SESSION II

Chairman: Dr E. Lebacq, M.D.

Problems in histological interpretation in sarcoidosis

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Summary

The sarcoid granuloma has a histological structure that is similar to that seen in many other diseases. Some of its diagnostic features are negative, but an accurate diagnosis can be made from biopsy tissues if numerous, monotonously uniform granulomata are present. Histological confidence is often proportional to the number of granulomata seen in the specimen.

Mediastinal lymph nodes taken at mediastinoscopy have been positive in 90% of seventy-four patients with sarcoidosis.

Problems in the histological interpretation of Kveim biopsies may be due to failure to include the injection site in the biopsy, to inadequate sectioning of the specimen and to equivocal cellular reactions. Despite these difficulties, dual blind reading of sections of mediastinal lymph nodes and Kveim reaction biopsies from patients with sarcoidosis has shown that the observer variation that is likely to be of clinical significance is approximately 5% in each group.

Biopsy plays an important part in the diagnosis of sarcoidosis, and this emphasizes the need to appreciate the difficulties that may arise in the interpretation of tissue sections. The problems encountered with naturally-occurring sarcoid lesions usually stem from the differential diagnosis of other granulomatous diseases. The need for a microscopic reading of the Kveim reaction has now been recognized, and although the diagnosis of other diseases does not arise in Kveim biopsies they cannot always be easily classified as positive or negative. Experience has been obtained from seventy-four mediastinal lymph nodes obtained at mediastinoscopy and eighty-two Kveim reaction biopsies, all from patients with clinical sarcoidosis. Sections of the mediastinal lymph nodes and the Kveim biopsies have been read on a dual blind basis and compared with the original service reading in order to determine the observer variation that is inherent in the histological method.

Sarcoidosis

The non-caseous epithelioid cell granuloma (Fig. 1) is the typical lesion of sarcoidosis, but this is not the only histological pattern that may be encountered. In the diffuse type, sheets of epithelioid cells are seen, but there is little or no attempt at discrete granuloma formation. The characteristic discrete granuloma may also be attenuated or submerged by the development of widespread hyalinization, usually assumed to be a late or healing manifestation of the disease. In both the diffuse epithelioid and hyaline types of sarcoidosis it is usually possible to demonstrate discrete granulomata in some part of the tissue, but these may not always be present.

Fig. 1. Epithelioid cell granulomata of sarcoidosis in mediastinal lymph node. Haematoxylin and Eosin × 90.
in small biopsy specimens. The number of times that these diffuse changes cause diagnostic difficulty is small, but they account for some of the histological diagnostic failures.

Intracellular inclusions, such as asteroids and Schaumann bodies, are seen in sarcoid granulomata and both can be helpful in suggesting the diagnosis; unfortunately neither is diagnostic. The Schaumann body (Fig. 2) is a rounded, conchoidal structure that is laminated and usually calcified. In its fully developed form the conchoidal body is associated with doubly refractile crystals that Jones Williams (1960) has shown to be endogenous and not exogenous. Table 1 gives the incidence of Schaumann bodies (conchoidal bodies with crystals) reported by Jones Williams (1960) and Burne (1953), together with the findings from Central Middlesex Hospital. These demonstrate that Schaumann bodies regularly occur in sarcoidosis and its morphological counterpart, chronic berylliosis, but the value of Schaumann bodies as specific indications of sarcoidosis is destroyed by the fact that they are also found in tuberculous granulomata, reaching a peak in chronic tuberculous salpingitis.

In the absence of specific cellular structure, the histologist must depend on general or negative features, such as the uniformity and compactness of the granulomata, the absence of caseation and negative Ziehl-Neelsen preparations. Using these criteria, the individual lesion of sarcoidosis may be exactly reproduced by tuberculosis, other tuberculoid diseases and by sarcoid-like reactions. The tuberculoid diseases are numerous and include the exotic granulomata, of which tuberculoid leprosy is a good example; the sarcoid-like reactions may be due to almost any extraneous material, may be seen in lymph nodes draining carcinoma and in Crohn's disease.

Tuberculosis can only be insecurely excluded by the two negative findings—lack of caseation and absence of acid-fast bacilli. Any central caseation in a granuloma suggests tuberculosis, but hyalinization in a sarcoïd granuloma does take place and fibrinoid necrosis may be seen. Necrosis resembling caseation has been described by many observers and is seen in Fig. 3. Whilst central necrosis does not always rule out sarcoidosis, negative Ziehl-Neelsen preparations are also unfortunately common in sections of tuberculous material. Acid-fast bacilli are seldom seen in sections or smears from non-caseous tuberculous lesions and even with caseous tuberculous disease bacilli are not always or easily seen on direct microscopy. Thus acid-fast bacilli are usually

**Table 1. Percentage incidence of Schaumann bodies (conchoidal bodies with crystals)**

<table>
<thead>
<tr>
<th>Tuberculosis</th>
<th>Berylliosis</th>
<th>Sarcoïdosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung lymphatic</td>
<td>Fallopian tube</td>
<td>All cases</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>6</td>
</tr>
<tr>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C.M.H. (1954-69)</td>
</tr>
</tbody>
</table>

![Fig. 2. A laminated calcified Schaumann body within a giant cell. Haematoxylin and Eosin × 360.](image1)

![Fig. 3. Central necrosis in an epithelioid cell sarcoid granuloma. Haematoxylin and Eosin × 110.](image2)
demonstrable in the typical tuberculous lesions which the histologist will confidently diagnose as tuberculosis from haematoxylin-eosin preparations, but bacilli are seldom seen in the difficult tuberculous granuloma that imitates sarcoidosis or other tuberculoid diseases. Bacteriological culture and/or animal inoculation are ways of overcoming these difficulties, and may be expected to be positive in at least 85% of tuberculous lesions, though this figure is reduced in the non-caseous type of tuberculosis that causes the most difficulty in the differential histological diagnosis of sarcoidosis. It is of the greatest importance that adequate material should be taken for bacteriological culture as well as for histological examination in all cases undergoing biopsy for the diagnosis of sarcoidosis.

One of the features of the tissue reaction of sarcoidosis that is of greatest positive value in diagnosis is the similarity in size and shape of the sarcoid granulomata. Often the granulomata may closely resemble each other, giving a mirror-image appearance (Fig. 4) that Pinner (1938) and Scadding (1967) have described as monotonously uniform. This uniformity is seen not only in individual tissues but is reproduced throughout the rest of the body. In order to use this for diagnostic purposes, biopsy material must contain multiple granulomata, preferably ten or more, and the confidence and accuracy of the pathologist's opinion will be directly proportional to the numbers of granulomata in the biopsy specimen. It is necessary that adequate tissue be available for bacteriology and for histology, and that this should come from an organ in which the density of sarcoid granulomata is likely to be high. Needle biopsies from liver or other organs with a lower incidence of sarcoid granulomata per unit area are likely to generate reports describing 'granulomatous disease of uncertain type' or 'as being consistent with sarcoidosis'. Such reports may be of value within the clinical context, but small biopsies from liver or bronchus, skin and even tiny lymph nodes from scalene pads of fat yield fewer granulomata than larger superficial (epitrochlear) or deeper (mediastinal) lymph nodes that immediately build up an impression of the monotonously uniform granulomatous disease of sarcoidosis. In mediastinal lymph nodes from ninety-three patients with clinical sarcoidosis Ross et al. (1970) obtained a positive histological diagnosis in 92%. This is higher than may be expected from biopsy of other organs. With needle biopsies from liver Israel & Sones (1964) reported granulomata in 80%, Foti & Moser (1969) 75%. Sarcoid granulomata were recovered in 24% of bronchial mucosal biopsies by Bybee et al. (1968) and in 63% by Friedmann et al. (1963) and by Liot, Lemoine & Chrétien (1963). Scalen lymph nodes of fat give higher results (90%, Foti & Moser, 1969, and 74%, Israel & Sones, 1964), but liver, bronchial mucosa and other tissues cannot be expected to yield as many granulomata as have been obtained in enlarged superficial or mediastinal lymph nodes. The pathologist's opinion becomes more authoritative if the biopsy not only contains granulomata, but also contains them in large numbers.

In an attempt to evaluate histological observer variation inherent in the interpretation of naturally occurring sarcoid tissues, lymph nodes from seventy-four patients were read by two pathologists on a dual blind basis. The results were compared with the original report and are shown in Table 2; the two sets of figures are similar, but could contain possible major differences (changes of positive to negative or negative to positive) of between nil and 17%. Further breakdown of these figures (Table 3)

**Table 2. Comparison of dual blind reading of seventy-four sarcoid biopsies with original service reading**

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Equivocal</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>67</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Dual blind</td>
<td>65</td>
<td>3</td>
<td>6</td>
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</tbody>
</table>

**Table 3. Histological observer variation in seventy-four sarcoid biopsies**

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Equivocal</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original reading</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>63</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Equivocal</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
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</table>

Fig. 4. Uniform sarcoid granulomata, showing similar size and structure. Haematoxylin and Eosin × 90.
Histological interpretation in sarcoidosis

indicates that there were only three major alterations (4%) of clinical significance (one positive changed to negative; two negatives changed to positive). Three minor changes (4%) were also made (three positives changed to equivocal) but these were less likely to have been of clinical importance.

The Kveim biopsy

The accuracy of the Kveim reaction has been shown by Siltzbach & Ehrlich (1954) to be increased if the injection site is biopsied and subjected to full histological examination. The cellular components seen in Kveim biopsies develop progressively (Rogers & Haserick, 1954) and are shown in Fig. 5. At 5 weeks it may be expected that sarcoid granulomata have become fully developed, whilst non-specific inflammatory changes have begun to regress. Sarcoid granulomata may persist in the fibrosing lesion and be recognizable after many months (Siltzbach & Ehrlich, 1954) but no practical benefit is to be expected by delaying biopsy beyond 5 weeks. The techniques of injection and biopsy have been described by Mitchell (1968).

The spectrum of histological changes that may be seen in Kveim reaction biopsies is shown in Fig. 6. On the left are the Kveim negatives, often thought

![Fig. 5. Evolution of the histological changes in the Kveim reaction.](image)

![Fig. 6. Histological changes in Kveim reaction (biopsy at 5 weeks).](image)
to consist of normal skin. This is seldom the case and serial sections will almost always demonstrate degeneration and swelling of dermal collagen, leucocytes of all types or foreign body reaction. If none of these is found, it suggests that the injection site may not be included in the biopsy or may not have been sectioned. Serial sections through the whole specimen are indicated. Careful marking of the injection site with Pelikan ink reduces the number of failed biopsies.

Equivocal reactions contain histiocytes in focal collections or diffuse epithelioid cells, usually between collagen fibres. Localized granulomata of sarcoid type are not seen, though aggregates of histiocytes or epithelioid cells can cause differences of opinion. Positive Kveim reactions contain epithelioid cell granulomata, usually discrete, but these become confluent with fibrinoid necrosis in strongly positive reactions; the diffuse epithelioid cellular infiltration or focal histiocytes of the equivocal reaction are often also present. In the strongly positive Kveim reaction there may be much fibrinoid necrosis surrounded by poorly developed granulomata, which may be scanty if the lesion is as large as the biopsy punch or if the nodule is not central in the biopsy. Thus the three types of Kveim reaction that cause the greatest difficulty to the histologist are the completely normal skin (that may not contain the injection site or be adequately sectioned), the equivocal cellular response and the very strongly positive reaction with much fibrinoid necrosis.

The results of dual-blind reading of eighty-two Kveim reactions in patients with clinical sarcoidosis are shown in Table 4. These figures, though similar, could conceal major differences of over 40%, but breakdown of these results, seen in Table 5, indicates that there were two instances of positive being changed to negative, and two negatives were changed to positive. The observer error of clinical importance in the interpretation of Kveim biopsies amounted to 5%, though minor alterations (changes of negative or positive to equivocal, or vice versa) were made in an additional 10%.

**General conclusions**

Kveim biopsies need careful technique during removal, and call for serial or step sections in order to identify the injection site. Equivocal reactions have been encountered in about 5% of specimens, and whilst there was some degree of observer variation in 15% of cases, the significant observer variation in the histological reading of the Kveim reaction was about 5%. With naturally occurring sarcoid lesions there is an apparent paradox, for the single sarcoid granuloma cannot be distinguished with certainty from that caused by many other diseases, yet histological accuracy with an observer variability of 5% has been obtained. This has been due to the fact that the most confident histological diagnoses of sarcoidosis were made on tissues in which large numbers of granulomata were seen. Reasonable sized mediastinal or other lymph nodes from patients with sarcoidosis can be expected to produce sections upon which accurate and reproducible interpretations can be made.

**Acknowledgments**

I am grateful to Dr D. N. Mitchell for much assistance with the blind reading of the histological material; to Dr J. R. Mikhail for help and encouragement; to Mrs I. Prentice and to Mr A. Booker for the diagrams and photographs.

**References**


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doi: 10.1136/pgmj.46.538.478

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