CASE REPORT

Guillain Barré syndrome precipitated by the use of antilymphocyte globulin in the treatment of severe aplastic anaemia

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This report describes the case of a 54 year old woman with very severe aplastic anaemia who was treated with antilymphocyte globulin (ALG) and developed Guillain Barré syndrome (GBS). No antecedent infective aetiology was identified. Although there are numerous reports of autoimmune disease after treatment with ALG in aplastic anaemia, and GBS after immunosuppressive treatment, there are none reporting GBS after the use of ALG for severe aplastic anaemia. The occurrence of autoimmune disease after immunosuppressive treatment, in particular ALG, is discussed, together with the possible mechanisms that result from T cell depression.

We describe a 54 year old woman with severe aplastic anaemia who was treated with antilymphocyte globulin (ALG) and developed Guillain Barré syndrome (GBS). No antecedent infective aetiology was identified. Although there are numerous reports of autoimmune disease after treatment with ALG in aplastic anaemia, and GBS after immunosuppressive treatment, there are none reporting GBS after the use of ALG for severe aplastic anaemia. We will discuss the occurrence of autoimmune disease after immunosuppressive treatment, in particular ALG, and the possible aetiology as a result of T cell depression.

CASE REPORT

A 54 year old woman was referred to our hospital with a diagnosis of very severe aplastic anaemia. She had presented two months previously predominantly with severe thrombocytopenia (haemoglobin (Hb), 10.1 g/litre; white cell count (WCC), 3.2×10^9 /litre; neutrophils, 1.7×10^9 /litre; platelets, 17×10^9 /litre) and had received a course of prednisolone. However, during this period her blood count deteriorated (Hb, 4.7 g/litre; WCC, 3.0×10^9 /litre; neutrophils, 0.1×10^9 /litre; platelets, 4×10^9 /litre) and she was referred for further management. Bone marrow examination revealed a hypocellular marrow consistent with a diagnosis of aplastic anaemia with normal cytogenetics. Investigation failed to reveal the underlying aetiology (hepatitis A, B, and C viruses, Epstein Barr virus, human immunodeficiency virus, and parvovirus were negative and an autoimmune profile, direct Coombs, sucrose lysis, and Ham's tests were all normal).

Therefore, the patient was given a five day course of equine ALG (lymphoglobulin; Sangstat, Cambridge, Massachusetts, USA) at a dose of 15 mg/kg/day (10 vials a day) after an initial test dose. During the treatment she developed culture negative fevers, which responded to hydrocortisone, consistent with serum sickness. Sixteen days after completion of ALG treatment and three days after reduction of the

hydrocortisone she awakened with lower limb weakness associated with absent reflexes, sensory loss in a stocking distribution, and urinary retention. The motor weakness progressed over the next 24 hours to involve her upper limbs. Magnetic resonance imaging of the spinal cord and computerised tomography of the brain were both unremarkable. Nerve conduction studies showed a generalised sensorimotor polyneuropathy consistent with the recent onset of acquired inflammatory demyelinating polyneuropathy (GBS). Screening for known precipitants of GBS (*Campylobacter jejuni*, cytomegalovirus, Epstein Barr virus, *Mycoplasma pneumoniae*, and human immunodeficiency virus infection) was negative. Lumbar puncture for cerebrospinal fluid was not undertaken in view of the thrombocytopenia. Antiganglioside antibodies were negative.

She received a five day course of intravenous immunoglobulin (IVIg) and intensive physiotherapy over several weeks. She was started on cyclosporin and required a short course of granulocyte colony stimulating factor support. A significant improvement was noted within 48 hours of starting IVIg. She was walking with support at four weeks and independently mobile eight weeks after IVIg treatment. Ten months later she has had a partial haematological recovery (Hb, 9.5 g/litre; reticulocytes, 3.0×10^9 /litre; WCC, 4.9×10^9 /litre; neutrophils, 2.2×10^9 /litre; platelets, 81×10^9 /litre) and is transfusion independent, although she continues to receive cyclosporin.

DISCUSSION

GBS is an acute demyelinating polyradiculoneuropathy, characterised by progressive, symmetrical weakness and areflexia, and in severe cases with respiratory muscle and autonomic involvement, although bladder involvement is unusual. It is believed to be caused by autoimmune mechanisms that are predominantly T cell mediated and is a rare but recognised event after autologous and allogeneic bone marrow transplantation, intensive conditioning regimens, and solid organ transplantation.¹ GBS is also well documented in conditions where immune dysfunction is a feature, notably Hodgkin² and non-Hodgkin lymphoma,³ HIV infection, and numerous autoimmune disorders such as chronic active hepatitis, hypothyroidism, sarcoidosis, Wegener's granulomatosis, and ulcerative colitis. It is postulated that in these situations GBS may arise as a result of viral infection/reactivation or as a result of immune dysregulation, in particular iatrogenically suppressed T cell function in the case of transplant patients.

Immunosuppressive treatment in itself is not thought to be a risk factor for the development of demyelinating

Abbreviations: ALG, antilymphocyte globulin; GBS, Guillain Barré syndrome; Hb, haemoglobin; IVIg, intravenous immunoglobulin; WCC, white cell count

Take home messages

- We describe a 54 year old woman with severe aplastic anaemia who was treated with antilymphocyte globulin (ALG) and developed Guillain Barré syndrome (GBS)
- This is the first report of GBS after the use of ALG for severe aplastic anaemia
- GBS is thought to be autoimmune in origin, and in this case was probably caused by a reduction in cytotoxic T cell responses that would normally restrict B cell activation as a result of the administration of ALG

neuropathies. Supporting data for this include reports of GBS developing as patients were weaned off steroids and the fact that GBS is also successfully treated by immunosuppressive treatments, such as cyclosporin A. Steroids can also be beneficial in the management of chronic inflammatory demyelinating polyneuropathy. However, there are instances where GBS developed after other immunosuppressive regimens. FK506 treatment in liver transplant recipients,⁴ cyclosporin A in renal transplant recipients,⁵ and cyclosporin A in rodent experimental studies resulted in demyelinating neuropathies.⁶ Other immunosuppressive agents, such as Campath-1H, are also reported to induce autoimmune conditions—for example, a high incidence of Graves' disease was reported after the use of Campath-1H in patients with multiple sclerosis.⁷ In some of these instances, an immune mechanism was suggested because symptomatic improvement was seen after plasma exchange or IVIg.

"Immunosuppressive treatment in itself is not thought to be a risk factor for the development of demyelinating neuropathies"

Aplastic anaemia is thought to be mediated by a cellular immune reaction directed against haemopoietic stem or progenitor cells. ALG derived from horse or rabbit serum appears to act by reducing cytotoxic T cells and by releasing haemopoietic growth factors from certain T cells, thereby dampening down the cellular immune response.⁸ Reduced cytotoxic T cell responses that would normally restrict B cell activation but allow growth of haemopoietic progenitor cells may increase the likelihood of autoimmune disorders arising. Although there are no reports of GBS after treatment with

ALG for aplastic anaemia, there are reports of other autoimmune disorders after ALG. Autoimmune thyroid disease, although rare, is described most frequently,⁹ and autoimmune haemolytic anaemia¹⁰ and fibrosing alveolitis have also been reported.¹¹ In addition, pre-existing multiple sclerosis and fibrosing alveolitis were exacerbated after ALG, suggesting the potential of ALG to trigger and perpetuate autoimmune disease.

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The patient gave her informed consent for this case report to be published.

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