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Serum soluble CD23 in patients with hypogammaglobulinaemia

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SUMMARY

Serum levels of the soluble form of the low-affinity receptor for IgE (FcERII, CD23) (sCD23) are elevated in autoimmune conditions associated with hypergammaglobulinaemia and B cell hyperactivity. Very high levels of sCD23 are found in patients with B-chronic lymphatic leukaemia (B-CLL) who are, however, frequently hypogammaglobulinaemic. We therefore compared the serum levels of sCD23 in healthy controls ($n = 33$) with three conditions associated with hypogammaglobulinaemia (HGG) and varying B cell numbers: X-linked agammaglobulinaemia (XLA, $n = 12$), common variable immunodeficiency (CVI, $n = 20$) and B-chronic lymphatic leukaemia ($n = 33$). Serum levels of sCD23 showed a significant correlation with the $CD19^+$ B cell count in both normals and patients with CVI ($r = 0{\cdot}65$, $P < 0{\cdot}0001$). Amongst the different clinical groups, serum levels of sCD23 were increased in the order XLA < CVI < normals < CLL (medians 2·5, 7·7, 11·1 and 540, respectively; $P < 0{\cdot}001$ for all comparisons except CVI *versus* normals $P < 0{\cdot}03$ in a one-tailed test). In the CVI group, serum sCD23 was lowest amongst four patients with low B cell numbers. There was no overlap in sCD23 between patients with XLA and this subgroup of CVI patients. Serum sCD23 is, therefore, derived predominantly from B cells, and is significantly related to the peripheral blood B cell count.

Keywords soluble CD23 X-linked agammaglobulinaemia common variable immunodeficiency chronic lymphatic leukaemia

INTRODUCTION

Maturation arrest at the pre-B cell stage is thought to underlie the absence of B cells and the hypogammaglobulinaemia (HGG) which characterizes X-linked agammaglobulinaemia (XLA) [1]. In contrast, the HGG observed in patients with common variable immunodeficiency (CVI) may be caused by a number of defects [2]. These include B lineage maturation arrest [3], defects of cytokine production [4], defective expression of the CD40 ligand [5] and abnormalities of T cell subsets [6] and function [7].

The low-affinity receptor for IgE (FcERII, CD23) exists as both a transmembrane protein on B and T cells, eosinophils, monocytes and platelets and as a soluble plasma protein (sCD23) [8,9]. Both transmembrane and soluble CD23 are involved in the differentiation of thymocytes, myeloid precursors and germinal centre B cells [8,9]. Soluble CD23 is also involved in B cell growth and, in synergy with IL-1, in the activation of CD4 T cells [10].

We have recently found serum levels of sCD23 to be elevated in patients with systemic lupus erythematosus (SLE), primary Sjögren's syndrome (pSS) and rheumatoid arthritis (RA) [11,12]. These conditions are associated with hypergammaglobulinaemia, autoantibody production and B cell hyperactivity. However, there was no correlation between sCD23 and serum levels of IgG, IgA and IgM [11].

Very high levels of serum sCD23 have been reported in patients with chronic lymphatic leukaemia (CLL) [13]. As HGG is a frequent accompaniment of B-chronic lymphatic leukaemia (B-CLL), the elevation in serum sCD23 would appear to reflect B cell numbers. We therefore compared serum levels of sCD23 in three conditions with HGG and variable numbers of B cells: XLA, CVI and CLL.

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PATIENTS AND METHODS

The diagnostic criteria for each patient group are detailed in Table 1. Health service employees in good health were used as controls.

HGG was defined as serum IgG < 6 g/l with IgA < 1·0 g/l and IgM < 0·6 g/l prior to any form of immunoglobulin therapy. In patients with XLA and CVI, sCD23 estimation was performed on blood samples venesected immediately before the patients' regular intravenous immunoglobulin therapy (IVIrt).

Table 1. Diagnostic criteria of patient groups

Patient group	Number (male:female)	Diagnostic criteria
XLA	12 (12:0)	Male sex, symptoms in infancy, absent CD19 B cells with normal CD3, CD4 and CD8 T cells
CVI	20 (11:9)	Symptoms in adult life, variable numbers of CD19 B cells and CD3, CD4 and CD8 T cells
CLL	33 (18:15)	Lymphocytosis > $10^{10}/l$, characteristic cell morphology and CD5/CD19/CD23 B cells on flow cytometric analysis
Controls	33 (17:16)	Health service employees in good health

XLA, X-linked agammaglobulinaemia; CVI, common variable immunodeficiency; CLL, chronic lymphatic leukaemia

Assay procedure

Soluble CD23 was measured using an enhanced chemiluminescent ELISA as described previously [10]. The capture monoclonal (EBVCS2) was a kind gift from Dr W. Sugden, and the detection monoclonal (BU38 conjugated with horseradish peroxidase (HRP)) was obtained from The Binding Site (Birmingham, UK).

Sera from patients and controls were mixed on each plate so as to minimize the effects of interplate variability.

RESULTS

The male:female ratio was similar amongst patients with CVI, CLL and normal controls (Table 1).

Figure 1 displays graphically the close association between serum levels of sCD23 and the peripheral blood $CD19^+$ B cell count in normal controls and patients with CVI ($r = 0{\cdot}65$ for the whole group, $r = 0{\cdot}69$ for CVI patients, and $r = 0{\cdot}62$ for the normal controls; $P < 0{\cdot}0001$, $P < 0{\cdot}002$ and $P < 0{\cdot}0001$, respectively).

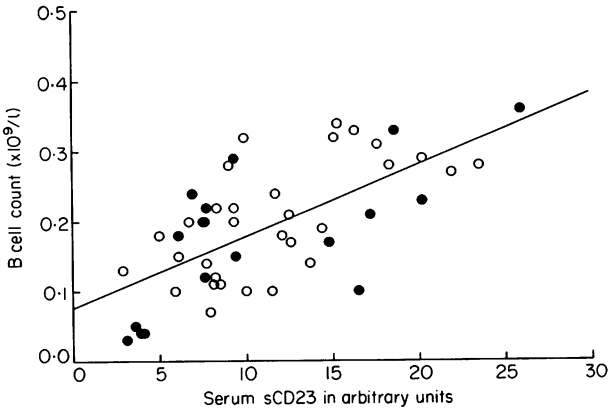

Fig. 1. Variation of serum sCD23 with $CD19^+$ B cell count in normals (○) and patients with common variable immunodeficiency (CVI) (●) ($r = 0{\cdot}65$, $P < 0{\cdot}0001$).

Figure 2 shows the serum levels of sCD23 in the groups studied. Patients with XLA had levels of sCD23 which were significantly lower than those in normal controls and in patients with CVI and CLL: there was no overlap between the levels in this group and those in the other three groups. Patients with CVI had sCD23 levels which were significantly lower than those in normal controls ($P < 0{\cdot}03$, one-tailed test). Patients with CLL had significantly higher levels of sCD23 than normal controls.

Amongst patients with CVI, four had $CD19^+$ B cell numbers which were recorded as less than 2% of the total lymphocyte population. The serum level of sCD23 in these four patients was the lowest in the CVI group. There was no significant difference in the median sCD23 between patients with CVI and normal controls when this subgroup of patients was removed from the full group of CVI patients (median 9·3 *versus* 11·1).

DISCUSSION

Recent work has shown a defect in a newly discovered protein tyrosine kinase (ATK) in patients with XLA [14]. Patients with CVI are both etiologically and clinically heterogeneous. Those with a pure B cell deficiency appear to behave like patients with XLA.

As indicated in Fig. 1, there is a good correlation between serum levels of sCD23 and the $CD19^+$ B cell count. This is shown by the very low levels of sCD23 in patients with XLA and CVI patients with absent/low numbers of B cells, normal levels of sCD23 in CVI patients with normal numbers of B cells, and very high levels of sCD23 in CLL patients with high numbers of B cells. Unfortunately, variations in treatment and stage of CLL disease prevented further correlation of sCD23 with B cell numbers.

The very low levels of serum sCD23 in patients with XLA who have no circulating B cells suggests that most of the sCD23

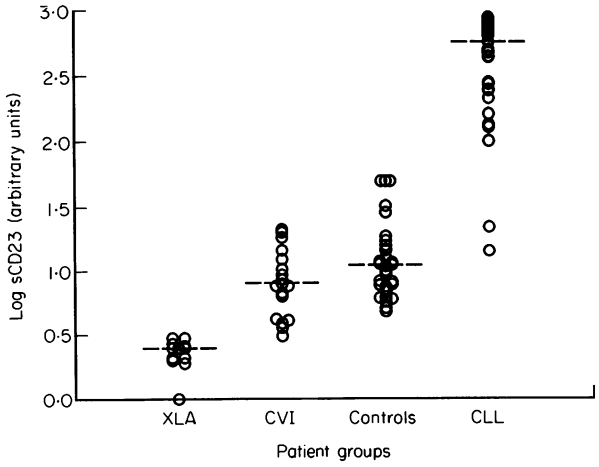

Fig. 2. Log serum levels of sCD23 in X-linked agammaglobulinaemia (XLA), common variable immunodeficiency (CVI), normal healthy controls and chronic lymphatic leukaemia (CLL) (medians 2·5, 7·7, 11·1 and 540, respectively) (CVI *versus* normal controls $P < 0{\cdot}03$ one-tailed test. In all other comparisons $P < 0{\cdot}001$ to $P < 0{\cdot}0001$).

in peripheral blood is of B cell origin. Nevertheless, sCD23 is detectable in these patients, supporting work showing that sCD23 is made by other cells, e.g. monocytes, eosinophils, platelets and T cells [8,9]. In normals and patients with CVI, another source may be follicular dendritic cells in the germinal centres of lymph nodes. In patients with XLA, germinal centres are absent and lymph gland tissue is very rudimentary.

In conjunction with IL-1, sCD23 has been reported to rescue follicular B cells from death by apoptosis by activating the bcl-2 proto-oncogene [15]. Defects in the regulation of the bcl-2 gene have been shown in about 80% of follicular lymphomas and in 10% of B-CLL [16]. IL-4 has been shown to increase bcl-2 expression in the fresh T cells of patients with CLL [15]. These cells were also found to express mRNA for IL-4 [17]. Since IL-4 increases CD23 and sCD23 expression [8,9], the B cell proliferation in B-CLL may arise from a combination of paracrine and autocrine stimulation accompanied by protection of the proliferating cells from death by apoptosis. In contrast, inadequate activation of the bcl-2 gene by low levels of sCD23 may leave follicular B cells susceptible to death by apoptosis. Thus the roles of sCD23 and bcl-2 clearly deserve further investigation in patients with CVI having low numbers of circulating B cells.

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