Frozen section simulation of trabecular adenoma and medullary cancer by papillary thyroid carcinoma

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Abstract

Two patients are reported in whom initial misdiagnoses of medullary cancer or trabecular hyaline adenoma for papillary carcinoma were made.

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The spectrum of usual papillary cancer frozen section appearances includes, at one end, the swollen papillae pattern and, at the other, the trabecular and infiltrative pattern. Diagnostic problems, as in the cases presented, can be anticipated mainly among the infiltrative trabecular cases. It is proposed that the particular cytoarchitectural pattern (presented) in such cases depends on (1) the degree of tumour papillae compression by surrounding tissues or pathologies; (2) the extent of ischaemia and associated sclerosis; and (3) compared with paraffin wax sections the absence of tissue fixation.

Case reports

CASE 1

A 64 year old woman presented with a neck swelling, clinically diagnosed as a multinodular goitre. Diffuse nodularity and a fixed 15 mm mass in the left lower lobe were found at surgery. A whitish-grey biopsy specimen contained sweeping ribbons of innocuous

cuboidal cells (fig 1), prompting frozen section diagnoses of either medullary cancer or, as a remoter possibility, hyalinising trabecular adenoma. Thyroidectomy, node excision, and parathyroid gland sampling were performed. Paraffin wax sections prepared from routinely processed unfrozen tissue showed a typical papillary cancer (fig 1, inset) normal parathyroid, and lymph node. Frozen section review showed scattered nuclear pseudoinclusions (fig 1).

CASE 2

A 76 year old woman presented with hoarseness, dysphagia, and a 40 mm white lump in the right lower pole of the thyroid. An incisional white frozen section showed trabeculae of regular cuboidal cells in eosinophilic, hypocellular amyloid-like stroma suggesting medullary cancer (fig 2). Paraffin wax sections prepared from frozen tissues, allowed to thaw, showed sclerotic papillary thyroid cancer (fig 2, inset). Spaces between papillae were readily visualised after formalin fixation, permitting accurate diagnosis. Frozen section review identified occasional nuclear pseudoinclusions.

Discussion

Hürthle cell and follicular thyroid carcinomas are notoriously difficult to diagnose at frozen section.¹ Definitive diagnosis of anaplastic carcinoma often requires deferral to paraffin wax section.² Papillary cancer, with the exception of the follicular variant, is regarded as "diagnosable".³ Misdiagnosis of papillary as medullary cancer has not been recorded.

These cases show the problems in frozen section cytoarchitectural assessment of papillary thyroid tumours. Snap-freezing the central sclerotic stroma resulted in apparent compression of papillae and an endocrine-like ribbon pattern of palisaded medullary carcinoma (figs 1 and 2). Two patterns each of medullary and papillary carcinoma have been described in frozen sections.¹ The spindle cell pattern medullary carcinoma and the "swollen papillae" pattern papillary carcinoma can easily be recognised. The alternative infiltrative trabecular-type papillary carcinoma, in an almost acellular stroma (fig 2), caused confusion with amyloid-rich medullary cancer. It can be surmised that the two frozen section papillary cancer patterns represent ends of a spectrum: formalin fixation with shrinkage of tissues is required to bring out the papillary pattern in sclerotic,

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Figure 1 Case 1: frozen section. Sinuous compact trabeculae of uniform cuboidal cells with occasional nuclear inclusions (→). No papillae are seen. Inset: Formalin fixed, paraffin wax section. Open papillae lined by overlapping ground glass nuclei.

Figure 2 Case 2: frozen section. Compact trabeculae between amorphous "acellular" stroma (upper and centre) resembling amyloid. Inset: Paraffin wax section prepared from frozen material after brief formalin fixation. Papillary pattern and stromal cellularity is becoming evident as well as a pseudofollicle (lower centre).

cellular "infiltrative trabecular" cases; cystic, or partly cystic, papillary thyroid cancers comprising papillae which are widely separated can be recognised as such even at frozen section. Interestingly, in each of the cases described there was good reason for compression of the papillae: in case 1 tumour was circumferentially compressed by nodules of a multinodular goitre, and in case 2 expansion of the large tumour mass was resisted by tracheal cartilage, deeply, and limited soft tissues and skin of the neck, superficially.

Cellular anisocytosis was seen in paraffin wax sections in case 1, but was less obvious in the frozen sections which, together with hyalinisation, prompted an alternative diagnosis of trabecular hyaline adenoma. This can simulate either medullary or papillary cancer microscopically.⁴ Trabecular hyaline adenoma is less than 40 mm in diameter, and very often below 20 mm, yellow-tan, unlike most carcinomas, and, unlike most papillary carcinomas, these cases are encapsulated on microscopy.⁴ Surgeons should be requested to submit tissue from the edge of the mass to include the capsule, if present.³

The "acellular" eosinophilic stroma simulating amyloid in case 2 at frozen section (fig 2) contained scattered fibroblasts without congophilia in the paraffin wax section (fig 2, inset). Overinterpretation of compact central ischaemic sclerosis, demarcated by malignant cells as tumour amyloid in frozen sections, has not been recorded before. Ischaemia may cause endothelial superoxide radical release, fibroblast proliferation, and collagenisation in fibromatosis,⁵ and a similar pathogenesis could be envisaged here.

Of three reliable papillary cancer cytology patterns, the ground glass nuclear pattern, present in both cases, is easily recognised in paraffin wax sections⁶; it is either less obvious¹ or absent,⁷ as in the cases presented, at frozen section. Grooved nuclei were seen in case 1 only in the paraffin wax section. On review, nuclear pseudoinclusions were seen in both cases: they are the only feature reliably to withstand frozen section processing.⁶ Time is required to scrutinise frozen sections for such detail more easily seen in touch preparations.¹ Inclusions have been described in medullary cancer⁸ and hyaline adenoma, albeit rarely.³

Fine needle aspiration is more sensitive than frozen section for carcinoma, though less specific,⁹ and the techniques are now regarded as complementary.¹⁰ When an incidental tumour is found at surgery, lobectomy without frozen section has been advocated.³ Medullary and papillary cancers may be multifocal and involve local lymph nodes early; medullary tumours can be complicated by parathyroid hyperplasia and are unresponsive to radioiodine. Such considerations have a bearing on the extent of surgery, so it seems preferable to establish diagnosis before or at operation. Papillary cancer can be reliably diagnosed at frozen section in about 70% of cases (personal observations). In the remaining cases compression of tumour papillae by impingement on surrounding structures or established pre-existing pathologies may result both in ischaemic sclerosis and a misleading "trabecular cellular infiltrative" pattern, causing confusion with medullary cancer or trabecular adenoma. Deferral to paraffin wax section may then prove judicious, particularly as medullary cancer is also a great mimic with many cytoarchitectural variations.

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