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HLA ANTIGENS IN HODGKIN'S DISEASE OF VERY LONG SURVIVAL

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Deepened understanding of the biodynamics of Hodgkin's disease and better methods for determination of the extent of the disease and its treatment have resulted in a great improvement in prognosis over the last 10 years. With the restricted diagnostic and therapeutic measures available in the 1960's, a 5-year survival rate of 22 per cent was reported (EASSON & RUSSEL 1963). With modern staging and treatment, today a 5-year survival rate of at least 70 per cent for all patients has been reported (KAPLAN 1972). In order to reach such high survival figures, it has usually been necessary to employ intensive radiation therapy or intensive chemotherapy. At the present time it is not clear to what extent late adverse effects may counterweight the beneficial effects of the intensive treatment. There is, for instance, increasing evidence that more intensive combined therapy results in an increased frequency of secondary malignancies, e.g. leukemia (CAVALIN-STÅHL et coll. 1977).

In recent years the interest has been concentrated on prognostic factors in Hodgkin's disease for the purpose of enabling a more differentiated therapy.

Among the well-known prognostic factors in Hodgkin's disease may be mentioned clinical stage (including systemic symptoms and signs), histologic type, length of history (stage by stage), leukocyte count, ESR (WESTLING 1955), type of therapy, and age of the patient. The last mentioned factors may be an indicator of the decreased immunologic competence in higher age, and it is well known that the im-

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Table 1

Sex, age, microscopic type, stage and length of follow-up in 40 patients with Hodgkin's disease

	10 long survivors	30 patients, untreated or with only short follow-up
Male:female	3:7	22:8
Age (years) range	15–52	15–78
mean	(29)	(36)
Microscopy		
Lymphocyte predominance	1	6
Mixed cellularity	2	8
Lymphocyte depletion	0	4
Nodular sclerosising type	7	12
Stage		
I	4	10
II	5	9
III	0	7
IV	0	4
II_e	1	0
Follow-up (years) range	18–29	0–10
mean	(23)	(2)

munologic status of patients with Hodgkin's disease has prognostic implications (HOLM et coll. 1976).

In experimental systems it has been demonstrated that the survival of mice who developed leukemia after infection with the Gross virus was dependent on the type of the major transplantation antigens (H-2, LILLY et coll. 1964). In man, extensive investigations have been performed for many different diseases, including tumors, of the relationship, if any, between the HLA-system and clinical parameters and prognosis.

However, the findings on HLA in Hodgkin's disease in different series have been partly contradictory (SVEJGAARD et coll. 1975). Usually, untreated patients have been examined and thus correlation, if any, between the HLA-system and prognosis has not been fully explored.

The present report analyses the HLA-system in a group of patients with Hodgkin's disease, some of whom were very long survivors.

Material and Methods

A report was given in 1973 (LANDBERG & AHLSTRÖM) on 13 patients with Hodgkin's disease who had survived at least 15 years after treatment. Since the diagnostic and therapeutic methods that had been used in these patients had been, when viewed

Table 2

HLA-types determined in 40 patients with Hodgkin's disease and in 1 623 normal subjects

A	B	C
1	5	w1
2	7	w2
3	8	w3
9	12	w4
10	13	
w25	14	
w26	15	
11	w16	
w19	w17	
w29	w18	
w32	w21	
28	w22	
	27	
	w35	
	w37	
	w40	

by modern concepts, very limited, these patients may be considered to have had either a benign form of Hodgkin's disease or a good reaction towards the disease. Of the 13 patients, 8 were alive at the time of the 1973 investigation and were tested for HLA-type. A further two patients with very long symptom-free survival were also included in the present material, thus consisting of 10 patients, all of whom had been symptom-free after the initial treatment, and then been followed for mean 23 years. Further information on the 10 long survivors is given in Table 1.

Another series consisting of 30 patients with Hodgkin's disease was also tested for HLA-type. Thirteen were consecutive new patients admitted during 1973, and 17 were follow-up cases the same year (Table 1).

HLA-typing of the 40 patients was done in 1973 according to a microlymphocytotoxicity test (KISSMEYER-NIELSEN & KJERBY 1973). Thirty-two different HLA-types in the A, B, and C series were determined (Table 2).

The distribution of the HLA-types in 1 263 normal subjects served as a reference.

Results and Discussion

Significant differences between different subgroups of patients with Hodgkin's disease and the reference group with respect to distribution of HLA-types is given in Table 3. The patients with Hodgkin's disease have been divided into (1) all 40 patients, (2) 10 long survivors, and (3) 19 patients with nodular sclerosing type. The

Table 3

Significant differences between different subgroups of patients with Hodgkin's disease and a reference group of normal subjects with respect to distribution of HLA types. p-values according to the chi-square test with Yates' correction

HLA	Reference group	All 40 patients	10 long survivors	19 with nodular sclerosing type
A 28	87/1263 (7 %)		3/10 (30 %, $p < 0.05$)	
B 18	63/1263 (5 %)	8/40 (20 %, $p < 0.001$)		5/19 (26 %, $p < 0.001$)

reason for listing nodular sclerosing type separately is the existence of the special morphologic, clinical and prognostic characteristics of this type, indicating that this subgroup may be basically different from the other types.

In all patients with Hodgkin's disease, not subdivided according to follow-up or histology, HLA B18 occurred more frequently than in the reference group. The same finding was made for the subgroup of 19 patients with nodular sclerosing disease, but not for the subgroup of 10 long survivors. An increased frequency of HLA B18 in Hodgkin's disease has also been reported by AMIEL (1967), SVEJGAARD et coll. and BJÖRKHOLM et coll. (1975).

The 10 long survivors (Table 3), but not the entire group of 40 patients or the subgroup of those with the nodular sclerosing type, had an increased frequency of HLA A28. Such an increase has also recently been reported by HANSEN et coll. (1977), who, however, presented no long-term data. The finding of an increased frequency of HLA A28 in patients with apparently good prognosis is contradictory to the finding made by BJÖRKHOLM et coll., who suggested that HLA A28 may be associated with advanced disease and poor prognosis.

HLA A1 has previously been reported to be frequently encountered in Hodgkin's disease. Thus, HENDERSON et coll. (1973) often found HLA A1 in patients with Hodgkin's disease without correlation to histologic type. KISSMEYER-NIELSEN et coll. also found HLA A1 to be frequent in Hodgkin's disease and also emphasized the association between HLA A1 and HLA A8. Subdivision according to histology in their series showed that HLA A1 and HLA A8 had the lowest frequency in patients with the nodular sclerosing type and the highest in patients with mixed cellularity. Further, a correlation with age was found, patients over 30 years of age often having HLA A1 and HLA A8. The results in their series were drawn from untreated patients. However, in a prospective investigation, BJÖRKHOLM et coll. found that the distribution of HLA-types in patients with Hodgkin's disease was not different from that of healthy controls. In the present series, HLA A1 occurred in about 40 per cent of all 40 patients with Hodgkin's disease and in about the same percentage of the 10 long survivors, compared with the figure 29 per cent for the reference group, the differences not being significant. This observation corresponds to that of BJÖRKHOLM et coll.

One may speculate that the very long survival in the present 10 patients despite only limited staging procedures and limited therapy implies that these patients had a good defence towards the disease. The finding of an increased frequency of HLA A28 may then, despite the small material, be of some importance when evaluating prognosis. It should be emphasized that when performing the statistical analysis, it was decided not to perform simultaneous inference. Therefore, even in the complete absence of any true difference, 1.5 significant differences will be expected at the level 0.05 when performing 32 separate tests.

Apparently HLA-typing in Hodgkin's disease has been reported to yield varying results. One explanation may be differences in the composition of the patient series, especially with respect to the length of follow-up.

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SUMMARY

Determination of 32 different HLA types in the A, B, and C series was performed in 40 patients with Hodgkin's disease, 10 of whom had a very long survival. A group of 1 263 healthy subjects was used as reference. HLA-B18 was seen significantly more often in all 40 patients and also in the subgroup of patients with nodular sclerosing Hodgkin's disease. An increased frequency of HLA-A28 was observed among the 10 long survivors, but only with weak significance.

ZUSAMMENFASSUNG

Bestimmungen von 32 verschiedenen HLA Typen in den A, B und C Gruppen bei 40 Patienten mit Hodgkinscher Erkrankung wurden durchgeführt, von denen 10 eine lange Überlebenszeit hatten. Eine Gruppe, die 1 263 gesunde Personen umfasste, wurde als Referenz verwendet. HLA-B18 fand sich signifikant häufiger in allen 40 Patienten und ebenfalls in der Untergruppe von Patienten mit nodulärer sklerosierender Hodgkinscher Krankheit. Ein Anstieg in der Frequenz von HLA-A28 wurde bei den 10 lang Überlebenden gefunden, jedoch nur mit einer schwachen Signifikanz.

RÉSUMÉ

La détermination de 32 types HLA différents dans les séries A, B, et C a été faite chez 40 malades atteints de maladie de Hodgkin dont 10 avaient une survie très longue. Un groupe de 1 263 sujets normaux a été utilisé comme référence. On a trouvé une fréquence significativement plus élevée de HLA-B18 chez ces 40 malades et aussi dans le sous-groupe de malades qui avait une maladie de Hodgkin nodulaire sclérosante. On a trouvé aussi une fréquence augmentée de HLA-A28 parmi les 10 malades ayant une longue survie, mais avec seulement une faible signification.

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