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COMPLEMENT C1-INACTIVATOR IN THE SERUM OF PATIENTS WITH MALIGNANT DISEASE

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Serum normally contains C1-IA, an alpha-2-neuramino-glycoprotein (PENSKY et coll. 1961). It inhibits the conversion of inactive to active complement C1, and thus the whole complement system (PENSKY et coll., ROSEN et coll. 1971).

Using an immunofluorescent technique and cytophotometry, OSTHER & LINNEMANN (1973) demonstrated the presence of C1-IA on the surface of cells from human carcinoma cell cultures and OSTHER et coll. (1974) in cell cultures from human brain tumours. A significant elevation of serum C1-IA was found by BACH-MORTENSEN et coll. (1975) in patients with malignant neoplastic diseases compared with patients with non-malignant diseases and healthy individuals. LACHMANN & WRAGGE-MORLEY (1976) assayed the function of C1-IA in serum from patients with malignancy and showed that no apparent correlation existed between the functional activity of C1-IA and the occurrence of malignant disease.

In the present report, serum C1-IA concentrations in patients with malignancy are compared with those of a control material, as well as the relation between the serum C1-IA concentration and the spread of cancer. An attempt to evaluate the determination of serum C1-IA concentration as an aid for the diagnosis of malignancy is also carried out.

Material and Methods

The clinical material comprised 423 individuals: 94 blood donors, 259 patients with non-malignant diseases and 70 patients with malignant neoplastic diseases. The

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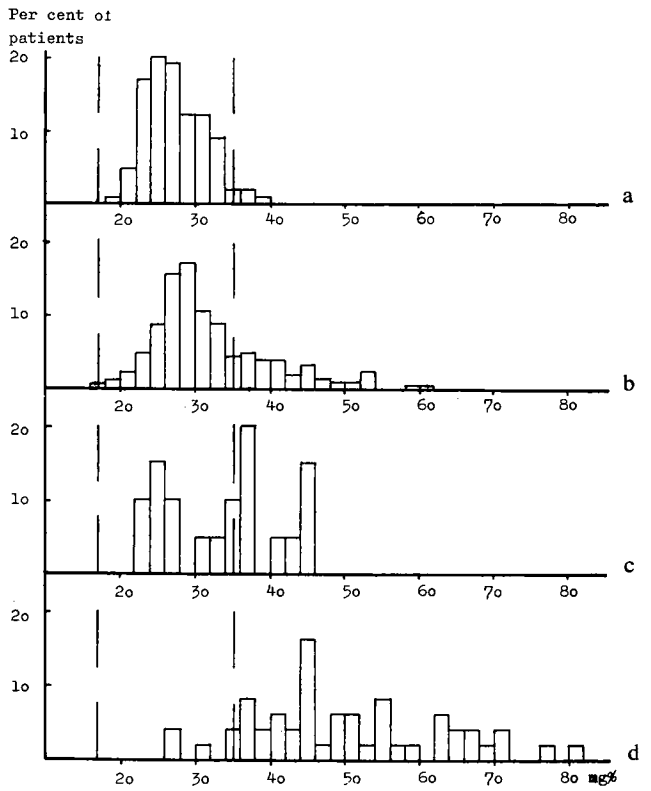

Fig. 1. Histograms of serum Cl-inactivator concentrations in the 4 groups. Abscissae, serum Cl-IA concentration in mg %. Ordinates, percentage of total number of patients in each group. a) Donors. b) Patients without malignancy. c) Group 1, patients with neoplastic disease but without metastases. d) Group 2, patients with neoplastic disease and metastases.

malignant group consisted of 20 patients without deep infiltration or metastases (group 1) and 50 patients in whom deep infiltration with or without metastases or systemic dissemination could be demonstrated (group 2).

Donor samples were collected in a single day in the blood bank. The 259 patients with non-malignant diseases comprised all patients over 12 years of age admitted to this hospital over a period of three weeks. Samples were taken on the day of admission, before treatment was initiated. No obstetric patients were included. The malignant group included all those patients from whom it was possible to take samples before surgery or other treatment during the period of the investigation. Some of these patients had been operated upon for malignant disease previously, or had been given anti-cancer treatments, but not within the 4 months immediately preceding sampling.

The diagnoses were confirmed by biopsy during operation or at autopsy. After

Table 1

Serum Cl-IA concentration in 20 patients with neoplastic disease but without metastases (group 1)

	No. of cases	No. with elevated values	Cl-IA (mg %)	
			Mean	SD
Carcinoma				
Mammary	4	2	33	4
Prostatic	5	3	36	11
Colonic	3	2	36	4
Uterine	2	0	32	5
Renal	1	0	24	—
Vesical	2	1	31	10
Pulmonary	1	0	34	—
Ventricular	1	0	22	—
Melanoma, malignant	1	1	46	—
Total	20	9	34	8

Table 2

Serum Cl-IA concentration in 50 patients with neoplastic disease and metastases (group 2)

	No. of cases	No. with elevated values	Cl-IA (mg %)	
			Mean	SD
Carcinoma				
Mammary	6	5	50	16
Prostatic	2	2	48	11
Colonic	12	11	52	14
Uterine	3	3	48	5
Renal	3	3	56	19
Vesical	2	2	47	4
Pulmonary	2	2	50	18
Ventricular	10	10	48	11
Pancreatic	3	3	68	13
Ovarian	2	2	48	12
Duodenal	1	1	36	—
Lymphoid	1	1	49	—
Esophageal	1	0	32	—
Leukemia	1	1	40	—
Seminoma, testicular	1	1	42	—
Total	50	47	50	13

Table 3

Serum Cl-IA concentration in 259 patients with non-malignant diseases

Disease	No. of cases	No. with elevated values	Cl-IA (mg %)	
			Mean	SD
Hepato-biliary	11	9	42	10
Kidney and urinary system	22	7	33	7
Systemic	6	2	35	7
Psychiatric	13	1	29	4
Appendicitis	4	0	27	2
Endocrinologic	11	3	34	4
Gynecologic	42	2	27	5
Colonic	12	5	35	8
Ventricular	18	6	33	7
Arteriosclerosis	9	7	42	9
Pulmonary emboli	8	6	39	9
Respiratory	7	1	32	5
Pulmonary infection	2	2	37	1
Heart and circulation	15	5	33	11
Orthopedic surgical	28	5	31	8
Reconstructive and plastic	47	8	30	5
Leptospirosis	1	1	60	—
Gonococcal infection	1	0	29	—
Megaloblastic anemia	2	0	25	—
Total	259	70	32	8

coagulation and centrifugation of blood samples, serum was removed and stored at −30°C until analysis.

Determination of complement Cl-inactivator. The content of Cl-IA in serum was determined by immunoelectrophoresis according to LAURELL (1966). Serum was diluted 1:10 with physiologic saline preceding electrophoresis. The heights of rockets in the electrophoresis were measured and concentrations read from a standard curve constructed on the basis of results from a standard (Behringwerke AG).

Results

The reference interval was calculated from the values obtained for 94 blood donors as the mean $\pm 2 \times$ standard deviations: 17–35 mg% (coefficient of variation 5%). There were no significant age variations.

For the 20 patients in group 1 the average value was 34 mg%, and 9 patients (45%) had elevated values. The 50 patients in group 2 had a mean value of 50 mg% and 47 patients (94%) had elevated values. The mean value for 259 non-malignant

patients was 32 mg% and 76 patients (29%) had elevated values of Cl-IA in serum. The distribution of serum Cl-IA concentration appears in the Figure.

A significant elevation of the average values was found between group 2 patients and donors ($p<0.001$), non-malignant patients ($p<0.001$), and group 1 patients ($p<0.001$).

No significant elevation was found between group 1 patients and non-malignant patients. Group 1 patients and non-malignant patients had significantly elevated values compared to the normal range ($p<0.001$, respectively).

Due to the relatively small number of patients with malignant disease no statistical comparison has been made between various types of malignancy.

Values in non-malignant patients as a whole are given in Table 3. Attention is specially drawn to the values in the groups, hepato-biliary diseases, pulmonary embolism, heart and circulatory diseases, and one patient with leptospirosis.

Discussion

A relationship exists between elevation of Cl-IA concentration in serum and the presence of malignant diseases (BACH-MORTENSEN et coll.). The present results seem to confirm this observation in patients with disseminated malignancy, but not in patients with a local malignant tumour.

As Cl-IA is found in normal serum and is subject to considerable normal variation the value of this determination for the early diagnosis of malignancy is small. In comparison with the reference interval calculated here, elevations of Cl-IA values are small, with increases up to only 100 per cent above the normal range. In patients with localized tumours, 55 per cent had values within the normal range; in the group without malignancy 76 patients (29%) had elevated values. Thus, in patients with local malignancy many false negative values were found and in non-malignant patients many false positive values.

The reason why higher values in serum are found in patients with disseminated malignant disease may be due to the fact that Cl-IA is produced by malignant cells. This is in agreement with previous reports (OSTHER 1974, OSTHER et coll., OSTHER & LINNEMANN 1973).

Non-malignant patients with elevated values were found mainly in diseases with cell destruction, for example in patients with pulmonary embolism, peripheral gangrene, disseminated infection disease, and in hepato-biliary disease. Therefore, a relationship between elevated values of Cl-IA in serum from patients with disseminated malignancy and cell destruction in the affected tissue may exist.

The present results and the observations made previously (OSTHER, BACH-MORTENSEN et coll.), implying that a correlation exists between malignant disease and elevated values of Cl-IA are apparently contradictory to the results obtained by LACHMANN & WRAGGE-MORLEY. This may be due to the fact that LACHMANN's group assayed the

functional activity of Cl-IA, whereas in the present investigation as well as in others Cl-IA concentrations were determined.

Determination of Cl-IA may be used to predict the prognosis in patients with malignant diseases. Therefore it is intended to follow up the present groups of patients, to further evaluate this possibility.

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SUMMARY

Complement Cl-inactivator (Cl-IA) in serum was determined in 423 individuals. The normal range for the concentration of Cl-IA in serum was calculated from values in 94 blood donors and the concentrations in the sera of 329 patients were determined in relation to this range. A significant correlation was found between widespread malignant neoplastic disease and increased quantity of Cl-IA in serum. Determination of Cl-IA may be used to evaluate the extent to which a malignant disease is disseminated.

ZUSAMMENFASSUNG

Der Komplement Cl-inactivator (Cl-IA) im Serum von 423 Personen wurde bestimmt. Der Normalbereich für die Konzentration von Cl-AI im Serum wurde von 94 Blutspendern bestimmt und die Konzentration im Serum von 329 Patienten im Vergleich zu diesem Bereich festgestellt. Eine signifikante Korrelation zwischen dem Ausmass der Streuung der malignen neoplastischen Erkrankung und dem Anstieg in der Quantität von Cl-IA im Serum wurde gefunden. Die Bestimmung von Cl-IA mag verwendet werden um das Ausmass der Verbreitung einer malignen Erkrankung festzustellen.

RÉSUMÉ

Les auteurs ont déterminé l'inactivateur de la fraction C1 du complément dans le sérum (C1-IA) chez 423 personnes. Ils ont calculé les variations normales de la concentration en C1-IA dans le sérum à partir des valeurs mesurées chez 94 donneurs de sang et les concentrations dans le sérum de 329 malades ont été déterminées par rapport à ces variations normales. Ils ont trouvé une corrélation significative entre les néoplasies malignes disséminées et une élévation de la quantité de C1-IA dans le sérum. La détermination de l'inactivateur de la fraction C1 du complément peut être utilisée pour apprécier l'étendue de la dissémination d'une affection maligne.

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