Alpha-1-antitrypsin phenotypes in malignant lymphoma

FRANCESCO CALLEA, GUIDO MASSI,* CHRIS DE WOLF-PEETERS, CARL LIEVENS,† VALEER J DESMET

*From the Department of Medical Research, KU Leuven, Belgium, the *Istituto Anatomia Patologica, UCSC Roma, Italy and the †Department of Oncology, St Rafaël Hospital, KU Leuven, Belgium*

SUMMARY The alpha-1-antitrypsin (α_1 AT) Pi phenotypes have been determined by isoelectric focusing in a series of 228 patients having a histologically diagnosed malignant lymphoma and in 250 healthy controls. The Pi MZ phenotype occurred in 13 patients with lymphoma (5.8%) and in five of 250 healthy individuals (2%). Furthermore, one patient with a Pi SS and three patients with an abnormal unknown phenotype, migrating slower than Z, were found in the lymphoma group. No prevalence for a special lymphoma type was observed among the abnormal Pi phenotype patients. The increased incidence of abnormal Pi phenotypes in malignant lymphoma's support the hypothesis of the possible role of α_1 AT in development of immunopathological disorders.

Alpha-1-antitrypsin (α_1 AT), a glycoprotein, is the major serum protease inhibitor, synthesised by hepatocytes.¹ It is a polymorphic protein, composed of eight fractions, each of them having a distinct isoelectric point. By using a high sensitive technique, about 30 inherited molecular variants have been described.² The slowest electrophoretic variants are called Pi deficiency alleles. The most common is the Pi MZ phenotype, classically associated with chronic pulmonary and liver diseases.^{3,4} Recently, an increase of the Pi MZ phenotype has been observed in patients with paraproteinaemia.⁵ In order to estimate the incidence of the Pi MZ (and others) phenotype in lymphoma patients, we carried out a prospective study on 228 patients with a histologically diagnosed malignant lymphoma and compared the results with those obtained in healthy controls.

Material and methods

The study comprised two groups:

Group 1 was composed of 228 consecutive patients with a histologically proven malignant lymphoma. In this group newly diagnosed cases as well as patients seen in the Oncology Department for control follow-up were included.

Group 2 was composed of 250 healthy blood donors of our hospital, as controls. Serum for Pi phenotyping was available from all subjects. The Pi phenotyping was carried out by isoelectric focusing on an ultrathin polyacrylamide gel layer.⁶ Serum concentration of α_1 AT was measured immunochemically on agarose plates (normal range 200-400 mg/dl). The relative significance of the results was ascertained by means of the χ^2 test.

Results

In group 1 (lymphoma patients), 13 cases were found to have a Pi MZ phenotype (5.8%). One patient with a Pi SS phenotype and three patients with an abnormal unknown phenotype, characterised by migration slower than Z, were also detected in this group. The serological and histological data on these 17 patients are summarised in Table 1. In the non-Hodgkin's lymphoma subgroup, five cases presented with paraproteinaemia. All of them had a Pi M phenotype.

In group 2 (controls), the Pi MZ phenotype was detected in five of 250 individuals (2%).

The incidence of other phenotypes and the comparison of frequencies between the two groups are given in Table 2.

Table 1 Clinical pathological findings in malignant lymphoma patients with Pi MZ, SS, unknown* phenotypes

No	Pi	Sex	Age (yr)	α_1 AT	Paraproteinaemia	Histological diagnosis
1	MZ	F	17	normal	No	Morbus Hodgkin's: nodular sclerosing type
2	MZ	F	13	normal	No	.. mixed cellularity + epithelioid cell reaction
3	MZ	M	37	increased	No	.. lymphocytic predominance
4	MZ	M	59	normal	No	.. lymphocytic depletion
5	MZ	M	23	decreased	No	.. lymphocytic predominance + epithelioid cell reaction
6	MZ	F	25	increased	No	.. nodular sclerosing type
7	MZ	M	58	normal	No	.. lymphocytic depletion
8	MZ	M	57	decreased	No	Non-Hodgkin's: diffuse lymphoblastic
9	MZ	M	54	normal	No	.. diffuse immunoblastic
10	MZ	F	34	normal	No	.. nodular, histiocytic
11	MZ	M	48	decreased	No	.. T cell lymphoma with epithelioid cell reaction
12	MZ	F	49	decreased	Bence-Jones prot	.. plasmacytoma
13	MZ	M	66	decreased	No	.. diffuse lymphocytic, well differentiated
14	SS	F	25	—	No	.. diffuse lymphoblastic
15	UN*	M	49	increased	No	.. nodular and diffuse, histiocytic
16	UN*	M	64	normal	No	.. diffuse, histiocytic
17	UN*	M	22	increased	No	Morbus Hodgkin's: nodular sclerosing type

*Phenotype slower than Z.

Discussion

Originally the Z allele of α_1 AT has been related with lung and liver pathology. Later on a variety of inflammatory disorders and immunopathological conditions, including lymphomas with paraproteinaemia,⁵ have been described in association with the Pi MZ phenotype.⁷ Moreover, there is good evidence that α_1 AT is involved in the regulation of the immune system.⁸

To evaluate the incidence of abnormal Pi phenotypes in malignant lymphomas, a Pi phenotyping was performed in 250 healthy blood donors and compared with that obtained in 228 unselected consecutive lymphoma patients.

In the control group (blood donors), five of 250 individuals presented with a Pi MZ phenotype (2%). This incidence is similar to the reported incidence in other European studies.^{9,10}

No Pi SS or abnormal unknown phenotypes were found in this group. In the lymphoma group, 13 patients (7 Morbus Hodgkin's, 6 non-Hodgkin's lymphomas) were found to have a Pi MZ phenotype (5.8%). Furthermore, one patient of this group showed a Pi SS and three other cases were characterised by the presence of an abnormal unknown

phenotype with a band slower than Z, probably corresponding to the recently described YPratt.¹¹ In order to confirm this correspondence, further investigations, including family studies, are needed.

These data point to an increased incidence of abnormal Pi phenotypes (MZ, SS, unknown migrating slower than Z) in lymphoma patients with no prevalence for a special subgroup (Tables 1 and 2).

Absolute comparisons of frequencies were difficult to perform because of the heterogeneity and the small sample size within phenotypic groups. However, when abnormal Pi phenotypes (MZ, SS, unknown) were analysed as a whole, their incidence was statistically significant ($p < 0.01$); when the Pi MZ phenotype was separately analysed, its incidence was just significant ($p \approx 0.05$) (Table 2). In this study no patient presenting with paraproteinaemia could be recognised as having abnormal Pi phenotypes. The Pi MZ and SS phenotypes are usually associated with a reduced serum level of α_1 AT.¹² However, because of the acute reactant nature of this protein, its serum concentration may change dramatically in the presence of inflammatory processes and malignant tumoral proliferations.¹ This might explain the variety of α_1 AT serum concentrations found in the patients of this study. The

Table 2 Incidence of α_1 AT Pi phenotypes in lymphoma patients and controls

Group	No	MZ	(%)	MM	MS	SS	Others (MF; MP)	Unknown*
Lymphoma	228	13	(5.8)	188	16	1	7	3
Hodgkin's	126	7	(5.4)	105	10	0	3	1
Non-Hodgkin's	102	6	(6)	83	6	1	4	2
Controls	250	5	(2)	217	22	0	6	0

*Phenotype slower than Z.

finding of an increased incidence of Pi MZ and other abnormal phenotypes in lymphoma patients, support the hypothesis of the role of α_1 AT in the development of immunopathological disorders.

The authors thank Dr B Van Damme, Dr J Van-deputte and Dr R Cotomaccio for criticism and valuable help.

References

- ¹ Morse JO. Alpha-1-antitrypsin deficiency. *N Engl J Med* 1978;**299**:1045-8.
- ² Fagerhol MK, Cox DW. The Pi polymorphism: genetics, biochemical and clinical aspects of human alpha-1-antitrypsin. In: Harris H, Hirschhorn K. *Advances in human genetics* 11. New York and London: Plenum Press, 1981:1-62.
- ³ Eriksson S. Pulmonary emphysema and alpha-1-antitrypsin deficiency. *Acta Med Scand* 1964;**175**:197-205.
- ⁴ Sharp HL, Bridges RA, Krivit W, Freier EF. Cirrhosis associated with alpha-1-antitrypsin deficiency: a previously unrecognised inherited disorder. *J Lab Clin Med* 1969;**73**:934-9.
- ⁵ Ananthakrishnan R, Biegler B, Demis PM. Alpha-1-antitrypsin phenotypes in paraproteinaemias. *Lancet* 1979;i:561-2.
- ⁶ Massi G, Fabiano A, Ragusa D, Auconi P. Characterisation of alpha-1-antitrypsin by isoelectric focusing on an ultrathin polyacrylamide gel layer. *Hum Genet* 1979;**53**:91-5.
- ⁷ Breit SN, Penny R. The role of alpha protease inhibitor (alpha-1-antitrypsin) in the regulation of immunologic and inflammatory reactions. *Aust N Z J Med* 1980;**10**:449-53.
- ⁸ Arora PK, Miller HC, Aronson LD. Alpha-1-antitrypsin is an effector of immunologic stasis. *Nature* 1978;**274**:589-90.
- ⁹ Cook PJL. The genetics of alpha-1-antitrypsin: a family study in England and Scotland. *Ann Hum Genet (London)* 1975;**38**:275-87.
- ¹⁰ Carlson J, Eriksson S, Hägerstrand I. Intra and extracellular alpha-1-antitrypsin in liver disease with special reference to Pi phenotype. *J Clin Pathol* 1981;**34**:1020-5.
- ¹¹ Hug G, Gail C, Bowles B, Fagerhol MK, YPratt: new alpha-1-antitrypsin variant migrates slower than Z phenotype on polyacrylamide but faster on starch gel electrophoresis. *Pediatr Res*. 1979;**13**:420.
- ¹² Kueppers F. Alpha-1-antitrypsin: physiology, genetics and pathology. *Humangenetik* 1971;**11**:177-89.

Requests for reprints to: Dr F Callea, Laboratorium Voor Cyto en Histochemie, K.U.L., Minderbroedersstraat 12, B-3000-Leuven, Belgium.