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Pathology☆,◊

Pathologie

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The present guidelines are based on French and international guidelines for the management and diagnosis of pancreatic endocrine tumour.

1. General case: pathology examination of a surgical specimen with macroscopically visible tumour

Pathological examination of a surgical specimen should provide all the information required for description, diagnosis and classification of the tumour, as for any other pancreatic neuroendocrine tumour; it should also shed light on the type of tumour. It may also provide information suggesting a syndrome of familial predisposition to neuroendocrine tumours, if not previously suggested.

1.1. Reception and initial conservation

The specimen should preferably be transferred fresh, not fixed. Even without presently validated diagnostic, prognostic or theranostic indications, it is recommended to sample a fragment of tumour tissue and, if possible and if the type of resection allows it, of surrounding tissue, for cryopreservation [1]; procedures should follow the current technical guidelines. After initial examination, the specimen is fixed; to allow possible molecular biology analysis, acid fixatives should not be used; buffered formaldehyde is recommended [1].

1.2. Macroscopic examination

Macroscopic examination, of both the fresh and the fixed specimen, should at least provide the following informations: number of tumours, size of tumour (or tumours, if multiple), general characteristics (cystic, solid), extra-pancreatic extension (exceptional in insulinoma), relations to neighbouring organs and large peripancreatic vessels, resection margin status (especially in case of tumorectomy), and presence of regional lymph-node metastases [1]. This information is especially essential for TNM staging.

1.3. Microscopic diagnosis

1.3.1. Identification of the neuroendocrine status of the tumour

The morphologic and immunohistochemical information determining the neuroendocrine status of the tumour should be included in the pathology report. Insulinoma is usually a well-differentiated neuroendocrine tumour with highly typical morphology (monomorphic aspect of the proliferation, tumour cell characteristics, hypervascular stroma). Presence or absence of signs of angioinvasion and perineural invasion should be noted in the pathology report, along with resection margin status.

Immunohistochemical markers are indispensable to confirm the neuroendocrine nature of the proliferation [1]. For pancreatic neuroendocrine tumours, European guidelines recommend two markers, considered complementary: chromogranin A and synaptophysin [1]. The main technical details of the procedures used (manual or automated; nature, origin and dilution of primary antibodies; revelation system) should be included in

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☆ Hypoglycemia in non-diabetic patient.

◊ L'hypoglycémie chez le patient non diabétique.

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the pathology report, as well as any involvement in a quality assurance programme. Immunodetection results should figure in the report; the important point is to determine whether immunodetection was positive or negative; if positive, it is not mandatory to specify the percentage of positive cells since this information is of no clinical interest [1].

1.3.2. Identification of the type of neuroendocrine tumour

Certain histological signs, such as amyloid stroma, confirmed by additional Congo red or thioflavin T stainings, are very suggestive of insulinoma; they are not, however, specific or sensitive.

To confirm the diagnosis of insulinoma, insulin expression in the tumour cells can be explored by immunohistochemistry using one of the commercially available anti-insulin antibodies. This is important in multiple endocrine neoplasia 1 (MEN1). If such techniques are applied, procedures should be specified as above: manual or automated; nature, origin and dilution of primary antibodies; revelation system. Results should be detailed, with assessment of the percentage of positive cells. In insulinoma, insulin expression is usually found in most or all tumour cells; however, there may be false negatives, even when the clinical diagnosis is certain [2]. Alternative markers, and notably beta-pancreatic cell specific transcription factors, have not been validated for diagnostic use; the sensitivity and specificity of the commercially available antibodies have not been established in pathology.

1.3.3. Evaluation of malignancy

Although malignant insulinoma is rare, objective or predictive signs of malignancy should be systematically looked for, as in any pancreatic neuroendocrine tumour. Objective signs include extension to peripancreatic tissue (sign of local invasion) and lymph-node and/or other organ metastases; predictive signs include vascular emboli and perineural invasion, which are not sufficient to establish malignancy but are alarm signals calling for particular follow-up. Elevated histologic grade is of bad prognosis, even in the absence of objective signs of malignancy. Finally, like in any tumour, resection margin status should be specified.

1.4. Classification

Once diagnosed, the insulinoma should be classified according to current guidelines. The pathology report should at least include:

- histologic classification on the WHO 2010 system (Box 1); the equivalent WHO 2000 classification may be indicated in brackets (see Table 1 for the correspondences) [3];
- histologic grade, according to mitotic and Ki67 indices, following the ENETS consensus [4] and WHO 2010 guidelines [3]: the absolute values of these two indices, and not just the grade, should be entered in the report [3];
- pTNM stage: several TNM classifications have recently been published [4,5]; the 2006 European Neuroendocrine Tumor Society (ENETS) TNM classification uses a specific system; the 7th edition of the UICC classification (2009) classifies pancreatic neuroendocrine tumours in the same way as pancreatic adenocarcinomas; given the difference between these two systems, it is presently recommended to give both: TNM (UICC) and TNM (ENETS) [6]; if only one is used, it must be clearly stated which.

Box 1: WHO 2010 classification of neuroendocrine tumours of the digestive tract and pancreas.

- Neuroendocrine tumor, G1
- Neuroendocrine tumor, G2
- Neuroendocrine carcinoma
  - Small-cell type
  - Large-cell type
- Mixed adeno-neuroendocrine carcinoma

Table 1
Correspondence between WHO 2010 and 2000/2004 classifications.

WHO 2010	WHO 2000
Neuroendocrine tumor, G1	Well-differentiated endocrine tumour of benign behaviour; Well-differentiated endocrine tumour of uncertain behaviour, with mitotic index < 2 and Ki67 index ≤ 2%; Well-differentiated endocrine carcinoma, with mitotic index < 2 and Ki67 index ≤ 2%
Neuroendocrine tumor, G2	Well-differentiated endocrine tumour of uncertain behaviour, with mitotic index > 2 and/or Ki67 index > 2%; Well-differentiated endocrine carcinoma, with mitotic index and/or Ki67 index > 2%
Small-cell neuroendocrine carcinoma	Poorly differentiated small-cell carcinoma
Large-cell neuroendocrine carcinoma	No corresponding category
Adeno-neuroendocrine carcinoma	Mixed tumour

Most insulinomas are benign, well-differentiated tumours without signs of local invasion or metastatic dissemination and very low proliferation indices: they can therefore be classified as grade-1 neuroendocrine tumour on the 2010 WHO classification. Less than 10% are deemed malignant, due to regional and/or distant metastasis [2]. A very few are grade 2 or sometimes even grade 3 [2].

1.5. Other information

Associated lesions should be looked for in surrounding tissue if the type of resection allows:

- other endocrine or non-endocrine tumours, or;

- endocrine microadenomatosis, revealed by an increase in the number and size of pancreatic insular structures, although diameter remains less than 5 mm.

Such lesions suggest a syndrome of familial predisposition to pancreatic endocrine tumour, especially type-1 MEN syndrome: between 5% and 10% of insulinomas are associated with MEN-1 syndrome; they are usually multiple, and may be metastatic [2].

Von Hippel-Lindau (VHL) syndrome (associating cystic lesions and pancreatic serous (cyst) adenomas) has not been described as being associated with insulinoma or with other forms of secreting neuroendocrine tumour. Exceptional cases of insulinoma have been reported in association with Bourneville's tuberous sclerosis.

There is at present no validated immunohistochemical screening technique for these genetic syndromes.

Microadenomas are also characteristic of insulinomatosis, a rare recently described entity with no recognised genetic underpinning, in which all microadenomas express insulin, strongly and exclusively [7]. It may be associated with a definite tumour (insulinoma, by definition > 5 mm) or comprise only microadenomas < 5 mm in diameter.

2. Special case: recommendations in absence of tumour identifiable on pathology

When there is no macroscopically visible tumour, the entire specimen should be included, in thin sagittal cross-sections. It is important to point out, however, that a very small tumour is unlikely to underlie the clinical symptoms associated with hormonal hypersecretion: rare pathologies involving a diffuse increase in β-cell mass are more probably implicated. Thus, adult nesidioblastosis is found in 3–5% of adults with hyperinsulinism [8], with no identifiable tumour; abnormal Langerhans islets with hypertrophic β cells suggest such a diagnosis.

3. Specific diagnostic issues

3.1.1. Diagnostic biopsy

Histologic examination of a biopsy sample targeting the pancreatic tumour usually enables precise diagnosis. Histologic examination is always possible, even if interpretation may need to take account of certain artefacts related to the sampling procedure. The sample is suitable for immunohistochemical analysis to confirm the neuroendocrine status of the tumour and the diagnosis of insulinoma. It is not, however, possible to assess the macroscopic characteristics of the lesion, nor is it always possible to assess all of the parameters involved in precise classification and staging: notably, mitotic index can only be determined on samples of sufficient size, although Ki67 index can be determined for almost all samples, since it may be established from as few as 500 tumour cells.

3.1.2. Diagnostic fine-needle aspiration cytology

Fine-needle aspiration of pancreatic tumour, especially under endoscopic ultrasound guidance, usually enables diagnosis of neuroendocrine tumour. Immunohistochemical analysis can be performed under suitable conditions using the cytoblock technique: wash the needle contents in fixative fluid to allow inclusion and preparation according to conventional histological techniques. This technique can even determine the Ki67 index if the sample is large enough. However, it is never sure that the aspirated material is truly representative.

3.1.3. Diagnosis of metastasis

Insulinoma is rarely metastatic, making it especially important to determine the nature of a presenting metastasis or a metastasis associated with a primary pancreatic tumour with suggestive clinical syndrome. The most reliable route to diagnosis is to demonstrate insulin expression by the tumour cells.

3.2. Mandatory insulinoma specimen pathology report information

Type of resection. Macroscopic characteristics: number of visible tumours, size, local extension, resection margin status.

Diagnostic evidence:

- histology;
- immunohistochemistry: chromogranin A, synaptophysin.

Hormonal profile, if performed:

- histoprognostic factors:
  - vascular emboli,
  - perineural invasion,
  - mitotic index,
  - Ki67 index,
  - resection margin status;
- 2010 WHO classification (correspondence with 2000 WHO classification may be indicated);
- histology grade;
- TNM stage (clearly indicating which classification is used);
- associated peritumoral lesions.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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