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CASE REPORT

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Allogeneic hematopoietic stem cell transplantation in a patient affected by large granular lymphocyte leukemia and multiple sclerosis

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Abstract We describe a 57-year-old man, affected by large granular lymphocyte (LGL) leukemia and concomitant primary progressive multiple sclerosis (MS), treated with allogeneic hematopoietic stem cell transplantation (HSCT) from an HLA-identical sibling. The patient was conditioned with fludarabine, busulphan, and cyclophosphamide. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine and short-term methotrexate. At 3 years follow-up, the patient is in complete remission of LGL with a marked improvement in neurological conditions. This is the first case of allogeneic HSCT in a patient with LGL leukemia and concomitant primary progressive MS. Allogeneic HSCT, performed in our patient to cure the lymphoproliferative disorder, improved the clinical course of MS.

Keywords Allogeneic BMT · LGL leukemia · Multiple sclerosis

Introduction

Large granular lymphocyte (LGL) leukemia is a chronic malignancy caused by the proliferation of monoclonal $CD3^+$ T-cell lineage or, less frequently, $CD16^+$, $CD56^+$, $CD57^+$ natural killer (NK) cell lineage [1]. Several reports suggest that LGL leukemia is triggered by antigen-driven cytotoxic T lymphocytes and that retroviral protein, with homology for the BA21 epitope of human T-lymphotropic virus (HTLV)-1, may play a role in the pathogenesis of LGL leukemia. The inhibition of the Fas apoptotic pathway may contribute to the expansion of leukemic LGL clones [1]. Multiple sclerosis (MS) is an inflammatory demyelinating disease with an extremely variable clinical course [2, 3]. Although its pathogenesis remains uncertain, current knowledge suggests that MS is a polyfactorial disease in which autoimmunity, genetic background, and environmental factors such as viral infectious agents may be involved [2, 3].

In the attempt to induce remission or stabilization of the clinical course of MS, autologous hematopoietic stem cell transplantation (HSCT) has been used with promising results [4, 5]. The rationale of this therapeutic procedure is based on the complete ablation of the immune system and consequently, of the autoreactive clones, and the generation of a new immune system from the HSC compartment. However, since self-antigens and antigen-presenting cells remain the same, the duration of remission after autologous HSCT is unpredictable.

Some reports describe allogeneic HSCT as a possible breakthrough in the management of refractory treatment-resistant MS, capable of preventing progression in patients with aggressive disease [6, 7]. In fact, allogeneic HSCT not only supplies a new stem cell source but it also generates an immunologic donor-mediated graft-versus-autoimmune effect in which donor cells modulate and induce apoptosis of recipient autoreactive lymphocyte clones [8, 9, 10]. However, for ethical reasons, this approach has only been experimented in MS patients with coexisting malignancies or other life-threatening pathologies [11].

Case report

We report a 57-year-old man affected by primary progressive MS and LGL leukemia who was successfully treated with allogeneic HSCT from an HLA-identical sibling.

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The patient's clinical history dates back to 1990 when he presented progressive hypoesthenia of the lower limbs. Subsequently, he presented mild ataxia, hypoesthenia of the upper limbs, dysesthesia of the lower limbs, urinary urgency, and diplopia. The diagnosis of primary progressive (PP) MS was made in 1993 according to the criteria of Thompson et al. [12]. From 1990 to 2000, the patient showed progressive deterioration of neurological function, truncal and cerebellar deficits characterized by nystagmus, dysphagia, and dysmetria of the upper and lower limbs, pyramidal signs such as spastic paraparesis, bilateral Babinski's reflex, and clonus. Despite treatment with azathioprine and occasionally methylprednisolone, there was no evidence during this period of stabilization or improvement of the disease. In particular, over the 12 months preceding HSCT the extended disability status scale (EDSS) [13] advanced from 6.0 to 6.5 points.

NK-like T-cell LGL was diagnosed in May 2000. Peripheral blood mononuclear cells were increased (25.3×10^9/l); 40% of them were lymphocytes with the following phenotype: TCR α/β^+, $CD3^+$, $CD8^+$, $CD16^+$, $CD56^+$, $CD94^+$, $NKG2A^+$, p70 $(NKB1)^+$, $CD45low^+$, and $ILT2^+$. Polymerase chain reaction (PCR) analysis detected clonal rearrangement of TCR-β genes. Pretransplant neurological evaluation revealed distal hypoesthenia of the upper extremities, pareto-ataxic ambulation, diplopia, right eye scotoma, nystagmus, dysphagia, dysmetria, and urinary and fecal urgency. Brain magnetic resonance imaging (MRI) showed multiple widespread lesions in white matter without enhancement following administration of a triple dose of gadolinium [14]. At this time, the EDSS score was 6.5.

The patient was conditioned with fludarabine 25 mg/m^2 once daily i.v. ×4 days (total dose 100 mg/m^2), busulphan 3.5 mg/kg p.o. in divided daily doses ×4 days (total dose 14 mg/kg), and cyclophosphamide 60 mg/kg once daily i.v. ×2 days (total dose 120 mg/kg). On day 0 (12 July 2000) he received 2.8 bone marrow-derived nucleated cells $\times10^8$/kg of body weight (CD34=2.2×10^6/kg) from an HLA-identical sex-matched sibling. Graft-versus-host-disease (GVHD) prophylaxis consisted of cyclosporine and short-term methotrexate. Allogeneic engraftment was documented on day +10 by microsatellite analysis. Cutaneous acute grade II GVHD occurred on day +16 and was successfully treated with low-dose steroids. A limited form of chronic GVHD appeared 1 year later and completely resolved after 6 months of treatment with mycofenolate. At 36 months post-transplantation the patient was in complete remission of LGL with a fully allogeneic reconstitution. There was a marked improvement in his neurological condition with an EDSS score of 5.5. Brain MRI revealed a stable pattern with no new T2 or T1 lesions.

Discussion

This is the first description of LGL leukemia in a patient with MS. According to our experience, allogeneic HSCT was able to cure the lymphoproliferative disorder and seemed capable of ameliorating the clinical course of MS.

LGL leukemia has often been found associated with autoimmune disorders, such as systemic lupus erythematosus or rheumatoid arthritis, but never with MS [1]. In our case, a likely hypothesis is that LGL leukemia may have contributed to the pathogenesis and/or persistence of MS. Moreover, it has been postulated that a retroviral infection may be involved in the pathogenesis of both MS and LGL leukemia [15, 16]. In MS autologous HSCT is still preferred to allogeneic HSCT [4, 5] because of safety reasons, but this therapeutic approach had to be excluded in our patient for the concomitant presence of LGL leukemia. Allogeneic HSCT seemed a rational choice for its ability to offer a new stem cell source and a potentially immunologic donor-mediated graft-versus-autoimmune effect [8, 9, 10]. In this context, it is interesting to note that the EDSS score of our patient improved after recovery from a limited form of chronic GVHD.

Primary progressive (PP) MS is different from the classic relapsing remitting (RR), or secondary progressive (SP) forms of MS. In fact, PP MS patients show fewer radiological inflammatory lesions [12] and are likely to be less informative than RR or SP MS patients with regard to the efficacy of allogeneic HSCT on disease evolution. Anyway, at 36 months follow-up, our patient enjoys stability of MS with an EDSS score of 5.5. This is obviously a single case report and until our results are confirmed by other reports, allogeneic HSCT can only be considered in MS patients with concomitant oncohematologic pathologies. However, the utilization of reduced-intensity conditioning regimens and the availability of manageable and more effective drugs to control GVHD may soon make it possible to reconsider the feasibility of allogeneic HSCT in patients with aggressive and rapidly worsening MS.

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