Letter to the Editor

Invasive hydatidiform mole of the lung with an implantation site intermediate trophoblast: Report of a case supporting the pathways of trophoblast differentiation
To the Editor:

An invasive hydatidiform mole is a type of hydatidiform mole in which molar villi invade the myometrium, cervical stroma, or uterine vasculature, which in rare cases can metastasize to extrauterine sites. The lung is the most frequent site of metastasis, although reports of the prevalence of pulmonary metastasis following complete hydatidiform mole range from 4 % to 65 % in the literature.¹ However, intermediate trophoblastic differentiation of molar villi in ectopic sites has not been clearly described, as current treatments are determined based on FIGO staging and risk scores, and metastatic lesions are rarely biopsied or histologically confirmed. Recently, we encountered a case of multiple lung metastases in a 34-year-old woman with a history of complete hydatidiform mole, which revealed an association between the villous and extravillous trophoblast in an extrauterine environment.

This patient had been diagnosed one year earlier with an intrauterine complete hydatidiform mole (CHM) at gestational week 11. During follow-up, her levels of serum β -hCG continually increased to ultimately reach 20,300 mIU/uL and she was found to have multiple lung nodules. Chest computed tomography revealed multiple well-defined 0.3 to 1 cm nodules in the left-upper, left-lower, and right-lower lobes. A total of four pulmonary nodules were biopsied.

The pulmonary nodules were well demarcated from the surrounding normal lung parenchyma. All nodules exhibited a centrally located single hydropic molar villus that was surrounded by a thick amorphous eosinophilic fibrinoid layer and blood clots in the pulmonary stroma (Fig. 1a). In two of the nodules, cleft-like free spaces were observed around the villi, which resembled the lacunar space at the normal implantation site of the endometrium or intervillous space (Fig. 1b). There were also focal direct attachment sites to the surrounding fibrinoid layer (Fig. 1c). The molar villi were lined by a single layer of inner cytotrophoblast and outer syncytiotrophoblast in those areas that faced the cleft-like free space (Fig. 1b), but at the site of attachment to the fibrinoid layer, no syncytiotrophoblastic layer was identified over the cytotrophoblast (Fig. 1c). Scattered individual trophoblasts were present within the fibrinoid layer (Fig. 1d), which had a single, round to ovoid nucleus, a conspicuous nucleolus, and abundant amphophilic cytoplasm, which is characteristic of implantation site intermediate trophoblasts (IT). The cytotrophoblast and villous stromal cells of the molar villi lacked immunoreactivity for p57^{kip2} (1:250 dilution, Neomarker,

Fremont, CA, USA), in contrast to that of cytotrophoblast and villous stromal cells of normal chorionic villi, which served as positive controls. These observations confirmed the diagnosis of CHM. The individually scattered IT in the surrounding amorphous fibrinoid layer showed immunoreactivity for CD146 on the cytoplasmic membrane (1:1000, Novocastra, Newcastle, UK) and for inhibin in the cytoplasm (1:100, Serotec, Oxford, UK). The proliferative activity of IT, as defined by Ki-67 immunoreactivity (1:200, DAKO, Glostrup, Denmark) was close to zero. In the remaining two nodules, molar villi were found to be in direct contact with the overlying fibrinoid layer throughout the entire circumference. The overlying syncytiotrophoblast had not formed; instead, numerous individual IT were found to be randomly scattered within the fibrinoid layer around the villi (Fig. 1d, arrows). The IT were admixed with lymphocytes at the periphery of the nodule, and several IT infiltrated alveolar septa beyond the nodules. Some trophoblastic nuclei were pyknotic or contained intranuclear cytoplasmic inclusions. No obvious mitotic figures were identified.

The serum β -hCG level of the patient dramatically declined 2 months after wedge resection and then was maintained within a normal range. She was treated with seven courses of EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine) chemotherapy. She showed no evidence of

Figure 1 (a) Representative image of a metastatic pulmonary nodule from the study patient composed of a centrally located single hydropic molar villus surrounded by a thick amorphous eosinophilic fibrinoid layer. (b) The molar villus was lined by single layers of inner cytotrophoblast and outer syncytiotrophoblast in the areas facing the cleft-like free space (arrows), which resembled the lacunar space of the normal implantation site. (c) The overlying syncytiotrophoblast did not form in areas where molar villi were in direct contact with the fibrinoid layer. (d) Numerous intermediate trophoblasts (arrows) were scattered within the fibrinoid layer around the villi.

residual or metastatic lesions during 28 months of post-surgical follow up.

The origin of extravillous or intermediate trophoblasts has not yet been elucidated; they may directly differentiate either from trophoblastic stem cells or villous cytotrophoblast. Identifying this origin will be important for understanding the pathogenic relationship between various forms of gestational trophoblastic diseases and trophoblastic tumors. It has been hypothesized that the cytotrophoblast itself represents a trophoblastic stem cell that can undergo two distinctive differentiation pathways—villous or extravillous.^{2,3} The choice of pathway depends upon the external milieu. On the free villous surface, the cytotrophoblast gradually loses its proliferative activity and directly fuses to form a syncytiotrophoblast. However, when a cytotrophoblast makes contact with a fibrinoid at the placental bed (decidua), the cytotrophoblast differentiates into a villous IT at the region of the trophoblastic columns, and then further differentiates into an implantation site IT at the implantation site.^{2,3} Chorionic villi and IT in the surrounding pulmonary parenchyma have also been previously identified in the villotrophoblastic pulmonary emboli, which consist of deported chorionic villi in a normal pregnancy.⁴ Fibrinoid is a nonfibrous, acellular, and relatively homogenous material that is derived from cellular secretions or cellular degeneration of trophoblast, which embeds postproliferative extravillous trophoblastic cells and can be found where trophoblastic migration or invasion occurs.⁵ The differentiation of IT around the villi occurs within a thick amorphous fibrinoid layer in both normal and molar pregnancy, which indicates that IT in both physiological and pathological contexts are derived from villous cytotrophoblasts. The histopathologic findings of this present case support two different differentiation pathways of cytotrophoblast into either syncytiotrophoblast or IT, depending on the surrounding environment of the chorionic villi (Fig. 1b and 1c). Notably, syncytiotrophoblast were only identified above the cytotrophoblast when villi were exposed to a cleft-like empty space; however, when the villus came into direct contact with fibrinoid materials, syncytiotrophoblastic differentiation did not occur and instead IT differentiation could be identified within the fibrinoid layer. In this present case, the fibrinoid layer of the pulmonary nodules contained numerous IT that exhibited

the features of implantation site IT. Considering the numerous IT scattered only around the molar villi in the fibrinoid layer in all four pulmonary nodules, we considered that IT were closely related to the molar villi, and must be differentiated *in situ* after metastasis and then migrated through the fibrinoid layer.

The histopathological findings in our present case support the previous hypothesis that IT, especially of the implantation site type, can differentiate from villous cytotrophoblast and indicate the plasticity of trophoblastic differentiation. It also provides histological evidence that this phenomenon can occur in an extrauterine environment after the metastasis of molar villi. The existence of mixed gestational trophoblastic tumors composed of various types of gestational trophoblastic cells can also be explained by the plasticity of trophoblastic differentiation between villous and extravillous trophoblasts.

DISCLOSURE STATEMENT

None declared.

Su Hyun Yoo,¹ Kyu-Rae Kim¹ and Stanley J. Robboy²

¹Department of Pathology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea and

²Department of Pathology, Duke University Medical Center, Durham, North Carolina, USA

REFERENCES

- 1 Sung HC, Wu PC, Hu MH, Su HT. Roentgenologic manifestations of pulmonary metastases in choriocarcinoma and invasive mole. *Am J Obstet Gynecol* 1982; **142**: 89–97.
- 2 Shih IM, Kurman RJ. New concepts in trophoblastic growth and differentiation with practical application for the diagnosis of gestational trophoblastic disease. *Verh Dtsch Ges Pathol* 1997; **81**: 266–72.
- 3 Shih IM, Kurman RJ. The pathology of intermediate trophoblastic tumors and tumor-like lesions. *Int J Gynecol Pathol* 2001; **20**: 31–47.
- 4 Song DE, Jang SJ, Kim KR. Villotrophoblastic pulmonary nodule with implantation site intermediate trophoblasts after induced abortion. *Int J Gynecol Pathol* 2007; **26**: 305–9.
- 5 Baergen RN. Development and histology of the nonvillous portions of the placenta. In: *Manual of benirschke and kaufmann's pathology of the human placenta*. New York: Springer, 2005; 107–18.