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PROGNOSTIC SIGNIFICANCE OF HISTOLOGIC SUBDIVISION OF HODGKIN'S DISEASE NODULAR SCLEROSIS

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The histologic classification of Hodgkin's disease (LUKES 1963, LUKES & BUTLER 1966) as modified at the Rye conference (LUKES et coll. 1966), is by now commonly used and has proved to be of relevant prognostic significance.

Nodular sclerosis represents in the majority of the published series one of the more frequent types of Hodgkin's disease (LUKES, LUKES et coll. CROSS 1968, KELLER et coll. 1968, COPPLESON et coll. 1970, STRUM et coll. 1970, BERARD et coll. 1971, FULLER et coll. 1971, PATCHEFSKY et coll. 1973, SCHNITZER et coll. 1973) with a frequency up to 74 per cent of all cases (DORFMAN 1971), and is usually associated with a favourable prognosis.

Because of this high frequency it has been considered of value to identify some additional histologic features enabling division of nodular sclerosis into subgroups which could better indicate the prognosis.

Cellular composition (relative number of mature lymphocytes and Reed Sternberg cells, anaplasia of reticulum cells) and amount of fibrosis have been the most used criteria to subdivide nodular sclerosis (CROSS 1968, KELLER et coll. 1968, PATCHEFSKY et coll. 1973). These authors also analyzed the relationship of the different subgroups with the main clinical parameters of disease and with survival.

CROSS, on a small group of 29 patients in all stages of Hodgkin's disease with nodular sclerosis (but mainly in stages I and II), found a better median survival

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Table 1

Hodgkin's disease stages I and II. Relapse after treatment according to the initial presentation group (248 cases—all histologic types)

Presentation group	No. of cases	Relapse	
		No.	Per cent
1	8	1	12.5
2	33	5	15.2
3	17	5	29
4	78	41	58.6
5	66	32	48.5
6	46	25	54.3

(8 years 3 months) in the group defined as well differentiated (with prevalence of mature lymphocytes and well developed nodular appearance of fibrosis) than in the group defined as poorly differentiated (2 years 2 months). On the contrary, no relationship with the number of involved regions was evident between the two groups.

PATCHEFSKY et coll., combining his series with that published by KELLER et coll. with the same subdivision, obtained a group of 177 cases in all stages of Hodgkin's disease with nodular sclerosis. The cellular composition and the amount of fibrosis were examined as independent variables. The cases with more lymphocytes and Reed Sternberg cells (defined as LP) and those with minimal or mild fibrosis (graded as +1, +2) were found in the earlier clinical stages (I and II) with higher frequency compared with the cases with mixed cellular composition (defined as MC) and advanced fibrosis (graded as +3 and +4). The first two groups were also associated with a better survival. Survival was also calculated for the LP and MC subgroups, in stages I and II only to avoid the influence of the different stage composition. This comparison confirmed the better survival of LP cases; the difference between the two subgroups was 12 per cent at 5 years and 22 per cent at 6 years.

All these data, even if suggestive, do not, however, reach statistical significance and further analyses are advisable better to define the existence in the nodular sclerosis group of patients with a different prognosis.

With this intention a group of patients with nodular sclerosis (Hodgkin's disease, stages I and II) was retrospectively analyzed and the occurrence of relapses after treatment was correlated with the differing histologic appearances.

The relationship of these histologic features with some other clinical factors was also analyzed: sex, presence of systemic symptoms or signs, and location of the primary involved areas.

The initially involved areas were referred to 6 main presentation groups (Fig. 1). In a previously published series (DE GIULI et coll. 1974) the first 3 groups appeared

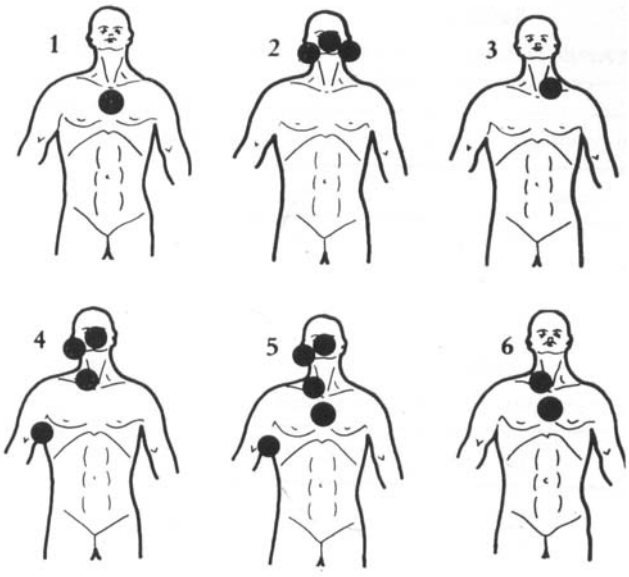

Fig. 1. Main sites at presentation. Hodgkin's disease, stages I and II. 1) mediastinum only. 2) upper cervical nodes, Waldeyer's ring. 3) single supraclavicular region. 4) multiple superficial areas. 5) mediastinum + multiple superficial areas. 6) mediastinum + supraclavicular.

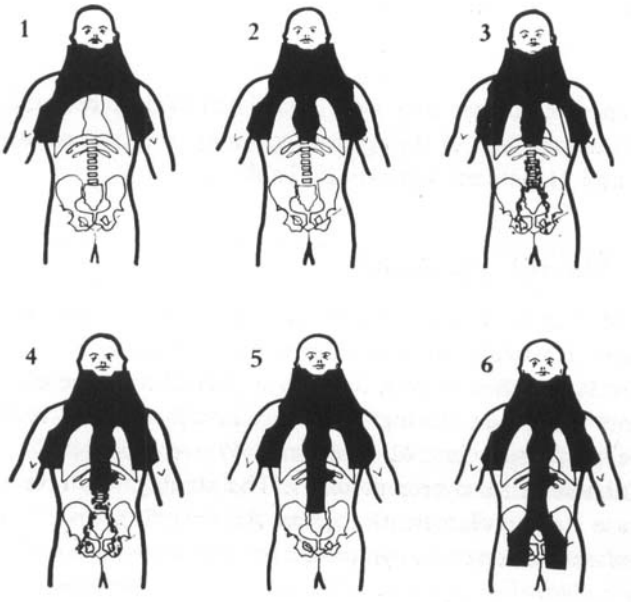

Fig. 2. Extension of irradiated areas between 1960 and 1974. 1) mantle omitting mediastinum. 2) mantle Thl0. 3) mantle Thl0, lymphography with ^{32}P labelled Lipiodol. 4) mantle L2, lymphography with ^{32}P labelled Lipiodol. 5) mantle + paraortic nodes. 6) Total nodal irradiation.

Table 2

Distribution of 67 cases of nodular sclerosis according to sex, presence of systemic symptoms or signs and initial presentation

Sex	No. of cases	Systemic symptoms		Initial presentation groups (no. of cases)					
		Absent	Present	1	2	3	4	5	6
Males	24	19	5	1	1	3	5	5	9
Females	43	39	4	4	—	5	11	16	7

Table 3

Subdivision of nodular sclerosis by fibrosis and cellular composition

Fibrosis	LP	MC	LD	No. of cases
+1 +2	7	22	1	30 (44.8 %)
+3 +4	10	25	2	37 (55.2 %)
Total No. of cases	17 (25.3 %)	47 (70.1 %)	3 (4.6 %)	67

to have a much lower incidence of relapse and were associated with a definitely more favourable prognosis. A comparison of the relapse frequency in the six groups in a larger series of stage I and II patients appears in Table 1.

Materials and Methods

The patients were treated at this Department of Radiology from 1960 to 1974. The total number of stage I and II patients submitted during that period to a radical form of radiation therapy was 248. Unfortunately, for only a part of them were the initial slides available, several being lost during the flood in Florence in 1966. Histologic revision could be performed in 142 cases and 67 were classified as nodular sclerosis and were included in the present series. The staging was revised according to Hodgkin's disease staging classification (Ann Arbor 1971).

The sex distribution and presence of systemic symptoms or signs and presentation appear in Table 2.

During the period 1960–1974 the irradiated areas were extended, resulting in six alternatives as illustrated in Fig. 2. The status of disease was assessed for all patients up to 31 Dec. 1975. The minimum follow-up was 12 months; 85 per cent of the patients were followed for periods of more than 2 years.

Table 4

Incidence of relapse after treatment compared with cellular composition and amount of fibrosis

Cellular composition	No. of cases	Relapse		Amount of fibrosis	No. of cases	Relapse	
		No. of cases	Per cent			Number	Per cent
LP	17	3	18	+1 +2	30	8	27
MC	47	19	40				
LD	3	1	33	+3 +4	37	15	41
		$0.10 < p < 0.05$				$0.75 < p < 0.50$	

Table 5

Distribution of systemic symptoms compared with cellular composition and amount of fibrosis

Cellular composition	No. of cases	Systemic symptoms		Amount of fibrosis	No. of cases	Systemic symptoms	
		Present	Absent			Present	Absent
LP	17	1	16	+1 +2	30	4	26
MC	47	7	40				
LD	3	1	2	+3 +4	37	5	32
		$0.50 < p < 0.25$					

The histologic revision was done at the Department of Pathology, University of Florence. The pathologists were intentionally not informed on the clinical stage and survival of the patients.

In 20 cases in which paraffin blocks with large tissue fragments were available, serial sections were prepared in order to determine if the microscopic appearances presented any substantial change in the various sections.

The specimens were stained with haemotoxylin-eosin and with the Mallory and Van Gieson methods. The specimens were also examined under polarizing light to assess the typical birefringence of the collagen.

The amount of fibrosis was classified according to PATCHEFSKY et coll. on an ascending scale, depending on whether it formed incomplete nodules (+1), or complete nodules involving less than one-half of the tissue specimen (+2), or well developed nodules with thick collagen bands (+3, +4).

The cellular composition was graded according to the criteria of KELLER et coll., scoring as LP the cases with predominance of mature lymphocytes and few Reed

Table 6

Sex distribution compared with cellular composition and amount of fibrosis

Cellular composition	No. of cases	Males	Females	Amount of fibrosis	No. of cases	Males	Females
LP	17	7	10	+1	30	15	15
				+2			
MC	47	15	32				
				+3			
LD	3	2	1	+4	37	9	28
			$0.50 < p < 0.25$				

Table 7

Presentation groups compared with cellular composition and amount of fibrosis

Cellular composition	No. of cases	Presentation group		Amount of fibrosis	No. of cases	Presentation group	
		1–2–3	4–5–6			1–2–3	4–5–6
LP	17	9	8	+1	30	4	26
				+2			
MC	47	5	42				
				+3			
LD	3	—	3	+4	37	10	27
			$p < 0.001$				

Sternberg cells, as MC the cases with mixed cell population of eosinophils, plasma cells and many Reed Sternberg cells and malignant reticulum cells. As LD were classified cases with depletion of mature lymphocytes, but still with a nodular appearance.

Results

The results of the histologic subclassification appear in Table 3. The two histologic types have been correlated with the relapse frequency and the other clinical parameters separately.

The adverse prognostic value of the occurrence of a primary post treatment relapse has already been demonstrated (KAPLAN 1968). Twenty-three patients of the present series (34% of total cases) developed a post treatment relapse. The distribution of the relapsing cases is compared with the cellular composition and the amount of fibrosis in Table 4.

The distribution of systemic symptoms or signs according to the cellular composition and to the degree of fibrosis is given in Table 5. Of the total cases only 9 presented systemic symptoms or signs.

Table 8

Extension of irradiated area compared with cellular composition and incidence of relapse

Irradiation area	LP		MC		LD		Relapse/No. of cases
	No. of cases	Relapse	No. of cases	Relapse	No. of cases	Relapse	
Mantle omitting mediastinum	—	—	3	2	1	1	3/4
Mantle Th10	7	1	22	12	1	—	13/30
Mantle Th10, lymphography with ^{32}P labelled Lipiodol	2	—	3	1	—	—	1/5
Mantle L2, lymphography with ^{32}P labelled Lipiodol	3	2	3	1	1	—	3/7
Mantle plus paraortic nodes	4	—	11	1	—	—	1/15
Total nodal irradiation	1	—	5	2	—	—	2/6
Total	17	3	47	19	3	1	

The distribution of patients according to sex appears in Table 6.

Table 7 gives the case distribution according to the presentation group. Most cases with involvement limited to mediastinum or upper cervical nodes or a single supraclavicular region (groups 1, 2, 3) belonged to the LP group. On the contrary, the majority of the MC cases (42/47) had involvement at multiple sites at presentation (groups 4, 5, 6).

The distribution of cases according to the extension of the irradiated area and to cellular composition appears in Table 8. The number of patients in each group is too small for any significant consideration except in the mantle Th10 group consisting of 30 cases. The incidence of relapse was 12/22 in the MC group and 1/7 in the LP group.

Discussion

The composition of the present series is comparable to series of nodular sclerosis reported previously.

The prevalence of females (ratio 1.97), the frequency of mediastinal involvement (42 cases of 67) and the rarity of constitutional symptoms are confirmed as biologic characteristics of nodular sclerosis.

The analysis of the results of the histologic subclassification shows that both the degree of fibrosis and the cellular composition have some correlation with the incidence of relapses after treatment, and they seem to distinguish groups of patients with a differing prognosis.

Because of the small number of cases, the correlations do not have statistical significance, but they are supported by the impressive analogy with the data reported by KELLER et coll. and by PATCHEFSKY et coll. In their series, as well as in the present one, the cellular composition seems to offer a better characterization of nodular sclerosis than the amount of fibrosis in predicting the post treatment outcome. The LP variety appears to be associated with a definitely lower incidence of relapse than the MC variety; the significance of the LD variety is uncertain due to its relative infrequency.

The advanced degree of fibrosis is associated with a higher incidence of relapse, but the difference is not as evident as for the cellular composition.

The analysis of the different treatment techniques employed shows that the better prognosis of the LP group does not seem to depend on a more frequent use of a larger irradiated volume; furthermore in the 30 cases treated with the mantle Th10 technique, the MC cases maintain a relapse incidence higher than the LP cases.

The more unfavourable prognostic significance of the MC variety is also confirmed by the association with other bad prognostic factors such as the presence of systemic symptoms or signs and the multiplicity of the involved regions at the presentation.

The present results seem to support the hypothesis that the M cellularity is an expression of a higher malignancy of the disease.

On the contrary, no correlation was found between the presence of systemic symptoms or the extension of the initial involvement and the amount of fibrosis as a further suggestion that this histologic parameter has less importance than the cellular composition in the prediction of survival.

Addendum in proof

An interesting report is that of COPPLESON et coll. (1973) correlating the cellular composition with survival in 358 biopsies of Hodgkin's disease: the lymphocyte frequency appeared to have the highest predicting value of prognosis both in the nodular sclerosis and in the mixed cellularity types.

SUMMARY

Sixty-seven patients with nodular sclerosis (Hodgkin's disease stages I and II) have been subclassified according to the cellular composition and the amount of fibrosis. Predominance of mature lymphocytes and rarity of Reed Sternberg cells were associated with less extensive disease at presentation and more favourable outcome. A less definite correlation to the amount of fibrosis was found.

ZUSAMMENFASSUNG

Siebenundsechzig Patienten mit nodulärer Sklerose (Hodgkinsche Krankheit, Stadium I und II) wurden entsprechend der zellulären Zusammensetzung und der Menge von Fibrose untergruppiert. Die Dominanz von reifen Lymphozyten und die Seltenheit von Reed-

Sternberg Zellen waren mit einer weniger ausgebreiteten Krankheit zur Zeit der Diagnose und einer günstigeren Prognose verbunden. Ein weniger gut definitiver Zusammenhang zum Umfang der Fibrose wurde gefunden.

RÉSUMÉ

Soixante sept malades ayant une sclérose nodulaire (maladie de Hodgkin, stades I et II) ont été répartis en une sous classification suivant la composition cellulaire et la quantité de fibrose. La prédominance de lymphocytes mûrs et la rareté de cellules de Reed-Sternberg sont associées avec une maladie moins extensive au moment du diagnostic et comporte un pronostic favorable. Les auteurs ont trouvé une corrélation moins nette avec la quantité de fibrose.

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