EVIDENCE BASED CYTOLOGY. WHAT'S EVIDENCE?

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Background. Cytopathologists become involved in evidence-based cytology because it concerns with quality of their personal and professional skills. To explore this meaningful definition we have to recall the concept of evidence-based (EB) medicine that is defined as “the conscientious, explicit and judicious use of current best evidence in making decision about the care of individual patient”. Since the evidence-based cytology is an offshoot of EB medicine, it deals with “generating a reproducible, high quality and clinically relevant test result in the field of cytology”\(^1\). This concept implies that we should build our decisions on solid bases rather than personal opinions, judgments of others, not either, as sometimes could happen, on superstitions. The “solid bases” should be represented by published literature even though personal experience and knowledge should not be excluded. Though EB cytology play a remarkable role in veterinary medicine, it is actually a dawning discipline, as well as many others branches. Current knowledge of veterinary cytopathologists is based mostly on learning from a few opinion leaders, conceptions acquired by local, national or international meetings, and books or scientific papers. A rationale analysis of publications in veterinary medicine reveals that only few articles meet the criteria of evidence. A bias is frequently present in the study premises, diagnostic guidelines are obtained from the analysis of a very small number of cases in many papers and sometimes diagnostic criteria originate from a single case report. Otherwise, cytologic guidelines are verified by hystopathologic examination since it is considered the “gold standard”. Unfortunately, histopathology is affected by the same limitations, so that cytologic guidelines should be also grew from clinical outcome and response to therapy as well. These are match points in veterinary medicine. Therefore some questions come out: What is the true evidence? What do we see? What do we read? What do we listen? What do we know? The aim of this lecture is to summarize my experience in EB cytology daily practice in addition to improve my personal knowledge.

The rules of evidence-based cytology. As previously stated, when dealing with cytological problems, the key question is not “is this evidence-based ?” but “what is the best interpretation, based on the evidence?”\(^2\). This scheme was recently proposed to establish the steps to practice EB cytology\(^1\)
Personal experience in practicing evidence-based cytology

First step: identify the question. Lot of queries take startle in everyday cytological practice, especially when we are supposed to work many cases out. Questions originate from lack of confidence in some topics, direct comparison with previous cases or at least cases of unusual presentation. Certain knowledge of normal cell aspect and their “usual” abnormalities could be considered the fundaments for every answer when “unusual” abnormalities are observed. For instance, I account as “unusual” abnormalities presence of “erythroid loops” in blood of envenomed dogs as unusual as spindle cells observed among hepatocytes. In other conditions questions could arise from specific features that being the case of specifical clinical outcomes or peculiar pathogenetic mechanisms.

Second step: analysis of previously published data. Prior to the diffusion of internet, books and papers were the preferred research source. Today the use of internet-based sources, such as PubMed, allows a wide and capillary access to a wide knowledge that helps in managing questions. Data retrieval could lead to different results:

- Published data are useful in answering the question. This is the most likely result when queries arise from lack of knowledge or when particular explanations are needed.

- Published data are unsatisfactory. Reviews of published data, issues addressed by mailing lists, open discussions with colleagues could not ever fit the purpose of solve
challenging cases. This failure recurs in presence of unusual morphological features or any pathological change that have not been previously described. At length the lucky event of finding additional cases displaying the same features could lead the observer to describe the new particular cytological outcome as a peculiar expression of some pathological process. In other situations analysis of published data, mostly in human cytology, could play a role in identify a suitable pathway to describe unusual features. For instance, the description of ghost cells in one human-medicine cytological paper was a good support for my publication on canine pilomatrixoma. In some quite few cases I contended with lacking data so that an end point or final diagnosis was precluded: good example is my personal experience with testicular tumors and hepatocellular carcinoma.

Third step: statistic, epidemiologic and informatics analysis. Once data are recorded, statistical evaluation is necessary in order to evaluate their diagnostic impact. If statistical analysis is supportive of the starting hypotesis, development of analytical criteria is allowed. The continuing discussion with experts in this branch is warranted. Epidemiologic analysis should be useful in determination, for instance, of risk factors and prevalence of disease in some population, but its scopes is beyond the target of this lecture. Informatic is useful in elaboration and publication of results.

Fourth step: elaboration of guidelines. Nowadays lot of main topics in veterinary cytology lack in solid guidelines. Results are mostly affected, for instance, by pre-analytical bias, low number of cases, lack of control series and financial limitations. I used to consider my results as preliminary achievements that need to be further verified to become reliable guidelines. In the case of testicular tumors, that I mentioned before, statistical data merging from my work, allowed to identify quite remarkable indications in cytological diagnosis of these tumors. On the other hand, guidelines for other main diseases need to be further addressed. For example, current guidelines for hepatocellular carcinoma are based on a very small number of cases; a comparative study between hepatocellular carcinomas and benign neoplasms is actually in progress.

Fifth step: application of guidelines in daily practice. This operation consist of the application of morphological criteria on daily samples. This is the heart of the EB-process: testing guidelines and verifying their efficacy in solving cytologic problems.
Sixth step: confrontation with the final diagnosis. This is a crucial point in the validation of criteria and guidelines. It is generally accepted that histopathologic examination play the role of diagnostic gold standard so that cytological findings must agree with histopathologic diagnosis. Some pathologists state that histopathology is a “brass” or a “tin” standard, rather than a gold standard\(^9\)! In fact not little of publications in the field of histopathology, both human and veterinary, are represented by opinions, case reports or case series, wrongly considered at the bottom of a pyramidal hierarchy of the evidence:

From this point of view, the relative weakness of histopathology considered as the conclusive evidence should be integrated with other data, for instance the response to therapy or the clinical outcome. However histopathology remain the reference for cytopathologists in evaluating the quality of their practice; the paper about cytological arrangements was an attempt to correlate cytologic features with histologic or architectural disposition and consequently to make the gap between the two disciplines smaller\(^10\). There are some cases in EB cytology that come out on the side of histopathology definitive role. I would mention one topic that I really care: cytological features of hepatic fibrosis. Even though in most cases cytology can give helpful informations for the management of chronic hepatopathy, the histopathologic diagnosis is necessary to characterize different types of fibrosis as, for instance, “porto-portal fibrosis” or “end-stage fibrosis”. Practically, cytologic examination can provide evidence of chronic hepatopathy (fibrosis)\(^4\) but histopathologic diagnosis is
fundamental in establishing fibrosis distribution and, consequently, in providing prognostic informations.

**Seventh step: modify data.** This operation should be encouraged. Everyone who trust in cytology and practice it according to EB purpous should enhance current knowledge with the aim of improve cytology diagnostic skill. This point is what I expect to happen in the near future considering the development of new analysis, modern elaboration and review of data and at last the EB method that was today’s talking point. At present in veterinary cytopathology, every guideline can be improved, because of new concepts acquisition, availability of large number of data and increased power in statistical evaluation.

**Others applications of EB in cytopathology.** The final report is a crucial component for a two-way communication between pathologists and clinicians: it expresses the likelihood a pathologic process can be presented and guides clinicians in therapeutic and prognostic choices. Results from one study suggest that “a standard terminology or limited set of terms, each with a defined range of numerical percentages to indicate probability, might decrease inter-individual variation in expressing probability and improve communication and understanding among clinical pathologists and between pathologists and clinicians”¹¹. An attempt to standardize the reports, as tried in human medicine, should be useful in improve the effects of “some words” (for instance: “consistent with…” or “suggestive of…”) in managements of clinical cases. Sampling and specimen adequacy in veterinary cytology is another important point because the proper way of sample collection has great impact on the test result. Since it is necessary to have adequate number of intact cells on the smear to obtain diagnostic results, the formulation of guidelines to obtain a satisfactory specimen should be warranted.

**The art and science of cytopathology.** This is the title of a wonderful book¹², written by professor Richard DeMay in 1996. Reading the pages of this book I developed a solid grasp in dealing with cells: cytology is a science but in some specific cases a quote of artistic skill could be helpful in elaborating concepts, features and relating evidences properly. In this cases my personal opinion is: trust in your feeling, when evidence cannot help you!

**Suggested readings**


