Pathol. Oncol. Res. (2012) 18:1091–1093
DOI 10.1007/s12253-011-9374-y

LETTER TO EDITOR

Primary Esophageal Small Cell Carcinoma with Brain Metastasis and with CD56, KIT, and PDGFRA Expressions

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Received: 27 May 2010 / Accepted: 26 January 2011 / Published online: 31 May 2011

To the Editor

KIT (CD117) is a product of an oncogene *KIT* mapped to 4q12 [1]. It is a transmembranous receptor tyrosine kinase oncoprotein whose ligand is stem cell factor. KIT plays an important role in cell differentiation, development and tumorigenesis. KIT is expressed in some normal cells (interstitial cells of Cajal, malanocytes, mast cells, blood stem cells, and germ cells) and their neoplasmic counterparts (GIST, melanoma, mast cell neoplasms, leukemia, and germ cell tumors, respectively) [1–4]. KIT expression is also noted in certain neoplasms such as some carcinomas and some sarcomas [1–4]. The majority of KIT-positive carcinomas are small cell carcinoma [1–4]. Platelet-derived growth factor receptor-alpha (PDGFRA) is a product of an oncogene *PDGFRA* mapped also to 4q12, like *KIT* [1]. PDGFRA is a transmembranous receptor tyrosine kinase. Mutations of *KIT* and *PDGFRA* genes are recognized in gastrointestinal stromal tumor [1–4].

Small cell carcinoma is a primitive neuroendocrine malignancy, and can occur in any organ though the vast majority develops in the lung. Primary small cell carcinoma of the esophagus is very rare; only several cases have been reported in the English literature [5]. Like small cell lung carcinoma, small cell carcinoma of the esophagus shows aggressive biological behaviors and the prognosis is poor [5]. However, KIT and PDGFRA expressions and mutations in esophageal small cell carcinoma have not been reported to date.

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The author herein reports a rare case of primary esophageal small cell carcinoma with CD56, and KIT and PDGFRA expression. The CD56, KIT and PDGFRA expression was an important clue of the small cell carcinoma. A 65-year-old man was admitted to our hospital because of headache. Imaging modalities showed a brain tumor. Resection of the brain tumor was performed. Pathological examination showed that it was a metastatic undifferentiated carcinoma composed of small cells with hyperchromatic nuclei, fine chromatin, molded nuclei and scant cytoplasm. Nucleoli were inconspicuous. There were many mitotic and apoptotic figures. The stroma was scant. Acinar or rosette structures were recognized in a few areas. Mucin stains showed a little cytoplasmic mucus. An immunohistochemical study was performed by Dako's Envision method as previously reported [6, 7]. The immunohistochemical study showed positive reactions for cytokeratins (AE1/3, MNF116, polyclonal, Dako, Glostrup, Demmark), and negative reactions for neuron-specific enolase (Dako), chromogranin (Dako), synaptophysin (Dako), cytokeratin 20 (Dako), cytokeratin 7 (Dako), cytokeratin 34βE12 (Dako), AFP (Dako), PSA (Dako), surfactant-apoprotein A (Dako), TTF-1 (Dako), HMB45 (Dako), S100 protein (Dako), CEA (Dako), and CA19-9 (TFB, Tokyo, Japan). The origin of the tumor cannot be estimated.

Clinical scrutiny for the primary site revealed an esophageal tumor, using endoscopy. Pathological diagnosis of the esophageal lesion was undifferentiated carcinoma composed of small cells with hyperchromatic nuclei, fine chromatin, molded nuclei, scant cytoplasm, and absent or inconspicuous nucleoli, being compatible with small cell carcinoma. The histological and immunohistochemical features were similar to those of the brain tumor, but no acinar or rosette differentiation was absent. Further immunohistochemical

analysis revealed that tumor cells were positive for CD56, KIT (Dako) and PDGFRA (Santa Cruz, CA) both in the brain tumor and in the esophageal tumor. Therefore, the tumors of the patient were diagnosed as small cell carcinoma. A new regimen of therapy was performed.

A molecular genetic analysis for *KIT* (exons 9, 11, 13, and 17) and *PDGFRA* (exons 12 and 18) genes was performed, in paraffin specimens of the esophagus, by the PCR-direct sequencing method, as previously described [8–11]. No mutations of the two genes were recognized.

KIT expression is recognized in several tumors [1–4]. In epithelial malignancies, KIT is expressed mainly in small cell carcinoma, though KIT expression has been noted in a few cases of adenoid cystic carcinoma, renal chromophobe carcinoma, thymic carcinoma, ovarian carcinoma, large cell neuroendocrine carcinoma of lung, and breast carcinoma [1]. Sihto et al. [4] reported that strong KIT expression was recognized in only 3 cases (breast carcinoma and teratocarcinoma) among 160 solid epithelial malignancies of various sites. In contrast, KIT expression was recognized in 10 among the 30 small cell lung carcinomas [4]. Thus, KIT shows a high specificity for small cell carcinoma. Extrapulmonary small cell carcinomas also frequently express KIT [12–14].

As to the sensitivity of KIT in small cell carcinoma, KIT expression in small cell lung carcinoma varies among researchers [4, 15–23]; it is reported to be from 33% to 100%. The prognostic implications of positive KIT protein in small cell lung carcinoma are controversial, and no definite conclusions were obtained [15–23].

The brain metastasis of the present case was at first diagnosed as undifferentiated carcinoma composed of small cells with a little adenocarcinomatous differentiation. However, the esophageal tumor was diagnosed as small cell carcinoma. The CD56, KIT, and PDGFRA immunostainings strongly suggested that the tumor was small cell carcinoma. Because it is well known that small cell lung carcinoma can be associated with adenocarcinomatous and squamous cell carcinomatous elements, the presence of adenocarcinomatous differentiation in the brain tumor does not hinder the diagnosis of small cell carcinoma.

Genetic analysis of *KIT* and *PDGFRA* was performed in the present case, and no mutations were identified. In the English literature, small cell lung carcinoma lacks *KIT* mutations [4]; Sihto et al. [4] showed that no mutations of *KIT* and *PDGFRA* genes were recognized in 31 small cell lung carcinomas. Extrapulmonary small cell carcinomas also show no mutations of *KIT* and *PDGFRA* genes [12–14]. The overexpression of KIT is reported to be derived from gene amplification of *KIT* [4].

In summary, the present case indicates that CD56, KIT and PDGFRA are useful markers of esophageal small cell carcinoma.

The author declares no conflict of interest.

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