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Methods by which mesothelioma can be diagnosed

by Ian Webster

The pathological diagnosis of mesothelioma has been beset by more difficulties than has any other industrial cancer. Before an occupational factor was considered in relation to other tumours, the pathological criteria of such a tumour had been clearly defined. From the early work of Wagner, Sleggs, and Marchand in South Africa, the relationship of mesothelioma of the pleura to asbestos exposure was suggested before the criteria for pathological diagnosis of the tumour had been completely elucidated. The wide variation of the histology of the tumour was not realized, and some experienced pathologists even denied the existence of mesothelioma of the pleura.

In 1924, Robertson of the Mayo Clinic introduced a comprehensive review of 'endothelioma of the pleura' by indicating that the confusing character of the clinical phenomena and the striking autopsy findings had constantly appealed to medical writers as worthy of study and report. He reviewed some 182 references, which indicated that what we now call *mesothelioma of the pleura* was known to the medical profession during the nineteenth century and before. 'So widely fundamentally important are the conclusions which may be reached', he wrote, 'that any review which attempts to clarify or harmonize these conclusions has full justification for the effort'.

In 1767 Joseph Lieutaud published an analysis of the findings on 3000 autopsies, and of these 2 may have been mesothelioma of the pleura. In 1819, Laennec, who is usually mentioned in association with the problem areas of pathology, considered that these pleura tumours were malignant (cancer). Although sarcoma was unknown at that time, the mesenchymal nature of some of these tumours was indicated by Hacke (1834) and Chaucelay (1837).

A few of the tumours described under the general term *cancer of the lung* up to 1870 could have been mesothelioma, but it was in that year that Wagner described a lesion *Das Tuberkelähnliche Lymphadenom* that was undoubtedly mesothelioma. In 1893, Virchow expressed his doubts on the primary nature of these tumours, and this undoubtedly influenced German thinking and that in many other parts of the world for a number of years. Had Peck presented his case to Virchow privately, instead of at a meeting of the Berlin Medical Association, Virchow may have reached a different conclusion.

Case records from different parts of the world were published, and in 1897 Weismayr emphasized the difficulty of deciding whether any given tumour of the pleura was really primary in that tissue, but he accepted that true carcinomas could originate in the pleural cavity and also drew attention to the sarcomatous nature of some of these tumours. By 1905, Bloch was able to review 58 cases of the *epithelial type* and 6 cases of *sarcomatous type*, but he insisted that those of epithelial type were derived mainly from endothelium of the lymph vessel. After 1905 other cases were reported, and a number were concerned with the origin of this tumour of the pleura.

In 1919, Bayne Jones indicated that most pathologists favoured the view that the tumour arose from the lining cells of the pleura, and that histologists regarded these cells as epithelial-like. These serosal cells were found when the cells of the mesoderm split to form the pleura, the peritoneal, and the inguinal extension of the coelomic cavity. Bayne Jones found 2 cases of endothelioma in 5000 autopsies.

Du Bray and Rosson, in 1920, following Adami, proposed the term *primary mesothelioma of the pleura* and concluded that the tumour arose from the surface of the parietal pleura. They could not see any justification for calling these tumours carcinomas, and considered that the term *endothelioma* was inappropriate. From 1921, *mesothelioma of the pleura* was used in the United Kingdom, except by Willis and the students who had trained under him. In the United States of America, the term *endothelioma* continued to be used for some time, and it appears that pathologists in France managed to describe some of these tumours without committing themselves as to whether they were endotheliomas or mesotheliomas.

In the early part of the twentieth century, papers were published on the origin of these tumours and their classification. Aschoff (1920) placed endothelioma and perithelioma under the heading of sarcomatous tumours, and noted that some people called these tumours *mesotheliomata*. In 1906 Kaufman reported these tumours as endothelioma, but in later editions of his book he emphasized that endotheliomas belong to the group of connective tissue tumours, and admitted that some of them

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may have arisen from the *Deckzellen* as described by Marchand. He considered that the term *endothelkrebs* should be avoided as true carcinomas come only from the epithelium.

These tumours of the pleura had certain features, especially those that could be observed macroscopically, that made them different from carcinomas.

Ewing, the doyen of American tumour pathologists, was of the opinion that, while these tumours should be called endotheliomas, 'all these tumours have sarcomatous qualities'. He urged 'in view of the uncertain position of endotheliomas as tumours, that the diagnosis should be accepted only when evidence was clear and conclusive'.

The opinions of Virchow, Kaufman, and Ewing influenced many succeeding generations of pathologists and caused many of the difficulties related to the classification of pleural tumours, but it must be stressed that much of their difficulty was one of terminology and not of whether such a pleural tumour existed or not. This aspect is often forgotten, sometimes conveniently so, by those who attribute greater difficulties to the diagnosis than have ever existed.

The term *mesothelioma* has gradually come to be accepted, but those who are not familiar with the history of pathology may consider that doubt has been cast on the existence of mesothelioma of the pleura. It must be remembered that, in the nineteenth century, a disproportionate amount of time was spent on the terminology, not only of primary tumours of the pleura, but indeed of many other tumours. It is now accepted that the tumour known as a mesothelioma does exist, and that pathologists have reasonably valid criteria for the diagnosis of a tumour at an autopsy, on a biopsy done at a thoracotomy or laporotomy, on a needle biopsy of the pleura, and even on a biopsy of cells exfoliated from a mesothelioma in pleural or peritoneal fluids.

Nobody will deny that it is easier to make a diagnosis of mesothelioma at an autopsy than it is on a biopsy specimen, but the degrees of facility are no different from those in the diagnosis of any other tumour. The concept that mesothelioma of the pleura can be properly diagnosed only at an autopsy is attributed incorrectly to McCaughey. What McCaughey required for the diagnosis of mesothelioma was an unequivocal predilection for the tumour to spread along a serosal membrane and definite evidence of a serosal origin. Even in 1965 he allowed that the diagnosis could be established on a biopsy done at a thoracotomy. Hourihane also indicated that the histological diagnosis on biopsy material is reasonably accurate and that the proportion of errors should be less than 5 per cent.

Other workers have reported in a similar vein, and it is considered that the case for the use of biopsy material rests on the evidence presented at the Conference on the Biological Effects of Asbestos held by the International Agency for Research on Cancer (IARC) in Lyons in 1972. The Advisory Committee on Asbestos Cancers, which met after the Conference, indicated, *inter alia*, that the National Consultative Panels had served a useful purpose and that the diagnosis of mesothelioma could be made on exfoliative cytology of the pleural fluid if the examination was conducted by a competent cytologist. By implication, therefore, it is accepted that the histological diagnosis of a mesothelioma on a biopsy specimen is valid.

Perhaps it would be of assistance if it were generally realized that pleural biopsies are done to show the nature of the thickened pleura in a patient who presents a pleural effusion or who has been found to show evidence of pleural thickening on radiological examination.

Certain workers have not advocated the use of needle biopsy because of the false negative results that can be obtained. However, a needle biopsy can be repeated; on occasions the procedure had to be repeated five times before a positive diagnosis could be obtained. The needle-biopsy procedure was introduced to minimize surgical intervention, which, it was considered, would lead to the spread of the mesothelioma into the thoracotomy wound. It now appears that there is a greater chance of such spread into the thoracic wall through a needle track than there is into a thoracotomy scar.

The South African Asbestos Tumour Reference Panel has issued a directive to thoracic surgeons and physicians that, in cases where the histological appearances of a tumour are not distinctive, a needle biopsy should be followed by a thoracotomy. Thus, it is hoped that as much of the tumour load as is possible will be removed before the start of radiotherapy, chemotherapy, or immunotherapy. It is realized that a thoracotomy requires a thoracic surgeon, an anaesthetist, and hospital facilities. For patients with pleural effusion at clinics that do not have these facilities and for patients showing pleural thickening, all that can be done to guide a diagnosis is a needle biopsy of the thickened pleura. However, it must be stressed that the report on the needle biopsy must be accompanied by clinical evidence of pleural pathology.

The earlier a mesothelioma can be diagnosed, the better are the results of therapy, and for this purpose exfoliative cytology and needle biopsy of the pleura are indeed useful.

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In 1957, in a publication with Smart, Hinson defined the problem areas (Hinson now accepts mesothelioma of the pleura). Most of these problems have been resolved as indicated by the following comments on the points and questions that Smart and Hinson raised.

1. If a mesothelioma exists as a tumour type, the tumour should arise from and be of the same type as the pleura, pericardium, peritoneum, and other derivatives of the primitive cavity.
   Comment
   Tumours do arise from the pleura, peritoneum, pericardium, and other derivatives of the primitive cavity, and the histological appearances are all within the limits of variation of mesothelioma. It is well known that the histological appearance of a tumour varies according to the type of tissue in which it is growing. The movement of the intestines may cause a different pattern to develop in the peritoneum from that in the pleural cavity.

2. As the presence of mucoproteins and hyaluronic acid (HA) are not specific for synoviomas, they are not specific for mesothelioma.
   Comment
   Many workers used stromal, instead of cellular HA, as indicative of the presence of a mesothelioma. The stroma of a bronchogenic carcinoma will contain HA, but it is most unlikely to contain intracellular HA. False negative results may be obtained because of the fixative used. Most pathologists now use the presence of HA only as supportive evidence of the diagnosis and not as a diagnostic feature *per se*.

3. There should not be a greater number of mesotheliomas of the pleura than of the peritoneum.
   Comment
   As the main route of entry of an industrial carcinogen into the body is the respiratory tract, there is every reason for the existence of more pleural than peritoneal mesotheliomas. Some workers are of the opinion that a peritoneal mesothelioma is secondary to a pleural mesothelioma.

4. It is difficult to understand why more tumours, in their series, should be on the right side of the chest.
   Comment
   The greater number of mesotheliomas on the right side has not been confirmed by all subsequent reports. However, as the development of mesothelioma is related to Kampmeier spots on the parietal pleura, and as there may be more of these on the right side, it is possible that a greater number of mesotheliomas will be found in the right pleural cavity.

5. In bronchogenic carcinoma the lymphatic spread is towards the periphery, whereas in pleural tumours it is towards the hilum (central).
   Comment
   It is suggested that the presence of a tumour at the root of the lung will interfere with the normal pressures in the lymphatic vessel, and, when this occurs, retrograde lymphatic spread can occur. In bronchogenic carcinoma, one would not expect the encasement of the root of the lung that one finds in mesothelioma.

6. As adenocarcinoma of the bronchus differs from other bronchogenic carcinomas in its longer survival and lymphatic spread, could not mesothelioma of the pleura be a type of adenocarcinoma or bronchioloalveolar carcinoma?
   Comment
   Adenocarcinoma of the lung does tend to have a better prognosis than a small-cell bronchogenic, and it may therefore spread in a different way from that of the small-cell bronchogenic. Should a small-cell or large-cell bronchogenic carcinoma survive, it is not expected that the spread in the lung would be different in any way from an adenocarcinoma. Electron microscopy has shown that the cells of a bronchogenic adenocarcinoma, and even those of the alveolar-cell carcinoma, differ from those of a mesothelioma.

7. Could not the mesothelioma arise from implantation of bronchioloalveolar malignant cells from the pleural cavity?

Comment

The answer to this question could possibly be obtained from a transplant of tissue from pulmonary adenomatosis, but it is understood that the survival of such transplanted tumours has not been good. The classic cases of alveolar-cell carcinoma described did not show pleural involvement of the nature of a mesothelioma, even though the alveolar-cell carcinoma was widespread.

8. As tissue culture has been inconclusive, can these findings be accepted as evidence of the epithelioid and sarcomatous areas in a mesothelioma?

Comment

This is still a matter for debate, even with modern techniques of tissue culture.

9. Involvement of the pleura in tumours can be found in malignant neoplasm of the stomach, colon, rectum, prostate, and breast. In the breast, pleural involvement has occurred thirteen years after the discovery of primary tumour and has been found in the contralateral pleura.

Comment

This is accepted, but the number of cases of pleural tumours in which no other primary malignancy could be found indicates that, although there may be some difficulty with metastatic carcinomas on a needle-biopsy specimen, the subsequent clinical evidence will correct any possible error.

10. Although true neoplasms of the pleura can be defined, the lesion is known to be produced from known primaries and there is no need to postulate an origin at this site.

Comment

This point is difficult to understand in that it appears to be contradictory, but it is submitted that there is a tumour of the pleura that can be classified as a mesothelioma. It is possible that the authors were indicating that many of the tumours diagnosed as mesotheliomas could have been metastatic. The clinical and pathological follow-up of patients has placed this problem in its true perspective.

The problem today can be defined as one of whether the pathological diagnosis of mesothelioma presents any greater difficulty than that encountered in the diagnosis of other malignant tumours. If it does present a greater degree of difficulty, is this sufficient to indicate that the diagnosis given should not be used in epidemiological studies, or in the determination of the effect of an environmental carcinogen?

It must always be remembered that the pathologist, together with the general practitioner, the chest physician, and the thoracic surgeon, is a member of a team that at all times does what is best for the patient. Anything extra that may be required for a more complete epidemiological study can be done in South Africa, and probably in other countries, only with the signed informed consent of the patient. This can be obtained only if the person requesting such a procedure is satisfied that he is not adding to or causing unreasonable suffering to the patient. This also implies that the patient must be told that he is suffering from a mesothelioma, which is often not in his best interests.

The patient presents to the medical practitioner in one of a number of ways:

(a) a subacute pleurisy that disappears with a feeling of heaviness in the chest due to a pleural effusion (Prieska Picture),

(b) a feeling of restricted chest movement or breathlessness, with or without pleural fluid (Kuruman Sickness),

(c) recurrent pleural effusion,

(d) thickening of the pleura that was detected on a routine X-ray or on an X-ray of the chest taken for another purpose.

When the general practitioner has satisfied himself that there is no acute etiological factor, the pathological investigation of the patient should proceed as follows.

(i) The pleural effusion should be tapped and the fluid submitted to the laboratory for general bacteriological culture and culture for *M. tuberculosis*. The fluid should be examined for malignant cells. Other tests can be carried out.

(ii) Either a needle biopsy of the pleura or a biopsy done at thoracotomy should be arranged, the pathologist being notified of the procedure before it is carried out.

(iii) Biopsy specimens should be so fixed that electron microscopy can be carried out and paraffin

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sections can be cut for light microscopy. Care must be taken that the biopsy specimen is imbedded so that the correct surface is cut, and sections at different levels of the biopsy specimen should be mounted. The initial stain used will depend on the laboratory processing the specimen, but the following special staining procedures should be available:

international stain for lung tumours,
alcian green or blue with and without hyalase,
periodic acid Schiff with and without diastase,
reticulin stain,
Southgate's mucicarmine.

In a needle-biopsy specimen, unless the specimen shows certain characteristic features, a diagnosis that 'the pathology suggests that of mesothelioma' should be sent out, recommending that a further biopsy specimen should be taken at open thoracotomy. The pathologist should be present at the thoracotomy.

It is realized, especially in South Africa, that there are clinics and general practitioners carrying out most valuable work to whom the facilities required by a thoracic surgeon are not available. Under these circumstances, either a clinical presentation consistent with a mesothelioma and the report of malignant cells in the pleural fluid, or a needle-biopsy specimen, should be sufficient for diagnosis and the commencement of therapy. However, whatever the therapy given (whether it be radiotherapy, chemotherapy, immunotherapy, or a combination of these), better results will be obtained if as much of the tumour as possible is removed from the chest at open thoracotomy.

In Johannesburg, it is the practice for the immunological profile of the patient to be established, and this is also being done on specimens submitted from the clinic at St. Michael's Mission, Bathlaros, in the Kuruman area. The immunological profile for each patient should be established before any major surgical procedure is undertaken or before therapy is started.

Even if therapy prolongs life, careful follow-up of the patient at intervals of approximately one month will confirm the diagnosis because of the typical but relentless progress of this man-made disease.

Presentation

In his presentation, Webster, illustrating the various pathologic presentations of these tumours with slides, made the following points additional to those in his written paper.

1. In all the last 60 cases of mesothelioma attending the National Research Institute for Occupational Diseases (Occupational Health Clinic), a history of asbestos exposure was elicited by careful questioning.
2. An expert cytologist can make the diagnosis of mesothelioma on cells in a pleural effusion. Electron microscopy is helpful in this connection.
3. HA is not necessarily present in the pleural fluid.
4. On needle biopsy of the pleura, a false negative diagnosis is more common than a false positive diagnosis. The biopsy may have to be repeated five times before a positive result is obtained.
5. The large amount of collagen in some tumours indicates their origin from an asbestotic plaque.
6. Occasionally tumours are encountered that contain myofibrils, and it is a problem whether such tumours, which resemble myosarcoma, are related to asbestos exposure.
7. Biopsy at thoracotomy should be deep to increase the chance of finding asbestos particles at the base of the pleural plaque, and it should include the lungs if possible, for medico-legal reasons.

Discussion

Wright

Wright added that there had been progress in this field in the past decade.

Webster

Webster, in answer to a question from Selikoff, averred that in only 1 per cent of needle biopsies would a false positive finding occur.

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The question of the importance of the pathologist's making the diagnosis 'blind' was raised. Webster stated that the South African Mesothelioma Panel usually did not have the exposure history available.

Wagner, Otto

Wagner and Otto affirmed that this was usually the case in their own material and material scrutinized by the British and European panels. In McDonald's studies in Canada, all the material had been reviewed blind, and sections of other tumours had been included in the series. There had been variations in the diagnoses of different pathologists, but the variation had been less than expected.

Wright

Wright pointed out that pathologists receive autopsy, biopsy, and cytology material, and that they should not need further information for epidemiological purposes.

Webster

In this connection Webster stated that, when atypical serosal cells were found in pleural effusions and they were accompanied by eosinophils, infarction should be suspected; if by other inflammatory cells, viral infection. On the other hand, when a small amount of fluid was associated with great pleural thickening, no cells at all might be found. He had no information on the incidence of false diagnosis on cytology.

In response to a question from Otto, Webster stated that he could distinguish mesothelioma from peripheral broncho-alveolar carcinoma. Long microvilli giving a bushy appearance, together with the absence of granules of the Clara-cell type and of lamellar bodies, were diagnostic. With electron microscopy he could distinguish the tumour from other lung cancers, and secondaries from gut, kidney, and elsewhere.

In answer to a question from Becklake, Webster indicated that he had not noted that any particular histological type of mesothelioma was more markedly correlated with asbestos exposure.

Elmes, Otto, Enterline, Webster

In response to a question from Sluis-Cremer, Elmes stated that mesothelioma should not be diagnosed from clinical data alone, but could be included in a general category of 'intrathoracic cancer' for epidemiological purposes. Otto agreed that a diagnosis could never be made in the absence of pathological material. Enterline was uncertain of the value of the term *mesothelioma* appearing on a death certificate. Webster stated that this was particularly unreliable in the case of Blacks in asbestos-mining areas in South Africa.

Hammond

Hammond criticized the procedure of intensive questioning of sufferers from intrathoracic malignancy about possible asbestos exposure unless a control group were used. He felt that this resulted in a large bias.

Bohlig, Elmes

Bohlig maintained that there was no radiological evidence that pleural plaques were a prerequisite for the development of pleural mesothelioma. Elmes reminded the meeting that in Finland pleural plaques do not lead to mesothelioma.

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