The Biopsy Specimen - Its Value and Limitations

Pages with reference to book, From 139 To 146

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Abstract

In an attempt to improve mutual understanding between clinician and pathologists on the matter of biopsy diagnoses, a brief review is made of the histopathologic method, and the information which can be extracted from it. Practical questions on the collection of the biopsy, its proper handling, the errors which may be due to sampling and comments on diagnostic errors and observer variation are offered. Some suggestions are offered with regard to second opinions, communication, and steps to make pathologic diagnoses more reliable (JPMA 33: 139, 1983).

In a recent visit to Pakistan (an honor conferred by the Khyber Medical College and its North American Alumni Association) I met an unreasonable and somewhat disconcerting amount of criticism between surgeons and pathologists in various cities. In abbreviated form, surgeons stated “Our histopathologists are uncooperative and incompetent; they disagree in their own diagnoses; they cannot tell benign from malignant; they cannot identify the primary site of a metastatic rumor; and cannot or refuse to give us from biopsies, the information we need to treat patients”.

Pathologists said, “Our surgeons are incompetent and uncooperative; they submit fat or fibrous tissue as diagnostic biopsies and expect an answer; they give us no clinical information to assist in making useful diagnoses; they ignore our reports and treat many patients without histologically confirmed diagnoses”.

Recriminations of this sort (by no means unique to Pakistan) suggest that each party has inadequate knowledge and appreciation of the others difficulties. It may therefore be helpful to review the place and limitations of biopsies, and of the histopathologic method of diagnosis in general, a task which I was asked to address in Peshawar.

Rationale

Pathology is the science of abnormality and disease, and thus covers any failure to attain or maintain the structure and function which is appropriate for different sexes at different ages; whether due to an intrinsic disorder, or to some extrinsic physical, chemical or parasitic injury. Microscopic Pathology is about 130 years old, and arose when Muller and Virchow in the 1840’s realized that disease could often be identified by examining histologic preparations, culminating in Virchow’s Cellular Pathology of 1858. Microscopy enables the description of number, size, shape, position, arrangement and staining, as these parameters may apply to foreign elements, to the tissues which constitute human parts; the cells which make up the tissues; or the subcellular elements which make up a cell. This is adequate for defining abnormalities of fixed structure, but not for the description of dynamic processes. For example, rate of growth, which is particularly important in tumors, cannot be directly measured by microscopy, but is inferred from increased cell mass, with associated architectural distortion; from increased number of mitoses, double nuclei and nuclear hyperchromatism. A direct evaluation in living tissue culture systems would be much better and might allow susceptibility to chemothe rapeutic agents and radiotherapy to be tested. In the same way, biochemical and biophysical properties are not well studied by microscopy but require other techniques. Parasitic agents of disease are not necessarily visible and are much better defined in microbiological laboratories. In brief, the histologic method

cannot provide all the information which might be desired and it is unfortunate that both pathologists and clinicians have come to expect more than can be delivered.

Applicability

The purpose of the biopsy is to obtain a pathologic diagnosis, usually by histologic examination, from a small sample of presumptively abnormal tissue, now obtainable from almost every organ and part. The skin and other accessible structures have been sampled by scalpel or punch for many years. The advent of biopsy needles and their accurate placement by radiologic guidance means that the majority of organs and specific areas within them can now be examined. Needle biopsies from the liver, thyroid or kidney are common; the lung parenchyma may be sampled through a bronchoscope or by a needle passed directly through the chest wall. The entire alimentary tract is open to endoscopic biopsy. Lymph nodes, endometrium, prostate, bladder, muscle, bone, synovium, and serous membranes are among the tissues routinely sampled.

The recent revival and extension of aspiration biopsy depends on long “skinny” needles of 20- or 24-gauge diameter and 6-8 inches in length. The general principles are by no means new, but the newer long needles may be passed directly though the abdominal wall and subjacent viscera apparently without harm, to reach deep structures such as the pancreas. This technique provides a very limited sample and does not allow the observation of tissue structure, which is such an important part of histopathologic diagnosis. Its greatest value is therefore in the identification of tumor cells, epitheioid cells and other distinctive cell types. The techniques require expert placement of the needle and largely become the problems of radiologists.

It is said that Willie Sutton (a celebrated U.S. bankrobber), when asked by the judge on one of his many convictions, why he persisted in robbing banks, replied, “Because that is where the money is”. This has become known as Sutton’s law;- to be useful, the biopsy specimen must be taken from the area where the pathology is. When biopsying lymph nodes, those chosen should be those most abnormal. Fatty nodes should be avoided. Nodes should not be taken from the inguinal region unless there is no alternative, since chronic inflammatory processes are common here and can interfere with the recognition of lymphomas and other diseases.

Handling the Biospy Specimen

The clinician must see that his specimen is properly treated and is sent to the appropriate laboratory area:-- histology, microbiology or biochemistry, depending on the information which is being sought. Not infrequently, more than one such examination is needed and it is therefore desirable to have some understanding of the use and limitations of fixatives. Their basic purpose is to stop the degradation of tissues by inactivating autolytic enzymes; and since fixatures penetrate tissues relatively slowly, the best results come when small specimens are rapidly immersed. While 10% formalin is generally adequate, some prefer Bouin’s solution for testicular biopsies. In muscle, Zenker’s solution is preferred, and the tissue should be pinned out while fresh on a tongue depressor or similar object, to avoid fixation artifact induced by shrinkage. For lymph node studies, Lilies B-5 fixative has been found superior. Sometimes, several methods of treatment are required. Thus a renal biopsy must in part be studied by fresh frozen section (for fluorescence microscopy) while glutaraldehyde is needed for electron microscopy, and formalin for routine examination.

Fresh material is preferable for frozen sections, chiefly because fixed tissue does not adhere well to the chucks on the cryostat. Fresh tissue is also required if biochemical assays. are to be performed as for the examination of estrogen or progesterone receptor activity. If bacteriologic examination is indicated, no fixative should be added; and if there is doubt on what exactly should be done, the pathologist should be alerted so that he may dissect the specimen under sterile conditions and act according to his findings.

Tissues are best examined when they have been oriented correctly, to avoid obliquely cut sections and to make sure that structures are seen in their proper arrangement. Clinicians can assist here, particularly with mucosal biopsies from the stomach or intestine which shrivel into round balls when placed

directly in fixative. Such specimens can be mounted face up on a piece of filter paper and allowed to adhere, before being placed in fix:.ative. If necessary, this can be done under a dissccting microscope. Along the same lines, the surgeon can greatly help in orienting larger specimens by placing large black ties on the cut ends of major vessels (as in a colonic resection) or may place ligatures to indicate lymph nodes or points of interest. Anatomic landmarks are much more obvious to the surgeon than to any one else.

While the surgeon is undoubtedly entitled to satisfy his interest in the interior of organs, cysts and tumors which he has removed, it is unfair if he cuts the fresh specimen by himself and then fixes it because this frequently results in a distorted, contracted organ, from which the pathologist may have great difficulty in making the adequate independent description which is required from him. This applies particularly to muscular organs such as the stomach, intestine or uterus. On the other hand, delay in fixation allows degenerative changes to occur as with the endometrium; and even more with the gallbladder, which undergoes extremely rapid autolysis in the unfixed state. The pathologist can do his best work when such specimens are examined fresh, dissected and possibly pinned out on paraffin or thin board, and then fixed.

It is perfectly appropriate to call the pathologist to the operating theatre so that the specimen may be demonstrated in situ, or jointly examined, in a side room.

On no account, must specimens be “split” with one part going to pathologist A and another to B. Adequate examination requires the whole specimen; the views from the front and back ends of a camel are quite different. It is also inadvisable to give the specimen to the patient himself and allow him to decide whether and by whom histologic examination should be made. He is not corn petent to do this. In most of the western world, it is accepted that all specimens removed from the operating theatre will be examined by the hospital pathologist in attendance; in the USA, this is a regulation for accreditation of hospitals. It is the responsibility of heads of departments to insure that their hospital pathologists are competent and meet the requirements of clinicians.

So that there is no mistake in identification, each container should be labeled and different specimens should be submitted in separate bottles is disturbing to receive in a single container two skin biopsies which prove to be malignant melanoma and seborrheic keratosis, without knowing which came from where. It is also helpful if the surgeon indicates whether he was making a complete “biopsy excision” or merely taking a sample. This guides the pathologist in how he cuts the specimen, to study whether margins are involved or not. It is also helpful to have the tentative clinical diagnosis, to guide in the particular stains which may be required and to provide a warning if appearances are totally unexpected: wrong identification is not unknown. The age of the patient should be also be given, since some tumors have a particular age distribution; more obviously, the interpretation of endometrial biopsies requires not only this information, but also the phase of the menstrual cycle.

SAMPLING ERRORS

There is always a chance when taking a blind biopsy or a random needle biopsy, that the suspected lesion will not be included in the tissue sample and only very small widespread lesions such as those in hepatitis or nephritis allow a random sample to be accepted as reliable. The ordinary needle biopsy of the liver, for example, includes approximately 1/10,000 part of the whole. From this biopsy, a five micron slide is cut for examination, or 1/200 of the material. Microscopic lesions again may be missed and the wonder is that pathologic changes are so frequently found and not that biopsy may fail.

Two obvious solutions are firstly to ensure that samples are actually taken from the lesion and secondly, to increase the amount of tissue examined.

If the lesion is visible by x-ray, the area which has been sampled can be accurately located. This is particularly important with bone tumors when it is necessary to be sure that the specimen represents the lesion itself and not some peripheral reparative process.

The amount of tissue which can be processed and the number of sections cut involve a compromise between time and cost, and the diagnostic returns. Complete serial sections of an entire specimen are in

practice an impossibility. Nevertheless, it is known that when examining lymph nodes, the greater the number which are sampled, the more blocks and the more sections, the greater the likelihood of finding metastases. In practice, all nodes which accompany a mastectomy specimen are submitted for microscopy, but there is evidence that the important prognostic information can be obtained from the nodes closest to the breast only:- this has allowed surgeons to submit limited lymph node samples from modified radical mastectomies. In putative thyroid adenomas, the best histologic evidence of malignancy is capsular invasion. If the nodule is large, some pathologists insist that 15 blocks are necessary to examine the capsule adequately; most settle for less, and it is clear that even 15 blocks represent only a part of the entire periphery. From transurethral prostatic resections, which may amount to 50 or 80 grams, it has been advocated that 8 grams should be examined as a minimum, with a further 2 grams for every additional 10 grams of wet tissue. The pathologist can help here by selecting fragments which from their yellow appearance he suspects to be neoplastic.

Frozen Sections

Frozen section techniques allow sections adequate for histologic diagnosis to be obtained within several minutes, in many situations. There are both technical and interpretive limitations. Bone and fat are not cut satisfactorily. All frozen sections are thick and the size of cells is greater than normally seen. Because lipids and most water soluble constituents are preserved, cytoplasm often appears muddy and detail is obscured. Nuclei may be distorted and appear hyperchromatic and mitoses may be missed. In brief, appearances differ. considerably from those which the pathologist is used to in paraffin sections. In lymph nodes, difficulties are so great that even the most eminent may refuse to attempt the diagnosis of lymphoma. It is therefore not to be assumed that, when the pathologist defers his opinion until he can examine paraffin sections it is a matter of incompetence. It is the nature of the technique itself.

Electron Microscopy

This form of examination is time consuming and expensive, partly due to the cost of the instrument, but even more to the cost of its maintenance. At the present time electron microscopy is a necessary part of renal biopsy evaluation. It is extremely valuable in the identification of certain tumors which are otherwise non-distinctive, although immunoperoxidase techniques will probably form an adequate substitute. The actual examination is done in the dark, by studying and photographing images on a fluorescent screen. The amount of tissue that can be examined is very small and the blocks from which sections are cut are literally of pinhead size. It is therefore necessary to have evidence from paraffin sections and thick plastic sections that the abnormality to be studied is actually present before cutting the extremely thin sections which are necessary, and which involve the use of special microtomes and glass or diamond knives.

The necessity for an electron microscope unit depends very much on the interest of clinicians. It is essential in modern practice that such studies be available, but it is quite common at small institutions to mail samples in glutaraldehyde fixative to special centers where photographs and a report will be furnished for a fee.

Differences in Diagnoses

This is of chief importance in tumor pathology. Every clinician knows that a pathologist may give different diagnoses on reviewing his own material, or on examining sections from a tumor which has been biopsied at different times, or from different areas. Every pathologist knows that he can be sure of obtaining a wide range of opinions from different consultants who have independently examined the same difficult slide. There is also reason to believe that the apparent unanimity reached by tumor boards or panels is frequently due to the persuasive personality of one member, rather than general conviction from demonstrable facts. It is not only desirable that clinicians should understand how these differences arise, but it becomes a necessity for the pathologist, in attempting to achieve greater reliability.

It should be recognised that histologic diagnosis is opened to subjective influences. Knowledge of the clinical condition may significantly sway opinion. Microscopic appearances can be surprisingly

different, 24 hours after the first scrutiny. It is thus safest to begin with unprejudiced observation, reserving the study of clinical data until histologic description has been taken as far as possible. It is also helpful to have more than one pathologist see any difficult slide.

Such generalities aside, some differences prove to be real, while others are only apparent; some diagnoses can be proven inaccurate by clinical outcome while others remain in the category of "observer variation", when there is no way of knowing which opinion is correct. Apparent differences may be due to the use of synonyms for the same tumor, where individual preference or the influence of one's teacher may come into play. Sometimes, the "official" name is changed, and the pathologist is merely keeping up to date. Here, the World Health Organization has made a useful effort to standardize tumor terminology; however, their names also change over the years, as the result of continued evaluation of the justification for separation or fusion of proposed entities.

Most differences stem from the fact that there is no consistent approach to tumor diagnosis and nomenclature. While the starting point is objective morphologic observation, several kinds of interpretation, of varying reliability, are then made, and incorporated in the diagnosis. Thus, "colloid adenocarcinoma of the colon" describes copious mucin production and glandular differentiation (objective), but also malignant potential (an inference) and anatomic origin(which may be provable or merely inferred). Observations themselves can be a cause of dispute. In some proliferations, the parameters available for definition are extemely few and susceptible to distortion by fixation and to misinterpretation because of random arrangement and oblique sectioning through cells. Thus, in lymphomas, the characteristics include the size of nuclei (large or small), their shape (round or notched), and the arrangement of cells (nodular or diffuse). Consideration of the number of points of identity required for fingerprint identification suggests that histologic definition from so few features, will establish broad groups only.

A second major difficulty is that many tumors are pleomorphic, and include tissues which have differentiated in different directions and appear as different types; or have reached different levels of maturation, so that they may include slightly dysplastic, as well as frankly anaplastic areas. Nevertheless, it is customary to provide a single name. In lung cancer, it is quite common to find mixtures of squamous cell carcinoma, undifferentiated tumor, and adenocarcinoma. One result is that a bronchial biopsy may be given a different name than the resected specimen. It also accounts for some differences in diagnosis. Thus, (Jones et al., 1957) in a 5 year review of his own diagnosis of lung cancer, agreed with his first report in 82%. When he enlisted the help of two fellow pathologists, their mutual agreement fell to 43%. Another report (Feinstein et al., 1970) gives disagreements among five pathologists of 2-42%, with different types of lung cancer.

The inferences drawn from morphology are of varying kind and strength. They include opinions on whether a proliferation is actually a physiological "nodular hyperplasia" or is an autonomous "true tumor", whether the proliferation is benign or malignant; and where and from what particular cell it has arisen.

The question whether focal proliferations in endocrine glands are dependent or independent of physiologic control mechanisms (nodules versus adenomas) cannot be answered by histology, but would require some physiologic methodology.

The prediction of a benign or malignant clinical outcome relies on correlation of tumor pattern with experience gained from patients who had similar tumors in the past. This must be individually established for each type of tumor. It also requires knowledge of the size and location of the lesion; the age, race, and sex of the patient, all of which may have some bearing. Thus, it is now known that small tumors, such as the occult carcinoma of the thyroid, the "pathologists' cancer" of the prostate, and the "minimal carcinoma" of the breast, may behave differently from their larger but otherwise identical counterparts.

The morphologic criteria found by experience to have predictive value, vary from tumor to tumor. In the thyroid, capsular invasion is highly significant; in the vilous tumor of the large intestine,

penetration of the muscularis mucosa. There is a continued active search for additional parameters, both structural and functional of reliability. A whole volume has been written on the histology of borderline cancer (Park, 1980). The varied clinical outcomes in patients with identical tumors preclude exact prognosis for any one person and require a statement of the probability of death or survival, as found for the entire group. Each type of tumor has its own behavior. Thus, in the white USA population, esophageal cancer carries a 5-year mortality rate of 95%, with a median survival time of 5 months; cancer of the colon, 55% and 26 months; while thyroid cancer has a 16% mortality at 10 years, with median survival over 15 years. Even a basal cell carcinoma has been known on very rare occasions to metastasize. Simple unqualified prognostic terms, such as “malignant” or “cancer” are inadequate descriptions.

Variation within single tumors also causes difficulty. When there are different types of tissue, the diagnosis may refer to the predominant area, as most representative; to the least-differentiated area, because most malignant; or to the best-differentiated area, as indicating the “real nature” of the tumor. The question is whether small areas of a more malignant type indicate poorer behavior. An attempt to examine this in lung cancer (Reid and Carr, 1961) showed that, except for undifferentiated small cell carcinomas, heterogeneity was frequent. If all tumors with any evidence of keratinization were called squamous cell carcinomas, mortality and survival times were not affected. If all tumors with areas of undifferentiated pleomorphic large cell carcinoma were grouped, there was only an unproven suggestion of slightly worse prognosis.

Variation also includes mixed levels of differentiation; e.g., half of prostatic cancers include at least two different grades. In the Gleason classification, each grade is assigned a numeric value (Murply and Whitmore, 1979) The number given to the predominant pattern is added to that of the secondary pattern, and the sum is thought to be a better prognostic indicator than was previously available. The reproducibility of this grading is probably about 70%.

In many proliferations, there is a gradual change from normal through dysplastic to neoplastic cells, and it may be difficult to determine the point at which a persisting growth process is indicated, as opposed to a resolvable inflammatory or a reparative proliferation; or the. point which indicates the likelihood of metastasis. The problem is comparable to that of dividing a sloping graph line into different segments. Most people can distinguish both ends from the center, but no more. This is how differences of opinion arise between inflammatory atypia and dysplasia; and between dysplasia and neoplasia. Examples, reflected in frequently different opinions, are the distinction between focal inflammatory infiltrates and pseudo tumors from lymphomas. In the skin, solar keratosis, keratoacanthoma, and squamous cell carcinoma may be difficult to distinguish. The same applies to activated nevus, melanocytic dysplasia, juvenile melanoma (epithelial and spindle cell or Spitz nevus) and malignant melanoma. In the cervix uteri, dysplasia, in situ carcinoma, and invasive carcinoma may be disputed. Attempts to divide dysplasia into multiple categories have not proved reliable, as judged by the criterion of diagnostic reproducibility, when many pathologists examine the same material.

Gradation of change also explains the use of terms such as “borderline cancer” or “of indeterminate prognosis-”. The meaning of a “borderline tumor” is that the histologic appearances are neither normal nor frankly malignant. This should imply a 50-50 chance that the tumor may behave as a metastasizing or as a nonmetastasizing lesion. As an example, if mucinous tumors of the ovary which are accepted as histolo gically malignant have a 33 % chance of resulting in death, it might be calculated that the borderline lesion has a lethal potential of 16%. The actual figure given is 4% (Hart and Norris, 1973) Other possibilities covered by the term “malignant” are that the lesion (if biopsied only) may progress and become more malignant; or (if excised) that there may be similar lesions remaining in other areas of the same organ (e.g. breast) or in a second of paired organs (e.g. ovaries). Each of these possibilities has a different probability, according to the nature of the tumor, but also according to the individual reaction of the patient, an aspect which is not measurably by histology.

Another component of diagnosis relates to the origin of a tumor. Sometimes this can be directly

established, by finding transitions from normal through dysplastic to anaplastic cells. More often, origin is an inference based on morphologic similarities, which may be more apparent to one observer than to another. In carcinoid tumors, different patterns have been thought to establish different anatomic origins: - foregut from hindgut. When a tumor has undergone anaplastic change, inference of origin becomes entirely unreliable; this is a phenomenon which is more common than generally accepted.

A category of tumor which has been the subject of recent discussion is that of the "APUDomas". These tumors were originally grouped because of common biochemical properties, which, however, proved on further examination to be non-discriminatory, because of their wide distribution. It had already been inferred that such tumors arose from neuroectoderm, a theory disproven for some and not proven for others. In other tumors, such as those of the breast or of the bronchi, attempts are made to identify which particular segment has given rise to the lesion. In the breast, it is not uncommon to find that both major ducts and terminal lobules are simultaneously involved; yet convention requires that the tumor is identified as infiltrating duct or infiltrating lobular carcinomas. Terminal bronchiolar, alveolar cell carcinoma, and metastatic carcinomaI in the lungs can also cause great difficulty because there are inadequate data to establish the origin. In the skin, basaloid proliferations are frequently stated to arise from one particular skin appendage or another, despite the fact that more than one appendage may be implicated and that differentiation may be proceeding in several directions simultaneously.

Having tried to identify causes for differences in diagnosis, it is only proper to attempt some suggestions for improvement. Most importantly, pathologists might benefit from a sharp separation, at least in their thinking, between primary description and secondary interpretation. Identification and naming of all tumors should be based on the types of tissue contained, rather than on presumptive origin; and where there are several types of tissue, each should be described. Inferences on the origin or nature of a proliferation require objective evidence, and if this is not obtainable, should only be given as possibilities. Prognosis should be expressed in terms of the probability of different possible outcomes:- e.g. local persistence; local lymph node involvement without further progression; metastasis and the probability of death. (The later is the figure complementary to the 10-year survival rate, and can thus be obtained from various statistical views). It is also possible to indicate the average lifespan before death will occur, for different tumors (National Cancer Institute, 1976). The word malignant should no longer be used in an unqualified manner, and the term cancer should not be used, except to mean what it means to the ordinary population: a tumor in which there is a high probability that it will cause death.

In dealing with observer variation, the only method of evaluating accuracy is reproducibility of diagnosis. If 80% of reviewers agree, such a diagnosis must be accepted. If the "consensus" figure is less than this, the process of "simplification to the point of strong agreement" is necessary. Thus, it may be agreed only that the tumor is a malignant epithelial lesion. In other cases, not even this might be accepted, so that the tumor must be described as "malignant tumor, undifferentiated". Finally, the additional functional parameters now available by immunocytochemistry should be diligently employed in the hopes of increasing the number of characteristics by which diagnosis can be reached, and inferences drawn.

Obtaining Second Opinions

It is helpful if both surgeons and pathologists understand and agree on the correct and ethical method for obtaining second opinions. A prudent pathologist will regularly obtain support for his opinion in any difficult case, by consultation with his own department; or by sending slides to some outside authority, without waiting to be asked. It is not improper for the surgeon, or for the patient to request a second opinion. However, the slides should be sent from pathologist to pathologist, so that they are not lost, and so that the pathologist will know what was thought, and that all parties may learn. This must not be viewed as a vote of no confidence, but taken as an educational experience; and something, which hopefully, by finding outside agreement, will inspire confidence from the surgeon. In the West, it

is usual when patients are referred from one hospital to another, to have the second pathologist review, not merely the original histology report, but the actual slides removed at the first operation.

SOME SUGGESTIONS

The purpose of this review is to assist in the development of mutual respect between clinicians and pathologists, by frank discussion of matters of difficulty and contention among pathologists, and areas where clinicians can help. One major problem is that of communication and surgeons are urged to see that the appropriate data are present on the "request for examination" form. Pathologists, on the other hand, have an obligation to be readily available for consultation and discussion. In their reports, they can greatly help by anticipating unstated questions and anwering them. Pathologists should appreciate the difficulties under which surgeons must work and realize that circumstances may force actions which are well recognized to be less than scienti fically optimal. All over the world, some patients are being diagnosed and treated for malignancies when this is not the case; it is also true that vigorous but misdirected therapy may be disastrous. Nevertheless, it is the clinician who has the ultimate responsibility to integrate all availabre information; make a diagnosis to the best of his ability; and propose appropriate treatment. This is the art of medicine. The ultimate beneficiary of all these efforts is the patient. In Pakistan I learned "And whoso save the life of one, it shall be as if he had saved the life of all mankind." In attempting this, goodwill and cooperation are urgently needed from all who have the privilege of practicing medicine, in any of its branches.

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