



Cytology ABCDE: A Practical ABCDE Algorithm for Cytology Diagnosis

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Abstract

An approach to the process of undertaking cytology diagnosis for medical students and those who operate with cytology specimens is presented. This simple mnemonic (ABCDE) can be used as a memory aid determining the order in which cells or tissue fragments should be evaluated. When receiving a slide for diagnosis and prior to examining it under the microscope we need to make sure that it is correctly labeled and prepared (Correct) and we also need to know or gather all available information concerning the patient (A, Available Information). Once under the microscope, we check the type of cells and the adequacy of specimen (B, Body & Being Adequate). Next, by taking into consideration the cellular morphology and potentially by performing ancillary studies we proceed to answer if the cells are neoplastic or not (C, Cancer). We then either form a differential diagnosis list or we end up with our final diagnosis (D, Differential diagnosis or Diagnosis), which is followed by the writing of the report (E, Exhibit). These sequential steps (Correct ABCDE) followed as an ad hoc procedure by most pathologists, are important in order to achieve a complete and clear diagnosis and report, which is intended to support optimal clinical practice. This ABCDE concept is a generic standard approach which is not limited to specific specimens and can help improve both cytology diagnoses and the quality of the final cytology reports.

Keywords: [pathology](#); [diagnosis](#); [cytology diagnosis](#); [cytology algorithm](#); [diagnosis report](#).



Practical points

Cytology ABCDE algorithm:

- is a new structured way to orientate cytology diagnosis
- describes a generic systematic procedure in cytology diagnosis and reporting
- is a useful practical and educational tool for pathology instructors, medical students, practitioners, cytologists and oncologists
- is a generic concept that can induce a similar pathology diagnosis and radiology interpretation algorithm.

Introduction

Cytology is a widely used diagnostic specialty, being relatively inexpensive, reliable and less invasive, compared with other methods. The correct diagnosis and complete report of pathologists are cornerstones to disease diagnosis, treatment and follow-up of patients. Patient management is conducted by a multidisciplinary team, including radiologists, pathologists, surgeons, radiation oncologists, and medical oncologists, all of whom should communicate effectively.

The diagnostic pathway begins when a test is indicated and a request is generated; it progresses via the diagnostic process and ends when a report is acted upon by the requester [1]. Specimen should be collected in the appropriate way, as documented in laboratory standard operating procedures. Minimum standards for the identification of patient and his tissue sample must be produced by the laboratory. All relevant clinical information should accompany the sample on the appropriate request form. Trained laboratory staff should record the gross appearance of the specimen and process it according to local protocols. The generated slides are interpreted by pathologists or trained biomedical scientists (cytotechnologists). The final report should include a gross description of the specimen, microscopic findings and ideally a final conclusion (i.e. either the diagnosis of a negative sample, or non-neoplastic abnormality, or neoplasm). Where ancillary studies are performed, the findings should be included in the body of the report [2, 3].

While an accurate assessment of cytology material is vital, the translation of pathological findings and interpretation into a report is an equally important exercise [4]. Different societies, associations and systems worldwide provide standard reporting and terminology guidelines that can be of paramount importance to both pathologists and treating doctors. Standard protocols are commonly followed to describe the required pathology results in up to 90% of all eligible cancer pathology reports each year in certain institutions [5] but only a few of them apply for cytology.

Even though protocols and forms can orientate pathologists when creating a report, there is a need for a clear and standardized cytology diagnosis pathway that identifies the order in which cells or tissue fragments should be evaluated. This article proposes a systematic framework for bridging the above gap. The proposed algorithm provides a step by step approach to cytology diagnosis primarily to medical students as well as to



biomedical scientists, pathology residents and pathologists who are involved with cytology specimens processing. In particular, the present article describes a practical and systematic ABCDE approach that can be used as a guide to cytology diagnosis pathway. The proposed procedure is a generic standard approach which is not limited to specific specimens and can help improve both cytology diagnoses and the quality of the final cytology report being issued to clinicians.

The procedure consists of six sequential steps. The underlying idea is that every step should be cleared before proceeding to the following one. If a step has not been cleared, additional clarifications that need to be taken into consideration are provided. The first three steps (Correct, A, B) are considered as prerequisite checkpoints before reaching the diagnosis phase (C, D). Cited data are meant to provide a uniform framework of thinking and reporting (E) across all health care professionals that use the relevant information. A detailed discussion of the general principles of collection, submission, preparation and staining of samples is outside the scope of this document. To the best of our knowledge the proposed ABCDE approach has not emerged in the open literature.

A Systematic Approach to Cytology Diagnosis

The proposed ABCDE procedure for the cytology diagnosis is summarized in Table 1.

<i>Correct</i>	<i>Correctly labelled and prepared specimen slides</i> (same number on slide and request form, stain and cover)
<i>A</i>	<i>AVAILABLE INFORMATION</i> (gender, age, medical history of the patient)
<i>B</i>	<i>BODY AND BEING ADEQUATE</i> (are the microscopic elements compatible with the expected histopathological findings according to topography of the lesion? & do we have an adequate sample?)
<i>C</i>	<i>CANCER</i> (is it a neoplasm or a non-neoplastic lesion?)
<i>D</i>	<i>DIFFERENTIAL DIAGNOSIS OR DIAGNOSIS</i> (we assess what we saw)
<i>E</i>	<i>EXHIBIT findings</i> (we write a report)



A flowchart of the suggested algorithm is depicted in Figure 1.

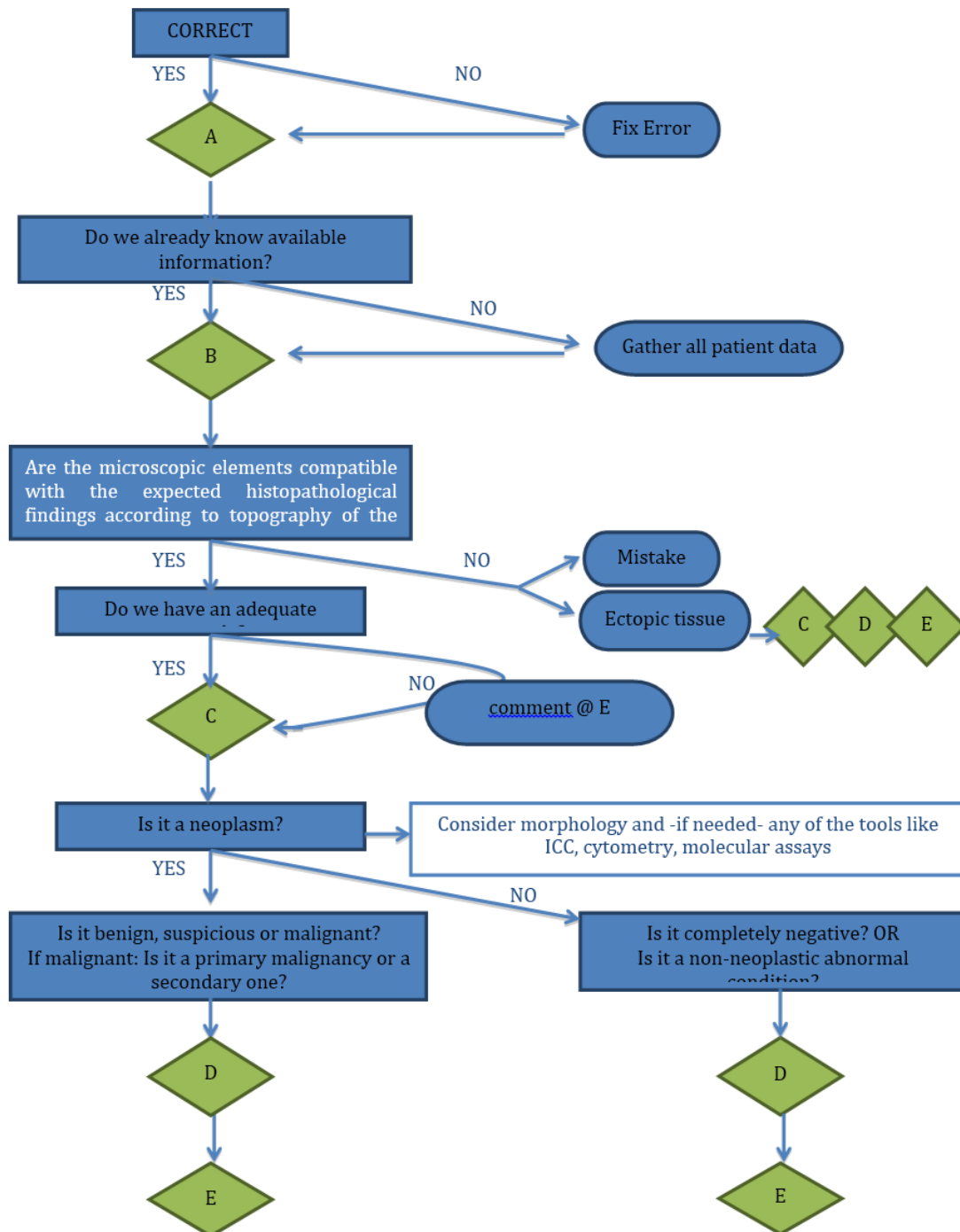


Figure 1. A Systematic Approach to Cytopathology Diagnosis.



The procedure follows six-step process, which commences with the “Correct” step.

Correct: At this stage, we ensure that the slides correspond to patient’s specimen and we look for optimal slide preparation technique.

After the evaluation of the material received by the laboratory, glass slides are being prepared. Slides should have the number that corresponds to patient’s specimen (correctly identified). This initial check – slides to patient – is fundamental for a correct diagnosis and usually it is carried out by biomedical scientists or trained medical laboratory assistants.

When receiving a slide for diagnosis and prior to having it examined under the microscope, we need to crosscheck that the number on the slide matches the one on the request form (correctly labeled). Slides should have the proper stain and be cover slipped without air (correctly prepared).

Available Information (A): At this stage, we establish the basis for our diagnosis.

Note that all relevant available information is a prerequisite for an accurate diagnosis. The first thing we need to register is the personal data and clinical information of the patient and in particular, the name, gender, age, medical history, previous specimens submitted if any, previous tumors if any, relevant treatment given (such as radiotherapy or chemotherapy), as well as all accompanying imaging information and laboratory results. The specimen type, the site and laterality must also be recorded. Table 2 shows indicatively an example of pre-test information collected prior to a Pap test. For certain specimens (e.g. urine), it is essential that the collection method is also documented on the request form.

Do we already have this data (best case scenario is that clinicians provided us all relevant information)?

If the answer is Yes, then we directly move on to step B.

If the answer is No, then we must gather all necessary information. We can communicate with the managing clinician for clarification; or, if we are in a clinical setting, we can search the medical records. Some may skip this step rushing forward with the microscopic examination of the slide. However, it is of paramount importance to acquire the missing data in order to correctly and rapidly form a complete and accurate differential diagnosis or a definitive diagnosis [6].

Note that current guidelines recommend that the clinician, radiologist, and pathologist work together towards establishing a diagnosis. Clinical and imaging information play a critical role to a pathology diagnosis.

Table 2. The ABCDE diagnosis pathway on a negative Pap Smear.



Correct	Correctly labelled and prepared specimen slides	
A	Available information	Gender: woman (only women can have a Pap smear!) Age: 64-year-old Last menstrual period: 52-year-old History (+any type of cancer, any kind of operation at cervix, medication, contraception, hormones, therapies): cryotherapy of cervix when she was young, 2 vaginal births, normal previous cytology results, HPV DNA test positive for 42, cancer of breast 4 years ago, radiotherapy, chemotherapy, medication for hypertension.
B	Body Being adequate	Cervix Endocervical cells
C	Cancer	No
D	DD Diagnosis	– Negative. Menopausal atrophy.
E	Exhibit	Identifications Macroscopic: 1 vaginal & cervical slide prepared with liquid-based cytology method; Pap stain Microscopic: ...large sheets of parabasal cells with round nuclei, containing clear chromatin... Conclusion: Negative. Menopausal atrophy.

The effectiveness of screening using the Pap smear relies on adequate sampling from the cervix. Although a conclusive definition of “adequate sample” remains elusive, the retrieval of endocervical cells from an area of the cervix known as the transformation zone or squamocolumnar junction, from which most abnormalities arise, has historically been considered an indication of quality [7, 8].

Body and Being Adequate (B): At this stage, we check the type of cells – tissue fragments and the adequacy of specimen.

It is essential to know what to expect, from a histological point of view. We need to know the topography of lesion, the part of the body that the sample comes from. For example, in a Pap smear we expect to see squamous and endocervical cells.

Are the microscopic elements compatible with the expected histopathological findings according to the topography of the lesion?

If the answer is Yes, then we proceed to the next question, which is “Do we have an adequate sample?”



If the answer is No, then we either consider it as a mistake that needs to be clarified before proceeding to C or consider it as ectopic tissue and proceed to step C. Awareness of possible ectopic tissue in erratic locations can help pathologists make the correct interpretation of samples.

Assessment of adequacy of the sample is a prerequisite for reducing the incidence of false results and in particular, false negatives. In case of sputum for example, if we do not see any pulmonary macrophages it is a superficial expectoration and we cannot have a representative image of the possible underlying lesion [9].

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Do we have an adequate sample?

If the answer is Yes, then we move on to step C.

If the answer is No, then we move to C, keeping in mind that at stage E a comment needs to be added, pointing out the inadequacy of the specimen. The reason for the inadequate smear should be clearly stated in the report [4].

Cancer (C): At this stage, we decide about the neoplastic or not character of the specimen.

The histopathological and cytological examination of a specimen is the basis of cancer diagnostics. Pathologic analysis in modern pathology practice follows several levels of examination, including:

Cellular morphology: First we evaluate cellular morphology. To view slides we make use of optical microscopy. Optical or light microscopy involves the transmission or reflection of visible light through or from a sample using a single or multiple lenses to allow a magnified view of the sample [10]. We are looking at the cells or tissue fragments by using routine stains, such as a Papanicolaou stain. Morphology can confirm a malignant lesion, as opposed to a reactive or infectious process. For most cases a morphologic examination is sufficient for conclusive determination of a lesion or a tumor type. However, sometimes, we are unable to characterise the cells, the cells may be cytologically malignant but the subtyping is uncertain or the full complement of cytological criteria may be lacking, leading to a suspicious rather than a definitive report. The next step is to take immunochemical stains out from our toolbox.

Immunocytochemistry (ICC): Immunocytochemistry comes next and is a technique used to assess the presence of a specific antigen on the surface, cytoplasm or nucleus of cells by use of a specific antibody that binds to the antigen. The antibody allows visualization of the protein under the microscope [11]. The goal of immunochemical examination is: i) to distinguish among different cancer types, such as carcinoma, melanoma and lymphoma; ii) to diagnose and further characterise, refine categorisation or classify the tumor type; iii) to determine – if possible – the site of



origin (where the cancer is originated) in case of metastasis; iv) to give prognostic information, and v) to give predictive information for malignant cells' drug response. In most situations, it is more useful to employ a panel of immunochemical markers instead of a single one and to always take into account cellular morphology and clinical information. The antibodies that make up the panel must be selected thoughtfully, on the basis of a carefully prepared differential diagnosis [6]. Table 3 gives an example of the use of ICC mainly for prognostic and predictive information.

Table 3. The ABCDE diagnosis pathway on a positive Fine Needle Aspiration (FNA) of breast.

Correct	Correctly labelled and prepared specimen slides	
A	Available information	Gender: woman Age: 42-year-old History (+any type of cancer, any kind of operation, medication, heredity): clear
B	Body Being adequate	Breast <i>Solid lesions:</i> No specific requirement for a minimum number of epithelial cells. Aspirator assumes the responsibility of sample adequacy based on the judgment that the FNA findings in the report are consistent with the clinical and radiographic findings. [19] <i>Cystic lesions:</i> There are no criteria for a minimal cell count. [19]
C	Cancer	YES Smears are hypercellular, with sheets and cords of malignant cells. Cells are crowded and enlarged. Nuclei are hyperchromatic with occasional prominent nucleoli. Myoepithelial cells are lacking. Abundant large cellular fragments with slender, well-formed papillary structures with narrow avascular stalks and wide bulbous ends = micropapillary form. ICC: ER+(2+) , PR+(2+) , c-erb-B2+(3+) , Ki-67>20%
D	DD Diagnosis	- Ductal carcinoma
E	Exhibit	Identifications Macroscopic: FNA of palpable mass ±2cm, close to areola of left breast; 3 slides: 1 prepared with liquid-based cytology method and 2 prepared with conventional method; Pap stain. Microscopic: narrative description of what we saw, plus ICC findings Conclusion: Ductal carcinoma

Flow cytometry: When the material is appropriate, flow cytometry can be used to measure cells number, size and shape. It is a laser-based technology that measures multiple characteristics of individual particles flowing in single file within a stream of



fluid as they pass by an electronic detection device. Flow cytometry is a method of cell counting and cell sorting according to size and shape; it is also employed in biomarker detection, such as the presence of tumor markers on the cell surface. Tumor markers are substances produced by tumor cells or by other cells in the body in response to cancerous or certain non-cancerous conditions. Flow cytometry is routinely used in the diagnosis, classification and management of blood cancers (i.e. acute leukaemia, chronic lympho-proliferative disorders and non-Hodgkin lymphoma) [12].

Molecular biology techniques: Last but not least molecular biology testing methods have to be taken into account. They are employed in the diagnosis of four main diagnostic areas, namely infectious diseases, inherited diseases, solid tumors and haemato-oncology. [13] Note that molecular alterations can provide important guidance to targeted therapies. Molecular testing can be performed on both aspiration and exfoliative specimens, plus effusions (a subgroup within the exfoliative category). The various preparations of cytology specimens be they liquid-based, cell block or direct smears, may all be utilized for molecular analysis each with its own advantages and disadvantages. [14] A large number of techniques are available for the design and implementation of molecular assays. Fluorescence in situ hybridization (FISH), Polymerase chain reaction (PCR), Real-time PCR or quantitative PCR, Reverse-transcriptase PCR, Southern and Western blot hybridization are some of the common techniques used for molecular assays [15, 16].

One could also consider histochemistry and electron microscopy, which are helpful supplements for diagnoses, but their usage has somewhat diminished.

The goal for pathologists today is not only to solely provide the most accurate diagnosis, but also to manage the specimen in a way that immunocytochemical and/or molecular studies can be performed to obtain predictive and prognostic data that will lead to an improvement in patient outcomes. This has implications regarding the strategic management of tissue, particularly for small biopsies and cytology samples, in order to maximize the high-quality tissue availability for molecular studies [17].

Returning back to the examination of cellular morphology, we need to look at the following specific cells characteristics: (i) specimen's cellularity; (ii) whether or not the cells population is monomorphic; (iii) if the cells are alone or in groups; (iv) the shape and size of cell groups; (v) the presence or not of cellular abnormality; (vi) the presence or not of pathognomonic elements of malignancy, and (vii) if there is invasion (cell block specimens only). We also need to observe the stroma. The cytologic features of malignancy include (i) tumor cell enlargement; (ii) increased nuclear to cytoplasmic ratio; (iii) nuclear pleomorphism; (iv) nuclear hyperchromatism; (v) clumping of nuclear chromatin; (vi) distribution of chromatin along the nuclear membrane; (vii) prominent nucleoli; (viii) increased mitotic activity, and (ix) atypical or bizarre mitosis.

Reaching stage C, we examine cellular morphology and the following question is posed:

Is it a neoplasm?



If the answer is Yes, then we have to differentiate between benign, suspicious and malignant conditions by looking for hallmark cytologic features that will enforce our decision. In case of malignancy, we must identify the cancer cells present and we must deduce if the morphology defines a primary malignant tumor or a metastasis. Note that if the cell morphology isn't straight-forward, we need to consider the use of ancillary techniques. Subsequently, we move on to step *D*.

If the answer is No, we need to examine the following complementary questions. Is it completely negative or do the special cytologic features imply a non-neoplastic abnormal condition (e.g. infection, atrophy, metaplasia, dysplasia)? In answering the above, we need to consider the following observations before we move on to *D*:

- Lymphocytic and plasmacytic inflammatory reaction indicates chronic conditions.
- The presence of neutrophils indicates active conditions.
- For inflammatory diseases look for the etiologic factor, that will provide direct targets toward which therapeutic measures can be directed e.g. Pap smear – cervicitis – Candida.
- Consider any repair mechanism that occurs after cell and tissue injury, including resolution (restoration of the native architecture and tissue), production of granulation tissue (if there is a large loss of tissue substance after injury), and scarring (production of fibrous tissue).
- Consider physiologic adaptive responses such as hypertrophy, atrophy, hyperplasia, metaplasia and dysplasia which occur in a variety of clinical and pathological settings.
- There is a natural history from metaplasia (an initial change from normal cells to a different cell type) to dysplasia (an increasing degree of disordered growth or maturation of the tissue) to neoplasia. This is best evidenced in development of uterine cervix and respiratory tract neoplasms [18].

Differential Diagnosis or Diagnosis (D): At this stage, we make our decision.

We have collected all clinical information, macroscopic description of specimen – if any – and microscopic findings. It is the right time to formulate a differential diagnosis or the diagnosis in our mind.

Should malignancy be the case, we should provide to the clinicians with the type of tumor and grade (how abnormal the cells look under the microscope; an indication of how quickly the tumor is likely to grow and spread). [20]

Sometimes, we may arrive at this stage only to form a differential diagnosis list, while we wait for ancillary studies to take place and lead us to a definitive diagnosis. Such an example is given in Table 4.



An accurate, specific and sufficiently comprehensive diagnosis will enable the clinician to develop an optimal plan of therapeutic intervention. If we are not able to completely identify the lesion, we provide a differential diagnosis list. Then, we move to the final step *E*.

Table 4. The ABCDE diagnosis pathway on a pleural effusion.

Correct	Correctly labelled and prepared specimen slides	
A	Available Information	Gender: man Age: 69-year-old History (+any type of cancer, any kind of operation, medication, heredity): repeated pleural effusion aggregation, dyspnea, exposure to asbestos, colon adenocarcinoma, resection surgery, radiotherapy and chemotherapy 4 years ago
B	Body Being adequate	Pleural cavity No criteria for adequacy or satisfactory sample have been defined for cytologic evaluation.
C	Cancer	YES Smears are hypercellular. Large tridimensional ball-like or papillary clusters of epithelial-like cells. Malignant tumor cells singly and in small clusters, with “cell-in-cell” arrangement. Nuclei are hyperchromatic with occasional prominent nucleoli. Thick endoplasm and fuzzy ectoplasm. Extensive cytoplasmic vacuolization. ICC: CEA-, MOC31-, Ber-EP4-, HBME1+, calretinin+, CK5/6+, WT1+
D	DD Diagnosis	Adenocarcinoma VS Mesothelioma ICC Mesothelioma
E	Exhibit	Identifications Macroscopic: pleural effusion, 1 litre of yellow turbid liquid; 1 slide was prepared by liquid-based cytology method; Pap stain Microscopic: narrative description of what we saw, plus ICC findings Conclusion: Mesothelioma

Exhibit (E): At this stage, we exhibit the macroscopic and microscopic findings by writing our report.

Good formatting of the pathology report is essential in order to optimise our communication with the clinician. Standardization, uniformity and consistency in the presentation of results between laboratories greatly facilitate the clinicians to read and understand reports coming from different laboratories. It is therefore of considerable



importance the adoption of a systematic reporting procedure regarding cytology diagnosis of cancer. [4] For this reason, there are standard protocols that can be followed to present the required data elements in many of the eligible cancer pathology reports. [5] The final report should include patient, doctor and specimen identification, a gross description of the specimen, microscopic findings and ideally a final conclusion [2, 3].

Patient, doctor, and specimen identification: This section contains the patient's name, birth date, and other personal information; the pathologist's and treating doctor's contact information; and details about the specimen, including the sampling method.

Macroscopic examination (or gross description): Certainly, this stage precedes the preparation of slides. Macroscopic information is taken into account during our D phase. The specimen should be carefully inspected and described in detail, including its volume, appearance, color, translucence and any special feature as seen by naked eye such as gel or clots.

Microscopic examination: This section comprises the main body of the report. All cell and tissue features observed and used for our diagnosis are presented in the microscopic examination part of our report. A narrative description of what we saw under the microscope is given here. Where infections are suggested, an indication of the likely causative organism should be made if possible. Where a neoplasm is diagnosed, this should be classified in as much detail as possible. It should be clarified whether the diagnosis was established based on optical microscopy alone or whether stains were required. Where special stains or immunocytochemistry assays have been performed, the findings should be included in this part of the report. Wherever nationally recognised, coded categories of diagnosis are agreed, these must be used in addition to the text. [2,3]

Note that in case of an inadequate specimen, an adequacy statement needs to be added in stage E of the report. Any notes and suggestions are also included here. [4]

Final conclusion: The report should ideally include a final conclusion; the diagnosis of negative sample, non-neoplastic abnormality or neoplasm. The report should detail if a specimen is diagnostic and if not, a differential diagnosis list should be given combined with a degree of certainty which should be described. [3] Our diagnosis must be as clear as possible so it can provide sufficient guidance to clinicians in planning further management of the case.

In Tables 2, 3 and 4, we present three examples on the application of the proposed ABCDE to cytology diagnosis procedure.



Discussion

To the best of our knowledge and after a careful search of all relevant literature, the only worldwide “ABCDE criteria” currently available in pathology is a heuristic ABCDE procedure for melanomas detection (ABCDE: Asymmetry, Border irregularity, Colour, Diameter, Evolving). There is also the “ABCD scheme”, the so-called Whitmore - Jewett prostate staging, previously used to stage prostate cancer, that has been replaced by the TNM staging system.

Diagnostic testing information supports many clinical decisions in both the identification of new conditions and the monitoring and treatment of existing ones. Proper pathological assessment of a specimen provides important prognostic information for the oncologist and points out patients that require further therapy. As such it sits within the overall patient clinical pathway. [1] The described Cytology ABCDE procedure is a well-structured and systematic way of thinking when examining a cytology specimen. The originality of this work is that all these steps have been structured to comply to an ABCDE procedure that provides a consistent set of steps and rules for reliable diagnosis. The proposed procedure is in its first edition and has not been through a full cycle of use, review and further refinement.

We believe that by using this ABCDE step-by-step approach a medical student cannot deviate from the right course of action. It should add an element of fun and guidance in a learning process. In addition, if medical students are all acquainted with the Cytology ABCDE algorithm, in their follow-up professional years, they will be inclined to provide all useful information to pathologists and can better understand and appreciate the role of pathologists.

Medical instructors can use this practical ABCDE guide to facilitate teaching Cytology. They can use it to present a case, to write a case report or to enrich their lectures.

Pathologists who teach residents could also make use of the ABCDE philosophy when they simultaneously view the slides under the teaching microscope. They can communicate their observations in a more coded way. For example, “what’s our A?”, “what did you find in C?”, “what do you think about D?”

Everyone who processes cytology specimens can probably find it useful and educational as well. It could also help improve outcomes in cytology reports by ensuring that all important elements for a complete diagnosis will be included.

Thus, we conclude that we do need the ABCDE algorithm for Cytology Diagnosis, which can give birth to an ABCDE algorithm for Pathology Diagnosis and Radiology Interpretation in the future.

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