Pathology and Nosology of Hodgkin’s Disease

By

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Lymphogranuloma is not localized and only linked with the RS in so far as its cells are of retothelial origin. Differentiation of the characteristic histological pattern has shown that the histogenesis of the lymphogranulomatous focus, with empty necrobiosis, granuloma formation and sclerotic obliteration, corresponds to the regular biopathological phases of inflammation. As a reactive process of varied duration and degree, lymphogranulomatosis can present various, including tumor-like changes, without satisfying the histological criteria of autonomous neoplasia or prospective sarcoma. Even though the etiology of Hodgkin’s disease is unknown, it is clinically, anatomically and histologically a separate disease. A survey of the various morphological findings leads to classifying it as an inflammation. It may be that the Hodgkin’s disease, like rheumatic diseases, nephritis or lupus erythematosus, is a poly-etiological reaction product, a course emancipated from the cause and proceeding by its own laws.

I

In his publication “On some morbid appearances of the adsorbent glands and spleen” Hodgkin described, in 1832, the histological pattern of a disease known as Hodgkin’s disease (Wilks 1865). In German medicine the condition is referred to as lymphogranulomatosis (Gross 1906). Hodgkin’s disease is a progressive illness, with intermittent fever, enlargement of lymph nodes and spleen, leukocytosis sometimes associated with eosinophilia, a positive diazo-reaction and wasting. Its classification is difficult. The clinical course is suggestive of an inflammatory nature, the etiology is unknown, and the morphological findings comparatively often indicate a tumor-like appearance. In this situation, the origin of the cells composing Hodgkin’s tissue appears particularly important, it will show the significance of a morphological analysis of histological changes and whether a correlation of the various patterns envisaged with the course of the disease enables Hodgkin’s disease (H.D.) to be differentiated as a disease entity.
II

A. The incidence of H.D. has been stated as about 2 cases in every 100,000 of population (Hoster) or 1.5 cases in 100,000 (Uddströmer). Some reports of a familial frequency are available. Records of connatal cases are few and agree that the mothers were affected by the disease during pregnancy. This is in clear contrast to leukemia in newborn infants of healthy mothers (Fresen, a).

B. There is a wide age range in Hodgkin's disease. If the questionable connatal

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cases are disregarded, are the time of its onset ranges from childhood to old age. The incidence is to some degree greatest in the third and fourth decades of life. So far as sex distribution is concerned, men appear to be generally more affected than women (Table I).

C. The interval between the appearance of the first symptoms probably relatable to H.D. and death due to it can be rated as the duration of the disease. This is not generally much influenced by the patient's age, although the course is usually more rapid in old age. Acute cases can, however, be seen in all age groups. The average duration calculated from the statistics on fairly large numbers of patients ranges between 2.4 years (Fresen a) and 3.7 years (Shimkin). About 30% of patients live longer, but only up to 21% of the men for 5 years and nearly 37% of the female patients. Untreated H.D. must not take a more rapid course than treated. However, the patient's life span increases with regular treatment (Heilmeyer et al.); for example 51% of those with radiotherapy can live for 5 years (Peters).

D. According to American statistics, the death rate from Hodgkin's disease has distinctly increased in recent years from 0.08% to 0.16%.

III

A. The pattern of the disease is one of its anatomical changes. A knowledge of these is important for a diagnostic understanding of the varied symptoms. The diagnosis can, in fact, only be established by biopsy. Necroptic examinations are, of course, limited. The significance of localization and spread for the symptoms, diagnosis and therapy of this progressive disease is evident. A survey of the most frequently found anatomical changes gives information on this (Table II).

B. The xanthous form (Letterer) is a rare variety, its particular feature is the storage of anisotropic lipoids which is not due to spontaneous or treatment induced regressive changes (Linke). Involvement of bone is common in advanced cases. Although there is some resemblance to lipoid granulomatosis, the two conditions differ in course, age and localization.

IV

Hodgkin's disease can affect all organs and tissues, and presents varied manifestations. Its most frequent situation is no doubt the lymphoreticular tissue. It is not, however, either restricted to anyone system or a systemic disease. The basis of the varied anatomical changes is the histological findings described by Hodgkin and later more precisely defined by Sternberg.

A. The giant cell granuloma is the basic element of the histological changes and enables the varied findings, which sometimes even are of a tumor-like ap-
It consists of a loose connective tissue stroma with lymphocytes, plasma cells, relatively sparse eosinophil granulocytes, epithelioid cells and the multi-nucleated giant cells (Reed; Sternberg). The histological diagnosis of H.D. depends on the finding of these giant cells (Fig. 1). In structure, function and occasional phagocytosis, the giant cells equal histiocytes or activated reticulum cells. Their formal origin is recognized from the characteristic structure of the granuloma. An argyrophil fiber reticulum is, by its arrangement and relation to the pre-existent tissue, distinctly new formed. The
reticulogenic so-called Hodgkin’s cell is considered to be the precursor of the
giant cell, it is not, however, only typical of lymphogranuloma but also found in
inflammatory hyperplastic lymph nodes, the non-specific sinus catarrh and infec-
tious mononucleosis (Fresen, a).

B. Fibrosis is another characteristic of the lymphogranulomatous focus; it develops from the hyaline degeneration of the fiber structure. Complete obliteration of an individual focus is recognized by degenerative atrophy of the cells, increasing clotting of nuclei and aggregation of remains of giant cells. Local hyaline sclerosis and extinction of a granuloma, as healing in the anatomical sense, is restricted to the individual focus; it does not influence the course of the disease, there being no concomitant general reaction (Fig. 2).

The phasic development of the granuloma through sclerosis to fibrotic nodule and in connection with the reversibility of progressive and regressive changes within the lymphogranulomatous single focus can be rated, according to generally valid bio-pathological rules, as the manifestations of an inflammatory process. The storage of double refractory lipoids in the histiocytes or reticulum cells which become foam cells, is certainly secondary (Letterer); it makes the transition from granuloma to fatty degenerated scar tissue particularly well clear (Linke).

C. The lymphogranuloma is therefore to be considered a special granulation tissue and, according to its histological structure, is to be classified with the retothelial determined granulomas (Fresen, a). The problem of clarifying the pathological course of the lymphogranulomatous process consequently requires the morphological demonstration of phases equivalent or adequate to an exudative stage.

1. Such early changes are seen in the sinus catarrh (Sternberg), the small foci of multiplication of reticulum cells, including those showing epithelioid transformation, and in circumscribed reticulocytosis of the sinus (Lennert). These changes however being restricted to within lymph nodes; this nonspecific reaction product cannot be considered generally valid for the histogenesis of a lymphogranulomatous focus, independent of the localization of the focus. There is no more diagnostic significance in these histological aspects than in the histological findings of para-granuloma. Exhibiting a clearly chronic and benign course, para-granuloma is considered to be a special type of lymphogranuloma which in 20% of cases leads to Hodgkin’s disease (Jackson and Parker) (Fig. 3). The localization of para-granuloma is also restricted to within lymph nodes. According to the critical evaluation of the findings in patients with such changes of lymph nodes para-granuloma appears to be a progressive disease of lymph nodes (Wright) which both in clinical prognosis and histomorphological pattern differs from lymphogranulomatosis (Loew and Lennert). Sinus catarrh, reticulocytosis and histological pattern, despite their non-specificity, as found in para-
granuloma can be well thought to be initial changes in Hodgkin's disease. But if it is taken into account that lymphogranuloma, independent of its localization, shows the same histological pattern, these conditions, as they are only found in lymph nodes, cannot be rated as generally valid early changes.

2. Irrespective of differences depending on the localization and considerable quantitative differences, the "caseous focus without remains of lymphogranulomatous tissue," already described by Sternberg, has actual significance for the histological diagnosis of the lymphogranulomatous process and its nosological determination. These foci of "spontaneous softening" demonstrate immediate necrobiosis of the affected place. They are neither due to local nutritional disturbances resulting from impairment of the blood supply to the affected tissue nor are they induced by treatment effects. They precede granuloma formation. Although the cause is unknown, it is a primary local tissue damage which is more likely to represent the initial phase of the lymphogranulomatous process. In contrast to para-granuloma, these foci are not restricted to lympho-reticular tissue. The regular successive order of granuloma and fibrosis is supplemented by the initial alteration of the tissue to the normal course of inflammation.

During the normally protracted course of lymphogranulomatosis, this primary phase may not, of course, be distinct or still observable in every biopsy specimen more or less accidentally obtained. As a typical example exudative processes in the lung have been described in lymphogranulomatous changes; as they precede the productive specific stage, the two phases together make up the pattern of lymphogranulomatous alveolitis (Nicod). This inflammatory nature with marked exudative component is also distinct in lymphogranulomatous meningoencephalitis (Wepler). The histogenetic course and its nosological determination as an inflammation are fully confirmed by the quantitatively extreme histological conditions in acute Hodgkin's disease (Fig. 4).

A comparison with the exudative phase of an inflammatory process is, thus, well applicable to lymphogranulomatosis. The productive stage in the form of the granuloma mainly composed of reticulo-histiocytic elements, becomes the particular diagnostic characteristic of the disease and by its spontaneous tendency to fibrotic obliteration leads to scarring of the individual focus. Local recurrences, with considerable quantitative differences as concerns exudative necrotic alteration, do complicate the lymphogranulomatous process, it is true, but do not reverse the regular successive course. No other conclusion can be reached from the course of the histological changes within a lymphogranulomatous focus (Fresen, a).

D. The clinical course and histo-morphological pattern of Hodgkin's disease are suggestive of an infective etiology.

No causal relation between Hodgkin's disease and tuberculosis has been proved, despite a frequent family history of tuberculosis (Wurm). All experiments
to transmit Hodgkin’s disease to animals, including monkeys, have failed. Reports of a virus as the cause have not yet been confirmed (Jacquez and Porter). The observation of freedom from symptoms for 8 to 11 years after exstirpation of the apparently first affected cervical lymph nodes (Jackson and Parker; Moeschlin et al.) causes to think of the pharyngeal or intestinal mucosa as the portal of entry of a causative agent, similar to the way of the primary tuberculosis infection. From the results of animal experiments, the histological substrate of lymphogranulomatosis has also been interpreted as an allergic reaction of lympho-reticular tissue, probably in the form of auto-immunization. This, however, also generally originates from an infection (Begemann).

For the present Hodgkin’s disease can only be explained as an inflammatory process; but whether this is due to a specific infection remains to be clarified.

V

On account of the comparatively frequent tumor-like findings, the tumor-like infiltration and destruction as well as the uniform histological pattern of the late sclerotic stage, Hodgkin’s disease has also been considered to be a neoplastic process, either a special tumor or a degeneration of the chronic inflammatory process to sarcoma.

A. A tumoral nature cannot even be concluded from the obtrusive morphological destructions. This has been particularly stressed for lymphogranulomatous bone changes (Uehlinger). A pre-existent neoplasia with local allergic inflammatory reaction (Berman) is contradicted by the necrobioses of the focus, which do not show any indications of it. The rarely found genuine tumors are of no statistic significance and not pathognomic of the nature of Hodgkin’s disease. The retothelial histiocytic elements of the granuloma develop, by reproducing their matrix, a reticular fiber structure which is seen, to varied degree, in all reticulogenic proliferations, including neoplastic manifestations of the RS. These, however, differ from Hodgkin’s disease both by their course and total anatomical pattern; their uniform structure is in contrast to the phasic development of Hodgkin’s disease; the uniform histological pattern differs from the morphological variations of lymphogranulomatous changes. These cytological specificities are only relative (v. Albertini) and do not allow principal morphological conclusions to be reached on malignancy generally or in the particular case of Hodgkin’s disease (Ruttner). Lymphogranuloma does not correspond to either retothelial sarcoma or reticulosis.

There is therefore not reason for grouping lymphogranuloma with the lymphoid tumors (Warthin). Brill-Symmer’s disease, with its fatal cataplasia to retothelial sarcoma, is no more likely to be a precursor of Hodgkin’s disease as this is a secondary malignant neoplasia of the RS (Fresen, b).

As essential argument for differentiating a special form of lymphogranulomato-
sis as Hodgkin's sarcoma has been derived from involvement of the central nervous system (Jackson and Parker), this stage being identical with retothelial sarcoma. This condition is, however, too rarely found for being accepted as to apply generally and to confirm the existence and development of so-called Hodgkin's sarcoma in lymphogranulomatosis. If the histological pattern of cerebral Hodgkin's sarcoma equals retothelial sarcoma (Losli), and there is no other indication of Hodgkin's disease, it can unquestionably be rated as a primary retothelial sarcoma which is apparently much more frequently found than brain involvement in the form of Hodgkin's sarcoma in Hodgkin's disease. Metastatic spread and neoplastic nature cannot be proved from either the total anatomical pattern of the histogenesis of the single focus.

B. Stipulation of an inflammatory nature of Hodgkin's disease does not rule out the possibility of malignant degeneration to sarcoma. The nosological positioning of lymphogranulomatosis as an inflammatory process on the basis of the histology of the individual focus is an indicative statement. A presumptive neoplastic property cannot be principally denied with equal certainty. One possibility in lymphogranulomatosis might be the neoplastic degeneration of the chronic relapsing inflammatory process. How often such a tumoral determination to the blastomatous form of lymphogranulomatosis takes place and becomes histomorphologically manifest is unknown. In retiothelial processes there is no possibility to differentiate between a local reaction in the form of inflammation and metastasis due to spread of tissue from another place. The retiothelial matrix is ubiquitous and forms as required, or there may be diseases of the system itself, for example reticulosis. Necroptic findings of so-called atypical lymphogranulomatosis are not a good foundation for this discussion if the definite histological characteristics of lymphogranulomatosis are missing. Many of the atypical cases do not obviously correspond to what is meant here by Hodgkin's disease. "Pseudoleukemia" and "lymphoid tumors" are such warning examples. In this connection the amount of therapy may need some critical consideration. All substances used for treatment are those which both inhibit but also precipitate tumors. The effect essentially depends upon the dosage-time factor.

References

2) Bogemann, H., Klinische und experimentelle Beobachtungen am immunisierten Lymphknoten, H.F. Schulz, Freiburg, 1953.
Fig. 1. Typical granuloma in Hodgkin's disease.
Spleen: *left*, hemat.-eos. 160 ×; *right*, silver impreg. 165 ×.

Fig. 2. Specific granulation tissue with marked cicatrization.
Vertebra: hemat.-eos. 70 ×.
Fig. 3. Paragranuloma picture in Hodgkin's disease.
Lymph node: hemat.-eos., left, 70×; right, 160×.

Fig. 4. Acute course of Hodgkin's disease with necrosis in:
left, lymph node (hemat.-eos. 70×); right, liver (silver impreg. 70×).