MOLECULAR PATHOGENESIS OF A PRIMARY MALIGNANT MELANOMA ARISING FROM A MATURE CYSTIC TERATOMA OF THE OVARY

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Background
Primary malignant melanoma of the ovary is extremely rare and no molecular pathogenesis has yet been reported. The mitogen-activated protein kinase and phosphatidylinositol
3 kinase pathways are activated in melanoma. KIT is also an important oncogene in melanoma and loss of hetrozygosity (LOH) in the PTEN region in melanoma is associated with the progression of melanoma. Here we analyzed the alterations of KIT and PTEN genes.
Design
Genomic DNA was extracted from malignant melanoma, mature cystic teratoma and normal tissues. The exon of KIT and PTEN genes were analyzed by polymerase chain reaction
(PCR) and direct sequencing of PCR products was performed.
The microsatellite markers, D10S1765 and D10S541 were used for the LOH analysis of the PTEN region. Two polymorphic markes, PTEN IVS4+109ins/delTCTTA and IVS+823T/G were used to analyze LOH within the PTEN gene.
Results and Conclusions
(1) A 66-year-old woman was admitted complaining of severe lower abdominal pain. Sonography and computed tomography scans revealed a cystic tumor of the ovary, and torsion of the ovarian cyst was suspected. The resected cyst was
7x5x4 cm and contained tooth tissue and hair.
Macroscopically, a mature cystic teratoma was indicated.
However, microscopical analysis showed a malignant melanoma in the mature cystic teratoma. (2) The LOH analysis using a PTEN-flanking microsatellite marker, D10S1765, showed allelic loss in the melanoma as well as in the mature teratoma. (3) Nucleotide sequencing to detect the polymorphism, IVS4+109ins/delTCTTA and
IVS8+32G/T revealed the allelic loss of the PTEN gene. (4)
LOH of the PTEN gene was found in one of five cases of mature cystic teratoma of the ovary. (5) A single-base substitution from A to G, resulting in K558E, was found in exon 11 of the KIT gene only in the malignant melanoma, and not in the mature teratoma. (6) Another mutation in the KIT gene was found in exon 17, resulting in D816H in the melanoma, but not in the mature teratoma. (7) No mutations of NRAS and BRAF genes were found.
These results indicate that LOH of the PTEN gene is one of the molecular alterations of an ovarian mature cystic teratoma and a KIT mutation is an additional promotional event associated with the oncogenesis of a melanoma arising from an ovarian mature cystic teratoma.