PATHOLOGISTS DO NOT HAVE HISTOLOGICAL EYES.

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Abstract

Laboratory medicine plays a very important role in medical field in relation to tissue diagnosis. It is based on a systematic analysis and comprehensive report from the laboratory that important therapeutic decisions are taken. In the current era after the advent of personalized medicine, targeted therapies and prognostication of a disease is also based on a complete pathology report. This underscores the importance of proper knowledge and understanding of the capabilities and limitations of laboratory medical professionals by the clinician, which will save a lot of hassles and help in optimal patient care.

KEYWORDS: Pathologist, Pre-analytical phase, Post-analytical phase

INTRODUCTION

“Pathologists are physicians and human beings. They have as great a capacity for error and susceptibility to subjective distractions as other practitioners of the art of medicine. Because of certain nineteenth century dogmas and because the teaching of pathology used to be relegated primarily to the long-forgotten pre-clinical phase, pathologists traditionally have been regarded to be more scientific than many of their colleagues. A mystic perversion of this assumption prevails among those clinicians who believe that the pathologist, given only a piece of a patient's tissue, has all of the other ingredients”

- DR. OSCAR N. RAMBO

By its very nature, surgical pathology depends heavily on the input of clinicians and surgeons who are fully aware of the potentials and limitations of the speciality. They should know that a microscopic diagnosis is a subjective evaluation that acquires full meaning only when the pathologist is fully cognizant of the essential clinical data, surgical findings, and type of surgery. The requisition slip for pathologic study should ideally be completed by a physician familiar with the case; too often the task is delegated to a medical student, a nurse, or the surgery resident who was requested to perform the biopsy. One of the most frustrating and potentially dangerous experiences that a pathologist can suffer is that of the requisition form lacking adequate clinical information [1]. In such instances, it becomes mandatory for the pathologist to take all measures to find out the history before making a diagnosis. And it should always be remembered by the clinician and the pathologist that in spite of all the precautionary steps taken and the meticulous evaluation of specimen behind every pathology report, it is only a portion of the tissue that is considered to be the most representative which is being sampled and there are still possibilities however remote, for the unsampled areas to contain the area of interest [2]. That is, pathologists do not and cannot study the entire tissue submitted and hence do not see the entire histology of the tissue submitted. In other words, pathologists have their limitations and that should be borne in mind by the clinician who is interpreting a pathology report [3].

Pathology is Not a Single Speciality:

Pathology, though thought to be single field of laboratory science, due to the enormity of knowledge explosion, has been categorized into surgical pathology, cytology, clinical pathology and molecular diagnostics. Surgical pathologists deal primarily with structure. Careful gross examination of excised tissue, first with the naked eye, is followed by a more detailed examination of tissue sections in the compound light microscope. Intraoperative examination making use of frozen tissue sections comes under their perview but in most instances, pathologists rely on the better preservation of structure afforded by permanent tissue sections stained with hematoxylin and eosin (H & E) and
Labelling and preservation of specimen –

PRE-ANALYTICAL PHASE:
Labelling and preservation of specimen –

Be it histopathology or cytology, a common error being done after the specimen is obtained is not understanding the importance of proper specimen preservation. For surgical specimens, 10% neutral buffered formalin is the ideal fixative in which the specimen needs to be placed immediately after surgery to facilitate proper interpretation by the pathologist [19]. For special studies consult your laboratory before putting specimen in formalin. Proper labeling of the containers is equally important as this will enable correct report for the correct sample removed from the correct patient. Some surgeons have the habit of dividing and sending the specimen to two different laboratories which might in all probabilities give different reports based on the material that each one receives. This is strictly not recommended as this will only lead to confusion [20,21].

ANALYTICAL PHASE AND THE ISSUES ENCOUNTERED:

Adequacy, orientation and macroscopic examination of the specimen:

Methodical gross examination of the resected specimen by an experienced pathologist is an absolute prerequisite for proper diagnosis and to provide accurate information regarding the margins and lymph node status. The pathologist must regard, and therefore properly triage biopsies, particularly excisional biopsies, as the definitive surgical specimen. To do this well, the pathologist must be informed about the clinical history, differential diagnosis, relevant laboratory results, gross tissue examination, and frozen section findings, if any, since they may individually or together dictate areas of sampling whether special studies are required. It becomes the responsibility of the operating surgeon to make the orientation of the specimen possible for the pathologist by drawing a rough sketch or by identifying the margins and suture. Once in the dissection room, before cutting, specimens should be marked with clips, sutures, or ink to provide anatomic orientation, and these should be described in the pathology submission sheet.

Frozen sections, being the method meant for rapid diagnosis, some examples for the limitations faced by pathologists during this process are in diagnosis of soft tissue tumors, ovarian tumors where an accurate distinction between borderline and malignant ovarian tumors is not possible. Breast lesions wherein a distinction between carcinoma in situ and invasive carcinoma should await more extensive sampling which cannot be done during frozen sections [21]. Here the three dimensional range of vision of a pathologists eye is

Accuracy Of Diagnosis Depends Heavily On Following Step-Wise Pre-Analytical And Analytical Procedures:

Occasionally other dyes [4]. Histochemistry, immunohistochemistry, and electron microscopy are helpful or necessary supplements for diagnosis in 10% to 15% of solid tumors. In addition, surgical pathologists collaborate closely with cytopathologists and with clinical pathologists. Cytology is used for both screening and diagnosis of lesions that may represent cancer or its precursors [5]. Specific benefits include cost-effectiveness, rapid turn-around time, and a diagnosis with minimal patient risk. Clinical pathologists are those who make use of other techniques, such as flow cytometry, and specialized laboratory tests of a biochemical, immunologic, or molecular nature [6,7,8]. The role of the clinical pathologist, however, has recently expanded into other areas of oncology. Particularly important is the molecular diagnostic diagnosis of tumors, for example, T-cell lymphomas, by the detection of gene rearrangements [9,10]. Demonstration of such rearrangements may be especially important as a supplement to the work of the surgical pathologist and immunohistochemist in distinguishing “clonal” and, therefore, presumably malignant lesions from benign but highly reactive lymph nodes [11]. At present, specific chromosomal abnormalities are of greatest clinical importance in only a few tumors, primarily lymphomas and leukemias [12,13]. However, it is now clear that non-random chromosomal changes are to be found in a variety of solid tumors, and it is likely that cytogenetic information will become increasingly useful in defining tumor progression and prognosis [14].

Although making use of radically different technology, electron microscopy seeks the same type of information as that gleaned from immunohistochemistry, that is, detection of differentiated organelles (or markers, in the case of immunohistochemistry) that permit more accurate tumor identification [15,16,17,18]. The molecular pathologist practices at the interface of anatomic and clinical pathology and utilizes the principles, theories and techniques of molecular biology to make or confirm diagnoses of cancer provide more specific classification of cancer and/or provide prognostic information. All these diverse informations converge into a final common pathway and that is, making use of them in wholesome patient care.
An important concern is the adequacy of the biopsy material for study within the short time available.

**Routine histopathology sections - Quality and quantity of the specimen** - Frequently the goal of a small biopsy is to determine whether the lesion is benign or malignant, with the expectation of performing additional surgery if the lesion proves malignant. Sometimes, however, the task is less straightforward. Not infrequently, tumors generate an extensive inflammatory response, and it is not unusual, for example, in endoscopic biopsies of gastric carcinomas, to find only after a prolonged search rare individual cancer cells “buried” in an extensive inflammatory cell infiltrate. In this case, the limitations are that the area of interest may not be included in the biopsy material. The surgeon might take significant chunk of tissue but that might contain just blood clot, necrotic material, non neoplastic tissue in between the tumor tissue. Here, a frank and healthy discussion between the clinician and pathologist will help in establishing what is right. Benign findings do not exclude the possibility that a tumor or any other significant pathologic condition is present but was not included in the tissue submitted for examination. Thus, the clinician must be prepared to perform a second, often more extensive procedure if the first does not yield sufficient diagnostic information. Artifacts induced by the procedure itself, such as thermal damage caused by an electrocautery or laser may hamper proper interpretation.

Quantity of the specimen submitted for study also matters a lot. The sample should include the required amount of material to identify and categorise the lesion under study. Image guided difficult biopsies of deep seated lesions offer limited material for study and in such cases, an accurate diagnosis and categorization of the pathology becomes difficult. The clinician should understand the limiting factor in these cases and not press and demand for more information.

**Excision margins** - An important concern is the adequacy of tumor excision. Depending on the tissue, this decision can be made on either frozen or permanent sections. If the tumor forms a discrete mass and the margins of the specimen are clearly recognizable, determination of excision margins is usually straightforward. Examples of tumors whose excision is likely to give clearly defined margins include those arising in the gastrointestinal tract, and nerve-invading tumors, such as adenoid cystic carcinomas of the salivary glands, gliomas, and glioblastomas) may be much more difficult to define. It must always be remembered that, in spite of the best possible efforts and the fact that sampling is done from the resected surgical margin closest to the tumor, for these diffusely infiltrating tumors, the unsampled areas might still harbor tumor cells however remote the possibility may be.

**Tumor grading staging and prognosis** - Pathologists are often called upon to grade tumors or to participate in their staging in order to estimate tumor prognosis. Tumor staging (eg, the well-known TNM system) has proved to be of great value in estimating prognosis. Staging attempts to measure the extent of spread of a cancer within a patient on the basis of such parameters as tumor size, lymph node involvement, and the presence of other metastases. It is obvious that objective determinations made by the pathologist on resected tumor specimens have a critical impact on accurate tumor staging. With rare exceptions, such as papillary carcinoma of the thyroid, the single most important risk factor in determining tumor prognosis is the presence of metastases to regional lymph nodes. Therefore, the pathologist must search diligently to find, examine, and prepare histologic sections from all lymph nodes included in resected tissue. But here, micrometasatasis can escape the eyes if the particular section of a lymph node submitted for histology does not include the tumour deposit. Serial sections of every node and immunohistochemistry to detect micro metastasis not visible to the naked eye have been proposed but practical issues in following this in day to day oncology practice remains.

**Cytology** specimens usually consist of a very small amount of cells or tissue fragments, optimal technique for both sample collection and slide preparation is crucial. Moreover, as in all areas of pathology, cytologic diagnosis should never be made “in a vacuum”; pertinent clinical data and communication between the cytopathologist and the clinician are essential, and will facilitate rapid, accurate and definitive cytologic diagnoses. In contrast to surgical pathologists, cytopathologists deal primarily with cells without regard to stroma. Cytopathologists usually report the result in one of four categories — positive, suspicious, atypical, or negative. [24-27] A positive diagnosis indicates that the pathologist is sufficiently confident of the malignant nature of the lesion that he/she is prepared to have the patient undergo definitive treatment such as surgical resection or chemotherapy based on that diagnosis alone. Where there is any doubt, the
The true communication of diagnostic intent of the pathologist is based on their understanding (or misunderstanding) of how clinicians interpret and act upon these phrases in different ways. Unsurprisingly, clinicians and others in the health professions feel confident to implement definitive therapy with a suspicious diagnosis. That should be the decision of the responsible clinician. When cellular abnormalities are present whose clinical significance is not known, the report should be in the atypical category. Other diagnostic tests may be in order, depending on the clinical situation. Definitive therapy should never be initiated solely on the basis of atypia. A negative cytology means that no abnormal cells were found in the sample examined. It is important for all to realize that this does not necessarily indicate absence of malignancy in the patient. False negative cytologies are often the result of sampling error. However, laboratory error may result in both false negative and false positive results.

The use of the Pap smear to screen for cervical cancer and its precursors in the general asymptomatic population has been instrumental in lowering the mortality rate from cervical cancer over the last four decades.[25,26] A problem inherent to all screening tests is the need to balance sensitivity and specificity.[26]

**POST ANALYTICAL PHASE:**

**Surgical pathologists report** - Communicating diagnostic uncertainty is an inherent part of all aspects of medicine. Pathology is presumed to be the final line in diagnosis, so when the pathologist expresses uncertainty in their diagnosis it could potentially lead to delayed treatment, repeat biopsy, and other interventions which increase medical expenditures and may negatively impact patient care.

It is common practice in the pathology community to use phrases of uncertainty in the diagnostic line, most commonly when dealing with biopsy specimens. This may understandably be due to inadequate tissue, or extensive artifact that makes definite interpretation impossible. Other cited reasons for uncertainty include nonstandard histomorphology, ambiguous immunohistochemical stains, lack of clinical information, uncertain criteria in the literature, lack of experience with the diagnosis, and hope (however unsubstantiated) to avoid legal liability for misdiagnosis. Unsurprisingly, clinicians and others in the health professions interpret and act upon these phrases in different ways based on their understanding (or misunderstanding) of the intent of the pathologist.

The findings should be presented comprehensively in terms that are understandable to both the pathologist and the clinicians caring for the patient. The report should provide enough information so that the clinician caring for the patient can follow the thought processes of the pathologist, much as if he were viewing the case with the pathologist at a double-headed microscope. The report should contain all the information to which the pathologist has access (ie, tumor size, grade, and nodal status) that is necessary to stage a patient with cancer. The report should include the results of all specialized tests performed, their interpretation, and the synthesis and coordination of all clinically useful information available to the pathologist that may be of aid in diagnosis and management. A potentially helpful method to standardize reporting of malignancies has been the introduction of synoptic reporting. Both the Association of Directors of Anatomic Pathology (ADASP) and The College of American Pathologists Cancer Committee (CAP) have produced synoptic reporting guidelines that are available on their websites. Finally, reports should be issued in a timely manner. Failure to report results promptly may delay patient care (thus uselessly adding to the cost of medical care), lead to error and confusion, and at the very least prolong anxiety in patients who are often already distraught [24,25].

**Confidentiality in surgical pathology reports** - The true owners of the reports are the patients as it is part of their personal medical record. Pathology laboratories act as guardians to store and archive the data generated in their laboratories as per the regulations of the ROYAL COLLEGE OF PATHOLOGISTS and the DATA PROTECTION ACT. The reports are to be directly issued to the health care professionals who requested the investigation. There are a few exceptions to this rule which are detailed in the revised guidelines published by the royal college of pathologists in January 2002 bulletin.

**Molecular pathology:**

There are additional specialties and fields which have an important role to play in the effective diagnosis, prognostication and therapy of tumours. The molecular pathologist practices at the interface of anatomic and clinical pathology and utilizes the principles, theories and techniques of molecular biology to make or confirm diagnoses of cancer, provide more specific classification of cancer and/or provide prognostic information. This is the field of pathology which promises bright prospects of routine usage in clinical
practice.

Hence, a proper judgment of the pathology by histology with a judicial use of ancillary techniques including immunohistochemistry and molecular biology is essential to give vital information regarding the diagnosis of a disease process. Meanwhile it is prudent to have a good rapport be aware of and remember the limitations of pathology report while a clinician tries to interpret the same.

Pathologists are from mars and clinicians from venus. Mars has been explored but venus, not yet. As pathologists we know our strengths and weakness. The message to you all is…never yield to pressure and attempt to give a diagnosis when you feel it is not justified. Discuss in case of any difficulty and explain yourself and your limitations.

Clinicians…Understand the do's and don'ts before expecting a categorical report from the other side. Be open to discussion and accept the limitations of this wonderful field which enables you to take your very next step.

REFERENCES:

CONFLICT OF INTEREST:

Dr. Chandramouleswari is a member of the editorial board, who has also authored this article was not involved in the selection, review and publication of this article.