DOUGLASS HANLY MOIR PATHOLOGY

Quality is in our DNA

Doctors' Newsletter

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Once more I'm delighted to provide an introduction to the DHM Doctors' Newsletter, the first for 2018. But not only to the Newsletter...

It's also my great pleasure to introduce and welcome five pathologists who have joined the practice since late 2017. They are Dr Ming-Celine Dubosq (Haematology), Dr Melanie Galea (Genetic Pathology), Dr Martin Jones (Anatomical Pathology), Dr Lawrence Mokgwathi (Anatomical Pathology, Newcastle) and Dr Renn Montgomery (Anatomical Pathology, Orange). With their arrival, the number of pathologists at DHM has reached 90, reflecting a depth and breadth of specialist pathologist expertise unmatched by any other Australian laboratory. Among them are individuals with national and international reputations who continue to contribute enormously in their sub-specialties.

A modern pathology practice depends on many other highly skilled individuals for its successful operation, but at its heart is the interaction between clinician and pathologist. A feature which differentiates DHM Pathology is that our service to you does not end with the issue of a lab report – instead, it is at this point that an in-depth, pathologist-driven resource aimed at optimal clinical care actually begins. Our reports reflect current opinion, best-practice and cutting-edge methodology. Each one is also accompanied by an undertaking that a pathologist in the relevant sub-specialty will be available 24/7 to interpret and discuss it with you.

Over many years, DHM Pathology has steadfastly committed itself to a unique style of pathology, one we call 'Medical Leadership'. This means that we endeavour to operate as a medical practice, rather than a business. Our reports and our team of 90 expert consultant pathologists proudly reflect one very important manifestation of our Medical Leadership model. We believe – and we hope you agree – that this is what a modern diagnostic pathology service looks like and the level of laboratory support a modern clinical practice requires!

Dr Colin Goldschmidt
MB, BCh, FRCPA, FAICD
CEO – Douglass Hanly Moir Pathology

Welcoming our new Specialist Pathologists


Haematologist

Dr Ming-Celine Dubosq
BSc(Med), MBBS (Hons), FRACP, FRCPA

Dr Dubosq graduated with Honours from the University of New South Wales in 2004. She specialised as a clinical and laboratory haematologist at Westmead Hospital and is interested in all aspects of haematology, with particular interest in lymphomas, myeloma and myelodysplasia.


Genetic Pathologist

Dr Melanie Galea
MBBS (Hons), BMedSc (Hons), FRCPA (Genetics)

Dr Galea is a medical graduate from the University of Sydney. She is the Royal College of Pathologists of Australasia's (RCPA) National Coordinator for Genetic Pathology Training and a member of the RCPA Genetic Advisory Committee. Her genetic pathology career to date has involved exposure to a broad range of molecular and cytogenetic techniques in constitutional, somatic and prenatal contexts.


Histopathologist

Dr Martin Jones
BSc, MBBS, FRCPA

Dr Jones graduated from the University of Sydney in 2007 and trained at Concord Hospital. He is interested in all areas of anatomical pathology, with a particular interest in genitourinary and gastrointestinal pathology. Dr Jones has been involved in the publication of peer-reviewed journal articles and teaching of junior doctors and medical students.


Histopathologist

Dr Lawrence Mokgwathi
MBBS, FRCPA

Dr Mokgwathi graduated from Monash University in 2010 and completed his internship and residency in Rockhampton Base Hospital, Queensland. He relocated to Sydney after admission into anatomical pathology training and attained his Fellowship with the RCPA in 2018. His areas of interest include general pathology and cytology. Dr Mokgwathi is based at our Newcastle Laboratory.


Histopathologist

Dr Renn Montgomery
BBiomedSc, MBBS, FRCPA

Dr Montgomery graduated from the Australian National University, Canberra, in 2010. His pathology training was at Liverpool and Canberra Hospitals, with a rotation to the Department of Forensic Medicine. He held conjoint positions with Western Sydney University and Australian National University Medical Schools. Dr Montgomery is based at our Orange Laboratory.

If you would like to read their full biographies, please visit our website www.dhm.com.au

Sebaceous gland tumour & colon carcinoma

The association of one diagnosis with the co-presence of another, despite apparent implausibility, is sometimes so compelling that the first diagnosis mandates an active search for the second. This case report illustrates the association and the implausibility.

Dr Esther Myint
MBBS, DP, MSc, FRCPA, Dip ICDP-UEMS
Histopathologist

Not all skin cancers are straightforward and some can be associated with internal malignancies or visceral cancers. Skin cancers can be syndromic; they can occur together and characterise a particular abnormality or condition and Muir Torre syndrome (MTS) is a good example. Syndromes are mostly inherited as autosomal dominant traits. MTS is characterised by the development of sebaceous tumours, often multiple, in association with visceral neoplasms, usually gastrointestinal carcinomas.

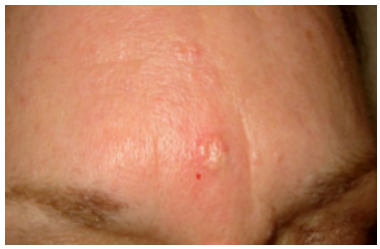
MTS is found as a variant of the autosomal dominant disorder, hereditary non-polyposis colorectal cancer (HNPCC), with tumours demonstrating microsatellite instability (MSI) and germline mutations in the DNA mismatch repair genes MutS homolog MSH2 and MLH1.

Epidemiology and disease association

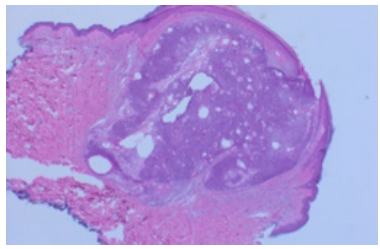
Sebaceous glands are holocrine glands, widely distributed in the skin. They are usually found in association with hair follicles, known as the 'pilosebaceous unit'. Ectopic sebaceous glands without attached follicles may be found in the upper lip, buccal mucosa and in the areolae of the breasts. Neoplasms of the sebaceous glands include sebaceous adenoma, sebaceoma and sebaceous carcinoma. They usually arise in adults and are commonly confused with basal cell carcinomas and squamous cell carcinomas.

A case report

A 56-year-old patient presents with a smooth, round, slightly scaly lump on the forehead, 2mm in maximum dimension. The clinical diagnosis was query basal cell carcinoma and it was excised.



Clinical photograph

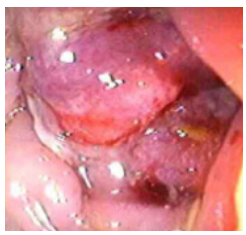


Histopathology (H+E) of excised skin lesion

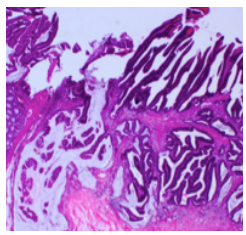
Microscopic findings were of sebaceoma and following immunohistochemistry staining shows loss of nuclear positivity of the DNA mismatch repair enzymes MSH2 and MSH6, which is usually associated with high-degree MSI, and raises the possibility of Muir Torre syndrome associated tumour.

The patient underwent investigations, including colonoscopy, and was found to have a fungating lesion in the sigmoid colon.

The patient had a left-sided hemicolectomy and the microscopic findings were of a moderately differentiated adenocarcinoma. It also has the same loss of nuclear positivity of the DNA mismatch repair enzymes MSH2 and MSH6, which further raises the possibility of Muir Torre syndrome associated tumour.



Endoscopic view of the adenocarcinoma



Histopathology (H+E) of the colon tissue

Muir Torre syndrome

This syndrome was first noted by Muir et al in 1967 and Torre in 1968, and is defined by occurrence of a sebaceous neoplasm and internal malignancy in the absence of other predisposing factors.

Cancers of the gastrointestinal and genitourinary tracts are the most common, with colorectal cancers often occurring at or proximal to the splenic flexure, contrary to most sporadic colorectal cancers.

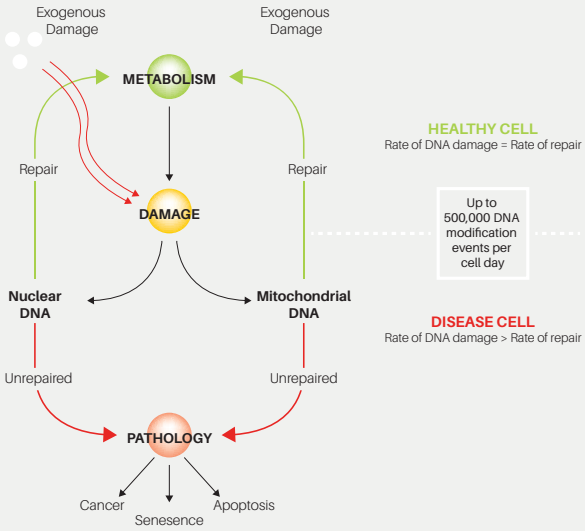
The skin lesions which develop in MTS include sebaceous adenoma, sebaceoma and sebaceous carcinoma. Multiple keratoacanthomas (with or without areas of sebaceous differentiation) are seen in some cases and reticulated acanthoma with sebaceous differentiation. Multiple sebaceous tumours and sebaceous tumours occurring before the age of 50 years are strong indicators of the syndrome. The cutaneous tumours may precede or follow the direct manifestation of the visceral cancer and may occur sporadically in family members.

The visceral tumours behave less aggressively than would be expected from the histologic findings and this is particularly true for tumours with MSI. Detection of MSI in cutaneous neoplasms may form the basis of a non-invasive screening technique for hereditary non-polyposis colon syndrome (also known as Lynch syndrome), of which the Muir Torre syndrome is regarded as an allelic variant and represents 1-2% of cases with Lynch syndrome.

MTS is inherited as an autosomal dominant trait. Mutations in one of the DNA mismatch repair genes MLH1, MSH2, MSH6 and PMS2 have been found in these patients.

What is the role of mismatched repair genes?

Up to 500,000 DNA (either nuclear or mitochondrial) modification events happen in a cell per day and, if unrepaired, lead to either apoptosis (programmed cell death) or senescence (lipofuscin) and ultimately malignancy. These modifications and damage are identified and repaired by these genes.



Role of immunochemistry

The role of immunochemistry is to:

1) Confirm the haematoxylin and eosin (H+E) diagnosis of sebaceous neoplasms from other mimicking differentials. Adipohilin and EMA will be positive and other melanocytic, squamous or basal cell markers will be negative
2) Stain for proteins from MSI markers, i.e., MLH1, MSH2, MSH6 and PSM2 for detection or as screening test for potential MTS
3) Provide prognostic biomarkers

At Douglass Hanly Moir Pathology, it is standard protocol to have immunohistochemistry staining for MSI proteins performed for all sebaceous neoplasms.

Recommendations in Muir Torre syndrome

- Consider MTS in patients presenting with a sebaceous neoplasm. Immunohistochemistry examination of tumours for MLH1 and MSH2 protein can be used as a screening test to identify patients.
- Individuals with or at risk of MTS or HNPCC should have:
  1) Colonoscopy every 1-2 years, beginning at age 20–25, or 10 years younger than the youngest age at diagnosis in the family is strongly recommended.
  2) Annual history and physical examination, including a complete skin examination and urinalysis, as well as periodic endometrial sampling and/or transvaginal ultrasound for women.

References

- Iacobelli J, Harvey N, Wood B. Sebaceous lesions of the skin. *Pathology* 2017; 49(7), pp. 688-697
- Weedon D. Skin Pathology. 4th ed. Elsevier: Churchill Livingston, 2015

HbA_{1c}: diagnosis & monitoring of diabetes mellitus

Dr Joyce Wu
MBBS, MAACB, FRCPA
Chemical Pathologist

Glycated haemoglobin (HbA_{1c}) has been used for monitoring patients with established diabetes for many years but its diagnostic application is a more recent development. This article provides some background to the test, explains dual reporting of results and discusses the use of HbA_{1c} in the diagnosis and monitoring of diabetes.

Key points

- When requesting HbA_{1c} it is vital that the clinician specify clearly the indication for the test, for example, 'diabetes monitoring' or 'diabetes screening'.
- HbA_{1c} ≥6.5% (≥48 mmol/mol) can be used to diagnose diabetes in asymptomatic, high-risk patients. HbA_{1c} ≥6.5% should be confirmed with glucose or another HbA_{1c} performed on a different day but as soon as possible, before any intervention has commenced.
- The recommended treatment target is HbA_{1c} ≤7.0% (≤53 mmol/mol). Treatment targets may need to be individualised to between ≤6.0% (≤42 mmol/mol) to ≤8.0% (≤64 mmol/mol), depending on patient-specific factors, such as type and duration of diabetes and risk of hypoglycaemia.
- Currently, HbA_{1c} is reported in both National Glycohemoglobin Standardization Program (NGSP) units (%) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units (mmol/mol), with the aim of eventually reporting in IFCC units only.
- A number of medical conditions affect HbA_{1c} results and preclude its use in both monitoring and diagnosis of diabetes mellitus.

What is HbA_{1c}?

Adult haemoglobin is predominantly (97% of total) HbA. HbA_{1c} is formed when a glucose molecule non-enzymatically attaches to the N-terminal valine of the β-chain of HbA. The amount of HbA_{1c} formed is directly proportional to the average plasma glucose concentration during the 120-day life span of the erythrocyte, with recent plasma glucose contributing more than earlier concentrations. HbA_{1c} is therefore a reflection of the average glycaemia over roughly the preceding 6–8 weeks and has a vital role in assessing the risk of an individual developing the complications of diabetes.[1]

HbA_{1c} for the diagnosis of diabetes mellitus

A 2012 position statement of the Australian Diabetes Society, the Royal College of Pathologists of Australasia (RCPA) and the Australasian Association of Clinical Biochemists (AACB)[2] contains the following:

- HbA_{1c} levels ≥6.5% (≥48 mmol/mol) are acceptable for diagnosing diabetes so long as the test is done in a laboratory and no conditions exist which preclude its accuracy.
- In an asymptomatic patient with a positive result, the test should be repeated to confirm the diagnosis.
- The existing criteria based on fasting and random glucose levels and on the oral glucose tolerance test remain valid and are the diagnostic tests of choice for gestational diabetes, type 1 diabetes and in the presence of conditions that interfere with HbA_{1c} measurement.

The use of HbA_{1c} simplifies the diagnostic process and may facilitate the detection of diabetes diagnosis. The test can be performed at any time of the day, does not require special pre-test preparation, such as a diet or fasting, and is stable when collected in the appropriate specimen tube.

Testing should be restricted to patients at high risk of undiagnosed diabetes and who are asymptomatic.[3] If one or more symptoms suggestive of diabetes are present in a low-risk patient, blood glucose tests should be used, because patients with rapidly evolving diabetes can have normal HbA_{1c}.

HbA_{1c} <6.5% (<48 mmol/mol) indicates that diabetes is unlikely but (since the patient is high-risk) the test should be repeated in 12 months. Patients should be given appropriate lifestyle advice and other modifiable cardiovascular risk factors should be assessed.[3]

There is uncertainty about the use of HbA_{1c} to diagnose pre-diabetes. While patients with HbA_{1c} above normal but below 6.5% (48 mmol/mol) are more likely to develop diabetes than is suggested by their AUSDRISK score alone, they have minimal risk of developing microvascular complications. Management is the same as for those at high risk of type 2 diabetes with HbA_{1c} within the normal range.[3]

HbA_{1c} ≥6.5% (≥48 mmol/mol) should be confirmed by another test (glucose or repeat HbA_{1c}). Repeat HbA_{1c} should be performed on a different day but as soon as possible, before any lifestyle or pharmacological interventions are initiated.[3]

It is important that clinicians state clearly the indication for the test when requesting HbA_{1c} testing, with wording such as 'diabetes monitoring' or 'diabetes screening'. This will allow the correct Medicare item number and interpretative comments to be used.

Individualisation of HbA_{1c} treatment targets

In monitoring patients with established diabetes, the general target is ≤7.0% (≤53 mmol/mol). Individualisation of target HbA_{1c}, taking into account patient-specific factors, such as type of diabetes and its duration, pregnancy, diabetes medication used, existing cardiovascular disease, risk of hypoglycaemia and comorbidities, may modify the target range from ≤6.0% (≤42 mmol/mol) to ≤8.0%(≤64 mmol/mol).[4] Douglass Hanly Moir Pathology includes these targets in its HbA_{1c} reports when diabetes monitoring is the indication for testing.

Dual reporting of HbA_{1c}

There are many assays for measuring HbA_{1c}. For many years, the NGSP in the US and other national and regional programs harmonised HbA_{1c} methods. This allowed valid, inter-laboratory comparison of results. The NGSP uses percentage (%) units.

The IFCC standardised glycated haemoglobin measurement by making it traceable to an international standard.[5] The IFCC uses mmol/mol (mmol HbA_{1c} per mol total Hb).

The improved specificity of IFCC-HbA_{1c} is reflected in results which are consistently 1.5%–2.0% lower than NGSP values.[1]

A 2007 consensus statement from the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), IFCC and International Diabetes Federation (IDF) was adopted and implemented by Australasian laboratories.[5] It recommended that HbA_{1c} results be reported in both IFCC units (mmol/mol) and derived NGSP units (%) to allow clinicians to become familiar with IFCC results before reporting of NGSP % units is withdrawn. Currently, there is no agreement on when dual reporting will cease and hence HbA_{1c} results are still reported with two units.

Conditions affecting HbA_{1c} results

As HbA_{1c} is simply haemoglobin with the addition of a glucose molecule, conditions that affect red blood cells or their survival time, such as haemoglobinopathies or anaemia, will affect the HbA_{1c} result.[3] Patients with abnormal haemoglobins may form other glycated products which may form at different rates to that of normal haemoglobin. Haemolytic anaemia can reduce HbA_{1c} by decreasing red cell survival, leading to reduction in the availability of haemoglobin for glycation. This occurs with autoimmune haemolytic anaemia, haemoglobinopathies and chronic renal failure. Any drugs that give rise to haemolytic anaemia will have the same effect. Red cell survival time is also reduced in severe liver disease, anaemia of chronic disease, vitamin B12 and folic acid deficiencies, and regular phlebotomy. Interestingly, iron deficiency anaemia can increase HbA_{1c} by up to 2%.[1] There are alternative ways of monitoring diabetes treatment in these patients, including the use of closer glucose monitoring and fructosamine testing.

Any discordance between glucose and HbA_{1c} levels should alert the clinician so that other testing options should be considered.

For any questions concerning HbA_{1c} results, please contact one of our Chemical Pathologists.

References

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Our Doctors' Newsletters contain articles written by our pathologists which focus on current issues and recent developments in pathology. Suggestions from you, which we invite wholeheartedly, are the best guarantee that our Doctors' Newsletter becomes a resource of maximum possible interest, information and relevance. If you have any topics you would like to suggest please feel free to contact Dr Ian Chambers (Medical Editor, DHM Publications) at med.ed@dhm.com.au.

Please note, this Newsletter can also be viewed on our website via the Clinician Publications link.

We look forward to hearing about your topics of interest and encourage your participation.

Dr Ian Chambers
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Medical Editor

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