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## Plasma Levels of Human Granulocytic Elastase $\alpha_1$ -Proteinase Inhibitor Complex (E- $\alpha_1$ -PI) in Leukemia

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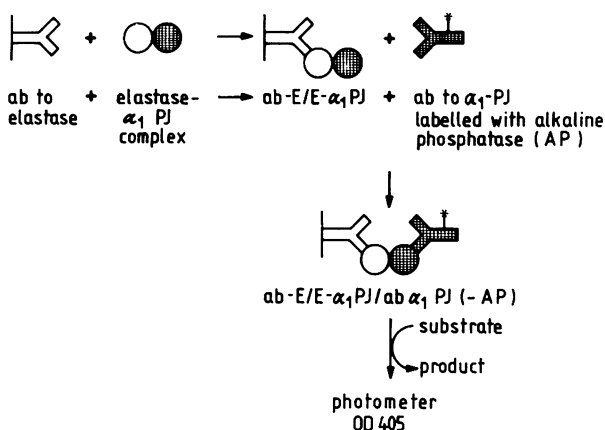
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**Summary.** There is evidence that polymorphonuclear granulocytes release neutral proteinases such as elastase (E) and cathepsin G in the course of acute leukemia. These proteinases may inactivate clotting factors by unspecific degradation before they are eliminated via complex formation with endogenous inhibitors, e. g. the  $\alpha_1$ -proteinase inhibitor ( $\alpha_1$ -PI). In this study it was attempted to correlate plasma levels of the E- $\alpha_1$ -PI complex with factor XIII and antithrombin III in acute leukemia. Using a newly developed, sensitive enzyme-linked immunoassay the concentration of E- $\alpha_1$ -PI in patients with various types of leukemia, malignant lymphoma or multiple myeloma was determined. Only patients with acute myelocytic or promyelocytic leukemia (AML, APL) and chronic myelocytic leukemia with and without blastic transformation (CML) showed moderate to high levels of E- $\alpha_1$ -PI (2- to 20-fold of normal). However, coagulation factor concentration observed in the different types of leukemia seemed to be independent of elastase liberation. Most of the AML-patients with elevated E- $\alpha_1$ -PI levels showed peroxidase positive blood cell smears.

**Key words:** Elastase –  $\alpha_1$ -proteinase-inhibitor – Factor XIII – AT III – Leukemia

Bleeding in acute leukemia is common and frequently caused by thrombocytopenia. However, consumption of plasmatic coagulation factors may also contribute to bleeding in leukemic patients. Generally it is thought that the release of procoagulant material (tissue factor) from leukemic cells specifically triggers the coagulation and fibrinolysis systems thus leading to disseminated intravascular coagulation (DIC) [4, 8, 17]. Possibly, even small amounts of monocytes account for most of the tissue factor activity [16].

Recent investigations indicate that lysosomal proteinases released from white cells may also contribute to the consumption of coagulation factors [1, 2, 3, 7]. Especially neutrophil elastase may destroy plasma proteins before inhibition occurs by  $\alpha_1$ -protein-



**Fig. 1.** Principle of the enzyme-linked immunoassay used for determination of the elastase- $\alpha_1$ -proteinase inhibitor complex (E- $\alpha_1$ PI). ab-E = antibodies against human granulocytic elastase; ab  $\alpha_1$ PI(-AP) = antibodies against human  $\alpha_1$ -proteinase inhibitor, labelled with alkaline phosphatase

ase inhibitor ( $\alpha_1$ -PI) and  $\alpha_2$ -macroglobulin ( $\alpha_2$ M). Because these inhibitors are present in excess direct measurement of the granulocytic proteinase activities in plasma is not possible. However, increased levels of the elastase  $\alpha_1$ -PI complex (E- $\alpha_1$ PI) would be an indirect but clear indication of elastase liberation. Such complexes have been demonstrated occasionally by others applying one- and two-dimensional Laurell electrophoresis to plasma samples of patients with septicemia or acute leukemia [3].

In our study quantitative estimation of the E- $\alpha_1$ PI plasma levels in patients with leukemia was performed with a highly sensitive enzymelinked immunoassay which has been developed recently by Neumann et al. [14]. To see whether a relationship exists between the concentration of E- $\alpha_1$ PI and the consumption of plasma proteins, we determined the levels of factor XIII (F XIII) and antithrombin III (AT III), because both clotting factors are known to be very sensitive substrates for granulocytic elastase in vitro [2, 6].

## Materials and Methods

Blood samples were obtained from 32 patients with acute leukemia (26 with AML, 6 with ALL), 8 patients with chronic myelocytic leukemia (CML), 3 patients with chronic lymphocytic leukemia (CLL), 6 patients with multiple myeloma and 4 patients with centrocytic-centroblastic lymphoma. Nine parts of blood were mixed with one part of 0.13 mol/l Na-citrate. Platelet-poor plasma was prepared in a refrigerated centrifuge (3000 g, 20 min, 4°C). The plasma samples were stored at -40° until assayed.

The enzyme-linked immunoassay for E- $\alpha_1$ PI was performed according to Neumann et al. [14]. The principle of the assay is outlined in Fig. 1. Briefly, plasma samples were incubated in plastic tubes coated with antibodies against elastase. After washing with buffer, the surface-fixed E- $\alpha_1$ PI complex molecules reacted with alkaline phosphatase (AP)-labelled antibodies directed against  $\alpha_1$ PI. Under the conditions used the activity of AP towards p-nitrophenylphosphate is proportional to the concentration of E- $\alpha_1$ PI in the sample.

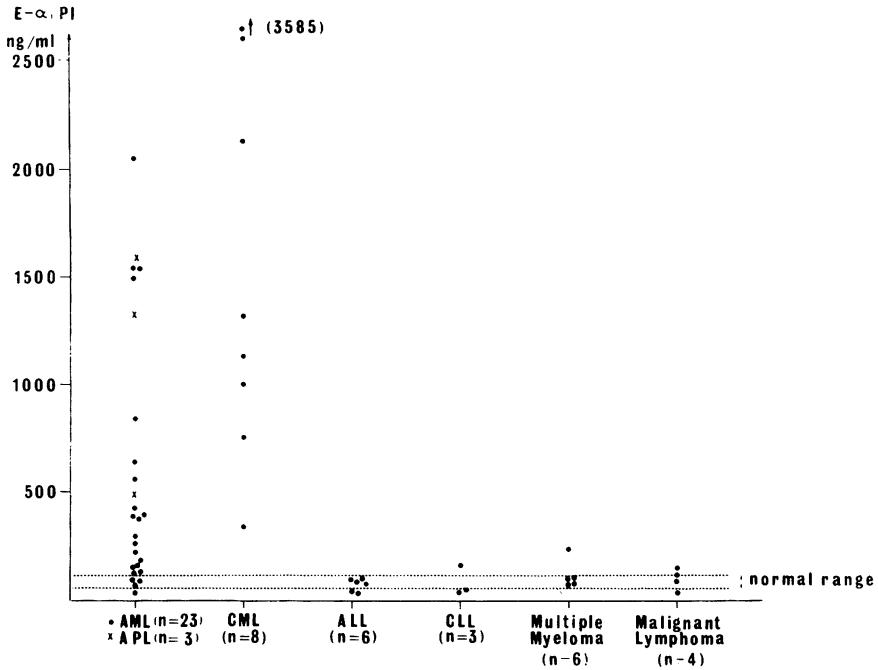


Fig. 2. Elastase- $\alpha_1$ -proteinase inhibitor complex (E- $\alpha_1$ PI) levels in plasma of patients with various types of leukemia, multiple myeloma or malignant lymphoma on admission. AML = acute myelocytic leukemia; APL = acute promyelocytic leukemia; CML = chronic myelocytic leukemia with blastic transformation; ALL = acute lymphatic leukemia; CLL = chronic lymphatic leukemia

Antithrombin III (AT III) was determined photometrically using the chromogenic thrombin substrate S-2238 (Deutsche Kabi, Munich) [15] and in some samples fluorimetrically (Protopath, Dade, Munich) [13]. The functional activity of the fibrin stabilizing factor (F XIII) was measured with a commercial test kit (Faktor XIII-Schnelltest, Behringwerke, Marburg) as described by Karges [10]. Plasma levels of F XIII subunit A and S were assayed with the Laurell electrophoresis [11] using monospecific antisera directed against either subunit A or S (Behringwerke, Marburg). The peroxidase staining was performed according to Kaplow [9].

**Results**

With the enzyme-linked immunoassay normal levels of complexed elastase were found between 40 and 150 ng/ml in 153 healthy individuals (mean value  $86.5 \pm 25.5$  ng/ml).

Plasma levels of the E- $\alpha_1$ PI complex were determined in 53 untreated patients with different types of leukemia, malignant lymphoma and multiple myeloma. Elevated levels were found only in patients with acute myelocytic and promyelocytic leukemia (AML, APL) as well as chronic myelocytic leukemia (CML) in the chronic phase and blastic transformation (Fig. 2). The highest amounts of E- $\alpha_1$ PI were observed in CML patients: in 5 of the 8 subjects more than 1000 ng/ml (i. e. 10 times the normal value) of complexed elastase were found. In acute and chronic lymphatic leukemia (ALL,

CLL), malignant lymphoma and multiple myeloma E- $\alpha_1$ PI plasma levels were normal or only slightly elevated (Fig. 2).

In 27 patients with the diagnosis of acute leukemia the peroxidase reaction was also performed. In 18 patients it was positive and 15 out of the 18 patients (83%) had elevated levels of E- $\alpha_1$ PI. In all 18 patients the diagnosis was acute myelocytic leukemia. Of the 9 patients with peroxidase negative smears only 1 (11%) had an increased concentration of granulocytic elastase. This patient had morphologically an acute myelomonocytic leukemia. The same diagnosis was true for a second patient whose E- $\alpha_1$ PI levels, however, were not elevated. In an additional patient with the morphological features of acute myelocytic leukemia a partial myeloperoxidase deficiency was present. The remaining 6 patients had acute lymphocytic leukemia.

In Table 1, the levels of E- $\alpha_1$ PI, F XIII and ATIII as well as the corresponding leukocyte counts are summarized for 24 patients with AML, APL, CML and ALL. In the remaining 14 patients whose E- $\alpha_1$ PI levels are depicted on Fig. 2 the coagulation data are incomplete and therefore not recorded. Obviously, there is only a poor correlation between the individual numbers of leukocytes and the complexed elastase as well as each of the clotting factors. The fibrin stabilizing activity of F XIII was reduced to 62.5% or less of the norm in more than half of the AML and APL patients. However, this reduction was independent of the amount of E- $\alpha_1$ PI present in the same samples. The extremely low F XIII activity in patients with ALL was especially striking considering their normal E- $\alpha_1$ PI levels. Moreover, CML patients showed F XIII activities in the normal range although the E- $\alpha_1$ PI complex was highly elevated. In a few cases, F XIII subunit A and S levels were also determined. No parallel decrease in either subunit characteristic for proteolytic degradation could be demonstrated. The AT III activity was in the normal range (75% up to 115%) in more than 70% of the patients studied. The reduced thrombin inhibitory capacity of the remaining subjects was correlated neither to the amount of complexed elastase nor to the F XIII activity.

Figure 3 depicts the rapid decrease in complexed elastase during remission induction chemotherapy in a patient with AML. E- $\alpha_1$ PI was normal following hematologic remission.

## Discussion

On the basis of *in vitro* and *in vivo* studies Egbring et al. [3] postulated that in addition to DIC direct proteolysis by granulocytic proteinases contributes considerably to the consumption of clotting factors in patients with acute leukemia or septicemia. Increased levels of complexed granulocytic elastase in the circulation were regarded as an indication of extracellular elastase release. Furthermore, the concomitant decrease in the fibrin stabilizing activity as well as the amount of F XIII subunit A and S were thought to be a consequence not only of clotting but also of proteolytic degradation by liberated elastase. Applying the Laurell technique for the determination of the E- $\alpha_1$ PI complex in plasma, the authors divided their leukemia patients into two groups: those with and those without  $\alpha_1$ PI-bound elastase. Reduction in F XIII activity, decrease in both subunits of F XIII and increased levels of fibrin (ogen) degradation product (FDP) correlated well with the presence, yet not with the absolute amount of complexed elastase in plasma. However, in a number of specimens without

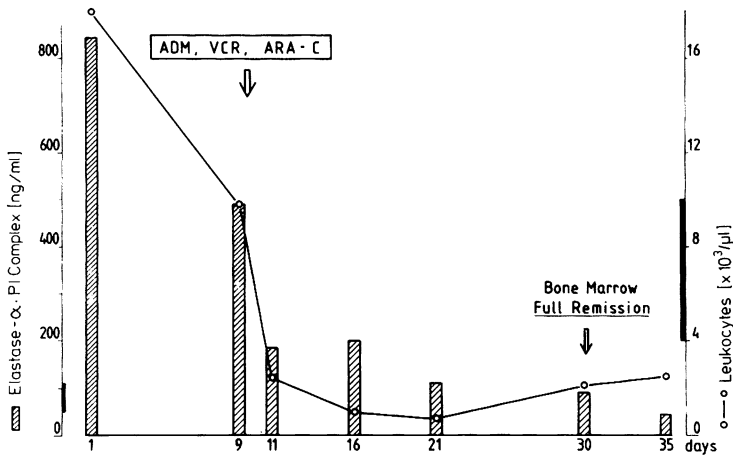


Fig. 3. Leukocyte counts and plasma levels of elastase- $\alpha_1$ -proteinase inhibitor complex (E- $\alpha_1$ PI) in a 51 year old patient with acute myelocytic leukemia (AML) during remission induction chemotherapy (ADM = adriamycine; VCR = vincristine; ARA-C = cytosine arabinoside). Abscissa: time after admission. First day of treatment day 8

$\alpha_1$ PI-bound elastase the levels of clotting factors were also pathological. This discrepancy might to some extent be due to the limited sensitivity and accuracy of the elastase assay applied by these authors. With the newly developed and highly sensitive enzyme-linked immunoassay, the lower working range for elastase in complex with  $\alpha_1$ PI is 0.2 ng per assay, i. e. 20 ng/ml plasma. Thus, even E- $\alpha_1$ PI levels in plasma samples of healthy individuals could be accurately measured (normal range: 60 to 110 ng/ml; Neumann et al [14]).

In our first approach to study E- $\alpha_1$ PI levels in leukemia, we found moderately to highly elevated levels in CML patients with and without blastic transformation. AML and APL patients showed a wide variety of E- $\alpha_1$ PI levels ranging from normal to more than twenty fold higher values, independent of the individual leukocyte counts. Interestingly, in most of the patients with peroxidase positive leukemic cells the E- $\alpha_1$ PI complex was clearly elevated, and vice versa. This might indicate various states of differentiation and maturation of the leukemic blood cells.

The present study of E- $\alpha_1$ PI levels in leukemia does not explain the significance of elevated amounts of complexed elastase in relation to the changes of F XIII and AT III in plasma. In contrast to the results of Egbring et al. [3] we could not find a correlation between the levels of E- $\alpha_1$ PI and F XIII in any of the leukemia groups studied. Whereas in the patients with AML a wide spectrum of F XIII values was obtained independently of the amount of E- $\alpha_1$ PI, the activity of F XIII in patients with CML was normal in spite of the high levels of E- $\alpha_1$ PI. There was also a striking discrepancy between the normal amount of E- $\alpha_1$ PI and the very low levels of F XIII in the 4 patients with ALL. It is well known that the treatment protocols for ALL patients include asparaginase which blocks hepatic protein synthesis [12]. This results in a decrease in coagulation factors such as fibrinogen, AT III and F XIII which are synthesized in the liver. The data of the 4 ALL patients, however, were obtained prior to the treatment with asparaginase.

**Table 1.** Leukocyte counts and plasma levels of elastase- $\alpha_1$ -proteinase inhibitor complex (E- $\alpha_1$ PI), factor XIII (fibrin stabilizing activity as well as subunit A and S), and antithrombin III (AT III) in patients with acute myelocytic leukemia (AML), promyelocytic leukemia (APL), chronic myelocytic leukemia (CML, o = chronic phase, x = blastic transformation), and acute lymphocytic leukemia (ALL). n. d. = not done

Patients	Diagnosis	Leukocytes ( $\times 10^3/\mu\text{l}$ )	E- $\alpha_1$ PI (ng/ml)	Functional	F XIII		AT III %
					A %	S	
Kh	AML	3.5	27	87.5			87
Re	AML	4	66	62.5			98
Ec	AML	10.6	96	37.5			66
Mi	AML	17.5	125	100	56.5	112.5	63
Schö	AML	163	170	50			70
Hi	AML	4.1	640	62.5			83
Bo	AML	17.9	840	50	50	74.5	88
Ha	AML	140	1140	50	62.5	80	98
Ri	AML	59.8	1540	87.5	53.5	100.5	n. d.
Ke	AML	49.9	2045	100	87.5	120.5	n. d.
Schn	APL	2	330	25	25	25	82
We	APL	1.6	1320	87.5			104
Si	APL	52	1600	n. d.			69
Me	CML <sup>x</sup>	7.8	132	120			109
Bo	CML <sup>x</sup>	174	336	75			109
Ri	CML <sup>o</sup>	381	750	75			110
Ay	CML <sup>x</sup>	76	1000	120			107
Eg	CML <sup>o</sup>	170	1025	87.5	76.5	136	n. d.
Vo	CML <sup>x</sup>	15	1140	100	59	110	n. d.
Ex	CML <sup>x</sup>	130	2120	100	45	106.5	n. d.
Rei	CML <sup>o</sup>	247	3585	100			67
He	ALL	32	64	25			85
Sa	ALL	35	64	25			70
Ri	ALL	69.5	68	25			100
Schi	ALL	36	76	37.5			105

Only recently was it demonstrated by serial determinations that a clear correlation exists between E- $\alpha_1$ PI increase and the decrease of both F XIII subunits in plasma of patients dying from postoperative septicemia [15]. In partial agreement with Egbring et al. [3] the conclusion was drawn that in patients with septicemia elastase or other lysosomal proteinases are involved to a significant degree in the depletion of F XIII. The data presented here, however, suggest that in acute leukemia the mechanism of F XIII depletion is independent of the liberation of elastase from leukocytes and, therefore, different from that postulated for septicemia. One reason for this discrepancy might be a different release mechanism in both diseases. In septicemia, elastase and other lysosomal proteinases should be liberated in high amounts preferably locally due to exogenous stimuli like endotoxins, opsonized particles, immune complexes etc. Hence, the inhibitory potential at or close to the infection focus might be temporarily overstressed thus allowing uncontrolled proteolytic degradation by lysosomal proteinases. In leukemia, however, elastase is probably released systemically

in amounts depending on the rate and mode of turnover of the leukocytes. In contrast to septicemia, the endogenous inhibitors are likely able to prevent unspecific proteolytic degradation of plasma proteins more effectively during a systemic release reaction. The low F XIII activity in some leukemia patients could be the result of either abnormal low synthesis or enhanced turnover of this protein due to factors not yet identified.

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