Passenger lymphocyte syndrome in liver transplant recipients: a description of 12 cases

Samuel Romero, Pilar Solves, Aima Lancharro, Isabel Cano, Federico Moscardó, Nelly Carpio, Miguel Á. Sanz

Department of Haematology and Haemotherapy, La Fe University Hospital, Valencia, Spain

Background. Passenger lymphocyte syndrome is an important cause of immune haemolysis after solid organ transplantation. It mainly occurs in minor ABO and Rh mismatched transplants. The haemolysis is usually mild and self-limited. We present our experience in passenger lymphocyte syndrome and liver transplantation and review the literature.

Materials and methods. We reviewed liver transplants performed in our centre from January 2002 to September 2013, searching for ABO or Rh incompatibility and serological findings of haemolysis. A direct antiglobulin test was systematically performed in each pre-transfusion assessment.

Results. A total of 1,217 liver transplants were performed and 12 passenger lymphocyte syndromes were detected: of the 56 cases with minor ABO incompatibility, ten patients developed passenger lymphocyte syndrome (17.9%) and of 147 cases with minor Rh incompatibility, two patients developed the syndrome (1.40%). All patients with passenger lymphocyte syndrome had haemolysis, a decrease of haemoglobin (median 6.8 g/dL) and an increase of bilirubin (median 5.15 mg/dL). The treatment of passenger lymphocyte syndrome consisted of increasing the dose of corticosteroids that the patients were receiving as post-transplantation immunosuppressive therapy and, in the majority of cases, transfusion of donor compatible red blood cells.

Discussion. Passenger lymphocyte syndrome in liver transplantation has significant clinical consequences. It is, therefore, important to make the diagnosis rapidly, performing pre-transfusion direct antiglobulin tests, and manage the problem correctly with donor compatible red blood cell transfusions and/or immunosuppressive treatment.

Keywords: direct antiglobulin test, haemolysis, liver transplantation, passenger lymphocyte syndrome, red blood cells.

Introduction

Passenger lymphocyte syndrome (PLS) is an important cause of immune haemolysis after solid organ and haematopoietic stem cell transplantation[1,2]. It mainly occurs in minor ABO and Rh mismatched transplants, although in rare cases Jk^{a} [3], Kp^{b} [4], Fy^{a} [5] and M[6] have been reported to be implicated. PLS consists of the production of antibodies by donor passenger lymphocytes, transplanted with the graft, against the recipient's red blood cell (RBC) antigens. It has been observed after kidney, lung, heart-lung, liver, pancreas, pancreas-spleen and hematopoietic cell progenitor transplantation[7].

The risk of haemolysis increases with a higher mass of lymphocytes transplanted with the graft, being more frequent in lung-heart transplants (around 70%) followed by liver transplants (around 40%) and kidney transplants (around 17%)[7]. When the donor lymphocytes infused proliferate, they produce an immune response that may be primary or secondary (anamnestic), with the onset of haemolysis occurring between 3 and 24 days after the transplant. The haemolysis is usually mild and self-limited. The direct antiglobulin test (DAT) becomes positive in the recipient and antibodies against A, B or both RBC antigens are detectable in serum and eluate. Antibodies against Rh and other RBC antigens have also been reported[5,8,9]. HLA compatibility is not usually considered in solid organ transplantation, however PLS occurs regardless of HLA compatibility[10]. The treatment includes transfusion of group O RBC or antigen-negative RBC units. In rare cases in which severe haemolysis occurs, additional treatments, such as stronger immunosuppression or plasma exchange, may be necessary[11-13].

La Fe Hospital in Valencia (Spain) has long experience in liver transplantation. Our objective was to analyse liver transplants performed in our centre and to describe the clinical and serological findings in the cases of PLS detected.

Materials and methods

Study population and data collection

The records of patients who underwent orthotopic liver transplantation during the period from January 2002 to September 2013 at La Fe University Hospital in Valencia were carefully reviewed, searching for ABO and/or Rh incompatibility. Minor ABO incompatibility was defined by the presence in the donor of ABO antibodies directed against the recipient's RBC. In most cases of PLS, the donor has O group blood and the recipient has A group and donor lymphocytes, therefore, produce anti-A antibodies against the recipient RBC antigen A. Other combinations, such as donor group O or A and recipient group B, occur more rarely. Minor Rh incompatibility occurs in liver transplants from Rh D-negative donors to Rh D-positive recipients.

The cases were also reviewed looking for serological and laboratory data of haemolysis which was evidenced by a decrease of haemoglobin concentration, increase of bilirubin level, the presence of a positive DAT and exclusion of other causes of decreased haemoglobin and increased bilirubin level. Clinical data and transfusion history were collected from an electronic hospital-based transfusion and clinical database. All clinical data concerning times refer to days after the liver transplant.

Once a case of PLS had been detected, clinical data were collected focusing on transfusion management and immunosuppressive treatment. The pre-PLS immunosuppressive treatment refers to the drugs that were administered in the period between the liver transplant and the detection of PLS.

Serological tests

The diagnosis of PLS was made when the recipient had a positive DAT and there were donor antibodies in the serum and eluate against the recipient's RBC antigens.

During the 3 months after transplantation, in addition to the routine ABO, Rh typing and RBC antibody screening test or indirect antiglobulin test (IAT), the DAT was systematically performed in pre-transfusion compatibility assessments in order to detect immunohaematological problems related to haemolysis. The DAT was performed routinely before every transfusion since 2006 while prior to that date, it was only performed if haemolysis was suspected.

The DAT was performed on RBC in samples collected into ethylenediaminetetra-acetic acid according to standard methods. RBC eluates were prepared by acid elution (Elu-Kit II, Gamma Biologicals, Houston, TX, USA). Eluates and sera of patients with positive results were tested for specificity using panels of RBC with known antigens (Ortho Clinical Diagnostics Inc., Raritan, NJ, USA; Bio-Rad GmbH, Cressier-sur-Morat, Switzerlandand; Makropanel, Menarini, Amsterdam, The Netherlands).

Patients who developed antibodies to RBC antigens, which were considered clinically significant, received blood that was negative for the identified antigen. RBC units were transfused following a type & screen, but when a significant antibody was detected a cross-match was performed.

Statistical analysis and literature review

Statistical comparisons were performed using the chi-square test or, when the number in any group was less than five, Fisher's exact test. p-values <0.05 were considered statistically significant.

A review of the literature was carried out through different search strategies based on data in the online U.S. National Library of Medicine (PubMed). Searches were conducted on July 01, 2013.

Results

Liver transplantation and passenger lymphocyte syndrome

During the study period, 1,217 liver transplants were performed at La Fe University Hospital, of which 156 (12.8%) with minor ABO incompatibility and 147 (12.1%) with minor Rh incompatibility. Of the 156 cases with minor ABO incompatibility, ten had PLS (17.9%), and two of the 147 patients with minor Rh incompatibility developed PLS (1.4%). Therefore, a total of 12 cases of PLS were detected.

Clinical features

Table I presents the patients' main clinical features. The median age of the patients was 46.5 years; 75% were males and 25% were females. Most of the patients had had a first liver transplant[14], although one patient had undergone a second transplant procedure. Currently two-thirds of patients are alive. Deaths were due to causes other than PLS.

All patients suffering PLS developed haemolysis. The median nadir haemoglobin level was 6.8 g/dL (range, 3.4-8.1 g/dL) on post-operative day 15 (range, day 10 to day 56) and the median peak bilirubin concentration was 5.15 mg/dL (range, 2.77-49.15 mg/dL) on post-operative day 13 (range, day 10 to day 59).

As shown in Table I, all patients received immunosuppressive treatment after their liver transplant. In most of the cases of PLS, the dose of corticosteroids that patients were receiving was increased up to 1 mg/kg/day; only one patient did not receive corticosteroids as treatment of PLS and in three cases information was not available. In addition, all patients received RBC transfusions during the episode of

PLS. All patients except one (case 3) were transfused with donor compatible RBC and received a median of four RBC units (range, 2-8 RBC units). Two patients (cases 6 and 9) received, besides the donor compatible RBC, several recipient compatible RBC units because of the short time between the first positive DAT and the need for RBC transfusion. Case 3 had a positive DAT on day 13; nevertheless, the test was not studied until day 18, when the diagnosis of PLS was made. The donor's ABO group was O+ whereas that of the recipient was B+. In the period between the test and its interpretation, the patient received six units of B+ RBC. In these three cases, the antibody screen before transfusion was negative. Moderate haemolysis occurred after transfusion.

Serological findings

Table II shows the main serological findings of all the cases. Of the 12 cases of PLS described, the antibody detected was anti-A in six cases, anti-B in four cases and anti-D in two cases. All the donors had a prior, negative IAT. The median post-operative time of detection of the first positive DAT was 12.5 days (range, 10-56 days). In half of the cases, the DAT was positive once, while it was positive more than once in the rest of the cases. Before implementing routine DAT prior to each RBC transfusion, we detected one PLS in 14 minor ABO mismatched transplants, while subsequently we detected nine PLS in 42 minor ABO mismatched liver transplants and two PLS in 110 liver transplants with minor Rh mismatching (p=non-significant).

Table I - Clinical features of the patients with PLS.

Case	Age	Gender	Haemoglobin		Total bilirubin		Haemolysis	IS pre-PLS treatment	Treatment PLS	
			Day of min. level	*(g/dL)*	*Day of max level*	*(mg/dL)*			*RBC (ABO Rh)*	*IS*
1	40	Male	18	6.6	17	49.15	Yes	CS + CSA	4 (0+)	nd
2	52	Male	29	7.9	36	6.87	Yes	CS + CSA	2 (0+)	CS
3	57	Male	15	6.6	13	11.46	Yes	CS + TAC	6 (B+)#	CS
4*	49	Male	16	6.4	14	4.80	Yes	CS + CSA + MMF	4 (A−)	CS
5	17	Female	13	3.4	13	8.20	Yes	CS + TAC	8 (0−)	CS
6	42	Male	11	5.0	11	4.79	Yes	CS + CSA	1 (AB+)#, 2 (0−), 1 (0+)	CS
7	45	Male	15	8.1	10	10.55	Yes	CS + CSA + MMF	2 (0−)	nd
8	49	Male	31	6.8	19	3.10	Yes	CS + MMF + TAC	4 (0+)	CS
9	48	Male	10	6.8	10	5.50	Yes	CS + MMF + TAC	1 (A+)#, 1 (0+)	nd
10	41	Female	12	7.9	12	2.95	Yes	CS + TAC	2 (0+)	CS
11	49	Male	12	6.8	11	4.34	Yes	CS + CSA + MMF	4 (0−)	CS
12	41	Female	56	6.8	59	2.77	Yes	CSA + MMF	4 (0−)	No

PLS: Passenger lymphocyte syndrome; IS: immunosuppression; RBC: red blood cell; CS: corticosteroids; CSA: cyclosporine A; MMF: mycophenolate mofetil; TAC: tacrolimus; nd: no data available; *CSA was decreased, because of renal toxicity, from 400 mg/12 h to 200 mg/12 h and MMF was added at a dose of 1,000 mg/12 h. #Transfusions of donor incompatible RBC.

Table II - Serological investigation of patients with PLS.

Case	ABO and Rh group		DAT IgG-C3d first positive*			DAT last positive	Eluate	IAT	Ab serum
	Donor	*Recipient*	*Day*	*IgG*	*C3d*				
1	0−	B−	17	nd	nd	30	Anti-B	Negative	Negative
2	0−	A+	24	Positive	Negative	24	Anti-A	Negative	Negative
3	0+	B+	13	Negative	Positive	18	Anti-B	Negative	Anti-B
4	A−	A+	11	Positive	Negative	16	Anti-D	Positive	Anti-D
5	0+	A−	13	nd	nd	13	Anti-A	Negative	Anti-A, anti-B
6	0+	AB+	11	nd	nd	11	Anti-B	Negative	Anti-A, anti-B
7	0−	A−	10	nd	nd	10	Anti-A	Negative	Negative
8	0+	A+	19	nd	nd	36	Anti-A	Negative	Negative
9	0+	A+	10	Negative	Positive	13	Anti-A	Negative	Negative
10	0+	B+	12	Negative	Positive	12	Anti-B	Negative	Negative
11	B+	AB−	11	Positive	Positive	16	Anti-A	Negative	Anti-A
12	0−	0+	56	nd	nd	56	Anti-D	Positive	Anti-D

PLS: Passenger lymphocyte syndrome; DAT: direct antiglobulin test; IgG: immunoglobulin G; C3d: complement 3d; IAT: indirect antiglobulin test; Ab serum: antibodies in serum. *When no data were available (nd), DAT positive refers to polyspecific antiglobulin.

Discussion

This study shows that PLS is a relevant clinical syndrome which must be kept in mind as an immune complication of solid organ transplantation. In our series the prevalence of PLS among minor ABO mismatched liver transplants was about 20% and all our patients had haemolysis, in contrast with the other large series of patients published by Ramsey[15]. This Author found that the frequency of PLS was between 29% and 40%, with haemolysis occurring in 44% and 18% of anti-A and anti-B antibody-mediated PLS, respectively. This probably means that we only diagnosed those cases presenting with anaemia and haemolysis and, therefore, requiring RBC transfusion. We are aware that at least the same number of cases of PLS without apparent haemolysis will have occurred, and that these cases went undetected.

Reviewing the literature (Table III), we found 56 cases in which antibodies against A and B antigens were detected[14-22], nine cases with anti-D[8,10,23-27] and seven cases in which other RBC antibodies were detected[3-6,10]. All cases except some of those published by Ramsey[15] and the case in which anti-M was implicated[4], presented with haemolysis and required at least donor compatible RBC transfusions.

Our Institution previously published data on PLS detected in a period from January 1991 to June 2001[21]. Two cases of ABO-related PLS (9% of ABO mismatched liver transplants) and two cases of Rh-related PLS (0.83% of all Rh mismatched liver transplants) were detected. Better knowledge of the syndrome and greater suspicion of its presence lead to more diagnoses.

The PLS detected in our Institution before and after implementing systematic DAT were not statistically different except for those involving minor Rh incompatibility. However, antibodies against Rh antigens are detected in the antibody screening, which becomes positive, so they can be diagnosed without DAT. It should be noted that the number of ABO and Rh mismatched transplants has increased with time. In our experience, performing DAT as a routine pre-transfusion test has been critical for a rapid diagnosis of PLS. As antibodies arising in PLS are transient (3 months in the case of ABO antibodies and even 1 year for Rh antibodies)[13], we support the use of DAT as usual practice during the first 3 months after liver transplantation.

Concerning treatment, all our patients received at least RBC transfusion with donor compatibles units,

Table III - Review of PLS reported in patients who underwent orthotopic liver transplantation.

Donor	Recipient	Ab specificity (n. of cases)	Haemolysis	Reference
O	A	Anti-A	Yes	Bracey AW, *et al.* (1987)[14]
O	A	Anti-A (32)	Yes 44 %	Ramsey G (1991)[15]
O	B	Anti-B (11)	Yes 18 %	Ramsey G (1991)[15]
O	A	Anti-A (5)	Yes	Triulzi DJ (1992)[16]
A Rh−	A Rh+	Anti-D	Yes	Kim BK, *et al.* (1992)[23]
Rh−	Rh+	Anti-D	Yes	Schwartz D, *et al.* (1992)[24]
A Rh−	A Rh+	Anti-D	Yes	Lee JH, *et al.* (1993)[25]
O	A	Anti-A	Yes	Sindhi R, *et al.* (1996)[17]
O	A	Anti-A	Yes	Jacobs LB, *et al.* (1996)[18]
B	A	Anti-A	Yes	Kunimasa JI, *et al.* (1998)[19]
O	B	Anti-B	Yes	Kunimasa JI, *et al.* (1998)[19]
O Rh+, K−, Fy^a−	O Rh+, K+, Fy^a+	Anti-K, anti-Fy^a	No	Seltsam A, *et al.* (2001)[5]
O Rh+	A1 Rh+	Anti-A	Yes	Au WY, *et al.* (2002)[20]
Jk^a−	Jk^a+	Anti-Jk^a	Yes	Hareuveni M, *et al.* (2002)[3]
O Rh+	A Rh+	Anti-A (2)	Yes	Aguilera V, *et al.* (2003)[20]
O Rh−	A Rh+	Anti-D	Yes	Aguilera V, *et al.* (2003)[20]
A Rh−	A Rh+	Anti-D	Yes	Aguilera V, *et al.* (2003)[20]
O Rh−	O Rh+	Anti-D	Yes	Fung MK, *et al.* (2004)[8]
O	B	Anti-B	Yes	Bae SH, *et al.* (2005)[22]
O Rh−	O Rh+	Anti-D, -C, -k	Yes	Shortt J, *et al.* (2008)[10]
A Rh−	A Rh+	Anti-D, -C	Yes	Grosskreutz C, *et al.* (2008)[26]
A Rh+	A Rh+	Anti-M	No	Makuria, *et al.* (2009)[6]
A Rh−	A Rh+	Anti-D	Yes	Turiño Luque J, *et al.* (2012)[27]
Kp^b−	Kp^b+	Anti-Kp^b	Yes	Koepsell, *et al.* (2013)[4]

PLS: Passenger lymphocyte syndrome;

except the three cases that we have already explained. Case 3 is an example of the importance of rapid, correct detection of the syndrome in order to implement adequate transfusion management. This patient suffered a delay of 5 days in the diagnosis, during which period he was improperly transfused with six B+ RBC units (recipient identical). For this reason, the patient had haemolysis associated with transfusion of donor incompatible RBC and received a higher number of RBC units than the median for all patients. Subsequently, the patient did not require additional transfusions. In the other two cases, patients received only one donor incompatible RBC unit and haemolysis was self-limited. Some authors have considered donor compatible transfusions during surgery as a prophylactic measure against the appearance of the syndrome in minor ABO mismatched liver transplants[28]. In this sense, the risk of haemolysis is highest (44%) after group O to A liver transplants[15]. Our Institution does not follow this policy.

The other point related to the management of PLS is the use of corticosteroids as a pharmacological treatment. All our patients but one received corticosteroids as additional treatment to donor compatible RBC transfusions. The dose given was 1 mg/kg/day which was maintained until resolution of haemolysis. It has been reported in the literature that most cases of PLS can be managed by transfusion of compatible RBC and the empirical use of corticosteroids[13]. However, in rare cases presenting with massive haemolysis it may be necessary to use other strategies, such as plasma or RBC exchange, intravenous immunoglobulins, monoclonal antibodies such as rituximab or even splenectomy[5,9-11,29]. None of our patients required additional treatment besides RBC transfusions and corticosteroids.

Conclusion

In conclusion, PLS is a cause of haemolysis that must be suspected in patients who have undergone ABO or Rh mismatched liver transplantation. This syndrome can have significant clinical consequences because of the haemolysis; it is, therefore, necessary to make the diagnosis and to initiate the correct treatment. We suggest implementation of DAT as a routine pre-transfusion test in order to make an early diagnosis. The appropriate management of PLS involves donor compatible RBC and/or immunosuppressive or immunomodulatory treatment.

Acknowledgements

The Authors thank the staff of the Blood Bank at Hospital La Fe (Valencia, Spain), including the trainee physicians who worked temporarily in the Bank.

Authorship contributions

SR and PS: study supervision. AL and IC: data collection. FM: data analysis. SR, NC and MAS critical revision and evaluation of the article.

The Authors declare no conflicts of interest.

References

1) Maheswari A, Mishra R, Thuluvath PJ. Post-liver transplant anemia: etiology and management. Liver Transplant 2004; **10**: 165-73.
2) Smith EP. Hematologic disorders after solid organ transplantation. Haematology Am Soc Hematol Educ Program 2010; **2010**: 281-6.
3) Hareuveni M, Merchav H, Austerlitz N, et al. Donor anti-Jk[a] causing hemolysis in a liver transplant recipient. Transfusion 2002; **42**: 363-7.
4) Koepsell SA, Landmark JD. Passenger lymphocyte syndrome: use of archived donor organ biopsy obtained at the time of transplantation for diagnosis. Am J Transplant 2013; **13**: 2227.
5) Seltsam A, Hell A, Heymann G, Salama A. Donor-derived alloantibodies and passenger lymphocyte syndrome in two of four patients who received different organs from the same donor. Transfusion 2001; **41**: 365-70.
6) Makuria AT, Langeberg A, Fishbein TM, Sandler SG. Nonhemolytic passenger lymphocyte syndrome: donor-derived anti-M in an M + recipient of a multiorgan transplant. Immunohematology 2009; **25**: 20-5.
7) Yazer MH, Triulzi DJ. Immune hemolysis following ABO-mismatched stem cell or solid organ transplantation. Curr Opin Hematol 2007; **14**: 664-70.
8) Fung MK, Sheikh H, Eghtesad B, Lopez-Plaza I. Severe hemolysis resulting from D incompatibility in a case of ABO-identical liver transplant. Transfusion 2004; **44**: 1635-9.
9) Nadarajah L, Ashman N, Thuraisingham R, et al. Literature review of passenger lymphocyte syndrome following renal transplantation and two case reports. Am J Transplant 2013; **13**: 1594-600.
10) Shortt J, Westall GP, Roxby D, et al. A dangerous group O donor: severe hemolysis in all recipients of organs from a donor with multiple red cell alloantibodies. Am J Transplant 2008; **8**: 711-4.
11) Hoffman PC. Immune haemolytic anemia-selected topics. Haematology Am Soc Hematol Educ Program 2009; **2009**: 80-6.
12) Audet M, Panaro F, Piardi T, et al. Passenger lymphocyte syndrome and liver transplantation. Clin Dev Immunol 2008; **2008**: 71569.
13) Petz LD. Immune hemolysis associated with transplantation. Semin Hematol 2005; **42**: 145-55.
14) Bracey AW. Anti-A of donor lymphocyte origin in three recipients of organs from the same donor. Vox Sang 1987; **53**: 181-3.
15) Ramsey G. Red cell antibodies arising from solid organ transplants. Transfusion 1991; **31**: 76-86.
16) Triulzi DJ, Shirey RS, Ness PM, Klein AS. Immunohematologic complications of ABO-unmatched liver transplants. Transfusion 1992; **32**: 829-33.
17) Sindhi R, Lansmark J, Shaw BW, et al. Combined liver/small bowel transplantation using a blood group compatible but nonidentical donor. Transplantation 1996; **61**: 1782-3.
18) Jacobs LB, Shirey RS, Ness PM. Hemolysis due to the simultaneous occurrence of passenger lymphocyte syndrome and a delayed haemolytic transfusion reaction in a liver transplant patient. Arch Pathol Lab Med 1996; **120**: 684-6.

19) Kunimasa J, Yurugi K, Ito K, et al. Hemolytic reaction due to graft-versus-host (GVH) antibody production after liver transplantation from living donors: report of two cases. Surg Today 1998; **28**: 857-61.
20) Au WY, Lo CM, Fan ST, et al. Life-threatening abo-mediated hemolysis after cadaveric orthotopic liver transplantation. Transplantation 2002; **74**: 285-6.
21) Aguilera V, Arriaga F, de la Rubia J, et al. [Anemia hemolítica por anticuerpos del sistema ABO o Rh en pacientes receptores de trasplante de órgano sólido]. Med Clin (Barc) 2003; **120**: 177-9. [In Spanish].
22) Bae SH, Jang JW, Kim MS, et al. A case of hemolysis in ABO-unmatched liver transplantation: use of washed group O red blood cells and steroids. Korean J Gastroenterol 2005; **45**: 369-73.
23) Kim BK, Whitsett CF, Hillyer CD. Donor origin Rh antibodies as a cause of significant hemolysis following ABO-identical orthotopic liver transplantation. Immunohematology 1992; **8**: 100-1.
24) Schwartz D, Götzinger P. Immune-haemolytic anaemia (IHA) after solid organ transplantation due to rhesus antibodies of donor origin: report of 5 cases. Beitr Infusionsther 1992; **30**: 367-9.
25) Lee JH, Mintz PD. Graft versus host anti-Rho (D) following minor Rh-incomptible orthotopic liver transplantation. Am J Hematol 1993; **44**: 168-71.
26) Grosskreutz C, Gudzowaty O, Shi P, et al. Partial HLA matching and RH incompatibility resulting in graft versus host reaction and Evans syndrome after liver transplantation. Am J Hematol 2008; **83**: 599-601.
27) Turiño-Luque J, Zambudio-Carroll N, Muffak-Granero K, et al. Early detection of biliary complications and graft rejection in a non-Rh identical liver transplant recipient from a non-heart-beating donor: a case report. Transplant Proc 2012; **44**: 2124-5.
28) Shanwell A, Eleborg L, Blomqvist BI, et al. Hemolysis in ABO-compatible liver transplantation--only after O grafts? Transplant Proc 1989; **21**: 3532.
29) Lee HJ, Gulbis A, De Padua Silva L, et al. Rituximab for passenger lymphocyte syndrome associated with allogeneic SCT. Bone Marrow Transplant 2008; **42**: 67-9.

Arrived: 12 June 2014 - Revision accepted: 3 March 2015
Correspondence: Samuel Romero Domínguez
Department of Haematology and Haemotherapy
Hospital La Fe
Avenida Fernando Abril Martorell 106
46026 Valencia, Spain
e-mail: romero_sam@gva.es