

論文の内容の要旨

Comprehensive histopathological and immunohistochemical analysis of ovarian mucinous tumors

(卵巣粘液性腫瘍の発生と進展に関する病理組織学的検討)

Sultan Ahmad Halimi

スルタン アハメド ハリミ

Mucinous tumors is one of the major histological subtypes of ovarian epithelial neoplasms along with other subtypes such as endometrioid, clear cell and serous. According to the current WHO classification, ovarian mucinous tumors have been classified into mucinous cystadenoma (MA), mucinous borderline tumor (MBT), and mucinous adenocarcinoma (MCa). Majority of these tumors are benign or cystadenomas. Only 20% of these tumors are borderline, non-invasive (intraepithelial or intraglandular) carcinomas, and invasive carcinomas. The interpretation of these tumors is usually difficult for surgical pathologists, since the histogenesis, immunophenotype, and diagnostic criteria of these tumors are controversial. Among these tumors, MBTs are further subclassified into intestinal-type mucinous borderline tumor (IMBT) and endocervical-type mucinous borderline tumors (EMBT). These two subtypes of MBTs are significantly different in clinicopathological behavior. Their distinction is usually difficult on histological examination. However, such distinction is usually not made for MAs and MCa. In addition, the MBTs have been given a variety of names in the past literature, and there is certain confusion with regard to their nomenclature. Differential diagnosis of ovarian mucinous carcinoma is also problematic. They are usually difficult to distinguish from non-mucinous ovarian carcinomas, and also from those tumors metastatic to the ovaries. The histogenesis of mucinous tumor has been controversial and different theories have been previously suggested. However, it is unclear, from where the gastrointestinal-type mucinous epithelium of the ovarian mucinous tumors initially arise.

In this study, we analyzed consecutive cases of ovarian mucinous tumors (MA, MBTs and MCa), resected at the University of Tokyo Hospital from 1984-2013. In addition, variety of benign teratomatous and metaplastic mucinous ovarian lesions, non-mucinous ovarian lesions, and normal Müllerian duct derivative were also analyzed immunohistochemically.

This work consists of three independent studies:

In the first study, we attempted to analyze the phenotypes and directions of differentiation of mucinous epithelium that constitutes MBTs, including IMBTs and EMBTs by immunohistochemistry. We studied 79 cases of MBTs including IMBTs (n=54) and EMBTs (n=25). For comparative analysis we have also added 22 cases of serous borderline tumors (SBTs) to the series. A panel of antibodies that included gastric differentiation markers (claudin-18 [CLDN18], MUC5AC, and MUC6), intestinal markers (MUC2 and CDX2), Müllerian markers (ER, PgR, CA125, and vimentin), and cytokeratins (CK7 and CK20) has been applied. Special attention was paid to the expression of CLDN18, one of the claudins that constitutes a family of 27 proteins essential for the formation of tight junctions, and the maintenance of polarity in epithelial, and endothelial cells. Our immunohistochemistry results demonstrated, that the CLDN18-positive immunophenotype is specifically observed in IMBTs, but not in EMBTs or SBTs. Other gastric marker, MUC5AC, which is also expressed in normal gastric foveolar epithelium, was also frequently expressed in IMBTs, supporting gastric-type differentiation of epithelium of the IMBTs. Expression of Müllerian markers was negative in IMBTs, while it was expressed in all EMBTs and SBTs. The expression of intestinal markers such as CDX2, MUC2 and CK20 were expressed focally in IMBTs, but not in EMBT and SBTs. Based on the results of this study, we conclude that intestinal-type mucinous borderline tumors are essentially composed of gastrointestinal-type mucinous epithelium, the predominant component of which is gastric rather than intestinal-type epithelium. This notion coincides with the morphological assessment of IMBTs by us and other researchers who also considered that most mucinous epithelium in IMBTs resembles foveolar-type gastric epithelium. Therefore, we proposed abandoning the conventional nomenclature “intestinal-type mucinous borderline tumor” and replacing it with “gastrointestinal-type mucinous borderline tumor” to avoid further confusion. Our immunohistochemical panel highlighted the differences between EMBTs and IMBTs. Lastly, similarities between EMBTs and SBTs have also been found from the morphological and immunohistochemical points of view.

In the second study, we analyzed ovarian mucinous carcinomas (MCa). Unlike MBTs, they have not been clearly subclassified into intestinal or endocervical subtypes. However, due to its histological features, most of these tumors considered as intestinal-type mucinous carcinomas (IMCas). These tumors are chemoresistant and have poor prognosis especially, when they present in advance stages. Since we suspected gastric-type differentiation of the epithelium of IMCas, we attempted to investigate the expression of gastric marker (CLDN18) in these tumors, and also to determine the utility of CLDN18 immunohistochemistry in distinguishing IMCas and other subtypes of non-mucinous ovarian carcinomas. In this study, we studied a large series of ovarian cancers that include: IMCa (n=19), clear cell carcinoma

(CCCa)(n=95), endometrioid carcinoma (EMCa)(n=38), high grade serous carcinoma (HGSCa)(n=58), and low grade serous carcinoma (LGSCa)(n=11).

Our result showed that CLDN18 is specifically expressed in IMCas. In contrast, almost all other subtypes of non-mucinous ovarian carcinomas were CLDN18 negative ($p < 0.0001$). After we realized that CLDN18 is a specific marker for IMCas, we attempted to investigate the utility of CLDN18 expression in distinction between IMCas and metastatic colorectal carcinomas (CRCs) involving the ovary. Metastatic CRC is one the most frequent extra-genital mucinous carcinoma that often metastasizes to the ovaries. Since, metastatic CRCs morphologically simulating IMCa, their distinction is often problematic. We performed immunohistochemistry for CLDN18, as well as other conventional markers such as MUCs (MUC2 and MUC5AC), Cytokeratins (CK7 and CK20), CDX2 and ER in IMCas (n=19) and metastatic CRCs (n=16) in the ovary. The overall objective was to establish a panel of markers which is useful for differential diagnosis between these two lesions.

Our results showed that unlike IMCas, nearly all CRCs metastatic to the ovary were completely CLDN18 negative with two exceptional cases, that revealed focal positivity ($p < 0.0001$). Therefore, we purpose CLDN18 as a novel marker which is useful in distinguishing IMCas from other non-mucinous ovarian primary carcinomas, and also from metastatic colorectal carcinomas involving the ovary. In addition, in this study, frequent expression of the gastric markers (CLDN18 and MUC5AC) with focal expression of intestinal markers (CK20, CDX2 and MUC2) observed in IMCas suggesting gastrointestinal phenotype of IMCas.

In the third study, we analyzed a large series of mucinous cystadenomas (MAs). Our aim was to elucidate the direction of differentiation of mucinous epithelium that constitutes MA and also to determine the histogenesis of gastrointestinal-type mucinous epithelium that arise in the ovary. We specifically sought for the possible histogenetic relationships between gastrointestinal-type mucinous epithelium and Müllerian-type epithelium in the ovary. Because we believed that CLDN18-positivity is the hallmark feature of gastrointestinal-type ovarian neoplasms, we attempted to determine their histogenesis by clarifying the distribution of CLDN18-positive gastric-type mucinous epithelium in variety of benign and metaplastic mucinous ovarian lesions, such as teratomatous, and metaplastic mucinous epithelium in Brenner tumor, and normal Müllerian duct derivatives. In this study of 139 cases of MAs, 14 cases coexisted with teratoma, 6 cases were in coexistence or with transition from endometrial cyst, 2 cases coexisted with endometriosis and one case coexisted with Brenner tumor. We performed immunohistochemistry for CLDN18 (as a gastric marker), CDX2 (as an intestinal marker) and ER (as a Müllerian marker) in all cases of MAs. Other benign lesions such as teratomatous mucinous

epithelium (n=13), metaplastic mucinous epithelium in Brenner (n=3) and metaplastic mucinous epithelium in endometrial cyst (n=5) and other non-mucinous lesions and Müllerian duct derivatives were stained with CLDN18 only.

According to our results, MAs consists of two different subtypes: gastrointestinal-type and Müllerian-type. Most of the MAs were gastrointestinal-type, characterized by CLDN18 and CDX2 expression (93%). The Müllerian variant was rare and showed CLDN18-/CDX2-/ER+ immunophenotype (6%). CLDN18-positivity of gastrointestinal-type MAs suggests that those tumors are a part of the ovarian gastrointestinal-type tumor spectrum. We considered, gastrointestinal-type MA as a benign subtype of gastrointestinal-type mucinous tumor category. The existence of CLDN18-positive mucinous epithelium in mature cystic teratomas and metaplastic epithelium in Brenner tumors, along with CLDN18 expression in nearly all MAs associated with mature cystic teratomas and Brenner tumors, support the hypothesis that the origin of gastrointestinal-type mucinous neoplasms of the ovary maybe these lesions. In addition, we found transitional areas between gastrointestinal-type epithelium (CLND18+/CDX±/ER-) and Müllerian-type epithelium (CLND18-/CDX-/ER+) of MA in 12 cases which is suggestive of possible histogenetic relationships between these two types of epithelium. This result suggests that a minor subset of gastrointestinal-type MAs is derived from Müllerian duct derivatives, such as endometriosis, through a metaplastic/neoplastic process.