COMPANION MEETING

ORELL FNA

Meeting Room : Bayside 102  
Time : 2:00 – 3:45

Convenor: Dr Afaf Haddad, Dorevitch Pathology, Heidelberg, VIC

Presenters:

1. Dr Felicity Frost, PathWest QEII, Perth  
   *Learning from errors in salivary gland FNA Cytology, PathWest QEII experience*

2. A/Prof Elizabeth Salisbury, Prince of Wales Hospital and University of NSW, Sydney  
   *Head and Neck Cytology from the Neck Down*

3. Dr Teik Beng Phung, Dorevitch Pathology, Melbourne  
   *Malignant hypertensive breast lump*

4. Dr Kris Kerr, Sullivan Nicolaides Pathology, Brisbane  
   *Is that a parathyroid in your FNA needle hub, or are you just happy to see me*

5. A/Professor Andrew Field, St Vincents Hospital, Sydney, NSW  
   *The FNA diagnosis of intraduct lesions of the breast.*
Case 2.

**Metastatic Medullary Carcinoma of the Thyroid presenting as Liver Metastases of Unknown Primary in a Young Adult Male**

Presented by: A/Professor Elizabeth Salisbury, Department of Anatomical Pathology, Prince of Wales Hospital, Sydney

University of New South Wales

University of Western Sydney

The predominant clinical presentation of thyroid cancer is either as a palpable neck nodule or ultrasound detected thyroid lesion. A subset of patients present with disease outside the neck which can produce a diagnostic challenge if a primary thyroid lesion is not suspected. The variety of subtypes of thyroid carcinoma contributes to difficult in correctly identifying these lesions in metastatic sites.

Medullary thyroid carcinoma (MTC), first described in 1951, is a malignancy which shows differentiation towards parafollicular cells of the thyroid gland and may follow an aggressive course with haematogenous and lymphatic spread. Presentation outside the thyroid gland is common and up to 50% of patients present with disease in the neck, often without an identified primary tumour. Pathologically, MTC displays a number of morphological variants which can make interpretation difficult, (small cell, spindle cell, polygonal cells) and the interaction of cells and stroma may produce trabecular, insular, epithelial-rich and amyloid-rich subtypes.

The classic cytological features include:
1. Cellular smears with individual cells and cohesive clusters. May see a pseudofollicular pattern which can mimic follicular carcinoma.
2. Variable cell types – spindle, plasmacytoid, small cells.
3. Cytoplasm may be scant or contain red granules.
5. Uniform hyperchromasia, smooth nuclear membranes, coarsely granular chromatin.
6. Amyloid in background.
7. Calcitonin/CEA/Chromogranin A staining positive.

There are a number of recognized variants of medullary carcinoma, including:
1. Microcarcinoma
2. Spindle cell
3. Papillary and pseudopapillary
4. Oncocytic
5. Clear cell
6. Glandular/trabecular/follicular
7. Amphicrine/composite calcitonin and mucin producing
8. Parangangioma-like
9. Small cell
10. Giant cell
11. Angiosarcoma-like
12. Squamous cell

A rare melanotic variant exists in which intracytoplasmic pigment is present, resembling malignant melanoma. Focal staining for HMB 45 has been reported. Staining for calcitonin and chromogranin helps establish the correct diagnosis.

Immunohistochemical markers are of great importance in the correct recognition of MTC. MTC may show positive staining for:
1. Low MW Keratin
2. Calcitonin – raised serum levels of calcitonin may also provide a useful diagnostic clue. There is also evidence to suggest that calcitonin may be measured in needle rinse material.
3. NSE, Chromogranin A, synaptophysin
4. CEA – follicular derived thyroid tumours are CEA negative
5. TTF-1
6. Neuropeptides (somatostatin, gastrin releasing peptide, ACTH, substance P, VIP)

Correct recognition of medullary carcinoma has important implications not only for treatment, but also because of the association with other endocrine lesions. 10-15% of patients with MTC have multiple endocrine neoplasm syndromes 2A (Sipple’s syndrome) or 2B (Gorlin’s syndrome) and other family members may be similarly affected. Sipple’s syndrome includes phaeochromocytoma, MTC and hyperparathyroidism. Gorlin’s syndrome (also called mucosal neuroma syndrome) includes mucosal neuromas, MTC and marfanoid changes. The hereditary forms of MTC show autosomal dominant inheritance and are associated with mutations in the RET oncogene on chromosome 10 which codes for tyrosine kinase receptor.

Metastatic spread to cervical lymph nodes is common and occurs in approximately 50% of patients, although frequency is closely related to tumour size with up to 90% of patients with tumours over 4cm having lymph node metastases. Disease may also spread haematogenously to liver, lungs, bones, brain and skin. Often multiple organs are involved and metastatic disease may be extensive.

The current total 5 year survival for MTC is approximately 70%. The treatment of early disease is predominantly surgical and there is a limited role for radiotherapy and chemotherapy in the management of metastatic disease and for these patients the outlook is grim. Clinical trials are currently investigating some new agents for treatment of MTC, including Vandetanib, which is a tyrosine kinase inhibitor and acts as an antagonist against EGFR and VEGF. In April 2011, Vandetanib became the first agent approved in the US for use in advanced MTC.

References:


Haugen BR, Kane MA. Approach to the Thyroid Cancer Patient with Extracervical Metastases J. Clin. Endocrinol. Metab. 2010 95:987-993

Nikiforov YE. Diagnostic Pathology and Molecular Genetics of the Thyroid. 2009. Lippincott Williams and Wilkins.

National Cancer Institute at the National Institutes of Health - http://www.cancer.gov/cancertopics/pdq/treatment/thyroid/HealthProfessional


A malignant hypertensive breast lump

Dr Teik Beng Phung
Dorevitch Pathology
Clinical History

- 33-year-old woman.
- Presented for Caesarean section.
- Developed a hypertensive crisis.
- Bone pain.
Work-up

Imaging:
- Left breast solitary soft tissue density
- Lesion in humerus

- Breast lesion related to the primary pathology or co-incidental finding? U/S-guided FNA performed.
- Bone biopsy.
Ultrasound-guided fine needle aspiration of the breast lesion

Pap and DQ-stained smears, and cell block prepared.

High cellular smears

Largely cohesive groups

“Clean” blood-stained background, lacking bare bipolar nuclei, stromal fragments, cellular debris.
Loose aggregates with “feathery” pattern predominantly. A smaller number of singly dispersed cells.
Fragile, moderate cytoplasm.
Round to ovoid nuclei; regular nuclear membranes.
Anisokaryosis.
Bland, finely granular nuclear chromatin. Occasional small nucleoli.
Cell block preparation
Cell block: Immunohistochemistry
Positive for chromogranin, synaptophysin and neuron specific enolase (NSE).
Negative for broad-spectrum cytokeratin AE1 / AE3 and TTF-1.
Occasional S-100 protein positive cells were identified at the periphery of the cell nests.
Summary of cytological findings

- Hypercellular lesion, predominantly in loose aggregates; capillary network.
- Low-grade nuclear features. N/C ratio preserved.
- No bare bipolar nuclei or stromal fragments.
- Clean background.
- Cell block shows nested “Zellballen” pattern.
- IHC: Neuroendocrine markers positive, cytokeratin negative, S-100 focally positive.
Further findings

- Lesion in the humerus displayed similar morphology and immunohistochemical profile.
- Urinary catecholamines elevated.
- Adrenal mass → phaeochromocytoma resected.

- *Malignant phaeochromocytoma with metastases to breast and bone*
Discussion

- Metastatic tumours involving the breast are rare.
- ~25% of metastatic tumours in the breast are the presenting manifestation of an otherwise occult extramammary malignant tumour, usually a lung carcinoma.
- Most common extramammary metastatic tumours include malignant melanoma, carcinomas from female genital tract, non-small cell lung carcinoma, neuroendocrine carcinomas from various sites (particularly carcinoid tumours) and haematolymphoid tumours.
- Malignant phaeochromocytoma metastasizing to the breast is extremely rare, and reported in a single case report in published literature.
FNA findings of a breast solid lesion

- **Primary “cellular” breast lesions**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Description</th>
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<tbody>
<tr>
<td>Epithelial hyperplasia of usual type</td>
<td>Absence of nuclear atypia and the presence of bare bipolar nuclei and myoepithelial nuclei.</td>
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<tr>
<td>Atypical ductal hyperplasia</td>
<td>Atypical features including focal crowding and overlap of nuclei, mild to moderate nuclear atypia.</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>Highly cellular, loss of cellular cohesion, atypical nuclei, single cells with intact cytoplasm. Bare bipolar nuclei and myoepithelial nuclei absent. Necrotic debris. Intracytoplasmic mucin vacuoles and intranuclear cytoplasmic invaginations.</td>
</tr>
<tr>
<td>Papillary lesions</td>
<td>Groups of cells with complex architecture and branching with finger-like processes.</td>
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Neuroendocrine lesions in breast

- Primary neuroendocrine breast carcinomas comprise 2-5% of breast tumours.
- Diffuse neuroendocrine differentiation c.f. focal neuroendocrine differentiation seen in 10 to 18% of usual (not otherwise specified) breast carcinomas.
- Cytological features are not unlike carcinoid tumours, particularly lung and GI origin, and other secondary neuroendocrine tumours.
Cytological features of breast neuroendocrine lesions

- Typically hypercellular aspirates.
- Dispersed population with loose aggregates and groups, rosettes or acinar pattern.
- Polygonal, spindled or myoid-like cells.
- Uniform, round to oval nuclei with inconspicuous nucleoli.
- Nuclear chromatin granular/stippled.
- Small amounts to scanty cytoplasm (small cell carcinoma)
- Background of capillary network (feathery pattern).
- Mucin production is also seen in 26% of neuroendocrine breast carcinomas.

**Phaeochromocytoma**
- May exhibit marked nuclear atypia.
- Distinct/prominent nucleoli.
- Intracytoplasmic inclusions and red granules in background due to fragmentation of cytoplasm (air dried preparations).
- Cytoplasm is usually fragile, finely granular and abundant with indistinct cell borders - lower N/C ratio c.f. other neuroendocrine tumours.
Immunohistochemistry on the cell block plays an important role in distinguishing these lesions, particularly primary from metastatic tumours.

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<tr>
<th>Primary breast lesions</th>
<th>Broad spectrum keratins, ER, PR, and GCDFP-15.</th>
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<tbody>
<tr>
<td>Primary and secondary neuroendocrine tumours</td>
<td>Neuroendocrine markers (synaptophysin, chromogranin, NSE and CD56). TTF-1 to exclude a lung primary, although bronchial carcinoids show variable expression of TTF-1.</td>
</tr>
<tr>
<td>Phaeochromocytoma</td>
<td>Negative for cytokeratins. Do not express ER, PR or GCDFP-15.</td>
</tr>
</tbody>
</table>
References

Case 4:

Presented by: Dr Kris Kerr, Sullivan Nicolaides Pathology, Brisbane

**FINE NEEDLE ASPIRATION OF PARATHYROID PARENCHYMA**

Their name says it all: the parathyroid glands are almost always located immediately adjacent to the thyroid gland. Whilst a normal parathyroid gland is usually less than 4 mm, there is some size overlap with a normal gland and a physiologically hyperactive gland, such that not all “enlarged parathyroid glands” occur in a setting of hyperparathyroidism or abnormal calcium metabolism. With high-resolution ultrasound imaging, the incidence of parathyroid incidentalomas has recently been estimated at 0.4%. In an era of readily available and frequently utilised imaging studies, radiologists are identifying lesions that they subsequently sample for cytological evaluation, with the clinical request stating “? thyroid nodule ? parathyroid”. This is a challenging area in cytopathology.

Most cytology texts acknowledge the significant cytomorphological overlap between thyroid and parathyroid parenchyma. Oft cited clues that favour the sampling of parathyroid parenchyma over thyroid parenchyma include dispersed epithelial cells and naked nuclei. Colloid and follicular structures on the other hand are said to favour thyroid parenchyma. These should not be absolute rules: for example, parathyroid glands may exhibit follicular structures with “colloid-like” material, and indeed the FNA may pass through colloid-rich thyroid parenchyma to reach the parathyroid gland. Those that sign-out endocrine histopathology will easily recall challenging cases where it has been very difficult to distinguish parathyroid from thyroid parenchyma and vice versa. Even Hurthle cell thyroid lesions are not spared, as a subset of parathyroid adenomata are composed of oxyphils, thus mimicking oncocytic thyroid nodules.

Some texts recommend correlating FNA findings with serum calcium/PTH studies, however not all enlarged parathyroid glands will manifest with hyperparathyroidism or serum calcium aberrancies.

In the event of a “cellular” cell block, immunohistochemistry may be informative, with parathyrocytes showing positive staining for PTH and chromogranin, whereas thyrocytes exhibit positive staining for TTF-1 and thyroglobulin.

In 2008, Christopher Owens et al published a paper which addresses this cytological conundrum. In this paper, he describes using the needle washout fluid to quantitate the level of parathyroid hormone present in the FNA material. If the sample has extracted thyroid parenchyma, the PTH level should be no higher than the serum PTH level (and will often be lower, given the dilution effect of the FNA washout fluid). In his study, if parathyroid parenchyma had been sampled, the rinsed fluid PTH level was at least three fold greater, and often several fold greater, than the serum level, even not taking into account the unavoidable dilution by the washout fluid.

Kwak et al determined that the diagnostic performance of FNA-PTH was excellent in their study: sensitivity of 93%, specificity of 100%, accuracy of 100%, PPV of 100% and NPV of 80%.

In several institutions, the cytopathologist is often not in control of whether an FNA is performed, and a broader issue is whether FNA of suspected parathyroid tissue should be undertaken at all. In their 2007 study, Norman et al demonstrated that FNA of parathyroid adenomata can cause severe local fibrosis, dramatically increasing the difficulty of surgical resection, often requiring
microdissection techniques to preserve nerves and assure complete removal. Furthermore, the fibrosis can cause confusing histological features that may mimic malignancy; so called WHAFFPT – worrisome histologic alterations following fine-needle aspiration of the parathyroid tissue. Two cases of FNA leading to seeding of parathyroid carcinoma along the needle track have also been reported.

To conclude, parathyroid and thyroid parenchyma show morphological overlap on cytological material. Biochemical analysis of the FNA washout fluid may assist in resolving this differential diagnosis. Performing an FNA on parathyroid parenchyma may lead to surgical complications and worrisome subsequent histology.

~ References ~

Kwak JY et al  Parathyroid incidentalomas detected on routine ultrasound-directed fine-needle aspiration biopsy in patients referred for thyroid nodules and the role of parathyroid hormone analysis in the samples  Thyroid  2009  Jul; 19(7): 743-8.


Norman J et al  Diagnostic aspiration of parathyroid adenomas causes severe fibrosis complicating surgery and final histologic diagnosis. Thyroid. 2007 Dec;17(12):1251-5


Agarwal, G et al  Implantation of parathyroid carcinoma along fine needle aspiration track Langenbecks Arch Surg  2006  Nov; 391(6).