

B-Cell Reconstitution After Autologous Bone Marrow Transplantation: Increase in Serum CD23 ("IgE-Binding Factor") Precedes IgE and B-Cell Regeneration

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The serum levels of IgE and the soluble cleavage product of CD23 (sCD23) were prospectively monitored for up to 1 year after transplantation in 34 patients who underwent autologous (n = 33) or syngeneic (n = 1) bone marrow transplantation (BMT). In 25 patients (74%), a transient IgE peak (two- to 2,750-fold increase) appeared in the serum 3 to 4 weeks after BMT. In 18 patients (51%), a two- to 125-fold increase in sCD23 coincided with the IgE peak. In only three patients was a sCD23 peak observed without a concomitant increase in IgE. The sCD23 increment pre-

ceded the IgE peak in each individual case. During the period of increased sCD23 serum levels, the absolute numbers of circulating B cells and other cell types expressing surface CD23 were extremely low. The biologic significance of these findings is discussed in light of present knowledge of regulation of B-cell growth and differentiation with special reference to the role of sCD23 as a multifunctional cytokine.

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AN EARLY TRANSIENT increase in serum IgE levels has been described after allogeneic bone marrow transplantation (BMT). Initially, this IgE peak was considered a sign of graft-v-host disease (GVHD).¹⁻³ It was, however, subsequently reported to occur without any correlation to GVHD or infectious episodes.⁴ The etiology and significance of the transiently increased IgE levels after BMT are unclear. A similar transient increase in IgD after BMT was recently described.⁵ Immunosuppressive treatment with corticosteroids,^{6,7} total body irradiation (TBI), and cyclophosphamide⁸ enhanced IgE synthesis and were thus considered to contribute to the IgE increase after BMT. However, since IgE elevations were reported even in infants with severe combined immunodeficiency (SCID) transplanted without prior myeloablative therapy,^{4,9} this possibility appears less likely. Furthermore, the alterations within T cell subsets observed after BMT may influence B-cell function with resulting dysregulation of IgE secretion.¹⁰

Recent studies of B-cell regulation/differentiation have focused on IgE and especially the B-cell 45-Kd low-affinity receptor for the Fc part of IgE (FcεR).¹¹ This receptor was recently demonstrated to be identical with the CD23 molecule earlier defined by monoclonal antibodies (MoAbs).^{12,13} A 25- to 35-Kd cleavage product of surface CD23 has been claimed to be capable of modulating the synthesis of IgE.¹⁴⁻¹⁸

We measured serum IgE in parallel with circulating soluble CD23 (sCD23) before and prospectively after autologous bone marrow transplantation (ABMT). The cell surface expression of CD23 on B cells was also monitored prospectively.

MATERIALS AND METHODS

Patients. We studied 33 consecutive ABMT patients and one patient who underwent syngeneic BMT. Eighteen patients had high-risk common acute lymphoblastic leukemia (cALL), nine patients had acute myeloid leukemia (AML), two cases had T-cell ALL (T-ALL), three had Hodgkin's disease (HD) and one had B cell non-Hodgkin's lymphoma (NHL). One patient with myeloma received marrow from his identical twin. All patients received high-dose chemoradiotherapy as conditioning therapy. All patients with cALL, T-ALL, and NHL received grafts purged with MoAbs and two rounds of rabbit complement.¹⁹ Patients with cALL were purged with RFAL3 (CD10) and SB4 (CD19). T-ALL marrows were purged with RFT2 (CD7) and B-NHL marrows were purged

with SB4 and RFB7 (CD20). The RF MoAbs were provided by Professor G. Janossy of the Department of Immunology, Royal Free Hospital, London. SB4 was provided by Dr C. Bouloux, Sanofi Recherche, Montpellier, France. Hematologic engraftment was successful in every case. Serum was obtained one to two times weekly during the first 5 weeks and then at every checkpoint. Sera were stored at -20°C. Heparinized peripheral blood was obtained regularly for quantitation of CD23 expression on B and T cells, natural killer (NK)-like cells and monocytes after ABMT. Approval was obtained from the Institutional Review Board for these studies. Patients were informed that blood samples were obtained for research purposes and that their privacy would be protected.

Determination of serum IgE. IgE levels were determined with a commercial standard radioimmunoassay (RIA, Phadebas IgE, PRIST; Pharmacia, Uppsala, Sweden).

Determination of CD23. A sandwich enzyme-linked immunosorbent assay (ELISA) with two CD23 MoAbs recognizing different epitopes on the soluble molecule was used as described in detail elsewhere.²⁰ The level of soluble CD23 in the serum of normal healthy volunteers was always below the detection level of the assay (<5 ng/mL).

Cell preparation and immunofluorescence analyses. Mononuclear cells were prepared from heparinized blood samples by centrifugation over Ficoll-Hypaque (Pharmacia). After counting and washings, cells were stored in phosphate-buffered saline (PBS) supplemented with 10% fetal calf serum (FCS) and sodium azide. For determination of CD23 expression on mononuclear cells, the following FITC-conjugated MoAbs were used: Leu-12²¹ (CD19)

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defining B cells, Leu-4²² (CD3)-defining all T cells, Leu-M3²³ defining monocytes/macrophages, and Leu-11²⁴ (CD16) defining NK-like cells. All Leu MoAbs were purchased from Becton Dickinson (Mountain View, CA). For dual-color analysis of CD23 expression, cells were first incubated with the MoAb MHM6²⁵ (anti-CD23, provided by Dr A. Rickinson, Bristol, England) followed by washings and incubation with phycoerythrin (PE)-labeled rabbit anti-mouse IgG (F(ab)₂ fragment; Serotech, Oxford, England). Thereafter, free binding sites were blocked by incubation with 1% normal mouse serum, and washed cells were finally incubated with FITC-conjugated MoAb. Cells were then analyzed on the FACStar (Becton Dickinson) flow cytometer, equipped with a 5 W Argon ion laser run at 0.5 W and emitting at 488 nm. Green fluorescence (FITC) was collected through a 530/30 filter, and red fluorescence (PE) was collected through a 585/42 filter. At least 10,000 viable lymphocytes were gated and analyzed for red (PE) and green (FITC) fluorescence. For analysis of CD23 expression on Leu-M3⁺ cells, scatter gates were set on lymphocytes and monocytes. Data were processed with a Hewlett-Packard 217 computer (Fort Collins, CO) and Consort 30 (Becton Dickinson) software. Absolute lymphocyte counts were obtained with an automatic blood cell counter (Technicon H1, Tarry, NY).

RESULTS

Levels of serum IgE. In 29 patients studied before ABMT (day -5-0), the mean serum IgE level was 20 ± 7 kU/L (mean $\pm$ SEM) (Fig 1). At six to ten days after marrow infusion, the levels began to increase. A maximum peak value of $1,736 \pm 804$ kU/L was recorded between days 21 and 25, after which a slow decrease was observed. At 12

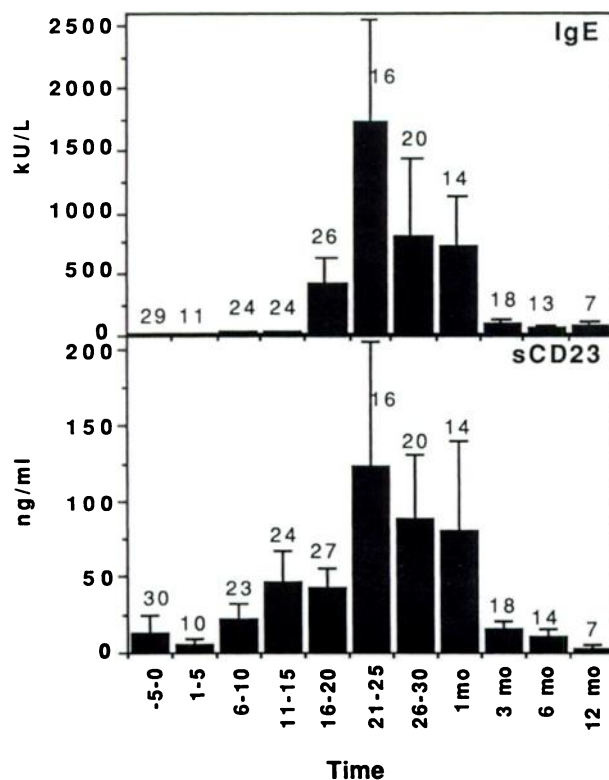


Fig 1. Serum levels of IgE and sCD23. Results are mean $\pm$ SEM. The numbers of patients analyzed at each time point are given. Normal control values: IgE 1.6-122 kU/L; sCD23 <5 ng/mL.

months after ABMT, many patients still had serum IgE values higher than pretransplant values. In 25 of 34 patients, an increase in IgE after ABMT was registered. In six patients, the pretransplant IgE levels were not determined because sera were lacking; therefore, peak values were compared with the earliest posttransplant levels. The mean increase was 536 ± 194 times the pretransplant level (range 2 to 2,750). Peak IgE levels were recorded at 3 to 4 weeks posttransplantation in every case. In four of the nine patients seemingly lacking IgE peaks, serum samples were lacking during the typical period of IgE elevation. These patients may also have had a transient IgE increase, since the half-life ($t_{1/2}$) of IgE is estimated to be two to three days.²⁶

Levels of CD23. In 18 of 34 patients analyzed, an increase in sCD23 occurred after ABMT (Fig 1). Before transplantation, only three patients had measurable amounts of CD23 in serum. Two of these patients, both of whom had AML, exhibited very high levels (320 and 3,150, respectively). They had no increase in sCD23 after transplantation; a decrease was recorded instead. The earliest increases in sCD23 were observed on day 6 through 10 after ABMT in ten patients. The peak value was recorded between 2 and 3 weeks after transplantation. Maximally, two- to 125-fold increases (18.2 ± 7.7) in the sCD23 levels were registered. In one patient with HD, sCD23 continued to increase up to +3 months, after which levels began to decrease. Three patients had a less prominent second elevation between 6 and 12 months after transplantation.

Correlation between serum IgE and CD23 values. In all patients with an increase in both serum sCD23 and IgE, the peak of sCD23 preceded that of IgE (Fig 2). Only three patients had an increase in sCD23 after ABMT without a concomitant IgE peak. However, in two of these three patients, sampling of sera was less frequent during the relevant period and an increase in IgE could thus not be fully ruled out. Conversely, six of the 25 patients with an IgE increase had no increase in sCD23. The levels or kinetics of serum IgE were not different in these patients as compared with patients who had a concomitant sCD23 peak.

CD23 expression on B cells. Because of the leukopenia during the first weeks, samples were analyzed before transplantation and then prospectively starting at +1 month. The absolute number of CD19⁺ B cells (Leu-12⁺) coexpressing CD23 (MHM6⁺) was already low before ABMT (Fig 3). Only 0.5 ± 1.4 (mean $\pm$ SEM) cells per microliter were positive for both markers as compared with 34.5 ± 14 in healthy controls ($P < .005$, Student's *t* test). At +1 month, the absolute number of CD23⁺CD19⁺ cells was again significantly lower than in controls ($P < .005$). The numbers did not reach that of normal controls until ~6 months. No correlation was observed between the numbers of total B cells, CD23⁺ B cells, and levels of sCD23.

CD23 expression on non-B cells. The expression of CD23 by non-B cells was analyzed in eight patients at +1 month after ABMT. No CD23 was detected on T cells (CD3), NK-like cells (CD16), or monocytes/macrophages (Leu-M3) (data not shown). At +1 month after ABMT, the mean number of CD23⁺ cells among all gated lymphocytes was 0.4% as compared with 2% in normal subjects. Virtually all CD23 expression was confined to B cells.

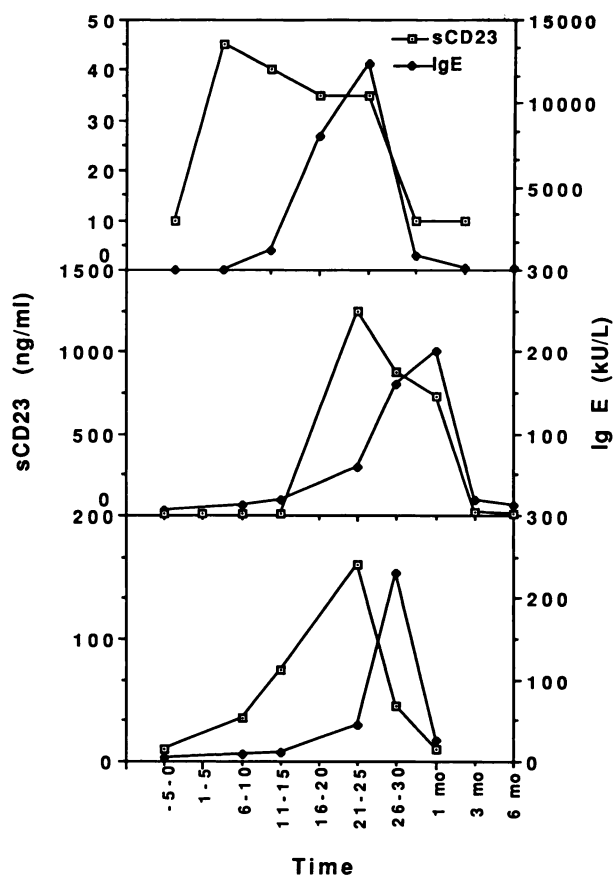


Fig 2. Typical changes in serum levels of IgE and sCD23 in three individual patients. In each case, the increase in sCD23 preceded the IgE peak.

DISCUSSION

High IgE levels after BMT were reported to be a sign of GVHD,¹⁻³ but were later also observed with no overt GVHD.⁴ Saarinen et al²⁷ studied IgE after ABMT but reported no elevated levels. In the present study, we showed that ~74% of patients after ABMT have a transient increase in serum IgE. This frequency should be compared with 80% to 95% reported after BMT.^{1-3,27}

The myeloablative chemoradiotherapy used as conditioning therapy for BMT/ABMT could induce the observed enhanced IgE synthesis, since immunosuppressive treatment is often followed by IgE elevations.^{6-8,28} Since IgE peaks are also reported in children transplanted without any conditioning therapy,^{4,9} myeloablative therapy is probably not the only major explanation for the observed changes in IgE. The origin, (ie, recipient or donor) of the IgE peaks is not clear, but indirect evidence for recipient origin was reported by Ringdén et al.¹⁰

Major imbalances of T-cell subsets are reported to occur after allogeneic BMT as well as ABMT.²⁹⁻³¹ Low numbers of the recently identified human T-suppressor/inducer subset³² were reported both after BMT³³ and after ABMT³¹ during the first 3 to 6 months after transplantation. Sarayan et al³⁴ recently demonstrated that B cells from marrow recipients during periods with high serum levels of IgE were capable of *in vitro* IgE synthesis when cocultured with autologous or

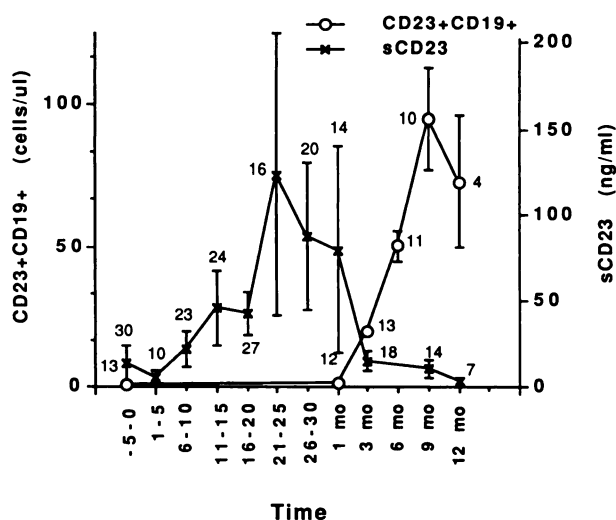


Fig 3. Absolute numbers (mean $\pm$ SEM) of CD23⁺CD19⁺ B cells in relation to serum levels of sCD23. The numbers of patients analyzed at each time point are indicated.

allogeneic T cells from BMT patients in the same phase after transplant. The *in vitro* IgE synthesis was, however, suppressed by normal allogeneic T cells and by autologous T cells obtained after the decrease in IgE levels. Therefore, the role of T-cell aberrations seems clear. Since most changes in T-cell subsets reported after BMT are also observed after ABMT,³¹ the increase recorded in IgE levels after ABMT in this study is not surprising.

The most novel feature of the present study was the indication of a direct causal relationship between the IgE peaks observed after ABMT and the appearance in serum of soluble fragments of an IgE receptor. Low-affinity receptors for Fc of IgE (FcεR) are found on the surface of human B cells, T cells, and NK cells and also on monocytes/macrophages,³⁵⁻³⁸ eosinophils,³⁹ and platelets.⁴⁰ Studies using MoAbs specific for FcεR have indicated that FcεR may be a B-cell-specific differentiation marker,^{41,42} and this structure was recently identified as CD23.¹³ IgE-binding factors (IgE-BF) are identified in culture supernatants of FcεR⁺ cells,⁴³ and at least one of these factors was a cleavage product of surface CD23.¹⁴ This relationship was further proved by comparison of the amino-acid sequence for IgE-BF and the predicted sequence from the cDNA encoding FcεR.^{44,46} The CD23-directed MoAb MHM6 was also recently shown to mimic the effect of the 12-Kd T-cell-derived low-molecular weight (low-mol-wt) B-cell growth factor (BCGF_{low}) on tonsillar B cells preactivated by the phorbol ester TPA.⁴⁷ Both MHM6 and BCGF_{low} downregulated the CD23 antigen on cells. Binding of MHM6 to the 45-Kd antigen on B cells also induced release of the 35-Kd antigen, which was the same as that observed for BCGF_{low}.¹⁴ Supernatants from Epstein-Barr virus (EBV)-immortalized B cells, from which affinity-purified preparations of shed CD23 were prepared, had autostimulatory activity.⁴⁸ The B-cell-derived BCGF and sCD23 are thus believed to be the same molecule.^{11,49}

In the present study, patients frequently exhibited a transient peak in serum levels of sCD23 after ABMT and this peak preceded, by a matter of days the peak in circulat-

ing IgE. Whether the two events are biologically linked remains to be established, but the possibility clearly exists. This notion is supported by recent *in vitro* studies on mature B cells showing that sCD23 could upregulate IgE synthesis promoted by the T-cell-derived lymphokine interleukin-4 (IL-4),¹⁸ indicating that sCD23 production is an essential feature of this response. Recent data also showed that FcεR on B cells are induced by IL-4,⁵⁰ followed by appearance of CD23 in culture supernatants.^{20,51} However, it is not clear whether the circulating sCD23 observed in our patients is derived from B cells. Indeed, strikingly low numbers of B cells expressing CD23 were observed up to at least 3 months after ABMT. Recently, IgE-binding factor(s) were demonstrated in sera from patients with chronic B-lymphocytic leukemia (B-CLL),⁵² and elevated IgE-BF levels were claimed to be capable of discriminating CLL from other malignancies. B-CLL cells are mostly CD5⁺ and ~20% to 40% of the cells are CD23⁺.⁵³ CD5⁺ B cells are among the earliest to recover after BMT.⁵⁴ In the present study, however, very low absolute numbers of CD23⁺ B cells were recorded early after ABMT. Therefore, that such cells can account for the sCD23 peak is very unlikely. Platelets are also an unlikely source, since platelet numbers are exceedingly low early after ABMT.

One possible source of sCD23 are large granular lymphocytes (LGLs), which may represent the predominant helper

cells early after BMT.⁵⁵ However, CD23 was undetectable on CD16⁺ (NK) and CD3⁺ (T) cells in our patients. Sarayan et al³⁴ demonstrated that supernatants of cultured T-cell-enriched blood lymphocytes, obtained from patients with high IgE levels after BMT, contained a factor able to induce IgE secretion in normal B cells. Alternatively, the peak of sCD23 observed after ABMT might result from proliferation of myelomonocytic elements, which occurs early. However, no CD23 expression by circulating monocytes/macrophages was detected at +1 month after ABMT. Thus, the cellular origin of sCD23 after transplantation remains to be established in later studies.

We showed in the present study that serum IgE peaks are recorded after ABMT in a way similar to that previously described after allogeneic/syngeneic transplantation. This peak of IgE is preceded by an increase in sCD23 which, because of the various functions attributed to this molecule, may also contribute to the overshoot in absolute numbers of B cells observed later after transplant.⁵⁶ Furthermore, the kinetics of events strongly suggests that sCD23 may be directly responsible for promoting IgE production in these patients.

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