospital 4 weeks after surgery, and 3 months later was symptom free, leading a normal life, and working full time. An MRI scan performed in October 1992, 18 months after excision of the xenoderm graft, showed no change by comparison with the MRI scan illustrated in Figure 1b which had been performed in January 1991, 2 months after the patient's original surgery.

Histology

Histology of the excised graft revealed areas of granulomatous inflammation containing fragments of Xenoderm, macrophages, giant cells, lymphocytes, and plasma cells, and small numbers of neutrophils. These areas

Table 1. Cerebrospinal Fluid Results

	March 21, 1991 (Lumbar)	March 27, 1991 (Lumbar)	April 2, 1991 (Lumbar)	April 3, 1991 (Ventric)
Leucocytes ^a	320	347	138	61
Erythrocytes	10	6	10	945
Protein (g/l)	1.6	1.5	1.3	0.9
Blood glucose (mmol/l)	6.3	9.3	Not done	Not done
CSF glucose (mmol/l)	0.4	1.5	1.4	3.2

Abbreviations: ventric, ventricular.

^a Predominantly lymphocytes: see text.

abutted pockets of acute inflammatory slough containing fragments of Zenoderm, cell debris, and occasional intact inflammatory cells. Where the graft remained intact, it had excited a hypocellular fibrous reaction (Figure 2 *a*). Under polarized light, the graft exhibited birefringence (Figure 2 *b*). The identity of the tissue fragments visible within areas of granulomatous inflammation (Figure 2 *c*) was confirmed by their birefringence under polarized light (Figure 2 *d*).

CSF Immunochemistry

We demonstrated oligoclonal bands (OCBs) of Immunoglobulin G (IgG) in both CSF and serum using isoelectric focusing, as previously described [8], in two sets of samples. The OCBs were more numerous and intense in CSF than in serum, suggesting the occurrence of both an intrathecal and a systemic oligoclonal response [12]. Screening of the CSF samples against a panel of common CNS pathogens (herpes simplex, varicella zoster, cytomegalovirus, rubella, mumps, measles, mycobacterium tuberculosis, *Treponema pallidum*) using an ELISA assay [9], and subsequent antigen-specific immunoblotting [10] revealed the presence of antibodies apparently directed against all the antigens tested. However, the affinities of these antibodies against mycobacterium tuberculosis and measles virus [assessed using sodium thiocyanate elution [9]] were extremely low, suggesting that these antigens were not, in fact, the primary target of the antibody response. Incubation of the patient's CSF with powdered porcine dermis (Zenoderm Corium implant kindly supplied by Ethicon Ltd) prior to isoelectric focusing led to the disappearance of three of the original OCBs (Figure 3) indicating that some of the oligoclonal antibody present may have been directed against antigens in the porcine dermis. By contrast, incubation of CSF samples containing numerous OCBs (from four control patients with multiple sclerosis) with the powdered dermis had no effect on the patterns observed.

Discussion

Pretreated porcine dermis has proved to be a very satisfactory material for repairing tissue defects in a wide variety of sites, including dura mater [11]. The dermis is treated with a proteolytic enzyme to remove noncollagenous elements, and the collagen is cross-linked with glutaraldehyde to increase its strength. It is subsequently cut to an appropriate thickness for a variety of applications, freeze- or air-dried, and sterilized by gamma irradiation. It must be reconstituted in normal saline before use. A previous study of its use as a dural substitute in 72 patients did not encounter a single inflammatory reaction attributable to the graft material itself [11].

Johnson et al [7] reported a case of subacute lymphocytic meningitis similar to ours occurring 6 months after the insertion of a lyophilized cadaveric dural graft in the course of a posterior fossa decompression. Histology of the excised graft revealed perivascular inflammation within the grafted tissue with some foreign body giant cells. Polyacrylamide gel electrophoresis of the patient's CSF suggested the occurrence of intrathecal IgG synthesis. The patient made an excellent recovery following removal of the graft.

Inflammatory complications may also occur long after the insertion of dural grafts. Cohen et al [5] described a chronic fibrotic inflammatory response to a polypropylene mesh graft causing symptoms identical to those with which the patient had been admitted to hospital 20 years before. The inflammatory mass was reproducing the effects of the convexity meningioma which had been identified and excised on her first admission.

We are not aware of any previous reports of lymphocytic meningitis following the use of porcine dermis as a dural substitute, although anecdotal accounts suggest that minor inflammatory reactions may not be uncommon. These usually respond to oral corticosteroids (R. Maurice-Williams, personal communication). We cannot absolutely exclude the possibility that a microorganism was responsible for our patient's illness, but a number of features suggest that the illness was the result of a delayed hypersensitivity reaction to the porcine graft: no organism was identified despite repeated microscopy, culture, and serological studies; the predominantly lymphocytic CSF response was more in keeping with granulomatous inflammation than with a postoperative bacterial infection; the histology of the excised dural graft indicated a more intense chronic inflammatory reaction than would normally be expected in a foreign body granuloma; the disappearance of at least some OCBs following incubation with the graft material raised the possibility that the immune response was directed against the graft; finally, the patient made a full recovery over a few weeks following removal of the graft, after 10 weeks of chronic meningitis which had persisted despite treatment with rifampicin, isoniazid, and steroids.

It is of interest that experimental studies of the host tissue response to implantation of Zenoderm into rat muscle reveal an early macrophage response, with a peripheral lymphocytic infiltrate by 90 days (I. Capperlaud, personal communication). Our patient's response to the implant, with granulomatous inflammation and CSF lymphocytosis, appears to have been similar in kind to, but much more marked in degree than, the response seen in experimental animals.

The depression of the lumbar CSF glucose in our patient was striking but it is well recognized that this may occur in chemical meningitis as well as in bacterial,

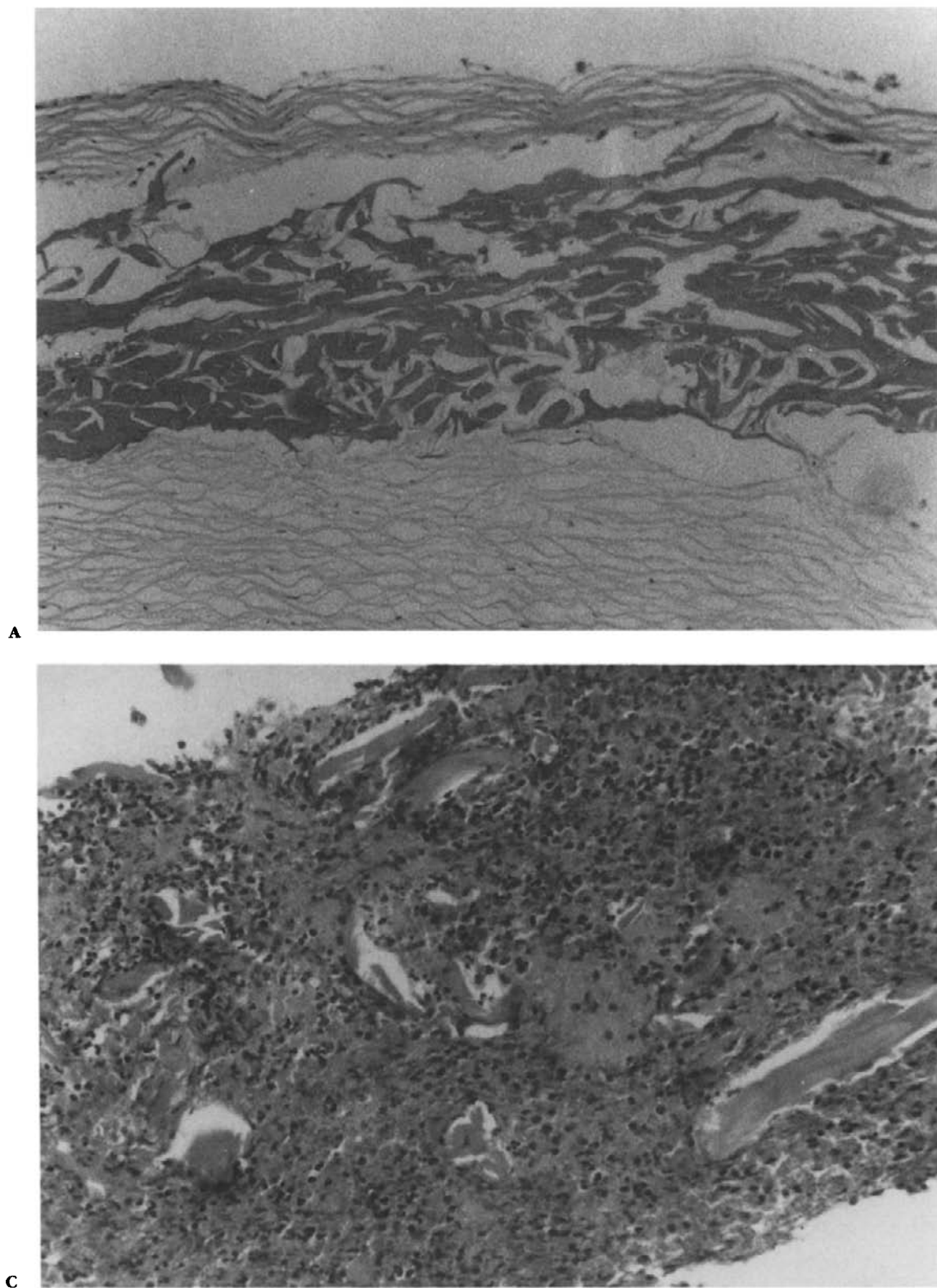
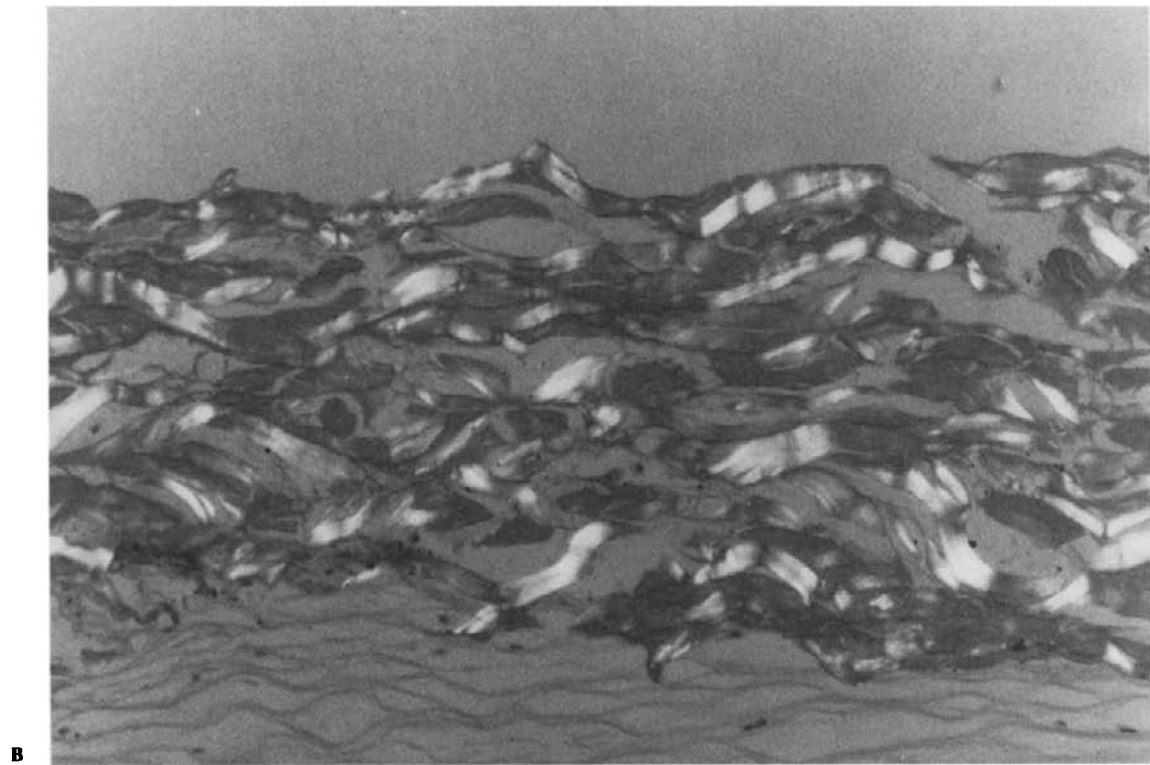


Figure 2. (A) The Zenoderm graft is surrounded by hypocellular fibrous tissue in an area relatively free of inflammation ($\times 100$). (B) Zenoderm another region of the excised tissue ($\times 190$). (D) The identity of the tissue fragments in Figure 1c is confirmed by their birefringence under polarized



from the same area shows birefringence under polarized light ($\times 190$). (C) Granulomatous inflammatory tissue surrounds fragments of Zenoderm in light ($\times 190$).

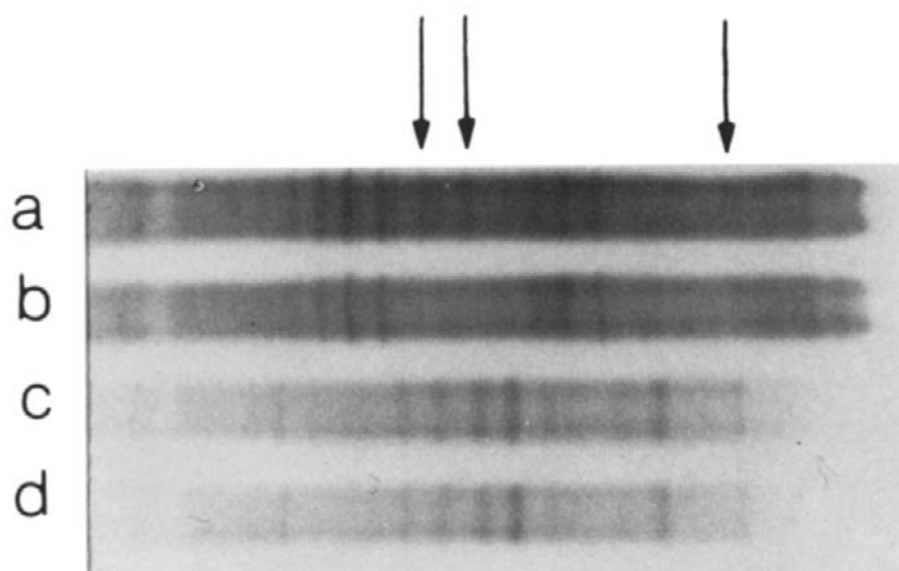


Figure 3. Oligoclonal bands of immunoglobulin G separated by isoelectric focusing, and visualized by immunoblotting, from the cerebrospinal fluid of the patient (lanes *a*, *b*) and a control (lanes *c*, *d*). Lanes *a* and *b* show the oligoclonal bands in untreated cerebrospinal fluid; lanes *b* and *d* show the bands following absorption with powdered Zenoderm. The arrows mark bands that disappear from the patient's native cerebrospinal fluid (lane *a*) following absorption with Zenoberm (lane *b*).

fungal, and other idiopathic inflammatory diseases of the meninges [6]. The case may, however, offer an exception to the general rule that "localized" meningitis does not lower CSF glucose [6].

Although the evidence of a single case is necessarily inconclusive, we suggest that porcine dermis may provoke a damaging immune response when it is used as a dural substitute. Such a response is clearly most unusual, and our case does not provide grounds for advising against the neurosurgical use of pretreated porcine dermis. However, the possibility of a hypersensitivity reaction should be considered in patients who develop lymphocytic meningitis following its insertion. It should be included among the many causes of such meningitis and of the mixed "systemic-intrathecal" pattern of oligoclonal bands of IgG.

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