Cell Transplantation
Volume 29: 1–7

DOI: 10.1177/0963689720950641
journals.sagepub.com/home/cll
SAGE

Autoimmune Cytopenias Developing Late Post Alemtuzumab-Based Allogeneic Stem Cell Transplantation: Presentation of Short Case Series from a Transplant Center

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Abstract

Stem cell transplantation remains the curative option for many patients with hematological malignancies. The long-term effects of these treatments on the patients and their immune systems have been extensively investigated, but there remains a paucity of data regarding autoimmune manifestations post-transplant, although these effects are well recognized. Herein we present the clinical picture and therapeutic approach in three patients (cases 1–3), with varied presentations of autoimmune disease post-transplant. Case 1 exhibited autoimmune hemolytic anemia and other autoimmune manifestations (serositis, thyroiditis), that were probably linked to graft versus relapsed leukemia effect. Cases 2 and 3 had pure red white cell aplasia and pure red cell aplasia, respectively, which were associated with hyperglobulinemia and a clonal T cell expansion.

Keywords

autoimmune disease, hematopoietic stem cells, t cells, graft versus host disease, bone marrow transplant

Introduction

Hematopoietic stem cell transplantation (HSCT) remains the only curative option for many patients with hematological malignancies. Disease relapse, graft versus host disease (GvHD), and infective complications have been under intense study resulting in great advances in terms of their diagnosis and management. On the other hand, there is paucity for data with regard to autoimmune complications post-HSCT, such as pure red cell aplasia (PRCA), pure white cell aplasia (PWCA), autoimmune hemolytic anemia (AIHA), and serositis. These complications are recognized but underdiagnosed in both allo-HSCT and auto-HSCT settings. In this article, we aimed to convey our reflections on the clinical features of three allograft patients at our Center who developed the aforementioned complications post-Alemtuzumab HSCT.

Case 1

The first case (case 1) refers to a 43-year-old man who underwent myeloablative Busulphan/Cyclophosphamide with Alemtuzumab 15 mg in the stem cell bag matched unrelated donor HSCT in first complete remission (CR1) for acute myeloid leukemia (AML) (FLT3 wild type, NPM1

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Submitted: March 25, 2020. Revised: May 16, 2020. Accepted: July 27, 2020.

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wild type, normal karyotype). Recipient and donor blood group were O RhD+ and O RhD−, respectively. Apart from the high body mass index (BMI), there were no other comorbid conditions at transplant. As part of his workup for initial induction chemotherapy, he was found to have past hepatitis B infection (HBcAb+, HBsAg−) with negative hepatitis B virus (HBV) DNA and was set on lamivudine and later entecavir prophylaxis. Frequent HBV DNA assessments have ensued regularly. The early term post-HSCT period was complicated by repeated cytomegalovirus (CMV) reactivation, effectively treated with valganciclovir. At day +94 post-transplant, the patient had mixed chimerism (93% donor in post-transplant whole blood, 3% donor in CD3+ T cell fraction) and underwent his first donor lymphocyte infusion (DLI) at a dose 0.5 × 106 CD3 cells/kg on day +180. The second dose was given 12 weeks later at a dose of 1 × 106 CD3 cells/kg resulting in abrupt full donor conversion only 2 weeks later. On day +305, the patient presented to the clinic with sickness, early satiety, and fatigue. He was diagnosed with Warm Antibody Coombs positive AIHA and upper gastrointestinal tract GvHD. The patient was started on prednisolone oral initially (1 mg/kg) to good effect. He exhibited recurred AIHA and thyroiditis on day +505 upon initial steroid taper. The latter manifested with palpitations and fatigue, undetectable thyroid-stimulating hormone, raised free thyroxine, and free triiodothyronine (26.1 pmol/l [9–19] and 7.5 pmol/l [2.6–5.7], respectively), with negative thyroid peroxidase antibodies. Steroid reintroduction at 1 mg/kg resulted in rapid resolution of thyroid function test abnormalities within 4 weeks. On day +520, cyclosporine was relaunched to enable steroid taper, but on day +560 leukocytosis, anemia, and blasts on blood film ensued. Bone marrow confirmed relapsed AML albeit with abnormal karyotype and two apparent unrelated clones one with del 2q and one with trisomy 3 and der(3), that is, 46 XY del(2)(q2q3)[6]/47 XY +3 der(3) add (3) (p?1)add(3)(q?1) [3] /46xy(3). Donor chimerism was 30% in the bone marrow and no Flt-3, NPM1, or IDH1/2 mutants were identified. Chemotherapy with Fludarabine/Cytarabine/Lenograstim/Idarubicin (FLAG-IDA) × 2 cycles was deployed and resulted in morphological CR2. This was followed by single DLI at a dose of 1 × 106 CD3+ cells per kg on day +650. On day +945, he displayed HBV DNA reactivation (13,150 copies/ml) without a picture of biochemical hepatitis. He was few weeks off lamivudine prophylaxis suspension. At that time, he was also off on steroids and without AIHA. CD4+ T cell count exceeded 300/μl. He was then set on entecavir with complete response (null viral copies since day +1069). On a separate note, on day +1035, the patient was admitted with recurred AIHA, moderate pericardial effusion, and moderate pleural effusions suggesting GvHD serositis. Steroids (prednisolone initial dose 1 mg/kg) elicited a good response. Four rituximab weekly infusions at a dose of 375 mg/m2 were also administered at the time. Although the patient has responded well to steroid therapy and his AML has remained in second complete remission (CR2) as of now (day +1533), it has been difficult to wean steroids altogether (the current dose is 5 mg on alternate days). Mycophenolate mofetil has been added to enable prednisolone taper over the last 12 months.

Case 2

Case 2 refers to a 62-year-old woman who received a Busulphan/Fludarabine/Alemtuzumab 30 mg reduced intensity conditioning (RIC) stem cell transplant from a matched unrelated donor for therapy-related AML (patient had previously received anthracycline-based treatment for breast cancer). The patient attained morphological CR but had the cytogenetically active disease (del 7q) prior to transplant. Early post-transplant course was uneventful, only complicated by CMV reactivation. On day +160, she was admitted with neutropenic sepsis and mouth ulcers (white cell count 3.38 × 109/L, hemoglobin 114 g/l, platelet 285 × 109/l, and neutrophil count 0.02 × 109/l). The bone marrow aspirate was consistent with PWCA revealing (1) reduced cellularity, profoundly suppressed myeloid series that comprised less than 5% of total marrow nucleated cells with virtually absent mature forms (metamyelocytes, band forms, neutrophils) and (2) normal erythropoiesis and slightly reduced megakaryocytes. In addition, the aspirate showed 42% lymphoid cells having a phenotype consistent with CD8+ T cells and natural killer (NK) cells on flow cytometry. A dominant T cell clone was demonstrated on T cell receptor analysis. The patient denied having a bone marrow biopsy at the time. Epstein–Barr virus, CMV, human herpesvirus 6, adenovirus, parvovirus B-19 viral PCR, and autoimmune screening were negative. Monoclonal gammopathy had been identified from day +90, but at diagnosis of PWCA, the clonal immunoglobulin G (IgG) kappa surged at 16.5 g/l. The condition had excellent response to intermittent Lenograstim. The agent was suspended 7 months afterward without recurring neutropenia. The patient has since received DLI for mixed chimerism. She has also been complicated by a high level (>20,000 copies/ml) EBV reactivation twice (days +270, +635) that responded promptly to rituximab intravenously (375 mg/m2) repeated weekly until viral clearance. She remains in remission from AML with normal neutrophils and full donor chimerism. She has never exhibited any acute, chronic, or post-DLI GvHD. Bone marrow T cell large granular lymphocytosis (T-LGL) clone has disappeared. Monoclonal IgG has been dwindling and is now barely detectable on immunofixation.

Case 3

Finally, we describe a 60-year-old man (case 3) who received a Busulphan/Fludarabine/Alemtuzumab 50 mg RIC allograft from a matched unrelated donor for inv(16)/trisomy 8 relapsed AML in CR post-FLAG-IDA salvage. Early transplant complications were recurring CMV reactivation, skin acute GvHD (overall grade1), and mild hemorrhagic

cystitis associated with BK virus infection. On day +266, pre-emptive DLI at a dose 0.5 × 106 CD3/kg for mixed T cell chimerism was administered (whole blood chimerism was 99%, and T-cell chimerism was 85% at the time). Very soon later, on day +277, the patient developed sudden onset, heavy hypoproliferative anemia with reticulocytes less than 5/μl (white blood cells 5.22 × 109/l, hemoglobin 59 g/l, platelets 262 × 109/l, neutrophils 2.03 × 109/l, lymphocytes 2.31 × 109/l, mean cell volume 95.6 fl, mean corpuscular hemoglobin 32.8 pg, mean corpuscular hemoglobin concentration 343 g/l, red cell distribution width 12.8%) without evidence of hemolysis, hematinic deficiency, or of disease relapse. Parvovirus, CMV, and EBV PCR were all negative. At that time, IgG peaked at 30 g/l with a monoclonal band 24.5 g/l, and no accompanying immunoparesis. Bone marrow aspirate revealed profoundly suppressed erythroid series (<1% on aspirate), whereas the trephine biopsy showed nearly aplastic erythropoiesis together with some hotspots of arrested erythroblast maturation and an excess of polyclonal plasma cells that comprised less than 10% of hematopoietic cells. On flow cytometry, CD8+ T cells comprised 7% of total marrow nucleated cells with confirmation of a dominant T cell clone from molecular diagnostics (T cell receptor PCR analysis). The diagnosis was of T-LGL-associated PRCA post-HSCT, and the patient was treated with the reintroduction of cyclosporine along with darbepoetin to good effect. The CD8+ T cell clone resolved in a subsequent bone marrow that was performed a few months later, whereas the monoclonal IgG has eventually subsided at 14.1 g/l. Over time, cyclosporine was successfully weaned off. The patient remains in remission with full donor chimerism some 5 years out from allograft.

Discussion

In this study, case 1 highlighted that AIHA might occur post-DLI in combination with rare, underdiagnosed forms of chronic GvHD, and this can potentially be linked to a somewhat unexpected Graft versus relapsed leukemia effect. Besides, through cases 2 and 3, we wanted to convey that clonal T cell (or NK-cell) expansions should be sought when isolated central cytopenias occur late post-allograft in the absence of viral/toxic causes (Table 1).

Autoimmune cytopenias are encountered following allogeneic stem cell transplantation, but there have also been reports of thyroid dysfunction, myasthenia gravis, vitiligo, and autoimmune hepatitis[1,2]. The incidence and pathophysiology of autoimmune complications post-transplant have not been adequately studied, but they are perceived to be linked to dysregulation of autoreactive T cells[3] not only from the transplant itself but from multiple previous chemotherapy treatments[4]. Treatment with highly immunosuppressive therapy, given primarily to eradicate disease and prevent GvHD, causes loss of regulatory T cells which can then lead to an expansion of recipient tissue reactive B and T cells[5]. Delayed immune reconstitution in patients receiving T cell depletes HSCT and may also predispose to autoimmune conditions[4].

In case 1, the late onset of AIHA, thyroiditis, and serosal inflammation 1-year post-chemo-DLI salvage might have been linked to vigorous Graft versus leukemia effect as the patient has remained in remission more than 29 months now despite that his AML relapse post-transplant with new complex karyotype clonal evolution. AIHA and serositis (inflammation of body serosal epithelium in pleural cavities, peritoneum, and pericardium) are classified as "other" manifestations of chronic GvHD. Their occurrence has been described in conjunction with other more frequent chronic GvHD manifestations, but there is a striking scarcity of data about their prevalence, clinical features, and impact on transplant outcomes. Case 1 is also unique in that these two aforementioned manifestations together with transient thyroiditis manifested as post-DLI or de novo chronic GvHD[6]. At that time, serositis was far more steroid responsive than the AIHA to steroids, which is in line with study data showing the latter is difficult to treat in the post-HSCT setting[7]. Although prednisolone is initially effective in controlling AIHA/Evans syndrome episodes, the majority of patients develop steroid dependency and receive second-line or third-line therapies, including rituximab, sirolimus, mycophenolate mofetil, intravenous immunoglobulin, and the recently proposed anti-CD38 antibody (daratumumab), with varied efficacy, as shown in Table 2.

With regard to the incidence and prognostic factors for autoimmune cytopenias post-allo-HSCT, a joint study of the Autoimmune Diseases and Severe Aplastic Anemia Working Parties (ADWP/SAAWP) of the European Society for Blood and Marrow Transplantation (EBMT) studied 530 adult and pediatric patients who underwent allo-HSCT for aplastic anemia[8]. Of these, $n = 25$ or 4.7% of patients were diagnosed with autoimmune cytopenia at a median 10.6 months post-allo-HSCT (32% with immune thrombocytopenia [ITP], 28% AIHA, 24% AIHA + ITP, and 16% autoimmune neutropenia). On multivariable analysis, the use of bone marrow and myeloablative conditioning was protective against autoimmune cytopenias. As the study was retrospective, the findings were limited by the absence of bone marrow biopsy and exhaustive differential diagnosis in some of the studied cases. Another large retrospective study from the Netherlands found that 30 out of 380 pediatric patients with both benign and malignant diseases developed autoimmune cytopenias post-allograft[9]. On univariate analysis, T cell depletion with ATG or Alemtuzumab, benign disease, and GvHD predisposed to autoimmunity. An interesting finding was that of a significant increase in IgG, IgA, and IgM levels shortly before autoimmune cytopenia onset. This is in line with cases 2 and 3 in this article, which displayed peaking IgG monoclonal gammopathy just before T-LGL-PWCA and PRCA, respectively.

LGL post-HSCT is often associated with cytopenias and nonclonal hypergammaglobulinemia[10]. It has been observed

Table 1. Salient Clinical and Treatment Details for Patients Under Study.

Patient; age; disease; disease status at onset	Conditioning type; intensity	Type of transplant/ stem cell source	DLI/timing to episode	CMV reactive/ presence at onset	GvHD and status at onset	Complication	Time (days [D]) from transplant at diagnosis of autoimmunecomplex	Treatment for autoimmune complex	Response to treatment
Case 1 male; 43; AML; CR2	Bu/Cy/Alemt 15 mg in the stem cell bag; MAC	HLA 10/10 MUD/PBSC	Y/Pre	Y/Low level, recurring through Tx for AIHA	Upper GI tract grade 2 post-DLI GvHD prior to AML relapse; CR	Warm antibody; autoimmune hemolysis, pericarditis; pleuritis	D +305 (AIHA) and D +1035 (AIHA and serositis)	Prednisolone × last 16 months; rituximab 375 mg/m^2 × 4 weekly twice months +12 and +23 post-BMT; MMF × last 12 months	Low-dose steroid dependence. Currently on prednisolone 10 mg OD and MMF.
Case 2 female;62; AML; CR1	Bu/Flu/Alemt 30 mg; RIC	HLA 10/10 MUD/ PBSC	Y/Post	Y/resolved	N	Pure white cell aplasia associated with NK and T-LGL expansion	D +160	Lenograstim weekly × 7 months	Complete response—off treatment
Case 3 male; 60; AML; CR1	Bu/Flu/Alemt 50 mg; RIC	HLA 10/10 MUD/ PBSC	Y/Pre	Y/resolved	Skin stage 2, overall Gr.1 CR	Pure red cell aplasia associated with T-LGL expansion	D +277	Cyclosporine × 8 months darbepoetin × 4 weeks	Complete response—off treatment

AIHA, autoimmune hemolytic anemia; Alemt, Alemtuzumab; AML, acute myeloid leukemia; Bu/Cy, busulphan/cyclophosphamide; Bu/Flu, busulphan/fludarabine; CMV, cytomegalovirus; CR, complete remission; CR1, first complete remission; CR2, second complete remission; DLI, donor lymphocyte infusion; GvHD, graft versus host disease; MAC; myeloablative; MUD, matched unrelated donor; MMF, mycophenolate mofetil; NK, natural killer; PBSC, peripheral blood stem cells; RIC, reduced intensity conditioned; T-LGL, T cell large granular lymphocytosis.

Table 2. Key Studies on Autoimmune Hemolytic Anemia Following Allogeneic Stem Cell Transplantation.

Patients analyzed	Cumulative incidence of AIHA	Median time to diagnosis	Number of patients/GvHD	Number of patients/CMV reactivation	Treatment outcomes	Reference
272 Adults. All had ATG	4.4% at 3 years ($n = 12$ pts)	147 days	10	6	Steroids—no response; rituximab—17% alive; AIHA contributed to mortality	Sanz et al (2007)
3 TYA patients. ALL, XLT/WAS, DNA-ligase IV deficiency	All patients had AIHA	180 days	NR	NR	Steroids, bortezomib—plasmapheresis no response; daratumumab CR in two-thirds; death to AIHA in one-third.	Schuetz et al (2018)
531 pediatric patients	5% at 3 years ($n = 26$ patients)		3	14	Steroids/IVIG—22% CR; rituximab—36% CR; bortezomib—57% CR; MMF, sirolimus—100% CR; stem cell boost—75% CR; overall CR—92%; overall OS—79%	Matthijis et al (2018)
530 adults and pediatric with AA, median age 21 years	2.6% at 6.4 years ($n = 14$ patients) with AIHA or Evans, another $n = 8$ patients ITP and $n = 4$ patients AIN)	10.6 months	No correlation with GvHD	NR	Steroids, IVIG, rituximab, G-CSF, AIHA—85% CR; Evans—14% CR; overall OS—85% at 5 years	Miller et al (2019)
380 pediatric patients	6.3% at 35 months ($n = 24$ patients). Most had additional AIN, ITP, or both	133 days	15	NR	Steroids—13% CR MMF, sirolimus, rituximab—all patients responded to additional treatment. Overall OS—83%	Szanto et al (2020)

AA, aplastic anemia; AIHA; autoimmune hemolytic anemia; AIN, autoimmune neutropenia; CMV, cytomegalovirus; CR, complete remission; G-CSF, granulocyte colony stimulating factor; GvHD, graft versus host disease; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; NR; not reported; OS, overall survival; WAS, Wiskott–Aldrich syndrome; XLT, X-linked thrombocytopenia.

that LGL is often associated with chronic CMV infection as well as patients with chronic GvHD through a process of chronic antigenic stimulation. LGL is a phenomenon estimated to affect between 0.5% and 18.4% of patients following HSCT[11]. The presentations can range from self-limiting polyclonal expansion to overt leukemia. Due to the lack of studies focusing on LGL, the data remain limited with interval between transplant and LGL estimated to be between 1 and 61 months. LGL is not always associated with cytopenias, but this is an important differential when investigating these cases in the post-transplant setting. Central cytopenias associated with an autoimmune mechanism to T-LGL expansion following an allograft are underreported, and they have been thought to complicate early post-transplant course due to unstable engraftment and evolving immune reconstitution. Therefore, cases 2 and 3 were notable because the autoimmune attack to bone marrow precursors causing PWCA and PRCA, respectively, was unraveled beyond day +150 following excellent engraftment with full donor status. In case 2, neutropenia was effectively controlled with Lenograstim, while case 3 patient had an excellent response to cyclosporine.

Finally, this study highlights that Alemtuzumab used for primary GvHD prophylaxis might elicit autoimmunity in selected stem cell transplant recipients. Alemtuzumab has long been associated with the development of secondary autoimmune diseases, with studies suggesting up to 30% of multiple sclerosis patients treated with Alemtuzumab develop secondary autoimmune manifestations[12]. which can occur years after the treatment, such as thyroid disorders and immune thrombocytopenia. It has been postulated that patients with preponderance for higher levels of interleukin-21 are more likely to experience secondary autoimmune complications due to greater levels of T cell apoptosis and cell cycling, increasing the likelihood for autoreactive T cells.

To conclude, this study illustrated rare post-HSCT autoimmunity, in particular hypoproliferative unicytopenia associated with clonal T-cell expansion, as well as autoimmune constellation of AIHA, thyroiditis, and serosal inflammation. The necessity to decipher autoimmunity post-HSCT through prospective clinical studies cannot be overstated.

Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Statements

This article does not contain any (experimental) studies with human or animal subjects. The article refers to a retrospective description of bone marrow transplant patients displaying unusual autoimmune manifestations.

Verbal informed consent was obtained from the patients for their anonymized information to be published in this article.

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