CASE REPORT

Bilateral Inflammatory Optic Neuropathy Related to Graft versus Host Disease Following Allogeneic Bone Marrow Transplantation for Hodgkin Disease

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ABSTRACT

Graft versus host disease (GvHD) is a common and often troublesome complication of allogeneic bone marrow transplantation. Neurological complications usually involve the peripheral nervous system and muscle, but the central nervous system may be affected. When an optic neuropathy develops, it is often difficult to determine the cause quickly; infective complications and drug toxicity may have arisen, but an inflammatory disorder due to GvHD should also be considered, particularly since treatment with steroids and immune suppression may improve the outcome significantly. This brief case report shows how this may be the case and reviews our current understanding of the pathophysiology and treatment of the disorder within the nervous system.

Keywords: Graft versus host disease, optic neuropathy, optic neuritis

CASE REPORT

This female patient presented at the age of 21 with stage IIA Hodgkin disease and was treated with four cycles of ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, and dacarbazine), followed by involved-field radiotherapy. Her condition improved radiologically, but recurrence was identified in the right hip 11 months later. This was treated with local radiotherapy; however, further investigations revealed more a widespread relapse throughout the skeleton, and she underwent further chemotherapy with DHAP (rituximab, dexamethasone, cytarabine, and cisplatin), which was complicated by the development of renal failure in the first cycle. Following recovery from this, she received high-dose BEAM chemotherapy (carmustine, etoposide, cytarabine, and melphalan), followed by an autologous stem cell transplant that was successful.

She remained well and disease free for 4 years before presenting with relapse in the abdomen and ribs. She received four cycles of gemcitabine, carboplatin, and dexamethasone with a radiological

response. She was referred to the Royal Free Hospital for consideration of further therapy, and after a computed tomography/positron emission tomography (CT/PET) scan had shown disease remission, she underwent a stem cell transplant from her human leucocyte antigen (HLA)-identical sister after conditioning with Campath, fludarabine, and melphalan. Following transplant she developed headaches, and brain imaging and cerebrospinal fluid (CSF) analyses were normal. She was taking cyclosporin A 125 mg per day and infection prophylactics.

The early post-transplant period was unremarkable aside from a protracted herpes simplex infection. Her immunosuppression was reduced, and a CT/PET showed no sign of disease 3 months after transplant. Her immunosuppression was stopped.

Six months after transplant, she received an infusion of donor leucocytes for mixed chimerism and shortly afterwards presented with a skin rash that was considered to be typical of that seen in graft versus host disease (GvHD). This was treated with oral then intravenous (IV) prednisolone and was slow to settle. Topical tacrolimus was added, then cyclosporin A

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reinstated. Her skin improved, but she developed breathlessness and was found to have bronchiolitis obliterans due to GvHD of the lungs. She was treated with high-dose steroids and cyclosporin A 160 mg b.d. Her condition stabilised with chronic GvHD, and there were repeated episodes of culture and serologically proven bacterial and fungal lung infection and herpes simplex of the oropharynx and oesophagus. It was decided a year after transplant to change from cyclosporin A to oral tacrolimus, mycophenolate, and rituximab. She improved and stabilised, and a CT/PET scan 16 months after transplant showed no recurrent disease. Two years after transplant, she was adjudged to be well. She remained in her home country and suffered repeated lung infections requiring intermittent intensive care for breathing support.

In November 2011, 4½ years following transplant, she developed a subacute, painless visual loss to no perception of light over 10 days. An ophthalmic examination in her home country was said to be normal. A magnetic resonance imaging (MRI) scan of the brain was normal, and a spinal fluid examination showed normal protein, cell count, and sugar differential. She was treated with methylprednisolone 500 mg and intravenous immunoglobulin 5 mg/kg without benefit. She was referred back to the Royal Free Hospital 3 months later.

On examination her acuities were perception of light with very depressed fields (Figure 1a), no colour vision, and slightly pale discs. The ocular mediae were clear.

Imaging was repeated and showed non-enhancing high-signal lesions within both optic nerves, no mass and no significant sinus disease, and no white matter lesions (Figure 2). The CSF showed no cells, a normal glucose differential, protein 0.23 g/dL, and matched oligoclonal bands. Serological tests against various herpes viruses, *Brucella*, *Borrelia*, *Cryptococcus*, and JC papovavirus and fungal antigens were negative, and tests for connective tissue diseases and vasculitis were negative (aside from a positive antinuclear antibody [ANA]). The serum antigen-converting enzyme (ACE) was normal. No antibody to aquaporin 4 was detected.

It was decided that the patient had an inflammatory optic neuropathy and a trial of high-dose (3 g) intravenous methylprednisolone was administered. This was associated with an improvement in her acuities and an enlargement of the visual field (Figure 1b). The dose of mycophenolate was increased to 3 g per day. Two further courses of 3 g methylprednisolone were prescribed, and the visual field improved further, with a final central visual acuity of 6/24 right, 6/36 left.

Six weeks later, she developed a painful red eye and was found to have an infiltration of multiple white patches of inflammation within the corneal stroma. There was no stromal vascularization or

anterior uveitis. Viral, bacterial, and fungal conjunctival cultures of corneal epithelium were negative. A keratitis related to her GvHD was diagnosed and resolved with topical dexamethasone and hypromellose drops, leaving a keratoconjunctivitis sicca requiring frequent administration of ocular lubricants.

DISCUSSION

We consider GvHD to have been the cause of the optic neuropathy. GvHD is a common and potentially life-threatening complication of bone marrow transplantation. It arises when donor T cells induce an immune response following activation by the host antigen-presenting cells, leading to inflammation and destruction of the tissue involved. It is a major cause of morbidity and mortality following bone marrow transplantation. In the chronic form, which may arise at any time following transplantation, the skin, eyes, liver, gastrointestinal (GI) tract, and lungs are affected most often, and shows distinctive clinical differences to the acute form.¹ This patient had continuing GvHD of the lungs and skin at the time of presentation.

Ocular involvement is usually limited to the anterior segment, with the development of a keratoconjunctivitis sicca in the majority of cases, with advanced and untreated cases developing secondary keratitis, ulceration and epithelial defects, and stromal scarring. Fifty percent are thought to develop ocular problems, with some 16% going on to develop chronic GvHD in a recent series.²

GvHD of the nervous system is not uncommon, particularly in the acute phase, in which it may be a feature of 40–50% of cases,³ but it is less prevalent in the chronic form. Involvement of the muscles and peripheral nervous system occurs, with myositis, a demyelinating peripheral neuropathy, isolated mononeuropathies, and a polyradiculoneuropathy resembling Guillain-Barré syndrome.⁴ A syndrome resembling myasthenia gravis may be seen.

Involvement of the central nervous system is less well characterised, with reports of cerebral vasculitis leading to stroke-like episodes, acute disseminated encephalomyelitis (ADEM), and a relapsing-remitting disease indistinguishable from multiple sclerosis.⁵ The neuropathology of this disorder is of an inflammatory infiltration with lymphocytes and plasma cells, of donor origin, and, in more florid cases, vessel wall necrosis in keeping with a vasculitis is seen.^{6,7} In these cases, treatment with steroids and immunosuppression led to neurological improvement and stabilisation in 3 of a series of 4 cases.⁷ A recent study from Memorial Sloan Kettering⁸ showed that of 1484 patients undergoing allogeneic stem cell transplants over an 18-year period, 7 developed neurological complications; 3 had ADEM and 4 had an

FIGURE 1. Visual fields (a) at presentation and (b) after 9 g intravenous methylprednisolone.

FIGURE 1. Continued.

FIGURE 2. MRI: coronal STIR showing high signal in both optic nerves.

inflammatory neuropathy. Those with ADEM each showed inflammation within the brain and spinal cord; biopsy in 2 cases showed demyelination with a heavy macrophage infiltration, although a less evident perivascularitis. The authors postulated that the absence of an inflammatory response meant that the disorder was a separate immunological phenomenon to GvHD of the nervous system.

Optic neuritis has been noted rarely in previous reports. A case reported by Matsuo et al.⁹ described a patient with a relapsing inflammatory illness of the nervous system that began with a unilateral optic neuritis before involving the other optic nerve, the brain, and spinal cord, and stabilised with steroids and cyclosporin A. Openshaw et al.¹⁰ described two patients with myelopathy, one of whom developed an optic neuropathy during steroid withdrawal.

An alternative explanation for the disorder is a toxic optic neuropathy related to medication; calcineurin inhibitors have been shown previously to be associated with neurological complications; the majority of case reports show a progressive, painless optic neuropathy that is bilateral.^{11–17} It follows transplantation of bone marrow, heart, and liver and appears not to be associated with recovery even when the drug is stopped forthwith. Most cases are associated with normal tacrolimus levels, and the disorder often arises many years into longstanding stable treatment. One case has been biopsied,¹³ and an infiltration of macrophages but few lymphocytes within an abundance of demyelinated axons was observed. Calcineurin inhibitors have been shown in vitro to have a toxic effect on optic nerve axons.¹⁸ Treatment of any kind has not been shown to improve vision,

although it is clear that the drug responsible should be stopped.

In this case there was no improvement after tacrolimus therapy was stopped, and had an alternative explanation not been postulated, the patient may have remained blind. There are more published cases of tacrolimus- or cyclosporine-associated optic neuropathy than that due to GvHD; it may be that some of these have improved with immunomodulatory treatment. It is of supreme importance, therefore, to consider an immune activation syndrome such as GvHD or immune reconstitution syndrome as a cause for optic neuropathy in cases such as this, since adequate treatment may be associated with a reasonable improvement in vision over time.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Note: Figure 1 of this article is available in colour online at <http://www.informahealthcare.com/oph>

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