

Case 1: Well Differentiated Breast Carcinoma (Peter Spieler)

Patient History

69year old female patient, 1993 with a benign lesion in the breast, now (2001) a new clinically cystic lesion (1.5x1cm), moveable, with slight indentation of the mamilla.

Patient was assigned by general practitioner to outpatient unit to perform a breast FNA.

Cytopathology

Here, the cytological diagnosis of malignancy is based on (importance declines in order): Chromatin pattern, nuclear polymorphism, isolated tumor cells with excentric cytoplasm, typical tumor cell formations (shape and border), cytoplasmic condensations, enlarged hyperchromatic nuclei.

Histopathology

See diagnosis.

DIAGNOSIS

C: Monomorphous (small cell) carcinoma of the breast (fairly well differentiated) with axillary lymph node metastasis

H: Well differentiated invasive ductulobular carcinoma of the breast and DCIS intermediate grade with microcalcifications pT1c, G1 (BRE Score 3,1,1)

In addition metastases measuring up to 1.4 cm in 3 from 10 axillary lymph nodes with infiltration of adjacent fatty tissue were found (Axilla level I and II).

Clues of cyto-histopathological correlation

Monomorphous (small cell) breast carcinomas count for about 5-10% of cytological diagnoses of carcinomas. A final cytological diagnosis of malignancy in these cases requests a highly cellular specimen. In our case the diagnosis was facilitated by the presence of a positive axillary lymph node puncture.

Discussion

If malignancy cannot be proven cytologically (insufficient criteria), the following differential diagnoses become relevant:

Intraepithelial neoplasia (CIS) of low grade type, sclerosing adenosis, radial scar, blunt (terminal) duct adenosis or microglandular adenosis.

Diagnostic procedure: If there is a sonographic equipment available, the clinical diagnosis of the palpable nodular mass should be confirmed, completed or corrected. In the actual case there was no typical cyst-like somorphology present, but an illdefined echo-poor area with a hypoechogenic shadow behind the lesion, a finding which is highly suggestive of malignancy. An extensive sampling by FNA is mandatory. In the present situation the axillary lymph nodes should be searched and punctured as well, again -if possible- guided by sonography.

Case 2: Lobular Carcinoma within a Fibroadenoma of the Breast (René Schönegg)

Patient History

87year old female patient with a tumor in the inner lower quadrant of the breast, measuring 4x3x2cm. Malignant? Senile dementia.

Slides from external FNA were sent in for diagnosis.

Cytopathology

The smears contain an overall rather small but regionally moderate amount of mostly isolated cells, sometimes arranged in small discohesive groups and rows. The nuclei are hyperchromatic, rather small, round to oval-shaped and now and then with irregular nuclear borders, dense and coarse to granular chromatin without significant nucleoli or some very small ones. Only few and excentric cytoplasm is present, containing some targetoid vacuoles. No myoepithelial cells are recognized. No stromal fragments.

Histopathology

See diagnosis.

DIAGNOSIS

C: Monomorphous carcinoma of the breast

H: Partially sclerosed fibroadenoma (5.5x3x2cm) with lobular carcinoma in situ and small focus of invasive lobular carcinoma (Ablatio mammae simplex).

Clues of cyto-histopathological correlation

The primary histopathological report revealed a partially sclerosed fibroadenoma. In consequence of the cytopathological diagnosis of a malignant tumor, several additional sections were made in which areas of a lobular carcinoma in situ and a small focus of an invasive lobular carcinoma were found. In the cytological smears no elements of a fibroadenoma were found. The puncture yielded an overall low cellularity which was probably due to the sclerosing nature of the fibroadenoma. The few cells however, were all malignant of type carcinoma.

Discussion

Carcinomas which arise within a fibroadenoma are very rare and are usually not suspected clinically and mammographically due to the lack of signs of malignancy. The mean age of these patients is usually higher compared to patients with inconspicuous fibroadenomas. Within fibroadenomas lobular carcinomas are more frequent than the ductal type with an in situ carcinoma being much more frequent than an invasive one. Fine needle aspirates from cellular fibroadenomas might show increased *intact single cells, nuclear enlargements, prominent nucleoli, moderate polymorphism and anisonucleosis of cellular elements*. In these cases an excision with histological examination of the nodule should be performed to rule out malignancy.

Case 3: Small Cell Carcinoma of Bronchus (Christine Egger/Rainer Kraft)

Patient History

59year old male patient with near total stenosis of the left superior lobe bronchus. Suspicious of central bronchial carcinoma in the upper lobe of the lung to the left. Sputum and bronchial washings.

Cytopathology

Adequate samples from sputum and bronchial brush and washings.

Histopathology

Bronchial biopsy (see diagnosis).

DIAGNOSIS

C 1. Adequate sampling with elements of squamous metaplasia and -dysplasia of the respiratory epithelium, without malignant neoplastic cells (*Sputum*)

C 2. Malignant neoplastic cells of type undifferentiated small cell carcinoma (SCCL) and elements of squamous meta- and dysplasia of bronchial epithelium (*Bronchial Brush and Washing*)

H: Undifferentiated small cell carcinoma with signs of neuroendocrine differentiation and high proliferative activity as well as foci of bronchial squamous meta- and dysplasia (biopsy of upper left lobe bronchus)

Clues of cyto-histopathological correlation

Foci of bronchial squamous meta- and dysplasia can be observed quite frequently in areas of bronchogenic carcinomas of all types and can serve as s.c. *indicator lesions*. Especially in exfoliative cytological material of airways (sputum, bronchial brush and washing fluid) in presence of a small cell carcinoma, indicator lesions might be easier to detect than the tumor cells themselves. For this reason the screening effort should specifically target possible paucicellular tumor elements when indicator lesions are present. If no tumor cells are found, a commentary to mention this circumstance and its practical relevance should be added to the descriptive diagnosis. Depending on the clinical situation further examinations are then indicated.

Discussion

An indicator lesion is a characteristic contextual cellular change that indirectly suggests another significant lesion. In cytopathology not only single cells are important but also their number, distribution or arrangement and neighbourhood as well as other accompanying changes and background morphology. Indicator lesions are especially useful in situations where tumor cells are difficult to find, degenerated or absent. Occasionally indicator lesions themselves request further investigations. In general *high cellularity, cellular monomorphism, mucus or necrosis/detritus* in the background should be considered to be indicator lesions.

Further examples are: -large flat sheetlike epithelial formations, multinucleated histiocytic elements and psammomatous calcifications in FNAs from the thyroid gland (papillary carcinoma); degenerated oncocytes or oxyphilic cells and oxyphilic "spheres" in FNAs from the parotid gland (Warthin's Tumor); numerous naked nuclei in FNAs from liver (hepatocellular carcinoma) or from salivary gland (acinus cell carcinoma); compact three-dimensional epithelial sheets in FNAs from prostate and so on.

Case 4: Oncocytic Follicular Adenoma of the Thyroid (Rainer Kraft/Christine Egger)

Patient History

55-year old female patient with hypoechogenic nodule of the thyroid (basal, left side), 1.5 cm in diameter. FNA sample from thyroid nodule.

Cytopathology

See diagnosis and clues.

Histopathology

See diagnosis and discussion.

DIAGNOSIS

C : Oncocytic tumor of the thyroid (Hürthle-cell tumor)

H: Oncocytic adenoma (Hürthle cell adenoma) of the thyroid (left) with central regressive changes

Clues of cyto-histopathological correlation

As a rule, oncocytic neoplasms of the thyroid are usually very cellular with little or absent colloid. A monomorphous population of large cells and isolated cells or loose cellular formations are observed with diminished cohesion in tissue fragments. Single cells are polygonal in shape, with extended finely granulated cytoplasm and distinct cell borders. The nuclei are eccentric with increased variation in size (anisonucleosis), granular chromatin and prominent nucleoli. There are no sufficient cytological criteria for distinguishing benign from malignant oncocytic neoplasms.

Differential diagnosis of Hürthle cell neoplasm of the thyroid includes

- *Focal oncocytic transformation (oncocytic metaplasia) of follicular cells within a nodular goiter (nodular hyperplasia)*
- *Graves' disease (M. Basedow)*
- *Hashimoto's thyroiditis (Autoimmunthyroiditis)*
- *Medullary carcinoma of thyroid, oncocytic variant (very rare)*

Discussion

Histopathology of oncocytic neoplasms of the thyroid:

- *oncocytic adenoma (Hürthle cell adenoma)*

- *oncocytic carcinoma (Hürthle cell carcinoma), micro- or macroinvasive (WHO 1988).*

Oncocytic neoplasms of the thyroid belong to the family of follicular neoplasms. The criteria to distinguish malignant from benign lesions equal the criteria used in common follicular neoplasms (angioinvasion and capsular infiltration).

Other lesions of the thyroid with oncocytes: *Chronic (autoimmune) thyroiditis, Graves' disease, nodular goiter (nodular hyperplasia).* *Oncocytes are also present after radio- and chemotherapy of the thyroid and in ageing and/or regressive changes.*

Regressive changes after the FNA procedure are more frequent in oncocytic neoplasias (adenoma/carcinoma) compared to other neoplasms of the thyroid. They include granulation tissue and inflammation, angiosarcoma-like proliferation of small blood vessels, fibrosis and scar formation after partial or total infarction and necrosis with hemorrhage. Pathogenesis: Probable trophic failure in encapsulated lesion due to edema and increased pressure in a closed compartment. Typically tumor infiltrates within the capsule are not affected.

Case 5: Metastatic Papillary Carcinoma of the Thyroid (Max Arnaboldi)

Patient History

33-year-old female patient with a cervical swelling (lateral neck) since 2 weeks, clinically suspicious of a lymphonodular enlargement. The family doctor included in her differential diagnosis a lateral branchial cleft cyst. FNA harvested 5 ml of amber coloured liquid. Excision and histological examination 1 month later.

Cytopathology

Cystic material with moderate cellularity. Clear to proteinaceous background, foam cells, hemosiderin-laden macrophages, lymphocytes. Little spherical epithelial fragments, with a smooth contour and palisaded nuclei, sometimes with psammoma bodies. No clearly viable papillary structures, no cytoplasmic nuclear inclusions, no linear grooves.

Histopathology

Lymph node metastases with typical growth pattern of papillary carcinoma. Some papillae with complex branching, some neoplastic follicles, typical nuclear changes.

DIAGNOSIS

C: Fine needle aspiration of a cervical lymph node, highly suggestive of metastatic papillary carcinoma of the thyroid

H: Lymph node metastasis of papillary carcinoma of the thyroid (Stadtspital Triemli, Zürich)

Primary: Multicentric papillary carcinoma of left thyroid (pT4)

Clues of cyto-histopathological correlation

(see also case 3 from Chr. Egger about indicator lesions). The typical 6 criteria of papillary carcinoma in cytology: *Papillary formations of atypical thyrocytes, nuclear vacuolation, nuclear grooves, crowding, three dimensional secondary structures, ground glass nuclei and psammoma bodies*. The cystic appearance with signs of residual hemorrhage, especially in lymph node metastasis, might dominate the picture while specific criteria are incomplete or missing.

Discussion

Papillary carcinoma is the most common type of thyroid cancer. Females are more affected than males (ratio 3:1). It can present in any age group, the mean age at the time of diagnosis being 31-38 years. Patients present with thyroid nodule alone in 67 percent and with cervical lymph nodes alone in up to 20 percent (1,2,3). A solitary cystic lateral mass simulating branchial cleft anomaly as first and sole presenting sign of the disease is somewhat less common, it is described in 6-8% of patients with thyroid carcinomas (4,5). Whereas marked cystic changes of the primary tumour are seen in about 10% of cases, they seem to be much more common in lymph nodes. However the cysts demonstrate the classical features of papillary carcinoma only in about 40% (5). In the remaining, you will find only focal papillae or nuclear features of papillary carcinoma.

References

1. Rosai J. Ackerman's Surgical Pathology, 8th Edition, Mosby, 1996
2. Rosai J, Carcangiu ML, DeLellis R. Tumors of the thyroid. Atlas of tumour pathology, third series, fasc. 5, Armed Forces Institute of Pathology, Washington D.C. 1992
3. Galera H, Gonzalez R, Bibbo M (Editor). Comprehensive Cytopathology, 2nd Edition, W.B. Saunders Company, 1997
4. Levy I, Barki Y, Tovi F. Cystic metastases of the neck from occult thyroid adenocarcinoma. Am J Surg 1992; 163: 298-300
5. Monchik JM, De Petris G, De Crea C. Occult papillary carcinoma of the thyroid presenting as a cervical cyst. Surgery 2001; 129: 429-32

Case 6: Metastasis of Squamous Cell Carcinoma (Max Arnaboldi)

Patient History

51-year-old male patient with, according to the radiologist, a "liquefied" left cervical lymph node. In his differential diagnosis he included a lateral branchial cleft cyst. Excision and histological examination 3 months later.

Cytopathology

Cystic material with high cellularity. Many structures suggesting epithelial pearls, many keratinized cells with or without nuclei, many "ghost" cells, many amorphous little fragments (micro-calcifications?), some multinucleated giant cells, some foam cells. No tadpole-like cells, no fibrocytes, practically no hyperchromatic or obvious atypical nuclei.

Histopathology

Metastatic keratinizing squamous cell carcinoma with marked cystic changes. Keratin plaques and keratin pearls, foam cells, multinucleated foreign-body giant cells. Basal cells and intermediate cells with marked dysplasia.

DIAGNOSIS

C: Fine needle aspiration of a cervical cyst with squamous cells (DD: lateral branchial cleft cyst, pilomatrixoma, epidermoid cyst)

H: Cervical lymph node with metastatic moderately differentiated keratinizing squamous cell carcinoma

Primary: Tonsillar carcinoma

Clues of cyto-histopathological correlation

Degenerated cellular elements should not be typed in cytology. Fragments of dead cells can suggest certain lesions in a differential diagnosis (see indicator lesions). An unequivocal (histologic-type) cytologic diagnosis is based on an intact nuclear morphology of an intact cell.

Discussion

Squamous cell carcinoma is the most common malignancy encountered in the head and neck area. Cystic changes in lymph nodes with metastatic squamous cell carcinoma are not uncommon (up to 17% in cervical/supraclavicular lymph nodes)(1). In patients with initial diagnosis of benign lateral branchiogenic/cervical cyst 10-17 percent turn out to have metastatic squamous cell carcinoma (2,3). The incidence of malignancy is significantly greater in patients older than 40 years (2). Cystic changes in lymph nodes harbouring metastatic squamous cell carcinoma are frequently (72%) associated with a tonsillar primary (lingual or faucial tonsil or nasopharyngeal tonsillar tissue) (4). The results of preoperative fine-needle aspiration are negative for malignancy in up to 66% of postoperative proven metastatic squamous cell carcinoma, and in up to 14% of fine needle aspiration of lateral cervical cyst (5).

Conclusion: Solitary cervical cysts in patients older than 40 years of age should be presumed to be metastatic carcinoma until proven otherwise.

References

1. Verma K, Mandal S, Kapila K. Cystic changes in lymph nodes with metastatic squamous cell carcinoma. *Acta Cytol* 1995; 39: 478-80
2. Gourin CG, Johnson JT. Incidence of unsuspected metastases in lateral cervical cysts. *Laryngoscope* 2000; 110: 1673-41
3. Flanagan PM, Roland NJ, Jones AS. Cervical node metastases presenting with features of branchial cysts. *J Laryngol Otol* 1994; 108: 1068-71
4. Thompson LD, Heffner DK. The clinical importance of cystic carcinomas in the neck: a study of 136 cases. *Cancer* 1998; 82: 944-56
5. Granstrom G, Edstrom S. The relationship between cervical cysts and tonsillar carcinoma in adults. *J oral Maxillofac Surg* 1989; 47: 16-20

Case 7: Poorly Differentiated Follicular Carcinoma of the Thyroid (Carlo Moll)

Patient History

69-year-old female patient with a large nodular goiter extending retrosternally. Suspicious mediastinal lymph nodes. FNA from left thyroid.

Cytopathology

Malignant cells with polygonal to round, rather polymorphic shapes, enlarged hyperchromatic nuclei, very few giant tumor cells. Few spindle-shaped neoplastic elements on a necrotic background with minimal inflammation. No elements of a lymph node.

Immunocytochemistry: Selected Thin Preps stained with Thyroglobulin revealed some positive tumor cells. Cytokeratin was heterogeneously expressed as well and Vimentin was coexpressed.

Histopathology

Extensively infiltrating poorly differentiated solid carcinoma with nodular growth pattern and abortive follicular formations (Tumorectomy). The immunohistochemical pattern was comparable to immunocytochemistry (above).

DIAGNOSIS

C: Malignant cells of type poorly differentiated follicular thyroid carcinoma

H: Poorly differentiated follicular carcinoma of the thyroid with extensive local infiltration (pT4 N1b M0)

Clues of cyto-histopathological correlation

Cytologically a progression into anaplastic carcinoma of the thyroid had been considered, from morphology and immunohistochemical coexpression of Vimentin and Cytokeratins. Expression of TG was very focal, in areas of recognizable abortive follicles.

Discussion

The cytologic diagnosis of *moderately (WHO)* and *poorly (WHO)* differentiated follicular thyroid carcinoma is straightforward. Difficulties arise with the appearance of oncocyctic variants. Malignant *well (WHO)* differentiated follicular neoplasias (well differentiated follicular carcinoma) cannot be distinguished from benign adenomas by cytology alone. The differentiation between follicular and papillary neoplasias is made by nuclear features exclusively. The texture of the cytoplasm is variable (inconspicuous small rimmed, large, oncocyctic etc.).

Reference:

DeMay RM: *The Art & Science of Cytopathology: Aspiration Cytology*. pp 726-728. ASCP Press (1996)
Horn A, Vosberg H and Wagner H: *Schilddrüse konkret*. 2. Auflage THIEME, Stuttgart und New York (1999)
Kini SR: *Color Atlas of Differential Diagnosis in Exfoliative and Aspiration Cytopathology*. pp 230-235 Williams & Wilkins, Baltimore (1999).

Case 8: Small Cell Lymphoid Neoplasia: Mantle Cell Lymphoma (Carlo Moll)

Patient History

86year old male patient with slowly growing cervical nodular enlargements. Malignant lymphoma? FNA of enlarged lymph node.

Cytopathology

Rather paucicellular aspiration sediment (Thin Prep) with unimorphous small to medium-sized lymphocytoid cells with slight irregular nuclear indentations in slightly enlarged nuclei and a narrow excentric perinuclear cytoplasmic rim resembling centrocytes/cleaved follicular centre cells (FCCs). The lack of polymorphism of the cellular population is evident. Tingible body macrophages are absent

Histopathology

Diffuse architectural effacement of the lymphonodular architecture and a monomorphic lymphoid proliferation with vague nodularity and mantle zone pattern. Pale hyalinised blood vessels. Typical IHC profile with positive *B cell markers, Cyclin D1 and CD5 positivity.*

DIAGNOSIS

C: Monomorphous small cell lymphocytoid population suggestive of mature B-cell neoplasia

H: Mantle cell lymphoma.

Clues of cyto-histopathological correlation

Of course an unequivocal and histology-type diagnosis of small lymphocytic lymphoma and associated neoplasias cannot be provided - but suggested. The most important criteria to differentiate a reactive from a neoplastic (small cell lymphoid) lymph node are:

Reactive

+ /+++ tingible body histiocytes
+ /+++ histiocytic groups
+ /+++ polymorphism (maturation)
+ /++ plasma cells
+ /+++ cellularity
round, smooth nuclear morphology

Neoplastic

- (except LL)
- /+
- /+
- /+ (except LPL)
+ /+++
enlarged, +/-irregular,
indented (cleaved)

Discussion

As a consequence a lymph node with a cytologic diagnosis of suspicious lymphoid neoplasia has to be excised and histologically sampled. Even in high grade (large cell and lymphoblastic) lymphomas a lymph node biopsy it is still necessary and standard procedure to type the malignant lymphoma on tissue slides, including immunophenotyping. Only as a crude diagnostic procedure or in a diagnostic emergency situation (e.g. acute upper congestion or incipient paraparesis), chemotherapy can be based on cytology and immunocytochemistry alone. In well fixed aspirates the differential diagnosis between a malignant lymphoma and an undifferentiated small cell carcinoma should be no problem.

Reference:

Jaffe SJ, Harris NL, Stein H and Vardiman JW (eds): Tumours of Haematopoietic and Lymphoid Tissues. World Health Organization Classification of Tumours: pp 168-170, IARC Press LYON (2001).

Case 9: Retroperitoneal Neuroendocrine Tumor (Paraganglioma) (Ivo Tosoni)

Patient History

60year old male patient with gastrointestinal discomfort, diarrhea and dehydration. Clinical diagnosis: Acute gastroenteritis (with positive stool cultures of Salmonella enteritidis). Incidental detection of a large interaortocaval retroperitoneal mass by ultrasound and CT scan ("Incidentaloma").

Additional Clinical Data

Abdominal ultrasonography and CT scan: Mass lesion measuring maximum 6.5 cm retroperitoneally at the level of the right-side hilum of kidney interaortocavally with no detectable connection with other organ structures Abdominal ultrasonography and CT scan for the rest inconspicuous (especially adrenal glands!). *Clinical differential diagnosis:* Paraganglioma, Lymphoma, Seminoma, Sarcoma

Cytopathology(1,2)

Pattern: Blood-rich smears with clearly dissociating, often loosely arranged cell connections, small groups of cells with alveolar and pseudoacinar arrangement; in the background many "naked" nuclei (cytoplasmic denudation); isolated ganglion-like cells; sustentacular cells (?)

Nuclear structure: Some marked variation in size; variable polymorphism; isolated scattered large bizarre nuclei; multinuclear cells in places; hyperchromatism with chromatin dense, finely granular or also "salt and pepper-like"; prominent, often central nucleoli; intranuclear inclusions

Cytoplasm: Fragile, loose appearance and not distinct; polygonal to fusiform; amphophilic to eosinophilic; granulation with globoid inclusions

Immunocytochemistry: LU5 negative; Chromogranin +; Synaptophysin +++; Vimentin +++; S-100-protein + (sustentacular cells).

Histopathology

See diagnosis and discussion.

DIAGNOSIS

C: Cell-rich neuroendocrine neoplasm, most likely paraganglioma (see ICC panel)

H: Paraganglioma

Clues of cyto-histopathological correlation

The case in question is a typical example of how, within the context of increasing interventional radiological investigation, fine-needle aspiration of retroperitoneal paragangliomas or pheochromocytomas takes place. Knowledge of the corresponding morphology and the *immunocytochemical profile* (3,4) is of primary diagnostic importance from the cytological point of view. Differential diagnosis between adrenocortical neoplasms, adrenomedullary neoplasms and metastases (clear-cell or oxyphilic carcinoma metastases!) solely on the basis of the morphology is cytologically difficult. In the case of a *cell-rich punctate with sufficient smears* (as in this case), the cytomorphological evaluation can therefore only be decisively optimized by means of an appropriate *immunocytochemical panel*.

Discussion

As yet, definitive evidence of malignancy of paragangliomas/pheochromocytomas is possible only through the detection of metastases (3). The significance of a possible malignant potential of a given paraganglioma/pheochromocytoma must be based on the definitive histology of the resected operation specimen.

References

1. R.K.Gupta, Y.K. Cheung, L. Wakefield, S.J. Wakefield, P. Johnson: Fine-needle aspiration cytology of malignant retroperitoneal paraganglioma, *Diagnostic Cytopathology* (1998) 18(4):287-290
2. R. S. Rana, P. Dey, A. Das: Fine needle aspiration (FNA) cytology of extra-adrenal paragangliomas, *Cytopathology* (1997) 8(2): 108-113
3. S. Schröder, P. Komminoth, B. Padberg and P.U. Heitz: Morphologische Typisierung, Dignitäts- und Prognosebeurteilung sowie aetiologische Einordnung adrenomedullärer und adrenokortikaler Neoplasien, *Pathologie* (1995) 16: 307-314
4. E. Achilles, B.-C. Padberg, K.Holl, G.Klöppel, S. Schröder: Immunocyto-chemistry of paragangliomas - value of staining for S-100-Protein and glial fibrillary acid protein in diagnosis and prognosis, *Histopathology* (1991) 18: 453-458.

Case 10: Signet Ring Cell Adenocarcinoma (Carlo Moll)

Patient History

85year old female patient with a tumorous mass at the right lateral pelvic wall, infiltrating the coecum. Ascites. Malignant? Typing? Smear from the sediment of ascitic fluid.

Cytopathology

Polymorphic epithelial "mesothelial-like" cells, building true secondary epithelial formations. Hyperchromatic homogenous to coarse chromatin, some nucleoli.

Histopathology

A variant of a paraffin section is presented, not from tissue but from a cellular pellet that was centrifuged from ascitic fluid. Especially from coagulated or clumped material the s.c. "cell block" can be used to cut series of sections to perform immunocytochemistry and thus represents an intermediate technique situated between cytology and histopathology. Small malignant tissue fragments with epithelial secondary formations surround polymerized fibrin and blood as well as reactive mesothelial elements.

DIAGNOSIS

C 1.: Malignant cells of type partly signet ring cell mucinous adenocarcinoma (Ascites)

C 2.: Cell block: Malignant cells and tissue fragments of a partly signet ring cell adenocarcinoma (Ascites)

H: Moderately to poorly differentiated partly signet ring cell adenocarcinoma at the site of colon coecum (biopsy thanks to Dr. Renata Flury, Winterthur)

Clues of cyto-histopathological correlation

Vacuolation of cells in cytological preparations, especially from fluids is very common but at a lesser extent significantly pathological or indicating malignant cells. Cytopempsis or passive uptake of watery content is optically "empty" or unstained, whereas mucinous substances or abortive secretory products usually are "thicker" and stainable (metachromatic to eosinophilic), see cover of this handout. The diagnosis of malignancy is never based on cytoplasmic but on nuclear changes.

Discussion

The primary site remains obscure, because there was no surface continuum from dysplastic to neoplastic tissue to prove it is a colon carcinoma, which still seems to be most likely. Further diagnostic interventions have not been performed because of the age and general status of the patient. The working title of this condition and stage is "*Metastatic adenocarcinoma of unknown primary origin*" (1).

To differentiate reactive mesothelials from malignant epithelial cells there are a couple of criteria: *bimorphic population without "intermediates", lack of "windowing" between cells in small secondary formations of truly epithelial cells, sometimes with abortive secretion pole and surface differentiation (e.g. typical globoid solid spheres in breast carcinoma).*

Immunocytochemistry: (Adeno-)carcinomas usually express the epithelial antigen BerEp4 and also CEA, mesothelials are not reactive. Important exception to the rule: Renal cell carcinomas are at a high percentage negative with BerEp4 and vice versa some malignant Mesotheliomas react positive with this antibody.

Reference

Hammar SP: *Metastatic adenocarcinoma of unknown primary origin*. Hum Pathol 29: 1393-402 (1998)

Case 11: HSIL (CIN III) of the Uterine Cervix (Carlo Moll)

Patient History

34-year old patient comes for a routine PAP smear, after having had a post partum PAP I finding 2 years ago.

Cytopathology

Extensive metaplasia with and without dysplasia is present. Squamous cells are mostly from the surface type. Dysplastic elements show a high N/C ratio with enlarged and slightly polymorphous nuclear forms, dense to coarse chromatin and some "pepper and salt" chromatin in one image with one naked nucleus. Some squamous intermediates with sign of HPV infection. An HPV-typing was not performed. The patient was immediately called for conization.

Histopathology

Short sector of severe dysplasia/carcinoma in situ with loss of the (metaplastic) squamous architecture within the T-zone. Numerous glandular structures beneath the lesion. In some sections small intraglandular dysplastic foci without invasion.

DIAGNOSIS

C: Moderate to severe dysplasia/carcinoma in situ (HSIL, eq. CINII-CINIII) of metaplastic squamous cells of the uterine cervix (s.c. metaplastic dysplasia). Signs of HPV infection.

H: Severe dysplasia/carcinoma in situ (CINIII) in transition zone of the uterine cervix.

Clues of cyto-histopathological correlation

The interpretation and grading of metaplastic dysplasia (of the s.c. T-Zone cells) might cause problems because of reactive hyperchromatic glandular cells and squamocolumnar junction cells with anisonucleosis and elevated N/C ratios. Metaplastic, squamocolumnar junction cells and dysplastic metaplastic cells can be distinguished by the regularity of tissue fragments and sheet formation. Syncytia with dyshesive cells with ill-defined cytoplasm and nuclei with moderate anisonucleosis, clumped or finely grained chromatin and enhanced chromocenters are typical for HSIL lesions of the T-zone.

Discussion

The entire lesion was hidden from colposcopy and measured only a few millimeters. If the endocervical fraction in a PAP exam is absent, the smear or the monolayer preparation has to be considered "satisfactory for evaluation but limited by absence of transformation zone component" according to the Bethesda System (1) for reporting PAP diagnoses.

Reference

Kurman RJ and Solomon D: *The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnosis*, Springer Verlag, New York, Berlin, Heidelberg (1994)
Kline TS and Nguyen G-K: *Critical Issues in Cytopathology*, Igaku-Shoin New York, Tokyo (1996)

Case 12: Papillary Urothelial Carcinoma of the Renal Pelvis (Carlo Moll)

Patient History

77year old male patient with hematuria. Suspicious pelvine irregularity of the right kidney. Sediment of pelvine washing fluid.

Cytopathology

Papillary sheets and dyshesive formations of enlarged, slightly irregular neoplastic urothelial cells besides reactive urothelials. In addition isolated urothelial cells are present with enlarged hyperchromatic nuclei and high N/C ratio, suggesting a flat component of a urothelial dysplasia and/or carcinoma in situ. Reactive pseudopapillary tissue fragments and formations represent regenerative (basaloid) deep non-neoplastic urothelial cells.

Histopathology

The slide in the set shows a here superficially infiltrating moderately differentiated papillary urothelial carcinoma (G2) with flanking urothelial (flat) dysplasia of the renal pelvis. In another section (not provided) there was extensive urothelial dysplasia and focal urothelial carcinoma in situ, extending into the ureter.

DIAGNOSIS

C: Malignant cells of type moderately differentiated papillary urothelial carcinoma and associated urothelial carcinoma in situ/urothelial dysplasia (renal pelvine washing)

H: Moderately differentiated papillary urothelial carcinoma (pT3 Nx G2) of the renal pelvis (nephrectomy left)

H: Associated urothelial dysplasia and carcinoma in situ of the ureter (in partial resectate left)

Clues of cyto-histopathological correlation

Diagnosis of well differentiated papillary tumors of the urothelium can be very difficult or nearly impossible (not here), especially in paucicellular washing specimen. In void urine the cells are usually degenerated by the toxic environment and difficult to interpret. Flat dysplasias/ carcinomas including the in situ carcinomas on the other hand reveal the classical criteria of malignancy (isolated cells with large hyperchromatic nuclei, high N/C ratio and polymorphism with irregular nuclear borders). The typical well differentiated papillary urothelial tumor or G1 carcinoma shows a highly cellular sediment with dyshesive feathery papillary sheets and three dimensional formations with isolated cells "dropping off". The enlarged nuclei are rather bright with distinct, slightly irregular nuclear cell borders and small chromocenters to several small nucleoli.

Discussion

The specificity and sensitivity of cytologic diagnoses of malignant neoplasias in therapeutic situations (recurrent tumor?) with marked reactive urothelial atypia due to therapy or in well differentiated papillary tumors with a morphology close to normal urothelial cells are low. They can be significantly enhanced by the FISH procedure for characteristic chromosomal aberrations of neoplastic cells (see Ref.).

Reference

Bubendorf L, Grilli B, Sauter G, Mihatsch MJ, Gasser TC and Dalquen P: Multiprobe FISH for enhanced detection of bladder cancer in voided urine specimens and bladder washings. Am J Clin Pathol 116:79-86 (2001).

Case *13: Chronic Lymphocytic Thyroiditis of Hashimoto Type (Carlo Moll)

Patient History

Extra case in reserve: 45year old female patient with multinodular enlargement of the thyroid, recently with increasing size (?). Adenoma? FNA from thyroid, left lobe.

Cytopathology

Trias: Lymphoid cells (few), some lymphoid blasts, oncocyctic change of follicular cells, pseudopapillary formations and some loss of cellular cohesion in tissue fragments.

Histopathology

Typical chronic lymphocytic thyroiditis with extensive oncocyctic change of the follicular epithelia and follicular damage with reactive focal hyperplasia. Some nodularity but no encapsulated neoplastic lesion.

DIAGNOSIS

C: Suspicious of follicular neoplasia, Hashimoto's to be ruled out.

H: Chronic lymphocytic thyroiditis (Hashimoto's thyroiditis). No follicular neoplasia present.

Clues of cyto-histopathological correlation

To rule out the differential diagnosis of a follicular neoplastic lesion of Hürthle cell type might be impossible by cytomorphological means alone if only few lymphocytes and/or plasma cells are present. It has to be mentioned that Hashimotos and neoplastic lesions of the thyroid can be associated and occur simultaneously. The serological identification of characteristic autoantibodies is helpful and should be suggested to the clinician, if not already done. A uninodular presentation of Hashimoto's would be highly unlikely.

Further differentials of Hashimotos might include *Graves disease and malignant Non-Hodgkins lymphoma in lymphoid rich findings with lymphoid blasts.*

Last not least

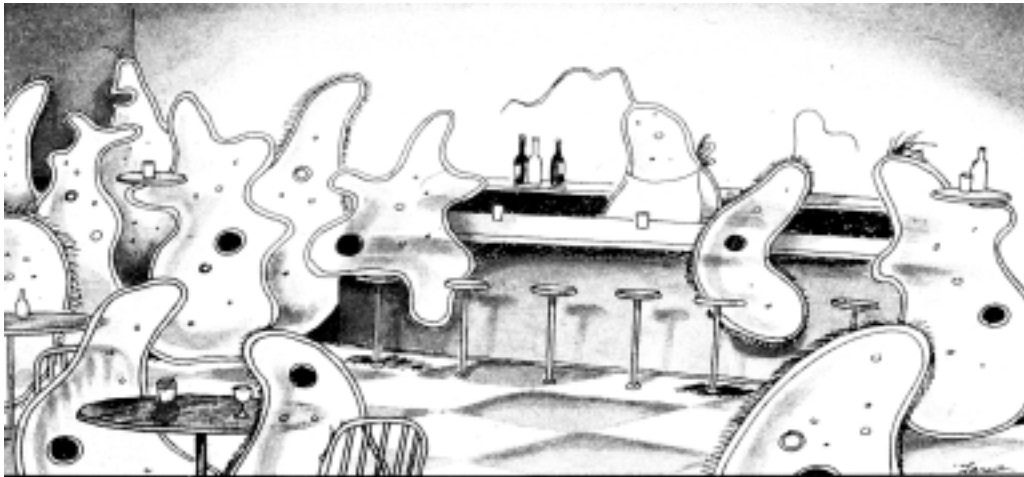
Thanks to the coauthors for their support and contributions and the thrilling experience to prepare this seminar. Thanks also to you participants for sending in your diagnostic proposals.

You have significantly contributed to the stimulating discussions. The next seminar will be about diagnostic pitfalls in cytology and histology in well documented cyto-histopathological correlations.

See you on the web at

<http://www.cyto-histo.ch>

Carlo Moll, January 26th 2002



Single-cell bars

G. Larson