Reconstruction of extensive nerve defects is hampered by the amount of autogenous nerve tissue available for transplantation and by donor site morbidity. Nerve allografts, being of foreign origin and potentially unlimited in supply, provide a solution to these problems. Studies have shown that nerve allotransplants require immunosuppression only until end-organ connections are made and that immunosuppressant therapy may be subsequently discontinued with no negative effect on functional outcome. Also, recent experimental and clinical focus has been on shorter periods of immunosuppression in order to reduce risk, even stopping immunosuppression after regeneration has reached the distal suture line rather than before recovery of end-organ connections. In the pediatric population, the increased disease burden and increased potential for nerve regeneration as well as the frequent availability of a living related donor make allografts all the more attractive as solutions to nerve reconstructive problems. Nevertheless, the risks of immunosuppression must not be underemphasized, and they deserve more attention in the current nerve transplantation literature.

The authors report on a child who, at the age of 1 year, received a nerve allograft from a living related donor who was positive for Epstein–Barr virus (EBV). The child quickly developed a symptomatic EBV infection concurrent with immunosuppressant drug therapy. The immunosuppression regimen was stopped prematurely, and the patient suffered only a short illness, but the EBV infection could have developed into a life-threatening posttransplant lymphoproliferative disorder (PTLD). The patient is consequently predisposed to develop PTLD and will have to be monitored for the rest of his life. This case highlights the importance of considering the potentially fatal risks associated with this elective procedure. Future studies are needed to quantify and minimize this complication. Nevertheless, it should be weighed against the potential functional benefit from using nerve allografts.

**KEY WORDS** • obstetric brachial plexus palsy • nerve allograft • Epstein–Barr virus infection • posttransplant lymphoproliferative disorder

Abbreviations used in this paper: CMV = cytomegalovirus; EBV = Epstein–Barr virus; Ig = immunoglobulin; PCR = polymerase chain reaction; PTLD = posttransplant lymphoproliferative disorder.
The EBV-induced PTLDs are a heterogeneous group of lymphoproliferative disorders associated with EBV infections; they develop as a consequence of immunosuppression in solid organ and bone marrow transplant recipients. The associated mortality rates are 60% in solid organ recipients and 80% in bone marrow recipients. Several risk factors for developing PTLD have been identified. Treatment with OKT3 (an anti-CD3 monoclonal antibody) and a serum mismatch (a negative recipient and a positive donor) for both CMV and EBV have been shown to synergistically increase the incidence rate of fatal PTLD by a factor of 654.

No case of EBV infection in a nerve transplant recipient has been reported in the literature to date. In the largest published review of a case series, the authors report on seven patients who underwent nerve allograft transplants, including one who experienced severe rejection, but they do not mention EBV serostatus or the danger of PTLD. Currently, surgeons at several centers are performing nerve transplantation using grafts from cadavers or living related donors.

The first case report describing nerve transplantation using an allograft from a living related donor was published in 1999; in this case, radial and ulnar nerve segments were transplanted from a man who had been declared brain dead shortly after he experienced an ischemic brain incident, to his daughter, who had suffered an obstetric injury to the upper extremities. The report primarily describes the consent and organ procurement process and does not mention EBV or CMV serostatus of the donor or the recipient.

A more thoroughly reported case was published recently: the recipient was an 8-month-old male infant with global obstetric brachial plexus palsy, and he was treated by cross-cast C-7 nerve transfer using sural nerve grafts from his mother. The results of both the donor’s and the recipient’s serological studies were negative, excluding the possibility of direct EBV transfer. Other infectious complications were not reported. The patient was treated with FK-506 from 1 week prior to transplantation. The dosage was gradually tapered every 6 months for the first year and maintained at a certain level after 1 year until discontinuation (total time not specified). No clinically significant functional improvement was observed as a result of the transplant. Other reports of nerve allografts from living related donors have appeared in the lay literature, but they are less well documented.

We report the case of a young child who developed a symptomatic EBV infection after receiving a nerve allograft from his father, who was EBV positive. Immunosuppression therapy was stopped prematurely, and the patient suffered only a short illness, but because he is now predisposed to developing PTLD, he will require lifelong monitoring. This case highlights the importance of considering the potentially fatal risks associated with this elective procedure, and with it we wish to give a word of caution to those who consider using this technique, which has recently been popularized in the lay and medical literature.

**Case Report**

This 5-year-old boy was referred to the Mayo Clinic brachial plexus team in July 2003 for a second opinion regarding a birth injury to the right brachial plexus that had resulted in a flail arm. The patient had a complicated history, including three surgeries that had been performed elsewhere. The first, which he underwent at 6 months of age, when he had begun to recover some biceps function, was a brachial plexus exploration. At 1 year of age, in April 1999, having recovered little additional function, he underwent a contralateral C-7 neurotization to the median nerve. This procedure was performed using a sural nerve allograft from his father, an EBV-positive, CMV-positive, kidney transplant recipient. At the age of 2 years and 6 months, the child underwent a tendon transfer procedure for shoulder abduction.

Postoperative immunosuppression had been instituted after the allograft procedure in April 1999, and the child was followed up immediately thereafter at the Mayo Clinic. The regimen consisted of prednisone, FK-506, and azathioprine (Imuran, GlaxoSmithKline). (Information concerning the dosages is no longer available.) Prednisone therapy was discontinued after 12 weeks and treatment with the other two immunosuppressive agents was continued until late July of 1999. At that time, treatment with these medications was discontinued because the patient developed a fever of 4 weeks’ duration that was associated with lymphocytosis and neutropenia (Table 1).

The patient’s blood values stabilized at the end of August, and FK-506 treatment was begun again at one half the regular dose. One week later, it was discontinued due to recurrence of lymphocytosis and neutropenia. Because of the time course of the patient’s symptoms and the degree of neutropenia during FK-506 therapy, an extensive blood workup was performed in September of 1999. The results showed elevated anti–Epstein Barr viral capsid antigen IgG and IgM levels and the absence of Epstein–Barr nuclear antigen antibodies. Together these results show a recent infection. The patient’s EBV status had not been tested prior to transplantation. The presence of viral DNA was found by PCR amplification of blood-derived DNA. Southern

**TABLE 1**

<table>
<thead>
<tr>
<th>Date†</th>
<th>FK-506</th>
<th>WBC</th>
<th>CBC, Differential, &amp;/or Platelet Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 11</td>
<td>yes</td>
<td>12,800</td>
<td>NA</td>
</tr>
<tr>
<td>May 26</td>
<td>yes</td>
<td>8,400</td>
<td>NA</td>
</tr>
<tr>
<td>July 23</td>
<td>yes</td>
<td>4,000</td>
<td>NA</td>
</tr>
<tr>
<td>July 25</td>
<td>yes</td>
<td>3,600</td>
<td>NA</td>
</tr>
<tr>
<td>July 26</td>
<td>stopped</td>
<td>July 26</td>
<td>50% atypical lymphocytes, differential 77% lymphocytes, 206,000 platelets</td>
</tr>
<tr>
<td>Aug 16</td>
<td>none</td>
<td>13,700</td>
<td>84% lymphocytes</td>
</tr>
<tr>
<td>Aug 23</td>
<td>half dose</td>
<td>13,400</td>
<td>NA</td>
</tr>
<tr>
<td>Aug 30</td>
<td>half dose</td>
<td>Aug 24–30</td>
<td>11,900</td>
</tr>
<tr>
<td>Sept 7</td>
<td>none</td>
<td>10,700</td>
<td>73% lymphocytes</td>
</tr>
<tr>
<td>Sept 13</td>
<td>none</td>
<td>6,600</td>
<td>91% lymphocytes</td>
</tr>
<tr>
<td>Sept 27</td>
<td>none</td>
<td>10,000</td>
<td>68% lymphocytes</td>
</tr>
</tbody>
</table>

* Aug = August; CBC = complete blood count; NA = not available; Sept = September; WBC = white blood count.
† All in 1999.
The immuno-

A recent experiment using cold-preserved allo-

In the mouse model, axonal re-

In our patient, the time

In the absence of other risk factors, PTLD

Nevertheless, during the clinical

Even in life-threatening conditions,

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Furthermore, cold preservation in University of

Despite

19

Pa-

In the first report of a

The uncontrolled expansion of a pool

FK-506.

that of isografts, suggesting a nerve regenerative effect for

That FK-506 was associated with partial

16

2

23

926

Discussion

Among composite tissue allografts, nerve allografts are

unique in progressively losing their antigenic stimulus as

they pass through a chimeric state to eventually being com-

posed of host tissue containing no donor allogeneic cells.

This quality theoretically allows for their application with a

limited period of immunosuppression.1,22,24,25 The immuno-

suppression dosage required for graft survival is unrelated to

the quantity of nerve tissue transplanted, supporting the

safety of this approach in particularly large nerve defects.27

Additionally, studies in nonrodent animal models have

proven the potential for nerve allografts to bridge long gaps

more closely resembling lesions encountered in clinical

practice.2,27 Furthermore, cold preservation in University of

Wisconsin cold-storage solution has been shown to work

synergistically with FK-506 to reduce the required duration of

immunosuppression.21 In the mouse model, axonal re-
geneneration of cold-preserved nerve allografts during treat-

ment with FK-506 has been shown to be superior even to that of isografts, suggesting a nerve regenerative effect for

FK-506.22 A recent experiment using cold-preserved allo-
grafts seeded with autologous Schwann cells allowed sig-
nificant regeneration across a 6-cm peripheral nerve gap in

primates not treated with immunosuppression.16 Despite

these results, however, the short 2-month course of FK-506

in primate allograft models was associated with partial

nerve rejection and inferior electrophysiological results

when compared with autograft controls.3,17

The significant health risks posed by the use of immuno-
suppressant drugs and the ethical issues surrounding the

use of composite tissue allografts for the treatment of con-
ditions that are not life threatening have been expounded in

previous papers.3,8 Even in life-threatening conditions,

composite tissue transplantation and the use of immuno-
suppression may add unwarranted risk, such as recurrence

or metastasis after tumor resection and reconstruction, and

the question of whether a procedure will truly benefit the

patient looms large.6 Strong support for the position of

nerve allografts in the hierarchy of reconstructive options

comes from their successful use in a number of clinical

cases. Several large peripheral nerve reconstructions with

allografts or a combination of allograft and autograft cables

have been reported recently.21–23 In contrast to attempts

made before the advent of modern microsurgical tech-
niques, immunosuppression, tissue matching, and pretreat-
ment methods, these recent efforts have resulted in verifi-
able recovery from long sciatic, ulnar, median, and tibial

nerve defects. According to the authors of these reports, the

risk–benefit balance favors the clinical application of this

technique, at least in the pediatric population, given that

these young patients theoretically have the most to gain

from a reduction in disease burden.22 In the first report of a

case of a nerve allotransplant from a living related donor,

this point is stressed, and other potential uses are men-
tioned, including spinal cord reconstruction and treatment

of degenerative neurological disorders such as dementia

and multiple sclerosis.7 Nevertheless, during the clinical

follow up in our case, as in a recently published case of a

nerve allotransplant from a living related donor,14 little or

no functional improvement attributable to the nerve allo-

graft could be observed.

Epstein–Barr virus infection in the setting of immuno-
suppression can present as an asymptomatic infection or

nonspecific viral syndrome and can result in PTLD. The

lymphoproliferation seen in these cases differs clinically and

histologically from the lymphoma that is seen in non-

immunosuppressed patients.10 Impairment of the cytotoxic

T-cell response to EBV-infected cells is thought to be the

main mechanism through which EBV-driven B-cell pro-

liferation occurs.32 The uncontrolled expansion of a pool

of EBV-infected B lymphocytes predisposes to cloning of

mutations and development of neoplasm.39 The clinical

presentation of PTLD is variable, ranging from a mononu-
cleosis-like syndrome to a true lymphoma, with lesions af-

fecting lymphoid organs or developing ectopically.30 Pa-

tients may respond to decreased immunosuppression, the

gold standard for initial treatment.28–30

Pediatric patients have an increased risk of developing

PTLD due to their relative underexposure to EBV, with 60

to 80% of pediatric patients who undergo transplantation

not yet having been exposed to EBV at the time of the pro-

cedure.28,30 In the absence of other risk factors, PTLD

occurs 24 times more frequently in seronegative recipients

than in seropositive recipients.39 In our patient, the time

course of immunosuppression and diagnosis of EBV infec-
tion with disproportionately severe symptoms are highly

suggestive of a causal relationship. With respect to solid

organ transplantation, several lines of evidence, including

HLA typing, sex chromosome analysis, minisatellite DNA
Nerve allograft with EBV infection

analysis, restriction fragment polymorphism DNA analysis, DNA fingerprinting, in situ hybridization, and PCR amplification, indicate that the origin of PTLD is usually in the recipient rather than the donor.26

Unfortunately, EBV PCR analysis was not available at the time of our patient’s transplantation procedure, so EBV viremia could not be evaluated by that method, nor was a tissue biopsy performed. A tissue diagnosis was not clinically indicated. Still, the body of evidence from solid organ transplantation demonstrates that the results of serological testing are positive for EBV in over 95% of early PTLD cases.11,12 In developed countries, primary infection with EBV most commonly occurs in early childhood and is generally asymptomatic or only mildly symptomatic.18 We therefore deduce that seroconversion took place in our patient around the time of nerve transplantation and initiation of FK-506 treatment. The source of the virus was almost certainly the nerve allograft. Other support is provided by the improvement in the results of the patient’s laboratory tests after cessation of immunosuppression therapy. Although the diagnosis of PTLD was not established in this patient, progression of the EBV infection was avoided by discontinuing immunosuppression.

The management of postransplant EBV complications is complex, but usually involves reduction of immunosuppression therapy as a first step. In most cases of PTLD, the B-cell epitope CD20 is expressed by the tumor cells, permitting the use of mouse anti-human CD20 antibody (rituximab) as an effective treatment.32 Although mortality rates have decreased, the overall incidence of PTLD has remained at 5 to 15% in most series.33 Early diagnosis is associated with a better prognosis, and therefore awareness of the clinical presentation of this condition is crucial. The most common symptoms are fever and impaired general condition, sore throat, hepatic or splenic enlargement, poor appetite, and weight loss.30 Our patient presented with the first four of these signs. Diagnosis of an EBV infection is confirmed by quantitative EBV PCR analysis of a blood sample—also used for viral load monitoring, in conjunction with a determination of tumor type and clonality, in cases in which tumors are detected, ideally by examination of a biopsy specimen.30 An excision biopsy would serve both diagnostic and therapeutic purposes.

A patient’s lifetime risk of PTLD is related to his or her EBV status and age at transplantation, the type of organ transplanted, and the duration of follow-up.26 The reported range of risk is from 0.5% in renal transplantation to 24% in T-cell depleted allogeneic bone marrow transplantation; PTLD does not occur sporadically.15,26

It is important to consider seronegativity for EBV as a risk factor for PTLD prior to performing surgery. It has been recommended that in cases in which initial EBV antibody profiles are incomplete, patients be retested prior to transplantation.33 Also, seroconversion in patients who were positive before surgery may be pathognomonic for PTLD, and the absence of seroconversion in a seronegative patient known to have received an organ from a seropositive donor may be a predictor of more serious PTLD.33 Asymptomatic viral replication can be detected by PCR analysis, allowing preemptive reduction of immunosuppression, which may prevent the progression to PTLD.20

The use of allografts that require short-term immunosuppression in the treatment of disorders that are not life threatening entails risks to the patient that include life-threatening disorders such as PTLD. These risks have been inadequately addressed in the literature to date on nerve transplantation. Outcome studies of clinical nerve allograft transplantation are needed to assess the safety and efficacy of the procedure in the light of the potential risks of immunosuppression. We suggest that, at the least, a pretransplantation assessment of the risk of PTLD should be performed by testing the EBV and CMV serostatus of the nerve recipient and donor.33 On the basis of the large body of evidence in solid organ transplantation, we conclude that very young patients who undergo this new allograft transplantation procedure are at some risk for EBV-related complications.11,12 Nevertheless, the unknown risk of viral transmission needs to be weighed against the potential for functional benefit from the nerve allograft. Future studies are necessary not only to quantify but also to minimize this complication.

References


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