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Spleen sizing by ultrasound scan and risk of pneumococcal infection in patients with chronic GVHD: preliminary observations

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Summary:

Encapsulated bacteria infections (EBI) can cause severe complications after BMT, usually occurring in patients with chronic GVHD (cGVHD) and attributed to functional hyposplenism. Using ultrasound (US) scan, we measured spleen size in 22 patients transplanted from HLA identical siblings, with or without cGVHD. No patient had received TBI, spleen irradiation or penicillin prophylaxis. Results were correlated with occurrence of EBI during a mean follow-up of 55 months (range 7–93). In the group without cGVHD, the difference between pre- and post-BMT spleen longitudinal diameters was not significant, and no patient developed EBI. In the cGVHD group, post-BMT spleen longitudinal diameters were significantly smaller than those pre-BMT (9.1 ± 1.6 *vs* 12.3 ± 2.2; $P = 0.0005$). Out of four patients with cGVHD who showed a major spleen size reduction, two developed a severe infection (an overwhelming sepsis and a pneumococcal meningitis). In our small series, we found a borderline relationship between spleen size reduction and duration of cGVHD ($P = 0.06$), as well as an increased risk of life-threatening infection in patients with extensive cGVHD and hyposplenism as detected by US scan. We conclude that US scan may be useful to detect spleen size reduction following allogeneic BMT and that penicillin prophylaxis is to be strongly recommended in patients with extensive cGVHD and spleen size reduction, even in those who have not received total body or spleen irradiation.

Keywords: ultrasound scan; hyposplenism; encapsulated bacteria infection; *Streptococcus pneumoniae*; chronic GVHD

Chronic GVHD (cGVHD) is a frequent complication of allogeneic BMT, and may have serious clinical implications. About one-half of patients undergoing BMT from an HLA-matched sibling develop cGVHD, which may affect various body sites.[1,2] cGVHD and subsequent immunosuppressive treatment may induce increased susceptibility to pneumococcal and other encapsulated bacterial infections (EBI),[1,3–6] for which long-term or life-long penicillin V (or other oral B-lactams) prophylaxis have been recommended.[3,7] However, the emergence of penicillin-resistant pneumococcal infections is a wordwide problem[8,9] occurring in both immunocompetent[10,11] and immunocompromised[12] patients. Since prolonged treatment with oral B-lactams may favor antibiotic resistance[13–15] and may produce side-effects such as diarrhea, colitis and pseudo-membranous colitis,[16] prudent and proper use of oral penicillin is suggested.

Although several factors may contribute to immune response failure after sibling transplant[17,18] the spleen seems to be a key element in host defence against encapsulated bacteria;[11] post-BMT functional hyposplenism, attributed to the TBI regimen, has already been documented.[19]

In this study we used ultrasound (US) scan to evaluate spleen size in bone marrow transplant patients and correlated spleen size with the occurrence of cGVHD and of EBI.

Patients and methods

From October 1991 to November 1998, we studied 22 unselected adult patients who had undergone BMT from an HLA-identical sibling for hematological malignancies and survived more than 6 months. About one-half of them presented with cGVHD, histologically documented and classified according to established criteria.[20] Patient characteristics are shown in Tables 1 and 2. All patients were given Bu-Cy as conditioning, except patients 11, 19 and 22, who received respectively Cy only, Cy-Thiotepa and Bu-Cy-Melphalan; all had CsA plus short course MTX as acute GVHD prophylaxis; none had TBI or spleen irradiation and none received penicillin prophylaxis in the post-BMT period. All spleen US scans were performed by the same operator, a hematologist trained in medical ultrasonography, using a portable Hitachi (Tokyo, Japan) instrument with a 3.5 MHz probe. The spleen was scanned in the longitudinal and transverse planes, with the subject in the supine position, until complete visualization of the organ was achieved.[21] Longitudinal and diagonal diameters (defined as the maximum length and width, measured with splenic borders and angles clearly defined) were measured and the perimeter was marked on the scan, so that the area was automatically calculated. Reference values were obtained from 10 age-matched normal subjects. In both groups of patients (with or without cGVHD), pre-BMT US spleen size (only longitudinal diameters were available) was compared with post-BMT size. Univariate analysis of quantitative variables was performed using Student's *t*-test.

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Table 1 Details of transplanted patients without chronic GVHD

Pt.	*Sex, age (years)*	*Basic disease*	*Splenic size by US scan*				*Encaps. bact. infection*	*Outcome (mo. from BMT)*
			pre-BMT	*post-BMT*				
			long	*long*	*diag*	*area*[a]		
1	F, 31	CML	10.5	9.1	3.5	25	none	A&W + 91
2	M, 24	AML	10	10.5	3	27	none	A&W + 89
3	F, 43	CML	9.5	11.2	4	41.4	none	A&W + 87
4	F, 32	CML	15	11.7	3.4	35	none	A&W + 84
5	F, 21	AML	9	11.7	3.4	40.4	none	A&W + 83
6	F, 23	AML	9.5	12.5	4.4	39	none	A&W + 78
7	M, 47	AML	12	12.5	3.9	44	none	A&W + 43
8	M, 45	AML	10	9.2	3	20	none	A&W + 39
9	F, 25	CML	10	10	4.3	38	none	A&W + 10
10	M, 34	CML	15	11	3.7	40	none	A&W + 10

US = ultrasound; long = longitudinal diameter, cm; diag = diagonal diameter, cm; AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia; CML = chronic myeloid leukemia.
[a]Automatically calculated from the longest spleen perimeter in cm^2.

Finally, we evaluated the incidence of EBI in all patients, as proved by positive cultures or by typical clinical findings, over a mean follow-up of 55 months (range 7–93).

Results

All US examinations were informative, accurately detecting spleen size (Tables 1 and 2). In the group of patients without cGVHD, there was no significant difference between pre- and post-BMT longitudinal diameters, nor between post-BMT spleen size and those of the control group. In the cGVHD group, post-BMT longitudinal diameters were significantly smaller than those pre-BMT ($P = 0.0005$). Post-BMT longitudinal diameters and areas were significantly smaller than those in the group without cGVHD and those of the control group. In particular, four patients with cGVHD (cases 14, 15, 18 and 19) had a post-BMT spleen size far below the mean normal value. Diagonal diameters were not significantly different among the three groups (Table 3).

Spleen size reduction was present in patients with both limited and extensive cGVHD, and with both short and long duration of cGVHD. While no relationship was found between size reduction and severity of the cGVHD ($P = 0.67$), a borderline correlation was present with the duration of cGVHD ($P = 0.06$). Two patients developed a life-threatening infection; both had the smallest US spleen size (Figure 1) and had extensive cGVHD. Patient 14 developed a rapidly fatal septic fever with disseminated intravascular coagulation and multiorgan failure, which was suggestive of pneumococcal infection. Patient 18 had pneumococcal meningitis proven by CSF culture, which responded to penicillin.

Discussion

Our data show that transplant patients suffering from cGVHD may develop significant spleen size reduction which may lead to life-threatening infections, even in the absence of total body or spleen irradiation. We could not find a statistically significant relationship between spleen size reduction and severity of cGVHD, while a weak correlation emerged between size reduction and cGVHD duration. Moreover, patients who developed a life-threatening infection had the smallest spleen size and extensive cGVHD. The mechanism(s) by which the splenic tissue is reduced in patients with cGVHD remains a matter of speculation. We were able to exclude a role for radiation during conditioning, since none of our patients had received radiation. It is also unlikely that the cause is graft-induced damage of the splenic lymphoid tissue, since after immunological reconstitution most of this should be of donor origin. Possible explanations are graft-induced damage of host-derived accessory or stromal cells, or atrophy of the lymphoid splenic tissue due to the treatment of cGVHD. Hyposplenism is described in other immune-mediated diseases, such as coeliac disease[22] and inflammatory bowel disease.[23] The shrinking of splenic tissue is also reminiscent of the immune-mediated pancreatic tissue hypotrophy that can be detected by US scan in diabetic patients.[24]

To the best of our knowledge, this is the first report that has employed US scanning to investigate spleen size in allograft patients. Compared to radionuclide techniques, US scan is a non-invasive, inexpensive, fast and easy tool for measuring spleen dimensions.[25] However, we concede that US assessment of hyposplenism is only partially reliable: longitudinal diameter may not represent the real volume of the organ,[21] and linear diameters may not correspond accurately to the area.

In conclusion, sequential spleen measurements by US in patients with cGVHD can help to distinguish patients with a higher risk of pneumococcal infection, and thus needing long-term antibiotic prophylaxis. Our current policy is to strongly recommend penicillin V prophylaxis in the patient subset with US splenic size reduction and extensive cGVHD. A study of larger cohorts of patients is needed in order to better define pneumococcal infection risk factors.

Table 2 Details of transplanted patients with chronic GVHD

Pt	*Sex, age (years)*	*Basic disease*	*Chronic GVHD*			*Splenic size by US scan*				*Encaps. bact. infection*	*Outcome (mo. from BMT)*
			Grade	*Duration (months)*	*Treatment*	*pre-BMT*	*post-BMT*				
						long	*long*	*diag*	*area*[a]		
11	F, 30	SAA	extensive	89	CsA+Prd, Az	12	9	2.8	28.4	none	A&W + 93
12	M, 25	CML	extensive	43	CsA+Prd	10.5	10.5	3.8	34.8	none	A&W + 68
13	M, 42	AML	extensive	56	Az	12	12	4.5	42.5	none	A&W + 66
14	F, 31	CML	extensive	60	CsA+Prd,Az	18	7	2.5	13	septic shock likely by SP	died of fulminant sepsis 61
15	F, 49	AML	limited	40	CsA+Prd	10	7.5	4.4	26	none	A&W + 60
16	M, 41	CML	extensive	27	CsA+Prd, Az	12.4	10	4.1	34.4	none	A&W + 58
17	M, 25	HD	extensive	16	Prd	13	9.2	2.5	21.1	none	A&W + 36
18	M, 39	AML	extensive	15	CsA+Prd, Az	11	7.1	2.6	17.8	meningitis by SP	died of leukemia relapse 35
19	F, 18	ABL	limited	14	CsA+Prd	10	7.5	2.5	14	none	A&W + 35
20	F, 22	CML	limited	13	Az	15	10.5	3.5	29.7	none	A&W + 34
21	M, 38	AML	limited	12	CsA+Prd	12	10	3.5	30.7	none	A&W + 30
22	F, 30	ABL	limited	12	none	12	8.6	3.5	24.5	none	A&W + 30

US = ultrasound; long = longitudinal diameter, cm; diag = diagonal diameter, cm; ABL = acute biphenotypic leukemia; CML = chronic myeloid leukemia; HD = Hodgkin's disease; SAA = severe aplastic anaemia; AML = acute myeloid leukemia; CsA = cyclosporin A; Prd = prednisone; Az = azathioprine; SP = *Streptococcus pneumoniae*.
[a]Automatically calculated from the longest spleen perimeter in cm^2.

Table 3 Spleen size comparison between normal subjects and post-BMT patient groups

Group	*Longitudinal*			*Diagonal*			*Area*		
	cm ± s.d.	*P*		*cm ± s.d.*	*P*		*cm² ± s.d.*	*P*	
Control[a]	10.63 ± 0.8	0.52	**0.01**	3.79 ± 0.39	0.52	0.11	33.05 ± 4.6	0.52	**0.04**
cGVHD absent	10.94 ± 1.22	**0.006**		3.7 ± 0.5	0.27		35 ± 8.1	**0.02**	
cGVHD present	9.06 ± 1.6			3.35 ± 0.75			26.4 ± 8.87		

[a]Ten age-matched normal subjects.
Bold, statistically significant difference.

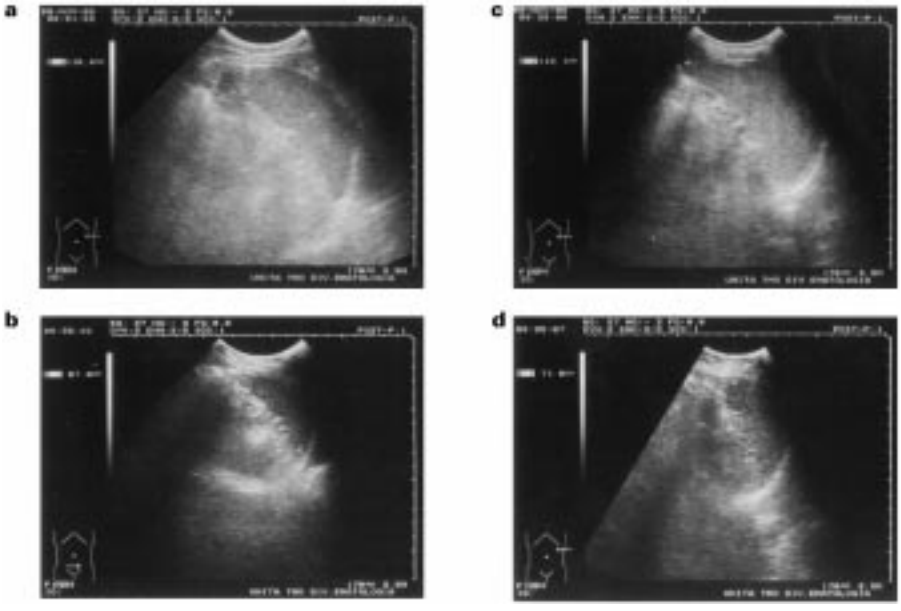

Figure 1 Ultrasound spleen size of two patients with cGVHD (**b** and **d**: cases 14 and 18) compared with that of sex- and age-matched transplanted patients without cGVHD (**a** and **c**).

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