PARTIAL BIOPSY AND CLINICAL INFORMATION IN THE DIAGNOSIS OF MELANOCYTIC LESIONS

- Dr Benjamin A Wood

Key Points
1. It is critical that the clinician indicate on the request form the location, clinical size, and operative intent for all pigmented skin lesions. Parenthetically, it is good practice to follow this approach for all skin lesions.

2. For diagnostic purposes an excisional biopsy with narrow (2mm) clinical margins and superficial subcutis is optimal to assess worrisome pigmented lesions.

3. If there are clinical indications for partial biopsy, both detailed clinicopathological communication and awareness of the potential sources of error are essential. Clinicians should be aware that in a study of melanomas treated at an Australian tertiary referral centre, partial punch biopsy sampling of larger melanomas was associated with a greater than 16-fold increase in rate of false negative diagnosis.

4. Clinicians should actively seek and communicate information regarding previous melanoma and previous biopsy sampling or trauma, both of which are well established as potential sources of misdiagnosis.

5. In all cases where there is significant clinicopathological discordance or other clinical concern, it is prudent to discuss the case with the pathologist.

The diagnosis of cutaneous melanoma, both clinically and pathologically, is among the ‘high stakes’ areas of medical practice. No one is unaware of the potentially life threatening nature of malignant melanoma. Conversely, because the large majority of melanomas occur on visible cutaneous sites, early recognition is both possible and increasingly common. In contrast to the poor prognosis of advanced disease, early melanoma can be entirely curable (in the case of melanoma in situ) or associated with >90% 5 year survival (for invasive melanoma less than 1mm in thickness).

For these reasons, the question “Is this melanoma?” is frequently asked, both implicitly and explicitly, by patients, clinicians and dermatopathologists in their assessment of many skin lesions. In this regard, it is timely to discuss the results of study which highlight the importance of biopsy technique and also to raise some important areas of clinicopathological correlation in the diagnosis of melanoma.

The Impact of Partial Biopsy on the Diagnosis of Melanoma

A study from the Victorian Melanoma Service examined 2470 cases of melanoma referred over the period from 1995-2006. The accuracy of initial pathological diagnosis was assessed, using VMS review (including definitive excision) as the gold standard. The majority of cases studied (2127) were excisional biopsies, while 163 punch biopsies and 180 shave biopsies were examined.

Of the 2470 cases studied, there were 83 false negative misdiagnoses and 135 false positive misdiagnoses. Some issues relevant to the subject of false positive diagnosis are discussed below, though detailed consideration is beyond the scope of this article. With regard to false negative misdiagnosis, punch biopsy was associated with a greatly increased risk of false negative diagnosis (OR 16.6; 95% CI 10.2-27.0), while shave biopsy was associated with a much smaller increase in odds (OR 2.6, with a 95% CI of 1.2-5.7).

Melanoma represents a challenging area of dermatopathology practice because the pathologist must assess and “weigh” numerous (sometimes subjective) criteria in coming to a diagnosis. Among the most important histologic criteria in the diagnosis of melanoma are lesion size, symmetry and circumscription. It is immediately apparent that these criteria cannot be fully assessed in a partial biopsy. When one adds the fact that many melanocytic lesions show significant morphological heterogeneity (even to the extent of some melanomas showing areas resembling non-melanocytic lesions such as solar lentigo or benign lichenoid keratosis), potentially leading to sampling error, the increased risk of misdiagnosis in partial (particularly punch biopsy) specimens taken from larger lesions is unsurprising.
Clinical Practice Points

1. The clinician should indicate on the request form for all pigmented lesions:
   A. The size of the lesion and its appearance.
   B. The intent of the biopsy procedure (e.g. excisional biopsy with a narrow clinical margin, punch excision of a small lesion, sampling punch of a larger lesion, complete saucerisation shave etc).

2. The ideal specimen for diagnosis or worrisome pigmented skin lesions is an excisional biopsy with narrow (2mm) clinical margins of surrounding skin.

3. In some circumstances (e.g. in cosmetically sensitive areas) partial biopsy methods may be appropriate. These may be particularly valuable if histology shows a non-melanocytic lesion. If these techniques are chosen, it is vital that the clinician communicates the circumstances to the pathologist and that both the pathologist and the clinician are aware of the issues relating to histological assessment and sampling which pertain. With care, the chances of inaccurate diagnosis leading to adverse outcome can be greatly reduced, and partial biopsy can be safely used in selected situations.

Other Clinical Information Relevant to the Diagnosis of Melanocytic Lesions

Though not directly related to partial biopsy, a number of related points regarding clinical information in the diagnosis of melanocytic lesions are also worthy of consideration in this discussion.

Site of Biopsy and Demographic Data

It goes without saying that these can be important factors in assessing a melanocytic proliferation. While patient age is invariably provided on pathology requests as part of the identifying data, specific details about the site of lesion are less reliably provided. The range of so-called “special site type” naevi which can show worrisome histological features is extensive. Naevi of acral sites can show prominent upwards scatter (Pagetoid extension) of melanocytes, easily remembered by the somewhat whimsical diagnostic acronym “MANIAC” - melanocytic acral naevus with intraepidermal ascent of cells.

Naevi on the breast, in the milkline and on genital skin can show somewhat enlarged melanocytes and irregular nesting, features which might lead to an erroneous interpretation as dysplastic naevus (or even melanoma). Naevi on the scalp and ear may also show site specific histological features which might lead to unnecessary concern. In contrast, dysplastic naevus is very uncommon on the face (with the possible exception of the sideburn region) and lesions which resemble dysplastic naevus on the sun-damaged face of elderly patients are very likely to be “dysplastic-naevus like” melanoma. Indication of the precise anatomical site of biopsy can obviously be important in facilitating a correct diagnosis.

History of Previous Surgery (or other trauma)

It is prudent clinical practice to actively enquire of every patient whether a lesion has been previously biopsied. If there is such a history, the clinician must indicate this on the request form, and if known indicate the date of prior biopsy, prior diagnosis and laboratory in which the initial biopsy was examined. Melanocytic lesions, both benign and malignant, may recur at a site of previous biopsy.

Typically naevi tend to recur more rapidly (most within less than 12 months of surgery), while melanoma often recurs more slowly. Just as the clinical appearances can be concerning, so prior surgery can induce a number of worrisome microscopic changes in benign melanocytic lesions. The degree to which these can mimic melanoma can be striking, hence the (somewhat outdated) appellation “pseudomelanoma.” While the pathologist can usually recognise such cases by the presence of dermal scarring, misdiagnosis is a well-recognised pitfall. In some difficult cases, dermatopathological review of the original specimen remains the most valuable diagnostic manoeuvre.

History of Previous Melanoma

A prior history of melanoma should always be indicated on the request form, including information as to whether the melanoma was invasive, and if so the Breslow thickness. Cutaneous deposits of metastatic melanoma are usually recognisable histologically, but in some cases may mimic primary melanoma, with significantly different prognostic and therapeutic implications. More rarely, metastatic melanoma may mimic blue naevus to a striking degree.

History of Recent Sun-Burn or Tanning Bed Use

It is well recognised that acute exposure to UV radiation can induce changes in melanocytic lesions which may histologically mimic those of melanoma. There is little data in the literature to indicate whether this is a significant cause of false positive diagnosis in clinical practice. Anecdotally, I have seen a case in which 3 naevi biopsied from a young adult female patient showed prominent upward scatter of melanocytes within the epidermis. This feature is generally a strong histological indicator of melanoma, though as with all criteria it is far from absolute. As the other features of the lesions suggested benignity and because the finding of 3 simultaneous similar lesions in a young patient was exceptional, further clinical history was sought. On directed questioning it was revealed that the patient had used a tanning bed on the day prior to the biopsies and the worrisome histological features were undoubtedly explained by this exposure.

References


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WHAT’S NEW IN PCOS?
- Dr Narelle Hadlow

Polycystic ovarian Syndrome (PCOS) is a common cause of infertility, menstrual abnormalities and metabolic disturbance in women. It is estimated to affect up to 20% of women in their reproductive years in Australia. However, surprisingly, 70% of these women are never diagnosed with PCOS.

In August of 2011 a new “Evidence Based Guideline for the assessment and management of Polycystic Ovarian Syndrome”, was released. (2) This document was the culmination of 2 years collaboration by experts, drawn from various areas of expertise who came together to form a PCOS Australian Alliance. Local contributors included Dr Bronwyn Stuckey, Dr Ee Mun Lim, Dr Elizabeth Davis and Dr Roger Hart. Dr Lim is Head of the Biochemistry Department, PathWest QEII Medical Centre and the appropriate use of biochemical laboratory tests have been well covered in this guideline.

The formulating group identified key areas of clinical priority and then developed guidelines for these priorities or knowledge gaps, according to NHMRC standards.

The 4 key clinical areas identified included:
1. Challenges of assessment and diagnosis
2. Assessment of emotional wellbeing
3. Lifestyle management
4. Fertility

The guidelines also give emphasis to the long-term complications of PCOS including increased risk of diabetes, cardiovascular disease, obesity, depression and anxiety.

What has Not Changed?
The diagnosis of PCOS itself remains unchanged. The “Rotterdam” criteria for diagnosis of PCOS are well known and this guideline supports the use of these criteria. These criteria are the presence of 2 of 3 of the following:
1. Oligo- or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries on Ultrasound

AND

The exclusion of other relevant pathology such as hypothyroidism, hyperprolactinaemia, congenital adrenal hyperplasia, Cushing’s syndrome or androgen secreting tumours.

What is New?
Some new emphasis has been given to the investigation of hyperandrogenism and the follow-up of the metabolic features of PCOS.

New Recommendations in Assessment of Hyperandrogenism

Hyperandrogenism is a key component of diagnosis of PCOS. This guideline further defines the most effective way to assess hyperandrogenism in a woman suspected of having PCOS. The guideline makes 2 recommendations regarding assessment of androgens in women with possible PCOS. The first of these was a clinical consensus recommendation. Although late onset congenital adrenal hyperplasia is rare, the guideline emphasized the need to exclude this condition before the diagnosis of PCOS is confirmed. The most practical way to do this is by measuring a 17 hydroxy progesterone (17 OH Prog) in the follicular phase of the cycle.

The second recommendation is an evidence based recommendation and confirms that the first line investigation for biochemical investigation of hyperandrogenism should be the measurement of calculated bioavailable testosterone, calculated free testosterone or the free androgen index. Second line tests include dehydroepiandrosterone sulphate (DHEAS) and androstenedione.

Metabolic Features of PCOS

These are also addressed in detail in this guideline with practical recommendations provided for assessment of cardiovascular risk and risk of type 2 diabetes.

Assessment of Lipids

Assessment of a complete lipid profile is suggested every 2 years for women with PCOS who have normal lipids and this should be done yearly in those who have abnormal lipid profiles or excess weight. In the clinical practice point information, it is recommended that total cholesterol target should be < 4.0 mmol/L in women with PCOS. The target LDL suggested for women without further risk factors for cardiovascular disease is an LDL < 3.4 mmol/L. In women with the metabolic syndrome or type 2 diabetes a target LDL of <1.8-2.6 or 1.8 mmol/L respectively should be the aim. Recommendations for HDL are that it should be > 1.0 mmol/L and that triglycerides should be < 1.7 mmol/L.

Assessment of Risk of Type 2 Diabetes

It is recommended that an oral glucose tolerance test be performed every second year in all women with PCOS and that this should be increased to annually in those women with further risk factors for type 2 diabetes. Further risk factors include age, ethnicity, parental history, previous high blood sugar, smoking, inactivity and waist circumference.

The reasons for the authors recommending this increased testing for type 2 diabetes are well argued in the guideline. They include the high prevalence of insulin resistance in women with PCOS (50-80% of women) and that this is further exacerbated by weight gain. These women are at increased risk of gestational diabetes and type 2 diabetes and the authors note that fasting glucose alone may lack the sensitivity needed to screen for type 2 diabetes in this group. They acknowledge however that glucose tolerance tests are onerous and inconvenient for patients and that in the future, glycated haemoglobin may be used for diagnosis of diabetes. Currently, however, glycated haemoglobin remains funded only for monitoring of known diabetes and Medicare does not support its use in screening.

Summary

The PCOS guidelines provide practical, evidence based information for the assessment and management of women with this condition. A range of resources are readily available to download with easy to follow links available on the internet. This comprehensive document will provide a valuable resource for a wide range of health care providers involved in the diagnosis and management of women with PCOS. In the future, glycated haemoglobin may be used for diagnosis of diabetes. Currently, however, glycated haemoglobin remains funded only for monitoring of known diabetes and Medicare does not support its use in screening.

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PATHWEST POSITION ON CARDIAC TROPOIN ASSAYS
- Drs Samuel Vasikaran & Dominic Mallon

How PathWest is Positioned with regard to Cardiac Troponin (cTn) Assay in Tertiary and Regional Routine Labs and PoCT

The three adult teaching hospitals all use the Abbott Architect platform for measuring cardiac troponin I (cTnI) in the laboratory setting. The current assay is a “sensitive” cTn assay as opposed to the conventional assays. In addition there is a “high sensitivity” cardiac troponin T (Hs-cTnT) assay available from other pathology providers on another platform. Clinically, the current generation sensitive TnI provided by PathWest performs virtually on par with the Hs-cTnT assay which is more sensitive but has a decreased diagnostic specificity for Acute Myocardial Infarction (AMI).

Early diagnosis of AMI can be achieved with sensitive cTnI testing either at baseline and/or at repeat testing at 2 hours in 90-95% cases. Abbott Diagnostics is developing a Hs-cTnT assay and we expect that to be introduced within the next 12 months time and we hope to work with the WA Cardiovascular Network to revise chest pain algorithms to incorporate the Hs-cTnT once it is available in WA. In order to improve diagnostic specificity and maximise the clinical utility of the Hs-cTnT assay for the diagnosis of AMI, the use of a higher cut-off in patients >70 years of age will be examined. Lesser, stable increases above detection limit in the elderly are still useful for risk stratification and, when absent, for early exclusion of AMI. Studies are now ongoing at each teaching hospital and the results of these would also help us decide on strategies for early diagnosis in acute chest pain patients.

In the PathWest branches with Vitros 5600 analysers (Albany, Armadale, Broome, Bunbury, Geraldton, Kalgoorlie, Rockingham, Swan Districts and Osborne Park) also provide “sensitive” cTnI testing via this analyser. However as these laboratories do not provide a 24-hour service (except Armadale), an iSTAT point-of-care (POC) TnI is provided in the emergency department (ED) for after hours use. Osborne Park hospital does not have an ED department and hence there is no requirement for iSTAT after hours. The POC instruments (iSTAT) currently have a cTn assay which has conventional levels of sensitivity (ie. less than the “sensitive” cTnI assay). All other PathWest branch laboratories continue to use the point-of-care Cobas h232 cTnT (Table 1). This will be reviewed when the current contract with Roche expires. There is no POC device that has a sensitive cTn assay.

Ideally, with staffing for 24-hour laboratory service, every laboratory would be using sensitive cTn assays performed on an automated platform. However, the staffing costs associated with providing a 24-hour laboratory service at all laboratories are prohibitive.

Changes Anticipated in our Testing Strategies

The main change in strategy when the Hs-cTnT assay is introduced would be to demonstrate a clear rise and fall (delta troponin) at low levels of cTn to diagnose acute cardiac damage (as opposed to just a raised TnI above a cut-off). The introduction of Hs-cTnT assays will potentially improve the early diagnosis of AMI, and therefore the ED’s ability to meet the four-hour rule for these patients. The adoption of Hs-cTnT assays will provide challenges as well as opportunities. Whilst the improved sensitivity of cTnT assays has significantly improved sensitivity of diagnosing AMI this comes at the cost of reduced specificity, especially in the elderly. PathWest is actively involved in a multidisciplinary team including cardiologists and emergency physicians to develop algorithms for the use of the Hs-cTnT assays before they are implemented. If Hs-cTnT assays become available on the POC instruments, similar protocols for using a rise and fall in cTn (delta troponin) at the lower levels would be introduced for these instruments too, but this is unlikely to happen in the near future.

Use of cTn in the Diagnosis of Acute Coronary Syndromes (ACS)

The clinician should be familiar with the sensitivity of the assay he/she is using and follow a diagnostic algorithm that is appropriate for that assay.

If there is a clear history and ECG changes of ACS, the patient should still be managed as for ACS, irrespective of whether the cTn testing is positive. In the event of negative tests further troponin testing should be performed.

With the use of sensitive cTn assays (Abbott and Vitros 5600), testing should be done at admission and 3 hours later / at least 6 hours after onset of symptoms.

With the use of conventional cTn assays (iSTAT, Cobas h232), we advocate a repeat cTn 6 hours later / at least 12 hours after onset of symptoms.

Community Based Testing of cTn

Appropriate management of patients with suspected ACS requires careful patient assessment (history, examination, CXR and ECG) and serial measurements of cTn in an acute care setting. Therefore cTn testing is discouraged in the ambulatory setting.

Summary

- PathWest provides sensitive TnI for the majority of patients accessing acute care facilities in WA. These methods demonstrate similar diagnostic performance to Hs-cTnT methods in clinical studies.
- For patients presenting to facilities when there is no laboratory service available (either after hours or in remote settings), at least conventional cTn measurements are available via POCT in all settings where a PathWest laboratory is on site, and in some more remote facilities.
- Appropriate management of patients with suspected ACS requires careful patient assessment (history, examination, CXR and ECG) and serial measurements of cTn in an acute care setting. PathWest would therefore recommend that this testing be confirmed to acute care settings.
- Clinicians need to be aware of the relative sensitivity of the assay they are requesting and use a testing algorithm that is suited to the assay.

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