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Dysplastic Nevus – What is it? Can we reproducibly recognize it?

A recent dermatopathology textbook gives a deceptively simple definition as follows: "Dysplastic (atypical, Clark's) nevi are clinically distinctive nevi with characteristic histology and an increased risk of melanoma change." That sounds straightforward. However, the following discussion casts doubt on whether things are this simple. The same text goes on to explain, "Despite repeated calls for the diagnosis of dysplastic nevus to be dropped, the diagnosis survives because proponents for its continued use can still be found and because alternative designations and definitions lack general support." Is it possible this concept is not as widely accepted, as some would lead us to believe?

There is a very nice description of the clinical features of dysplastic nevus:[1] "Clinically, dysplastic nevi are usually larger than ordinary nevi and often show a mixture of tan, dark brown and pink areas. There is often persistence of a somewhat indistinct peripheral macular area in a lesion, which by its size, would be expected to be solely papular. The surface texture is often pebbly." That sounds straightforward as well. However, it is also noted that "not all nevi with these characteristics have the histologic features of dysplastic nevi." In fact, a recently published study looked at the correlation between clinical atypia and histologic dysplasia in nevi. They measured the degree of concordance between the clinical and histologic findings of dysplasia (or lack thereof) in acquired melanocytic nevi. The authors identified two groups of nevi, one group of unequivocally atypical clinical features and another group with unequivocally non-atypical features. These nevi were then excised and examined by a single experienced dermatopathologist who was blinded to the clinical features. Overall the agreement between the clinical and histopathologic diagnosis of dysplasia was 58.4%, and agreement regarding the absence of dysplasia was present in only 66.6%. The kappa score for overall agreement was 0.17, which is considered negligible. The conclusion from this study is that dysplastic nevus does not exist as a clinicopathologic entity because of the poor agreement observed between the clinical and pathologic diagnosis of dysplasia. It was noted that histologic evidence of dysplasia is found in a variety of nevi, including many without clinical features of dysplasia (a fact cited in multiple references). Some clinically dysplastic nevi have no histologic evidence of dysplasia. A recent review of this study in Practical Reviews in Pathology commented: "The debate about whether or not dysplastic nevus exists as a meaningful clinicopathologic entity continues, and will not be settled by this study, which provides more evidence against. Although there is ample precedent for the existence of identifiable preneoplastic lesions in other organ systems, the empirical evidence for a clinically useful, identifiable preneoplastic melanocytic lesion remains scant."

While this debate continues today, there has been discussion and dissent regarding melanocytic lesions for many years. A particularly provocative paper from Dr. Ackerman includes a wealth of insight into the nuances of this problem, too extensive to cover in a short document such as this; however an excerpt from the concluding remarks is as follows: "Recently, we, with colleagues in our laboratory, reviewed 244 specimens of melanocytic nevi that had been seen consecutively in the dermatopathology laboratory at New York University Medical Center in 1978, prior to the introduction of the term dysplastic nevus. Many of these nevi (68) would now be called dysplastic nevi, but they were designated then as banal junctional and compound melanocytic nevi. A good number of these nevi (32) were removed for histologic examination by the shave technique. Follow up evaluation of 21 of these *partially* removed dysplastic nevi failed to reveal a single one that eventuated in malignant melanoma, and not even one that persisted as a pigmented melanocytic nevus at the biopsy site." This begs the question of whether re-excision of any of these nevi is required. Dr. Ackerman goes on to say: "In conclusion, we view the dysplastic nevus as one of many variants of melanocytic nevi; it is, in our experience, a very common nevus. Although clinically and histopathologically dysplastic nevi must be differentiated from malignant

melanomas, they are not malignant melanomas, nor, in our view, are they common forerunners of malignant melanomas. Use of the term dysplastic nevus is unfortunate, because it conveys a sinister connotation to what may be a rather conventional melanocytic nevus."

To further emphasize that this debate continues today, I have become aware of a study now being conducted by dermatopathologists, coordinated at the University of Pennsylvania Health System, University of California San Francisco, and Massachusetts General Hospital Harvard Medical School, to assess current opinion about dysplastic nevi in the dermatopathology community. The survey questionnaire acknowledges several interesting points. The introduction targets the significance of dysplastic nevi and their relationship to melanoma, noting that each participant is recognized as having their own individual concepts about these two conditions. It also notes that there has never been a systematic examination of the thoughts of the dermatopathology community on the topic. One of the survey questions asks what term the respondent prefers for a compound nevus with lateral extension of the junctional component beyond the dermal component, papillary dermal fibrosis, bridging nests, increased vascularity, mild surrounding lymphocytic infiltrate and some degree of nuclear variability (all descriptors used in the constellation of findings discussed for dysplastic nevus). Options include atypical nevus, dysplastic nevus with mild, moderate, or severe dysplasia, dysplastic nevus (without grading degree of dysplasia), nevus with architectural disorder (with or without comment on cytologic atypia) and compound nevus (with no qualifiers). The survey goes on to ask if dysplastic nevus has a higher probability of developing into melanoma in the future than an ordinary nevus. It asks if an incompletely removed dysplastic nevus should be re-excised and why. The fact that these questions need to be asked of experienced dermatopathologists around the country reveals the uncertainties surrounding these issues.

OK. So if we accept that dysplastic nevus as an entity is controversial, at least pathologists can diagnose this imperfect category reliably,….right? Well, several studies have assessed the interobserver and intraobserver concordance in the diagnosis of dysplastic nevi and the histological grading of their atypia and have reported limited or 'only fair' concordance for one or both of these features, particularly at the mild to moderate (low grade) end of the spectrum. Although there is usually agreement on the presence of architectural disorder, problems can arise in the subjective assessment of cytologic atypia. Furthermore, cytologic atypia is required for the diagnosis of dysplastic nevus, as there is reasonable agreement that if you are going to use the term dysplastic nevus, architectural disorder alone is insufficient[3]. How much cytologic deviation from "normal" is enough to qualify for the atypia that defines dysplasia, whatever that may or may not be? In a Yale University study of interobserver variation in the diagnosis of dysplastic nevus, they found agreement rates between pathologists of only 0.32 to 0.71. Another study found "fair" interobserver agreement in which the rates for identification between six pathologists looking at the same set of slides varied from 7% diagnosed as dysplastic nevus by one pathologist up to 32% diagnosed by another pathologist. An additional study evaluated 100 consecutive melanocytic lesions for interobserver reproducibility of the histologic criteria proposed for the dysplastic nevus. Analysis of the kappa statistics showed poor reproducibility of nuclear features, while reproducibility of architectural features was acceptable. They concluded "we cannot apply the combined criteria of cytological and architectural features with any confidence in the diagnosis of dysplastic nevus."

In light of this uncertainty revolving around the existence of dysplastic nevus as an entity, its clinical significance, and its diagnostic reproducibility, it becomes apparent that there is no standard or single truth, regardless of who interprets the slides or where this action takes place.

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References

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Surepath® vs. Cytyc Thinprep®

The Pap Smear has done an excellent job of reducing morbidity and mortality from cervical carcinoma during the last 45 years. Despite this, there are well-known sources of error involved with the collection, preparation and screening of traditional Pap Smears. These errors can include both false positive and false negative results. In an attempt to help reduce these limitations of the conventional Pap smear, liquid-based cytology preparations have been developed. Two of these products, Cytyc ThinPrep® and SurePath®(formerly Autocyte® Prep) are currently available. Each has been approved by the Food and Drug Administration (FDA) as replacements for the conventional Pap smear. The Cytyc ThinPrep® was FDA-approved in May 1996 with SurePath® receiving FDA approval in June 1999. The Rex Healthcare laboratory has been utilizing the Cytyc ThinPrep® since May of 1998 and implemented SurePath® in June of 2001

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The SurePath® methodology differs significantly from that of Cytyc ThinPrep®. ThinPrep® obtains a thin layer sample by using a membrane filter, to which a vacuum is applied. This traps the cells of interest onto the membrane and allows them to be applied to a glass slide for examination. Unfortunately, if the sample contains blood, inflammation or necrotic debris, this extraneous material will adhere to the membrane and block the adherence of cells. In many instances this can lead to an unsatisfactory or less than optimal specimen. This is especially true for bloody samples. SurePath® obtains a thin layer sample using a density sedimentation method. This enriches the cell sample by excluding blood and the majority of inflammatory cells as well as necrotic debris. Because of this enrichment process, SurePath® consistently provides adequate samples regardless of the presence of extraneous material in the sample.

SurePath® has a simple, uncomplicated collection method in that the gynecological sample is obtained using the Rover Cervex-Broom. Since this type of broom device has a detachable head, after the sample is collected by the clinician, the head of the broom device is then simply popped off into the preservative vial and sent to the laboratory. This process not only simplifies the collection process but also allows the **entire specimen** to be submitted for evaluation. For clinicians that have concerns regarding small or stenotic cervical os, the option exists of going back with a new endocervical brush with detachable head and collecting a second endocervical sample. The Cytyc ThinPrep® sample may be collected with either a broom device or a brush/spatula. Unfortunately the sample then must be manipulated significantly by the clinician before it is submitted to the laboratory and the collection device is ultimately discarded.

As far as billing issues go, both SurePath® and Cytyc ThinPrep® utilize the exact same CPT billing codes and thus enjoy the same reimbursement rates.

The FDA position is that both devices have been approved as safe and effective alternatives to the conventional Pap smear.[1] From a morphologic perspective, SurePath® and Cytyc ThinPrep® have much in common, as both provide a superior specimen than the traditional Pap smear. Several studies, including two performed in our laboratory, have shown that SurePath® and ThinPrep® are equivalent in disease detection.[2-6] Because of the density sedimentation technique, SurePath® has been shown to improve specimen adequacy relative to ThinPrep®. [2-5] In our laboratory ThinPrep® specimens are five times more likely to be unsatisfactory than SurePath® samples.[3] A recent study performed at the Cleveland Clinic indicated that ThinPrep® specimens from

patients with squamous cell carcinoma are "strikingly hypocellular" making this important diagnosis difficult to render using ThinPrep®. The authors attribute this hypocellularity to tumor diathesis blocking the ThinPrep® membrane filter.[7] In our laboratory we recently experienced a situation in which an unsatisfactory ThinPrep® sample on a patient was followed up by a SurePath® sample which convincingly demonstrated keratinizing squamous cell carcinoma.

The ThinPrep® collection medium has been approved by the FDA for use with the Digene Hybrid Capture II® assay for the detection of HPV subtypes only if the sample is collected using a broom device. However, off label HPV testing using the Digene assay is available for either ThinPrep® specimens or SurePath® specimens collected using either broom or brush devices through several reference laboratories.

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Lab Notes: Viral Skin Cultures, LDH-1

We occasionally receive viral culturettes containing swabs obtained from skin lesions with a request to perform viral culture. Virtually all viruses isolated from dermal culture are either Herpes Simplex or Varicella-Zoster. Herpes virus cultures are performed in the Rex Laboratory. All other requests for viral culture are referred to Mayo Medical Laboratories. Mayo will no longer accept dermal swabs for viral culture. They have replaced viral culture with PCR testing for Herpes Simplex and Varicella-Zoster DNA, because of increased sensitivity. Accordingly, all dermal swabs submitted to the Laboratory with a request for "viral culture" will be forwarded to Mayo Medical Laboratory for "Herpes Simplex and Varicella-Zoster DNA Detection by PCR".

Effective immediately, the Laboratory will no longer offer LDH-1 (lactic dehydrogenase isoenzyme 1) analysis. Troponin is a superior marker for the detection of myocardial infarct with a delayed (3 – 9 days after onset of chest pain) presentation.

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