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Lymphoepitheloid Cell Malignant Lymphoma (Lennert)

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Summary. Typical epitheloid cell formations were found in 175 of 500 cases of various types of Hodgkin's disease. No distinctive behaviour was found in cases with epitheloid structures.

Close attention has been devoted to a further series of 23 lymphoepitheloid cell malignant lymphomata marked by focal nuclear atypicality in their epitheloid cell granulomas, which destroyed the basic neoplastic structure of the lymph node in many cases, necessitating further biopsy. In this series not only Hodgkin's disease (7 cases) but also some malignant lymphomas of non Hodgkin's types (3 × immunoblastoma, 3 × immunocytoma and 2 × T-lymphoblastoma) were found. In 6 cases only a tentative diagnosis of lymphoepitheloid cell malignant lymphoma could be made.

The epitheloid granulomatous reaction tended to disappear gradually in all cases by repeated check-ups, and was apparently a secondary phenomenon. The cause of the epitheloid cell atypia was not evident although it proved to be an important diagnostic feature identifying an independent form of lymphoepitheloid malignant lymphoma. The subsequent development of this lesion suggested a mildly pleiomorphic highly malignant lymphoma, which might be of B cell origin, but was sometimes demonstrably of the T cell series.

Key words: Lymphoepitheloid cell malignant lymphoma independence – Behaviour – Epitheloid cell atypia.

Introduction

The basis for the definition of lymphoepitheloid malignant lymphoma (LML) was provided by Lennert (1968). His original communication was concerned

List of abbreviations used: HD = Hodgkin's disease, ML = malignant lymphoma, LML = lymphoepitheloid cell LM, RS = Reed-Sternberg cells, LH = lymphoid-histiocytic (polyploid variant of RS) cells, HE = hematoxylin-eosin

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merely with the consistantly high content of epitheloid cells in Hodgkin's disease (HD); the series of 60 cases was heterogenous although HD constituted the major subgroup. The epitheloid granulomatous structures were considered to be a special response to the neoplastic process. There were fewer HD in Lennert's subsequent larger series (1975) and in the study referred to by Scully (1977). HD was diagnosed in only 45 out of the initial 121 cases; there were 36 cases of angioimmunoblastic lymphadenopathy and 40 cases of other types of ML. A number of more recent studies have suggested that Lennert's interpretation of lymphoepitheloid lymphoma as a subvariant of Hodgkin's disease was no longer viable, as neither its clinical course nor its therapeutic response could, as a rule, be fitted into the currently used pattern of classification of Hodgkin's disease. Some authors, therefore, prefer to include LML among non-Hodgkin malignant lymphomas (Dorfman, 1975), and the possibility of including it among T lymphomas has also been suggested (Klein, 1977). In our own material the problem has developed in what is now quite an extensive series. I wish to present some of the findings.

Material

In a retrospective study 500 lymphnode biopsies in HD were revised in order to determine the frequency of typical epitheloid cell granulomas and the prognostic value of these structures.

Close attention has been devoted to another prospective series of 23 malignant lymphomas, in which cellular atypicality in epitheloid cell granulomas was the most prominent feature of the biopsy finding and the diagnosis of LML was often only tentative. Repeated biopsies and longitudinal follow-up led to the diagnosis of ML other than LML and HD in some of these cases.

In the last few years the problem of ML has been approached systematically and so part of the results were based on comprehensive morphological-histochemical, immunological and electron-optical analyses carried out under standard conditions. However, the main emphasis was placed on clinical biopsy and necropsy correlations. In six cases biopsy findings were verified at autopsy.

Results

The basic feature of the retrospective larger series was that admixtures of granulomas of typical epitheloid cells were found so frequently in all forms of Hodgkin's disease (175:500) that doubts were cast on the diagnostic usefulness of this particular sign, and on the very independence of the problem of lymphoepitheloid malignant lymphomas. We were unable to find any convincing prognostic or diagnostic significance in the finding.

Different results were obtained in the prospective series that had been taken for close analysis. Some of the epitheloid cells in the granulomas showed cytological irregularities or even atypicality, including enlargement of the nuclei, coarsening of their chromatin, thickening of the nuclear membrane, often running into irregular invaginations (Fig. 1), enlargement of the nucleoli, polyploidy or binuclearity. These atypical epitheloid cells also had the appearance of RS cells or lacunar cells in places. Not all the epitheloid cells were atypical, most

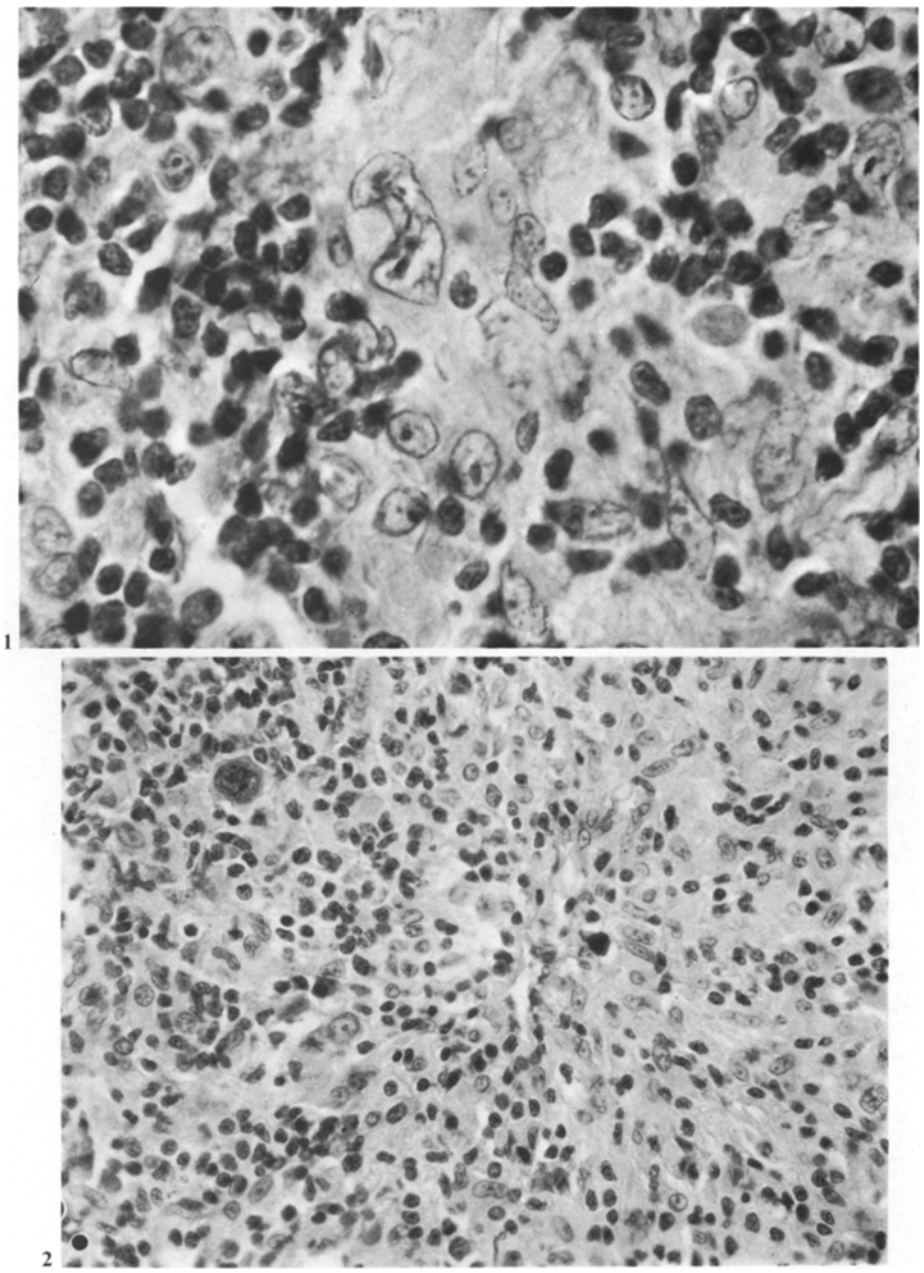
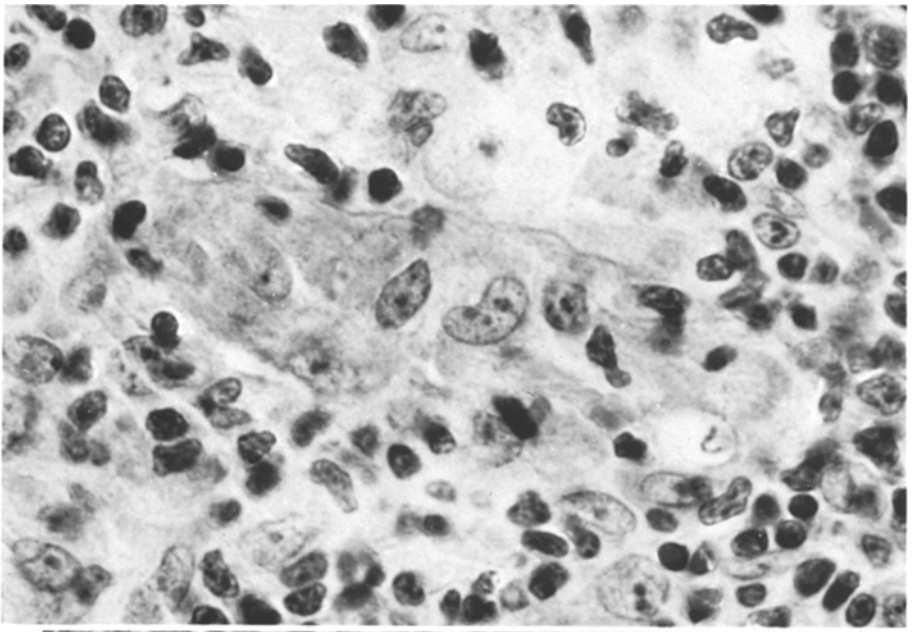


Fig. 1. Epitheloid cells of different size, irregularly shaped nuclei, thick nuclear membranes, and well defined nucleoli. Case 11 (Hodgkin's disease). HE. ×1,200

Fig. 2. Radial pericytic-like perivascular arrangement of epitheloid cells. Case 4 (Hodgkin's disease). HE. ×600



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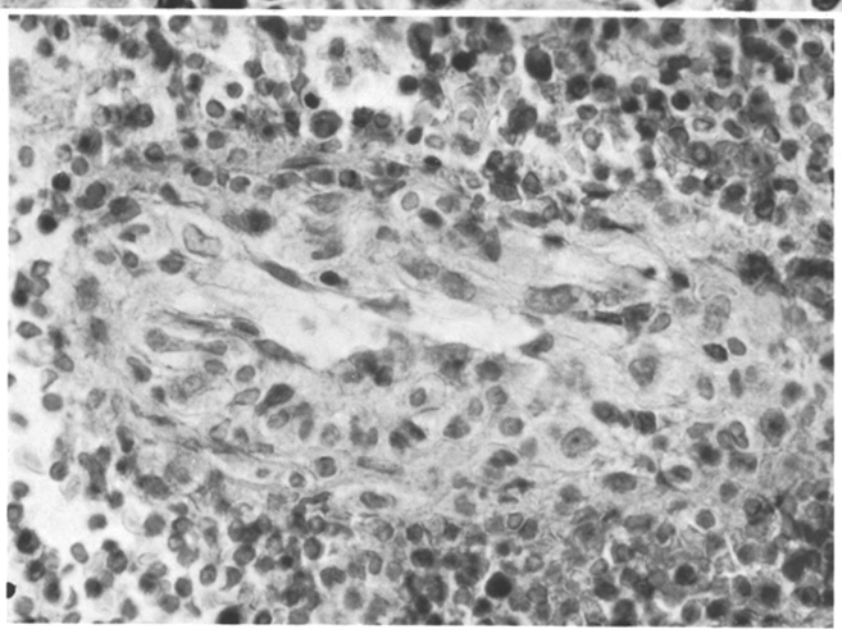

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Fig. 3. Endothelial epitheloid cells. Case 18 (Angioimmunoblastic lymphadenopathy). HE. ×800

Fig. 4. Epitheloid cells in the muscular wall of a vessel. Case 6 (Hodgkin's disease). HE. ×600

Table 1

Atypical epitheloid cells seen in	
Hodgkin's disease	7 cases
angioimmunoblastic lymphadenopathy	2 cases
immunoblastoma	3 cases
immunocytoma	3 cases
T lymphoblastoma	2 cases
others	6 cases
Total	23 cases

resembled those seen in sarcoidosis or tuberculosis. Other basic lymph node changes did not differ from those found in other types of malignant lymphoma.

Differences in the nature of granulomas were comprised not only of cytological deviations but also changes in their interrelationship and their relationship to the original node structures. It was possible to identify smaller sarcomatoid nodules and also large, vaguely defined atypical epitheloid formations. There were also however, nodules bound to the existing node structures, e.g. nodules associated with follicles, and perivascular (Fig. 2), endothelial (Fig. 3) and intramural vascular epitheloid transformations (Fig. 4).

The structure of the node in the nongranulomatous part was always fundamentally altered, though not always in the same way. Of the 23 cases (see Table 1) there were two instances of the predominance of immunoblastic infiltration with admixtures of eosinophils and plasmocytes. Lukes'polyploid LH cells were present as were cells close resembling RS cells (Fig. 5a). There were also two instances of a similar basic node structure but with only lacunar cells present (Fig. 5b); three cases showed a predominance of basophil polyploid immunoblasts. All in all, the findings in seven cases permitted the diagnosis of Hodgkin's disease in the absence of the characteristic Sternberg cells, although sometimes repeated biopsy was necessary.

In two cases endothelial cell proliferation was so prominent (Fig. 3) that the picture closely resembled that of angioimmunoblastic lymphadenopathy. In three instances, atypical immunoblasts (Fig. 6) were the basic element clustered among the epitheloid granulomas. There were also three instances of an abvious preponderance of immunocytes, or lymphoplasmocytoid cells (Fig. 7). In two further cases a predominance of pleomorphic cells without cohesion was seen reminiscent of malignant lymphoma with convoluted nuclei. One of them was proved to be a T lymphoma by repeated biopsy and T rosetting in 60% of cells in an necropsy material (Fig. 8).

On six occasions the cytological pattern between granulomata was not definitive and a malignant lymphoma was considered only because of the presence of atypia in the epitheloid cells. Sufficient data could not be obtained for precise diagnosis in these cases but the clinical course was compatible with the diagnosis of ML.

Repeated biopsies and comparisons with post-mortems (see Table 2) usually demonstrated a gradual disappearance of epitheloid formations and a transition to a picture of obvious malignant lymphoma. Only once was complete remission found.

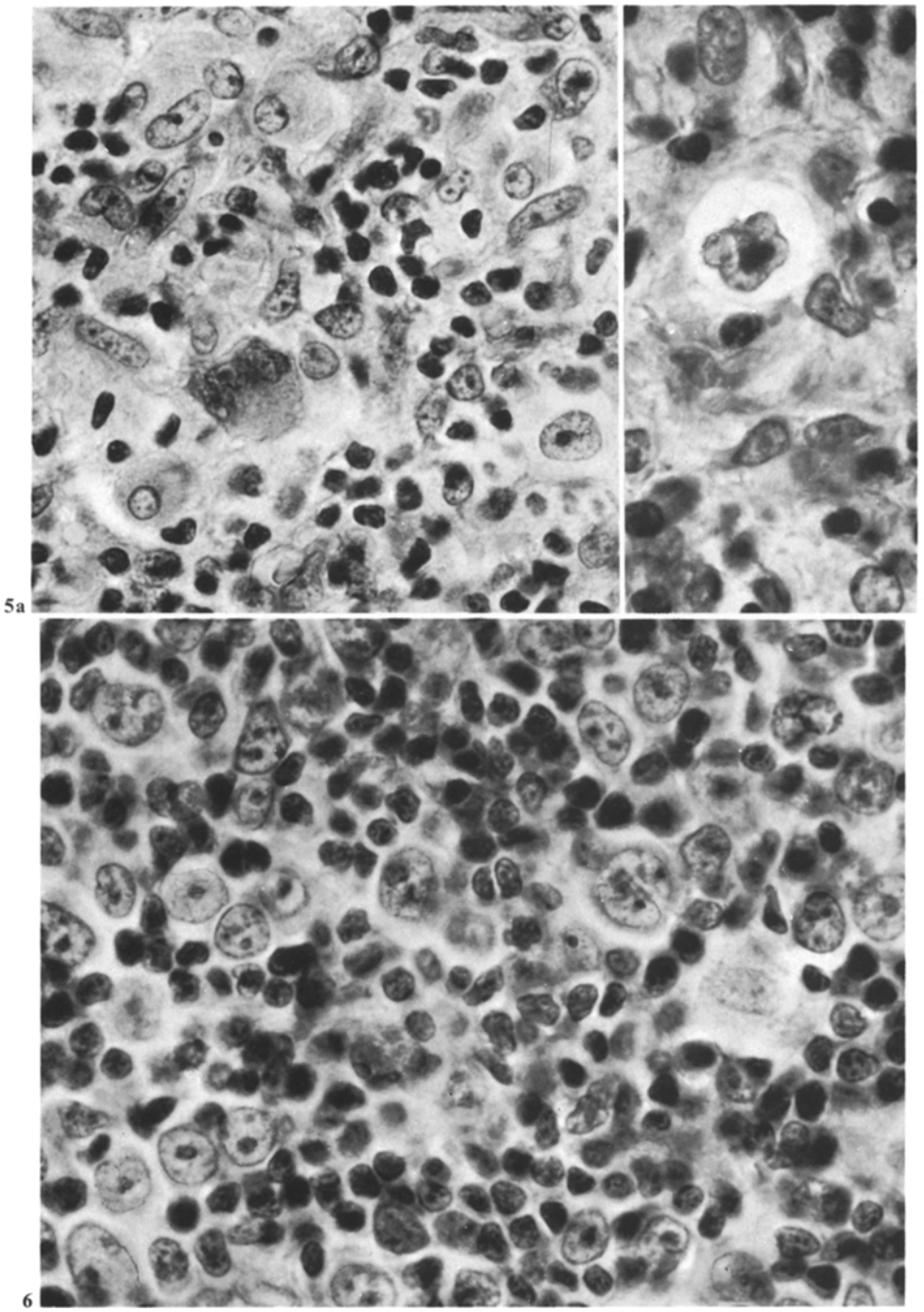
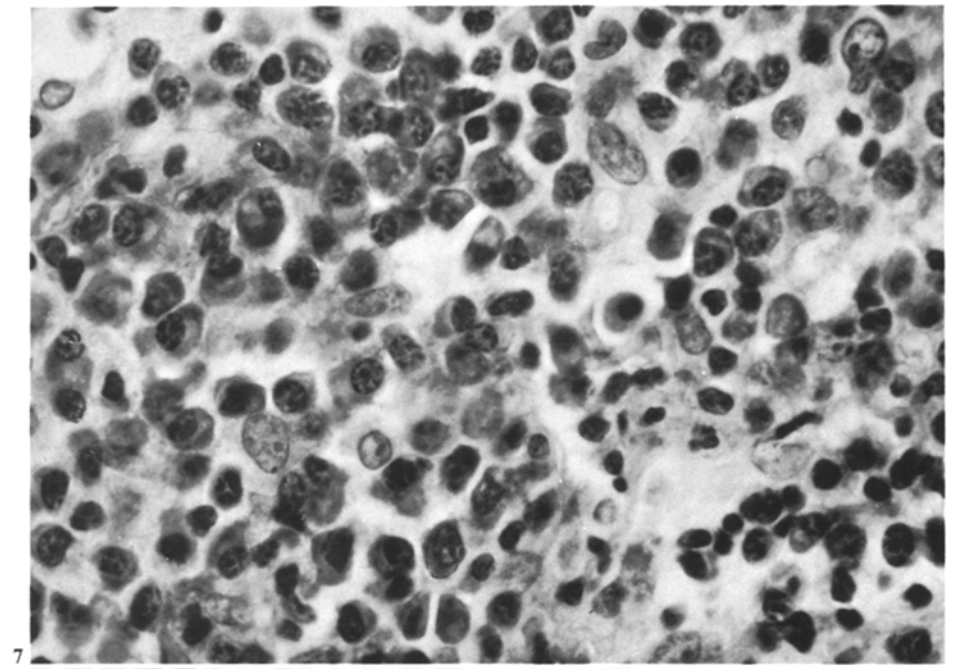


Fig. 5. a Epitheloid, lymphoid-histiocytic and Reed-Sternberg type cells. **b** Lacunar type cell. Case 5 (Hodgkin's disease). HE. ×1,200

Fig. 6. Clumped atypical immunoblasts. Case 12 (Immunoblastic lymphoma) HE. ×1,200



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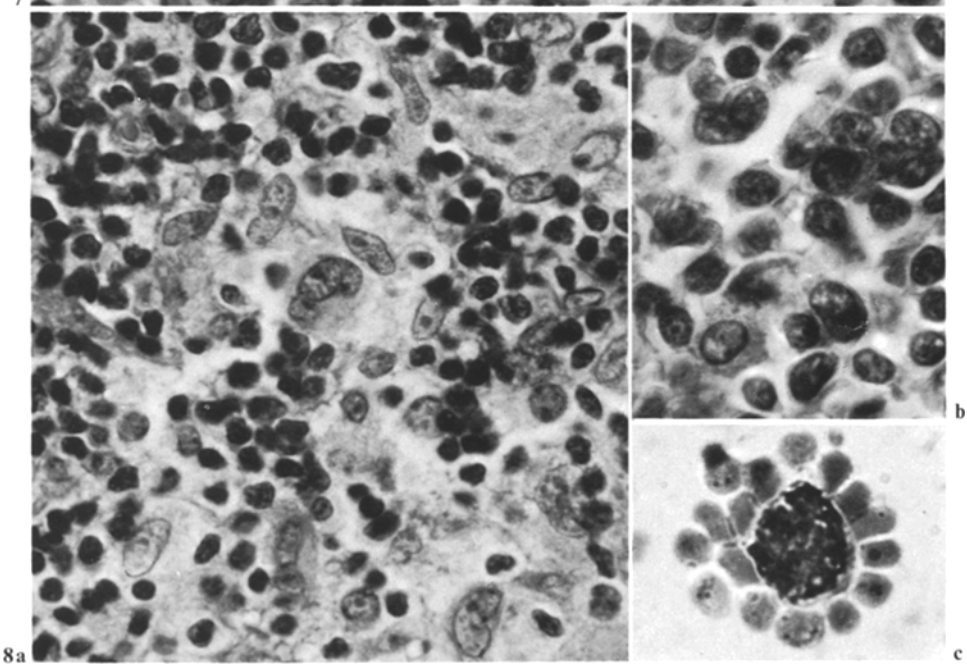

8a b c

Fig. 7. Predominant lymphoplasmocytoid cells. Case 23 (Immunocytoma) HE. ×1,200

Fig. 8a–c. Case 20 (T lymphoblastoma). **a** Characteristic epitheloid granulomas in biopsy. HE. ×600. **b** Slightly pleomorphic T lymphoblasts in necropsy. HE. ×600. **c** T rosetting. HE. ×2,000

Table 2

Case	First biopsy	Repeated biopsy	Necropsy
M.B.	no conclusion	LML	ML (Type), no epitheloid formations
M.B.	LML		ML pleiomorphic, no epitheloid formations
U.J.	LML		ML pleiomorphic, no epitheloid formations
H.J.	sarcoidosis	paragranuloma	ML immunocytic, no epitheloid formations
V.A.	LML		ML pleiomorphic, scanty epitheloid formations
Š.F.	epitheloid granuloma	ML immunocytic	complete remission

The number of lymphocytes was evaluated in the whole of the series along lines similar to those in Hodgkin's disease. The differences were considerable; in 12 cases the number of lymphocytes was undiminished, but in 11 cases it was markedly reduced.

The basic data on the patients were similar to previous reports though tonsillar involvement was not frequent (Editorial 1976; Burke et al., 1978). Our patients' average age was rather high, in the region of 50 years, and there was a slight preponderance of males. The course of the disease was very different. Remission was achieved in about two thirds of the patients, following the usual therapeutical measures, or occasionally spontaneously. However, in five of the postmortem cases the disease appeared to have progressed very rapidly, and therapy had obviously had little effect. Deaths occured between 6 and 18 months after the appearance of the first signs.

Discussion

If we are to form any clear idea of the picture of lymphoepitheloid malignant lymphoma on the basis of our prospective study, only two common features stand out:

1. Epitheloid cells clumping to form small epitheloid granulomas; some of the epitheloid cells had variably atypical nuclei.

2. There were different degrees of prominence of the malignant lymphoma among the epitheloid formations. In about one third of the cases there were so many epitheloid granulomas as to obscure the ML structure. A tentative diagnosis of ML could then be based only on focal epitheloid cell atypicality. Definitive diagnosis was made from the repeat biopsy. "Extraepitheloid" histopathological features were those of Hodgkin's disease or angioimmunoblastic lymphadenopathy. In other cases the picture was more pleomorphic, resembling sarcoma, lymphoplasmocytoid in nature, or appearances suggesting a T-lymphoblastoma.

The interrelationships between epitheloid and other tumour structures cannot be defined except in vague terms. Different elements of malignant lymphoma may possible produce substances of the lymphokine type (Lennert et al., 1968), which are responsible for the epitheloid granulomatous reaction. As tumour anaplasia progresses production may dwindle, providing a plausible explanation for the gradual disappearance of the epitheloid granulomatous component in individual cases. It is also possible that epitheloid cells are like polyploid cells in Hodkin's disease. However, epitheloid cells in LML usually have the ultrastructural features of histiocytes and do not have basophilic cytoplasm nor do they resemble polyploid immunoblasts. They also show a tendency to the development of giant cells of the Langhans type which do not resemble any of the variants of RS cells. One cannot overlook that in epitheloid transformation a number of different non-lymphocytic node structures take part (endothelia, muscle cells of the vessels and pericytes) most of which are not of lymphocytic or monocytic origin.

The cause of the epitheloid cell nuclear atypicality is not clear since no epitheloid transformation of tumour cells appears to be involved. If the epitheloid cells were neoplastic many more would show nuclear atypicality. It is always a relatively small proportion of these cells that are strikingly different from the majority.

The diagnosis and differential diagnosis of LML would prove to be a difficult task if lymphoepitheloid lymphoma were to be regarded as an oncological entity. As our experience accumulated the term LML gradually began to be used as a group designation only. A third of the cases involved could be identified as Hodgkin's disease. In another third a different lymphoma was suspected because of the presence of certain other signs, depending on the course of the disease or the results of necropsy. In many of the cases concerned no specific diagnosis could be made and the diagnosis depended on the fact that atypical epitheloid cells were signals of some malignant lymphomas.

Prognostic conclusions proved difficult to draw because of the variegated nature of the basic patterns. Where Hodgkin's disease was diagnosed the biological behavior was typical for that type of tumour. Sarcomatoid lymphocytedepleted forms took a very unfavourable course, as seen in three cases. In contrast, patterns associated with structures close to the first type of Hodgkin's disease behaved relatively favourably.

In the cases of poorly classifiable pleomorphic malignant lymphomas, the disease took an unfavourable course particularly where malignant lymphoma, probably of the T series (with a tendency to simultaneous skin affection) was involved. In the group in which the first biopsy was not diagnostic, there was also poor prognosis. A poor prognosis was also found when the tumour became differentiated to form a picture of lymphoplasmocytoid lymphoma with hypergammaglobulinaemia.

In conclusion, prognosis proved to be relatively favourable only where the picture was one of Hodgkin's disease without lymphocytedepletion. Lymphocytedepleted variants of Hodgkin's disease and other malignant lymphomas of the non-Hodgkin type, with epitheloid structures, were highly malignant.

Lymphoepitheloid lymphoma is a problematical nosologic entity. There is no denying its conspicous structure. It would perhaps be convenient to single out those cases where diagnosis rests merely on the presence of atypical epitheloid formations, obscuring the rest of the lymphatic tissue. There are relatively few of these cases. In our series they were distinct from the other entities under discussion, and were finally identified as malignant lymphomas of both B and T series, and as pleomorphic malignant lymphoma probably of the T series. In some cases the picture was undoubtedly distinct from Hodgkin's disease and from angioimmunoblastic lymphadenopathy. This relatively independent picture could be identified in about a quarter of our prospective series of 23 cases.

Hodgkin's disease and some other ML have distinctive characteristics, if they have an epitheloid granulomatous or atypical reaction and are best not considered in the discussion of LML. Only if the approach is made substantially more selective, lymphoepitheloid lymphoma could be defined in more detail as regards its clinical features and prognosis.

Therefore, although little is likely to remain of the original concept of lymphoepitheloid lymphoma and although we prefer to refer to lymphoepitheloid reaction in some malignant B and T lymphomas, it is undeniably to Lennert's credit that he drew attention to this problem and that he made the tentative diagnosis of this type of ML possible.

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