

Distinctive immunohistochemical profile of mucinous cystic neoplasms of pancreas, ovary and lung

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Summary. Mucinous cystic neoplasms (MCNs) of the pancreas, ovary and lung have a similar histologic appearance. We investigated if immunohistochemical (IHC) studies could help in separating these neoplasms. Twenty-six ovarian MCNs (invasive carcinoma and borderline tumor), 12 pancreatic MCNs (invasive carcinoma, and with moderate or high-grade dysplasia), and 3 pulmonary MCNs (only invasive carcinoma) were retrieved. Our study demonstrated that pancreatic MCNs are positive for CDX-2 (67%), PDX-1 (100%), CK7 (83%) and CK20 (100%), while are negative for CA-125. The IHC profile of ovarian intestinal type MCN is similar to that of pancreatic MCNs, except for lower frequency of CDX-2 expression (29% vs. 67%). Ovarian endocervical like MCNs are positive for CA-125 (100%) and CK7 (100%), while are negative for CDX-2, PDX-1 and CK20. Pulmonary MCNs are positive for CDX-2 (100%), CK7 (100%) and CK20 (100%), while are negative for PDX-1 and CA-125. All tumors are negative for TTF-1, D2-40 and WT-1. We concluded that an IHC panel of CDX-2, PDX-1, CA-125, and CK20 is useful in separating MCNs of the pancreas, ovary and lung.

Key words: Mucinous cystic neoplasm, Lung, Pancreas, Ovary, Immunohistochemistry

Introduction

Mucinous cystic neoplasm (MCN) is much more common and best defined in the ovary (Scully et al., 1998; Lee et al., 2003) and pancreas (Thompson et al., 1999; Zamboni et al., 1999, 2000; Hruban et al., 2007) than those arising in the lung (Colby et al., 2004).

Pancreatic MCN accounts for approximately 2-5% of all exocrine pancreatic tumors (Thompson et al., 1999). Patients with pancreatic mucinous cystic adenocarcinoma are approximately 10 years older than patients with adenomatous or borderline tumors (MCN with moderate dysplasia) (54 versus 44 years), suggesting an adenoma - carcinoma sequence (Zamboni et al., 1999). The borderline ovarian MCN accounts for approximately 10% of mucinous ovarian tumors and 30 - 50% of ovarian epithelial borderline tumors (Scully et al., 1998). Patients with ovarian intestinal type MCN (MCN-I) are generally older than those with endocervical-like MCN (MCN-E) with an average age of 41 vs. 34 years old (Scully et al., 1998; Lee et al., 2003). All pancreatic and ovarian MCNs have similar histologic features, consisting of cysts lined by mucin-secreting cells and surrounded by ovarian-like stroma, which may result in difficulty in diagnosing the primary site of a metastatic lesion in especially core needle biopsy (CNB) or fine needle aspiration (FNA) specimens.

Pulmonary MCN like ovarian and pancreatic MCN can show a spectrum from mucinous cystadenoma, borderline to mucinous cystadenocarcinoma (Devaney et al., 1989; Graeme-Cook and Mark, 1991; Davison et al., 1992; Dixon et al., 1993; Nakamura et al., 1993; Roux et al., 1995; Tangthangtham et al., 1998; Monaghan et al., 2002; Gao and Urbanski, 2005). Pulmonary mucinous cystic adenocarcinoma (MCA) is very rare with less than 50 cases reported (Graeme-Cook and Mark, 1991; Davison et al., 1992; Dixon et al., 1993; Roux et al., 1995; Tangthangtham et al., 1998; Gaeta et al., 1999; Gao and Urbanski, 2005). It was first proposed as a distinct entity in 1989 (Devaney et al., 1989). It occurs in patients between 40 to 73 years old and involves both men and women (Nakamura et al., 1993; Tangthangtham et al., 1998; Gao and Urbanski, 2005). It is not certain if pulmonary MCA is related to smoking, since some patients are non-smokers. Pulmonary MCA is characterized by fibrous-walled cysts lined with

mucinous epithelium that can vary from benign features to malignant epithelium, histologically similar to the better-recognized counterparts in the ovary, pancreas and appendix (Nakamura et al., 1993; Tangthangtham et al., 1998; Monaghan et al., 2002). Following initial limited resection, mucinous cystic neoplasm of borderline malignancy can recur (Mann et al., 2001). Prognosis of pulmonary MCA is much better than conventional pulmonary adenocarcinoma (Devaney et al., 1989; Graeme-Cook and Mark, 1991; Davison et al., 1992; Dixon et al., 1993; Nakamura et al., 1993; Roux et al., 1995; Tangthangtham et al., 1998; Gaeta et al., 1999; Mann et al., 2001; Monaghan et al., 2002; Gao and Urbanski, 2005) and rare metastasis has been reported in the literature (Gao and Urbanski, 2005).

Organ specific transcription factors, such as TTF-1 and CDX-2, and differential cytokeratins, such as CK7 and CK20, have been widely used in identifying an adenocarcinoma of unknown site. Ovarian MCN was reported to express CDX-2, CK7 and CK20 (Wauters et al., 1995; Cathro and Stoler, 2002; Park et al., 2002; Werling et al., 2003; Kaimaktchiev et al., 2004). Pancreatic MCN is reported to be positive for CK7, CAM5.2, EMA and CEA (Bloomston et al., 2006). Varying expression of CDX-2 has been noted in acinar cells, islet of Langerhans cells (Jin and Drucker, 1996) and less than 32% of pancreatic adenocarcinoma (Silberg et al., 2000; Moskaluk et al., 2003; Werling et al., 2003; Kaimaktchiev et al., 2004), but it has not been reported if pancreatic MCN express CDX-2. Pulmonary MCA is reported to be positive for CK7 and CK20 with focal EMA positivity, and negative for CEA and chromogranin A (Monaghan et al., 2002). Based on the published data, it can be challenging to diagnose the primary site in a metastatic MCN with IHC stains.

Although the diagnosis of the site of a MCN is usually not difficult based on clinical history and radiographic studies, it can occasionally be challenging to exclude a metastatic MCN from a primary MCN due to their histological similarity. In this study, we investigated if immunohistochemical (IHC) studies could help in better classifying these neoplasms.

Materials and methods

Selection of cases

This study was approved by the institutional review board of Allegheny General Hospital, Pittsburgh, PA. In this study, 26 ovarian mucinous cystic neoplasms (MCN) consisting of 14 intestinal type (MCN-I) and 12 endocervical like (MCN-E) including borderline tumors and invasive carcinomas, 12 pancreatic MCNs (including MCNs with moderate and high-grade dysplasia, and invasive carcinomas) and 3 pulmonary MCNs (invasive carcinoma only) were evaluated. In the 3 patients with primary pulmonary MCN and 26 patients with ovarian MCN, no lesion was identified in other organs by computed tomography (CT) and magnetic

resonance image (MRI) studies at the time of surgery. The gross findings of the 3 pulmonary MCA are similar to the counterparts of pancreas and ovary.

Our clinical data showed that pancreatic MCN is more frequently seen in women than men with a ratio of 5:1. The average age of patients with pancreatic MCN is 46±15 years old with a range of 32-69 years old. Ovarian MCN affects women with an average age of 52±16 years old and a range of 21-74 years old. Pulmonary MCN affects both men and women with an average age of 60±12 years old and a range of 49-72 years old.

Pathologic evaluation and immunohistochemistry

Formalin-fixed (10% buffered formalin), routinely processed, hematoxylin and eosin-stained (H and E) tissue sections were evaluated independently by 2 pathologists (XL and YL).

Paraffin-embedded blocks were sectioned, deparaffinized, rehydrated, and blocked with methanolic 3% hydrogen peroxide. Antigen retrieval was performed in citrate buffer (pH 6.0). The immunostaining for CDX-2 (BioGenex, San Ramon, CA, catalog number: MU392-UC, mouse IgG1, 1:70 diluted), TTF-1 (DakoCytomation, Carpinteria, CA, catalog number: M3575, mouse IgG1, 1:100 diluted), PDX-1 (Santa Cruz Inc., Santa Cruz, CA, catalog number: ab47383, goat IgG, polyclonal, 1:80 dilution), CA-125 (DakoCytomation, Carpinteria, CA, catalog number: M3520, mouse IgG1, 1:20 dilution), CK7 (Cell Marque Inc., Hot Springs, AR, catalog number: CMA539, mouse IgG1, neat), CK20 (Ventana, Tucson, AR, catalog number: 760-2635, mouse IgG2a, neat), WT-1 (DakoCytomation, Carpinteria, CA, catalog number: M3561, mouse IgG1, 1:100 dilution), D2-40 (Signet, Dedham, MA, catalog number: 730-01, mouse IgG1, 1:50 dilution) on these slides were performed in an automated immunostainer with appropriate positive and negative controls. The detection was performed with Iview DAB detection kit (Ventana, Tucson, AZ, Catalog number: 760-091). It is classified as negative if either <5% of cells are positive for staining or the cells are weakly stained. All slides were counterstained with hematoxylin and then were evaluated independently by 2 pathologists (XL and YL).

Statistics

The stained slides were independently reviewed by 2 pathologists and the results were compared. Chi-square and Fisher test was used for statistical analysis.

Results

Distinct IHC profiles of MCNs of the pancreas, ovary and lung

In this study, we found that pancreatic MCNs were positive for CDX-2 (67%), PDX-1 (100%), CK7 (83%)

Mucinous cystic neoplasms' IHC profiles

and CK20 (100%), while were negative for CA-125, TTF-1, D2-40, and WT-1 (Table 1 and Figure 1). The IHC profile of ovarian MCN-Is was similar to that of pancreatic MCNs except for lower frequency of CDX-2 expression (29% vs. 67%). Ovarian MCN-Es were positive for CA-125 (100%) and CK7 (100%), while were negative for CDX-2, PDX-1, CK20-1, TTF-1, D2-40 and WT-1. The pulmonary MCNs were positive for

CDX-2 (100%), CK7 (100%) and CK20 (100%), while negative for TTF-1, PDX-1, CA-125, D2-40 and WT-1. Therefore, PDX-1 positivity of a MCN supported either a primary pancreatic MCN or an ovary MCN-I. Combination of a positive staining for CA-125 and negative staining for CK20 and CDX-2 supported a diagnosis of ovarian MCN-Es, but negativity for CA-125 and positivity for CK20 could not exclude ovarian MCN

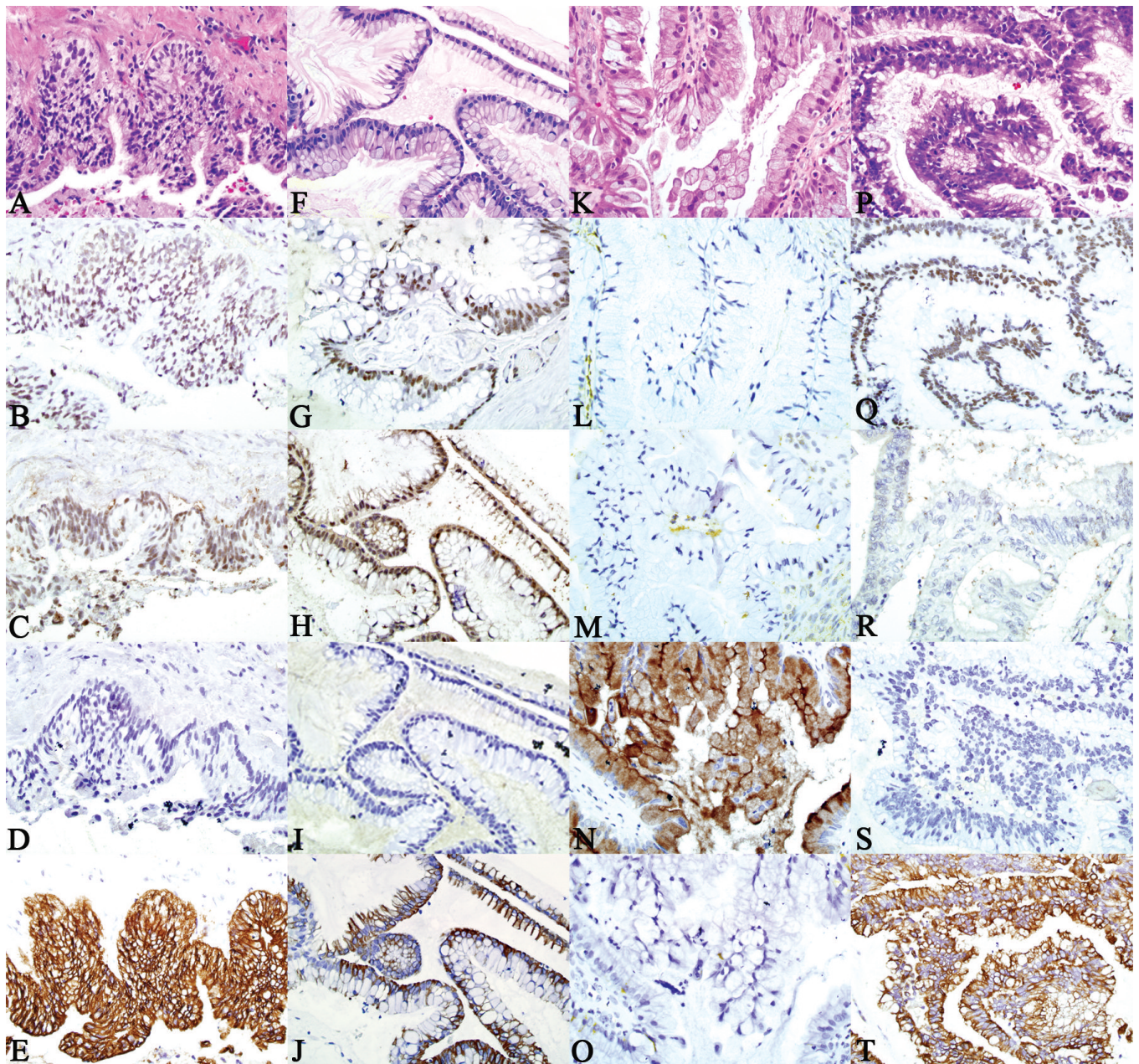


Fig. 1. Immunohistochemical results of the pancreatic, ovarian and pulmonary mucinous cystic neoplasms. Pancreatic MCN (A-E), ovarian intestinal type MCN (F-J), ovarian endocervical like MCN (K-O) and pulmonary MCN (P-T) with stains with H and E (A, F, K and P), CDX-2 (B, G, I and Q), PDX-1 (C, H, M and R), CA-125 (D, I, N and S), and CK20 (E, J, O and T). x 400

Table 1. Expression of IHC markers in MCNs of pancreas, ovary and lung.

MCN	No.	CDX-2	PDX-1	CA-125	CK7	CK20
Pancreatic MCN	12	8 (67%)*	12 (100%)*	0 (0%)	10 (83%)	12 (100%)*
Ovarian MCN-I	14	4 (29%)	14 (100%)*	0 (0%)	14 (100%)	14 (100%)*
Ovarian MCN-E	12	0 (0%)	0 (0%)	12 (100%)*	12 (100%)	0 (0%)
Pulmonary MCN	3	3 (100%)*	0 (0%)	0 (0%)	3 (100%)	3 (100%)*

MCN: mucinous cystic neoplasm; MCN-I: intestinal type MCN; MCN-E: endocervical like MCN. All tumors were negative for TTF-1, D2-40 and WT-1. *: P<0.01.

(ovarian MCN-I). CDX-2 was positive in all 3 pulmonary MCNs, the majority of pancreatic MCNs (67%) and only a minority of ovarian MCN-I (29%). Therefore, a combination of CDX-2 positive staining and PDX-1 and CA-125 negative staining supported a diagnosis of pulmonary MCN. This panel of IHC markers could not separate pancreatic MCN from ovarian MCN-I, suggesting that these two neoplasms had the same or very similar differentiation. Most pancreatic MCNs, all ovarian MCNs (MCN-Is and MCN-Es) and all pulmonary were positive for CK7 and all MCNs of the pancreas, ovary and lung were negative for TTF-1, D2-40 and WT-1. Therefore CK7, TTF-1, D2-40 and WT-1 are not useful in separating these neoplasms.

Discussion

Mucinous cystic neoplasms most commonly occur in the ovary, appendix and pancreas than in other organs, such as lung, liver, skin, prostate, retroperitoneum, bladder and breast (Hart and Norris, 1973; Albores-Saavedra et al., 1987; Dixon et al., 1993; Thompson et al., 1999; Zamboni et al., 1999, 2000; Honma et al., 2003; Lee et al., 2003; Colby et al., 2004; Bloomston et al., 2006) MCNs from all sites appear virtually identical to MCNs of the ovary and pancreas. Although the MCNs of various sites have similar histologic and cytologic features, our study shows that the IHC profiles of ovarian, pancreatic and pulmonary MCNs are different.

The diagnosis of primary MCN is usually not difficult based on the clinical history, imaging studies and histologic findings, but it can occasionally be challenging to identify the primary site of a metastatic MCA. In this study, we found that a panel of IHC markers of PDX-1, CA-125, CDX-2 and CK20 can help in separating pancreatic, ovarian and pulmonary MCNs. A MCN positive for PDX-1, CDX-2 and CK20 and negative for CA-125 is most likely either pancreatic MCN or an ovarian MCN-I. A MCN positive for CA-125 and negative for PDX-1, CDX-2 and CK20 is most likely ovarian MCN-E. A MCN positive for CDX-2 and CK20 and negative for PDX-1 and CA-125 is most likely of a pulmonary primary. Therefore, when a metastatic MCN of possible pancreatic, ovarian or pulmonary primary is suspected, the IHC panel (CDX-2,

PDX-1, CD-125 and CK20) is recommended in addition to comprehensive clinical and radiological findings in determining the primary site.

The pancreatic MCN and ovarian MCN-I show very similar histologic and cytologic features. In this study, we found that ovarian MCN-I expresses a similar IHC profile to that of pancreatic MCN, except for less frequent expression of CDX-2 (29% vs. 67%). These features suggest that these two neoplasms share the same differentiation. The reported frequency of CDX-2 expression in ovarian MCN is controversial in the literature, ranging from 10.5 - 64% (Moskaluk et al., 2003; Werling et al., 2003; Kaimaktchiev et al., 2004). But these published paper did not clarify the expression of CDX-2 in ovarian MCN-I or ovarian MCN-E. In this study, we found that CDX-2 was only expressed in the ovarian MCN-I (only 29%), but not in the ovarian MCN-E. We do not know the exact reason why the reported frequency of CDX-2 expression in the ovarian MCNs was so quite different. One possibility is misdiagnosis of a metastatic intestinal adenocarcinoma as primary ovarian MCN, as recently, it was found that nearly all tumors previously diagnosed as metastatic ovarian MCNs are instead metastatic mucinous carcinomas from extraovarian sites (Hart, 2005). Another possibility is the percentage of ovarian MCN-I versus MCN-E. Although previous reports showed low frequency of CDX-2 expression in pancreatic neoplasms (< 32%) (Silberg et al., 2000; Moskaluk et al., 2003; Werling et al., 2003; Kaimaktchiev et al., 2004), our data showed that pancreatic MCN has high frequency of CDX-2 expression (67%).

PDX-1, a transcription factor, is encoded by pancreatic duodenal homeobox 1 and required for the development and differentiation of duodenum and pancreatic exocrine and endocrine cells (Offield et al., 1996; Hui and Perfetti, 2002; Ashizawa et al., 2004). In adults, PDX-1 is expressed in islet beta cells, normal duodenal and colorectal epithelial cells as well as in pancreatic adenocarcinoma and mucinous cystic neoplasms (Ashizawa et al., 2004). In this study, we found that PDX-1 is expressed in 100% pancreatic MCNs and ovarian MCN-Is. Therefore, in our opinion PDX-1 is not an "organ-specific" transcription factor, and can be used as a sensitive marker of pancreatic MCN and ovarian MCN-I.

Primary pulmonary MCN exhibits distinctive pathologic features (Devaney et al., 1989; Cook and Mark, 1991; Davison et al., 1992; Dixon et al., 1993; Nakamura et al., 1993; Roux et al., 1995; Tangthangtham et al., 1998; Gaeta et al., 1999; Graeme-Mann et al., 2001; Monaghan et al., 2002). Pulmonary mucinous cystadenocarcinoma (MCA) shows a spectrum ranging from mucinous cystadenoma, borderline malignancy and mucinous cystadenocarcinoma, histologically similar to its counterparts of ovarian and pancreatic MCNs except for stroma (fibrous stroma vs. ovarian stroma), and different from other subtypes of pulmonary adenocarcinoma. Sufficient sections need to be submitted for evaluation similar to the pathologic work-up of pancreatic and ovarian MCN, as invasive carcinoma may be present only in a small area of the neoplasm. The distinctions between pulmonary MCA and cystic mucinous bronchioloalveolar carcinoma (BAC) or mucinous (colloid) adenocarcinoma with cystic degeneration can be challenging, especially in small specimens (such as core needle biopsy, fine needle aspiration and wedged biopsy). Mucinous BAC usually has a characteristic alveolar distribution with preservation of the lung architecture, and a lining by mucin-containing columnar cells without desmoplastic stromal reaction. Occasionally mucinous BAC can be multifocal in distribution, which is not seen in pulmonary MCN. Mucinous adenocarcinoma shows scant to abundant malignant glandular cells in the mucin, while pulmonary MCN shows abundant extracellular mucin with few malignant cells in the mucin. Cystic degeneration of mucinous adenocarcinoma contains necrotic debris and often is not lined by glandular epithelium, while the cysts of pulmonary MCN contain mucin rather than necrotic debris and are lined by mucin producing epithelium. A spectrum of changes from benign cystadenoma to cystadenocarcinoma has not been described in conventional pulmonary adenocarcinoma and mucinous adenocarcinoma, while pulmonary MCA can show a spectrum ranging from benign, borderline and malignant. Besides histological difference between pulmonary MCN from pulmonary mucinous adenocarcinoma or mucinous BAC, IHC can help in separating them. Mucinous adenocarcinoma is positive for TTF-1 (100%) (Tsuta et al., 2006). In this study, we found that all 3 pulmonary MCNs were negative for TTF-1. Mucinous BAC is reported to be positive for TTF-1 (0-67%) and negative for CDX-2 (Lau et al., 2002; Rossi et al., 2004; Saad et al., 2004; Simsir et al., 2004). In this study, we found that all 3 pulmonary MCNs were positive for CDX-2 and negative for TTF-1, in contrast to a recent study reporting that pulmonary MCNs are positive for TTF-1 (30%) and negative for CK20 (Gao and Urbanski, 2005). One possible reason for the discrepancy is the criteria that they used to define pulmonary MCN. Their criteria include mucinous (colloid) adenocarcinoma according to WHO classification, which is different from the criteria of WHO classification for pulmonary MCN (Colby et al.,

2004). Their cases include mucinous (colloid) adenocarcinomas based on their case descriptions. In addition, at least one case included in their study should be classified as signet ring cell adenocarcinoma according to WHO classification (Colby et al., 2004). Another possible explanation is that only 3 primary pulmonary MCNs were included in the current study due to rarity of the cases. From our current results, we believe that an IHC panel including CDX-2, TTF-1 and CK20 should be used in the work-up, when the differential diagnoses include pulmonary MCN, mucinous adenocarcinoma and mucinous BAC, especially in small biopsies. Considering the relative excellent prognosis of pulmonary MCA, these tumors should be distinguished from other subtypes of pulmonary adenocarcinomas.

In conclusion, although the MCNs of the pancreas, ovary and lung are histologically very similar, they express different IHC profiles of CDX-2, PDX-1, CA125 and CK20. This IHC panel can be helpful in separating them and identify the primary site once needed.

References

- Albores-Saavedra J., Angeles-Angeles A., Nadji M., Henson D.E. and Alvarez L. (1987). Mucinous cystadenocarcinoma of the pancreas. Morphologic and immunocytochemical observations. *Am. J. Surg. Pathol.* 11, 11-20.
- Ashizawa S., Brunnicardi F.C. and Wang X.P. (2004). PDX-1 and the pancreas. *Pancreas* 28, 109-120.
- Bloomston M., Chanona-Vilchis J., Ellison E.C, Ramirez N.C. and Frankel W.L. (2006). Carcinosarcoma of the pancreas arising in a mucinous cystic neoplasm. *Am. Surg.* 72, 351-355.
- Cathro H.P. and Stoler M.H. (2002). Expression of cytokeratins 7 and 20 in ovarian neoplasia. *Am. J. Clin. Pathol.* 117, 944-951.
- Colby T.V., Otori P., Noguchi M., Rami-Porta R., Henschke C., Franks T., Vazquez M.R., Schimosato Y., Geisinger K. and Matsuno Y. (2004). Adenocarcinoma. In: *Pathology and genetics: Tumors of the lung, pleura, thymus and heart.* Travis W.D., Brambilla E., Muller-Hermelink H.K. and Harris C.C. IARC Press. Lyon, France. pp 40.
- Davison A.M., Lowe J.W. and Da Costa P. (1992). Adenocarcinoma arising in a mucinous cystadenoma of the lung. *Thorax* 47, 129-130.
- Devaney K., Kragel P. and Travis W. (1989). Mucinous cystadenocarcinoma of the lung: A tumor of low malignant potential (abstr). *Am. J. Clin. Pathol.* 92, 524 (Abstract).
- Dixon A.Y., Moran J.F., Wesseliuss L.J. and McGregor D.H. (1993). Pulmonary mucinous cystic tumor. Case report with review of the literature. *Am. J. Surg. Pathol.* 17, 722-728.
- Gaeta M., Blandino A., Scribano E., Ascenti G., Minutoli F. and Pandolfo I. (1999). Mucinous cystadenocarcinoma of the lung: CT-pathologic correlation in three cases. *J. Comput. Assist. Tomogr.* 23, 641-643.
- Gao Z.H. and Urbanski S.J. (2005). The spectrum of pulmonary mucinous cystic neoplasia: a clinicopathologic and immunohistochemical study of ten cases and review of literature. *Am. J. Clin. Pathol.* 124, 62-70.
- Graeme-Cook F. and Mark E.J. (1991). Pulmonary mucinous cystic tumors of borderline malignancy. *Hum. Pathol.* 22, 185-190.
- Hart W.R. (2005) Mucinous tumors of the ovary: a review. *Int. J.*

- Gynecol. Pathol. 24, 4-25.
- Hart W.R. and Norris H.J. (1973). Borderline and malignant mucinous tumors of the ovary. Histologic criteria and clinical behavior. *Cancer* 31, 1031-1045.
- Honma N., Sakamoto G., Ikenaga M., Kuroiwa K., Younes M. and Takubo K. (2003). Mucinous cystadenocarcinoma of the breast: a case report and review of the literature. *Arch. Pathol. Lab. Med.* 127, 1031-1033.
- Hruban R.H., Pitman M.B. and Klimstra D.S. (2007). Mucinous Cystic Neoplasms. In: *Tumors of the pancreas*. Hruban R.H., Pitman M.B. and Klimstra D.S. (eds). American Registry of Pathology in Collaboration with the Armed Forces Institute of Pathology. Washington, DC. pp 51-74.
- Hui H. and Perfetti R. (2002). Pancreas duodenum homeobox-1 regulates pancreas development during embryogenesis and islet cell function in adulthood. *Eur. J. Endocrinol.* 146, 129-141.
- Jin T. and Drucker D.J. (1996). Activation of proglucagon gene transcription through a novel promoter element by the caudal-related homeodomain protein *cdx-2/3*. *Mol. Cell. Biol.* 16, 19-28.
- Kaimaktchiev V., Terracciano L., Tornillo L., Spichtin H., Stoios D., Bundi M., Korcheva V., Mirlacher M., Loda M. and Sauter G. (2004). The homeobox intestinal differentiation factor CDX2 is selectively expressed in gastrointestinal adenocarcinomas. *Mod. Pathol.* 17, 1392-1399.
- Lau S.K., Desrochers M.J. and Luthringer D.J. (2002). Expression of thyroid transcription factor-1, cytokeratin 7, and cytokeratin 20 in bronchioloalveolar carcinomas: an immunohistochemical evaluation of 67 cases. *Mod. Pathol.* 15, 538-542.
- Lee K., Tavassoli F., Prat J., Dietel M., Gersell D., Karseladze A., Hauptmann S. and Rutgers J. (2003). Surface epithelial-stromal tumors. In: *Pathology and genetics: Tumors of the breast and female genital organs*. Tavassoli F.A. and Devilee P. (eds). IARC Press. Lyon, France. pp 124-129.
- Mann G.N., Wilczynski S.P., Sager K. and Grannis F.W. Jr (2001). Recurrence of pulmonary mucinous cystic tumor of borderline malignancy. *Ann. Thorac. Surg.* 71, 696-697.
- Monaghan H., Salter D.M. and Ferguson T. (2002). Pulmonary mucinous cystic tumour of borderline malignancy: a rare variant of adenocarcinoma. *J. Clin. Pathol.* 55, 156.
- Moskaluk C.A., Zhang H., Powell S.M., Cerilli L.A., Hampton G.M. and Frierson H.F. Jr (2003). *Cdx2* protein expression in normal and malignant human tissues: an immunohistochemical survey using tissue microarrays. *Mod. Pathol.* 16, 913-919.
- Nakamura H., Tanaka Y., Hori H., Ishiguro S., Hara H. and Mori T. (1993). A case of mucinous cystic adenocarcinoma of the lung with signet-ring cells. *Kyobu. Geka.* 46, 990-993.
- Offield M.F., Jetton T.L., Labosky P.A., Ray M., Stein R.W., Magnuson M.A., Hogan B.L. and Wright C.V. (1996). PDX-1 is required for pancreatic outgrowth and differentiation of the rostral duodenum. *Development* 122, 983-995.
- Park S.Y., Kim H.S., Hong E.K. and Kim W.H. (2002). Expression of cytokeratins 7 and 20 in primary carcinomas of the stomach and colorectum and their value in the differential diagnosis of metastatic carcinomas to the ovary. *Hum. Pathol.* 33, 1078-1085.
- Rossi G., Murer B., Cavazza A., Losi L., Natali P., Marchioni A., Migaldi M., Capitanio G. and Brambilla E. (2004). Primary mucinous (so-called colloid) carcinomas of the lung: a clinicopathologic and immunohistochemical study with special reference to CDX-2 homeobox gene and MUC2 expression. *Am. J. Surg. Pathol.* 28, 442-452.
- Roux F.J., Lantuejoul S., Brambilla E. and Brambilla C. (1995). Mucinous cystadenoma of the lung. *Cancer* 76, 1540-1544.
- Saad R.S., Cho P., Silverman J.F. and Liu Y. (2004). Usefulness of *Cdx2* in separating mucinous bronchioloalveolar adenocarcinoma of the lung from metastatic mucinous colorectal adenocarcinoma. *Am. J. Clin. Pathol.* 122, 421-427.
- Scully R., Roung R. and Clement P. (1998). Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Armed Forces Institute of Pathology. Washington, DC. pp 23.
- Silberg D.G., Swain G.P., Suh E.R. and Traber P.G. (2000). *Cdx1* and *cdx2* expression during intestinal development. *Gastroenterology* 119, 961-971.
- Simsir A., Wei X.J., Yee H., Moreira A. and Cangiarella J. (2004). Differential expression of cytokeratins 7 and 20 and thyroid transcription factor-1 in bronchioloalveolar carcinoma: an immunohistochemical study in fine-needle aspiration biopsy specimens. *Am. J. Clin. Pathol.* 121, 350-357.
- Tangthangtham A., Chonmaitri I., Tungsagunwattana S. and Charupatanapongse U. (1998) Mucinous cystadenocarcinoma of the lung. *J. Med. Assoc. Thai.* 81, 794-798.
- Thompson L.D., Becker R.C., Przygodzki R.M., Adair C.F. and Heffess C.S. (1999). Mucinous cystic neoplasm (mucinous cystadenocarcinoma of low-grade malignant potential) of the pancreas: a clinicopathologic study of 130 cases. *Am. J. Surg. Pathol.* 23, 1-16.
- Tsuta K., Ishii G., Nitadori J., Murata Y., Kodama T., Nagai K. and Ochiai A. (2006). Comparison of the immunophenotypes of signet-ring cell carcinoma, solid adenocarcinoma with mucin production, and mucinous bronchioloalveolar carcinoma of the lung characterized by the presence of cytoplasmic mucin. *J. Pathol.* 209, 78-87.
- Wauters C.C., Smedts F., Gerrits L.G., Bosman F.T. and Ramaekers F.C. (1995). Keratins 7 and 20 as diagnostic markers of carcinomas metastatic to the ovary. *Hum. Pathol.* 26, 852-855.
- Werling R.W., Yaziji H., Bacchi C.E. and Gown A.M. (2003). CDX2, a highly sensitive and specific marker of adenocarcinomas of intestinal origin: an immunohistochemical survey of 476 primary and metastatic carcinomas. *Am. J. Surg. Pathol.* 27, 303-310.
- Zamboni G., Scarpa A., Bogina G., Iacono C., Bassi C., Talamini G., Sessa F., Capella C., Solcia E. and Rickaert F. (1999). Mucinous cystic tumors of the pancreas: clinicopathological features, prognosis, and relationship to other mucinous cystic tumors. *Am. J. Surg. Pathol.* 23, 410-422.
- Zamboni G., Longnecker D., Kloppel G., Adler G. and Hruban R. (2000). Mucinous cystic neoplasms of the pancreas. In: *Pathology and genetics: Tumors of the digestive system*. Hamilton S.R. and Aaltonen L.A. (eds). IARC Press. Lyon, France. pp 234-236.