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Case report

Disappearance of lupus anticoagulant after allogeneic bone marrow transplantation

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Summary:

Lupus anticoagulant antibodies have never been reported to disappear after either allogeneic or autologous bone marrow transplantation in humans. We report the first case of disappearance of lupus anticoagulant antibodies in a patient without systemic lupus erythematosus or clinical evidence of other autoimmune disorders, who received an allogeneic bone marrow transplant as treatment for chronic myeloid leukemia. Although marrow transplantation is not a recognized therapy for antiphospholipid syndrome, our observation should be considered another example of the capability of intensive chemo-radiotherapy followed by stem cell transplantation to ablate a pathologic marrow clone resulting in an autoimmune disorder and improve, or even cure, some severe autoimmune diseases.
Keywords: antiphospholid antibodies; lupus anticoagulant; bone marrow transplantation; autoimmune diseases

Lupus anticoagulant (LA) is an antiphospholipid antibody (APA) which reacts with negatively charged phospholipids. The antigen recognized *in vivo* by this antibody, if any, is unknown. The clinical spectrum associated with its presence when there is no clinical evidence of systemic lupus erythematosus (SLE) or other well-defined autoimmune disorder (ie primary antiphospholipid antibody syndrome (PAAS)), includes thrombocytopenia and several clinical manifestations of thromboembolic events, such as recurrent arterial and venous thromboses, cardiac valvular disease, recurrent pregnancy loss and stroke.[1]

Due to the heterogeneous expression of these antibodies, there is no uniform opinion regarding minimum criteria for demonstrating LA. Such antibodies are usually detected through their ability to interfere with phospholipid-dependent coagulation assays, such as the activated partial thromboplastin time (aPTT), Russell viper venom time (RVVT) and kaolin clotting time (KCT) (at least one of these is required for the diagnosis of LA). This defect is not corrected in a 1:1 mixture with normal plasma. Neutralization of the inhibitor through an excess of phospholipid (ie platelet neutralization procedure (PNP)), is the usual confirmatory test.[2]

In the last few years, various authors have suggested that both allogeneic (BMT) and autologous (ABMT) bone marrow transplantation, may play a role in the treatment of different autoimmune pathologies, such as SLE, rheumatoid arthritis, myasthenia gravis (MG), inflammatory bowel disease, autoimmune thyroiditis (AT), and a wide variety of diseases in which immune phenomena are assumed to be the pathogenic determinant or, at least, an important contributor to the final clinical picture.[3–11] In most cases, these have been casual observations in hematological patients who have received high-intensity chemo-radiotherapy followed by either allogeneic or autologous hematopoietic reconstitution. Nevertheless, several authors have described selected cases in which, because of their severity, ABMT has been performed in these pathologies.[11–13] On the other hand, transferral of MG,[14] AT[15] and some autoimmune phenomena of SLE[16] from donors to recipients of a BMT has also been described, as if there were a direct correspondence between the activity of the disease and marrow immunocompetent cells.

Although disappearance of APA has been described after both BMT and ABMT in SLE, as far as we know, neither LA without clinical evidence of SLE nor PAAS, have ever been reported to disappear after these therapeutic procedures. We report the first case of disappearance after BMT of LA without PAAS or clinical evidence of SLE, in a patient with chronic myeloid leukemia (CML).

Case report

A 23-year-old woman was diagnosed as having Philadelphia-positive CML in chronic phase. At diagnosis, basic coagulation studies were performed, which showed a lengthening of the aPTT (43 s/29 s) and a reduction in the percentage of prothrombin activity (PA) (54%). No further investigations were performed. Initially, hydroxiurea (HU) was administered at doses ranging from 1 to 1.5 g/day. The patient did not receive interferon (IF) at any stage of the disease.

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Fifteen months later, the patient underwent BMT from an HLA-identical sibling donor. Preliminary coagulation studies showed the persistence of the abnormalities present at diagnosis. Further studies showed the results given in Table 1. Thrombin time was normal (19 s/21 s). Biological probes for syphilis were negative, as were anti-cardiolipin antibodies. A remarkable finding was the low levels of factors VII (50%), VIII (54%), IX (53%) X (64%), V (26%) and II (47%). This defect was not corrected by a 1:1 mixture of normal plasma, and the PNP (Staclot PNP; Diagnostica Stago, Asnieres-sur-Seine, France) was positive. All these data fulfil the criteria for the presence of LA. Additionally, PTT-LA (PTT-LA; Diagnostica Stago) was positive.

She had normal levels of lactic dehydrogenase, urea, uric acid and creatinine, slight splenomegaly of 14 cm on abdominal ultrasound, and the t(9;22) translocation in 100% of the metaphases evaluated with the additional finding of del(21) in 20% of metaphases. Peripheral blood counts showed a leucocytosis (15×10^9/l with 8% basophils), and 796 000 platelets per ml; the hemoglobin was 13.4 g/dl.

In June 1993, she underwent marrow transplantation from an HLA-identical sister, after conditioning with cyclophosphamide (60 mg/kg/day × 2 days), and total body irradiation (13 Gy). Graft-versus-host disease (GVHD) prophylaxis included methotrexate, cyclosporin A (CsA) and prednisone (PRD).

The most relevant events after transplantation included onset of fever on day +10 which lasted for 7 days and was treated with ceftazidime, amikacin, vancomicine and amphotericin B. Exclusively cutaneous grade II GVHD was present at day +19. No systemic therapy was given. At day +22, she developed epigastric and right hypochondrial pain and was found to have oedema of the lower extremities and a 13 kg weight gain. Abdominal ultrasound showed marked splenomegaly (17 cm), dilatation of the suprahepatic arteries and swelling of the walls of the gallbladder. Alkaline phosphatase was 339 U/l, gamma GT 151 U/l and both ALT and AST were in the normal range. The bilirubin reached 1.5 mg/dl, so that a diagnosis of hepatic veno-occlusive disease (HVOD) was made. Fluid restriction and diuretic treatment were started with complete resolution of this episode.

A coagulation profile performed on day +27 showed complete normalization of all previously abnormal parameters. At this time, the patient was receiving PRD (1 mg/kg/day) and CsA (3 mg/kg/12 h). These data are shown in Table 1.

In month +6, re-evaluation was performed, and she was found to be in cytologic, cytogenetic and molecular remission. A basic coagulation profile which included PA, aPTT and TT, was entirely normal. The patient was not receiving any kind of immunosuppressive therapy, and had limited chronic GVHD.

At present, 4 years and 8 months after marrow transplantation, she is in hematological and cytogenetic remission, and coagulation parameters are completely normal, as shown in Table 1. No further investigations were performed, as the most sensitive tests for LA were negative.

Discussion

Casual observations of improvement and even disappearance of autoimmune disorders after both BMT and ABMT for hematological diseases have been reported many times over the last few years.[3–9,11]

Experiments in murine models have shown that PAAS, as well as SLE can be cured by BMT[17,18] but as far as we know, disappearance of LA without evidence of SLE or cure of PAAS through these procedures has never been described in humans.

Diagnosis of LA was made immediately before any BMT-related maneuver, so that pharmacological interactions can be excluded and, although no specific tests were undertaken when the patient was diagnosed with CML, LA was probably already present 15 months before BMT. In our opinion, these two findings are independent, because no association between LA and CML has ever been reported. Some authors have reported the appearance of LA after immunotherapy with IF,[19] but our patient received HU as cytotoxic treatment, and an association between LA and HU has also never been reported.

The patient underwent BMT from an HLA-identical sibling donor. The coagulation studies performed at day +27 (ie while she was receiving immunosuppressive drugs) and month +6 (after CsA and PRD had already been withdrawn) were normal, and showed the disappearance of LA.

The first study was performed during a clinical episode

Table 1 Coagulation studies performed 8 days before (prior to marrow conditioning) and 27 days and 4 years after bone marrow transplantation

	Plt	*PA*	*APTT*	*F*	*APTT + NP (mins)*				*KCT*	*RVVT*
					5	*30*	*60*	*120*		
Day −8 before BMT	533	57	48/35	280	34/30	42/36	47/43	53/45	145/96	31/28
Day +27 after BMT	16	83	24/30	309	25/29	25/30	28/31	40/40	105/100	28/28
4 years after BMT	170	100	27/31	278	NP	NP	NP	NP	98/101	NP

The first study showed a clear prolongation of the APTT which was not corrected by a 1:1 mixture with normal plasma, and a marked prolongation of the KCT. These abnormalities were corrected by the addition of an excess of phospholipids (see text for details). Twenty-seven days after transplantation, all parameters were within the normal ranges. All pretransplantation abnormalities are currently absent.

Plt = platelets (× 1000/μl); PA = prothrombin activity (%); APTT = activated partial thromboplastin time; F = fibrinogen (mg/100 ml); APTT + NP: APTT after 5, 30, 60 and 120 min of incubation at 37°C with normal plasma at a concentration of 1:1; KCT = kaolin clotting time; RVVT = Russell viper venom time; NP = not performed.

Except for platelets, fibrinogen and prothrombin activity, all the values are expressed in seconds over control.

of HVOD, and the second while chronic GVHD was present. These circumstances are of special interest, because LA has been reported in both clinical settings, HVOD[20] and GVHD.[21] The most striking finding is the absence of this coagulation inhibitor more than 4 years after transplantation.

In general terms, we can assume that LA antibody production is due to an aberrant clone of immunocompetent marrow cells. Levite *et al*[22] demonstrated that SLE autoantibody production in mice is determined by bone marrow-derived cells, and not by other extramedullary immune cells. This provides an acceptable explanation for the different experimental findings such as transfer of both PAAS and SLE from affected mice to healthy recipients,[23] which has also been reported in humans for MG,[14] AT[15] and some auto-antibodies related to SLE.[16] It is difficult to elucidate whether these observations are merely due to high-intensity chemo-radiotherapy or whether there is an additional role for immune reactions after transplantation. Clinical evidence supports the idea that it is probably just the absolute ablation of the pathological clone through cytotoxic drugs which is responsible for clinical improvement or cure, as complete responses have been described for different autoimmune disorders with ABMT.[8,9,11–13]

ABMT is beginning to be considered an acceptable choice of treatment for patients with severe forms of autoimmune diseases. It is difficult to decide which patients should be considered candidates for this therapeutic approach. At present, ABMT is a widely used therapeutic modality for hematological pathologies such as low-grade non-Hodgkin lymphomas, when the expected survival rate may be up to 5–10 years without treatment, while some severe forms of autoimmune diseases have a shorter survival and a higher morbidity rate due to complications in spite of treatment.

In our opinion, PAAS patients do not fulfil the criteria for ABMT, especially if, as in our patient, clinical complications due to AL are not present. Nevertheless, our observation should be considered as further proof of the capability of immune ablation followed by stem cell transplantation to eradicate a pathological clone responsible for an autoimmune disorder.

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