Mitogen-activated protein kinase 3 (MAPK3) and human epidermal growth factor receptor 2 (HER2) on recurrent intracranial meningiomas: A case report

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INTRODUCTION

Meningiomas are tumor originated from arachnoidal cap cells of the leptomeninges, and it is by far the most common primary intracranial tumor in adults. It accounts for 15-30% of all central nervous system (CNS) tumors in adults. Despite their high prevalence, it remains challenging to predict their biological and clinical behavior. To date, it has been accepted that the extent of surgical resection and histological grade are the most reliable factors to predict the recurrence of meningiomas. HER2 and MAPK3 represent a well-known prognostic factor in various tumors, however only a few studies on the relationship between meningioma recurrence, HER2, and MAPK3 expression. This report presents additional data that support the relationship between the expression HER2 and MAPK3 with recurrent meningioma.

INTRODUCTION

Meningiomas are tumor originated from arachnoidal cap cells of the leptomeninges, and it is by far the most common primary intracranial tumor in adults. It accounts for 15-30% of all central nervous system (CNS) tumors in adults. Despite their high prevalence, it remains challenging to predict their biological and clinical behavior, especially regarding its recurrences.

Study regarding demographical data and its association with meningioma recurrence shows conflicting results. Several studies have reported higher recurrence rates in male patients compared to female patients. However, other studies, have found no significant difference in gender for recurrence rates. Nakasu et al. and several other authors reported no association between tumor development in young patients (< 40 yrs) and a high likelihood of recurrence. However, Perry and associates found a strong relationship between age and recurrence, while Adegbite and colleagues demonstrated that gender and age have no significant association with recurrence.

It has been proposed that certain medical condition, including hormone replacement therapy and hormone-related disease or state such as breast cancer, ovarian cancer, pregnancy, or obesity, are linked to a higher incidence of meningiomas. Exposure to cranial radiation was also documented linked to a higher incidence of meningiomas. According to WHO classification (2007), meningiomas are divided into three grades (I, II, and III). With this new grading system which includes the brain invasion into the diagnostic criteria for aggressiveness, the percentage of atypical meningiomas grow to 20-35% of newly diagnosed meningiomas. This classification is important because together with the extension of resection, it may help in predicting the recurrence rate and thus the global prognosis.

To date, it has been accepted that the extent of surgical resection and histological grade are the most reliable factors that help predict the recurrence of meningiomas. However, the quest to search a marker to predict its clinical behavior continued. The potential candidates were HER2 and MAPK3. Both HER2 and MAPK3 represents a well-known prognostic factor in various tumors such as breast carcinomas. However, there are only a few studies on the relationship between...
meningioma, HER2, and MAPK3 expression, and the results are conflicting as well. This report aimed to present a case that supports the relationship between the expression HER2 and MAPK3 with recurrent of meningioma.

CASE REPORT

A thirty-nine years-old female with recurrent meningioma that had craniotomy tumor removal a year ago (Figure 1 and 2). Patient came back to the hospital one-year after the surgery, with decreased consciousness, intracranial hypertension, and bulging defect on the head (Figure 3). Histopathologic examination result Meningothelial Meningioma (WHO Grade I). Head CT Scan contrast shows the isodense lobulated lesion, with homogeneity enhancement.

The patient had second craniotomy tumor removal, and histopathologic examination of the sample taken during surgery confirm the presence of Meningothelial Meningioma (WHO Grade I). Based on the second pathologic sample, we performed immunohistochemical staining. We used c-erbB-2 Oncoprotein (SP3) Rabbit Monoclonal Antibody with catalog number RMAB008R manufactured by Diagnostic Biosystems and Anti-ERK1 antibody [Y72] with catalog number (ab32537) manufactured by Abcam. The result from immunohistochemical staining showed positive expressions of HER2 and MAPK3 (Figure 4).

DISCUSSION

HER2 (erbB-2) is a transmembrane glycoprotein with tyrosine kinase activity which is known as a member of the human epidermal growth factor receptor (HER/EGFR/ERBB) family. Known as an oncogene, amplification or over-expression of this gene has been shown to play an essential role in the development of certain types of cancer.\textsuperscript{17–21}

After discovering its role as an oncogene in human carcinoma and its association with the aggressive form of the cancer, researchers pay more attention to HER2 in cancer research for the past two decades. Since then, a lot of studies had confirm the overexpression of HER2 in several types of cancer, including breast cancer, ovarian cancer, and gastric cancer.\textsuperscript{19,21–25}

The MAPK/ERK cascade also plays a role in the initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating several transcription factors.
Activation of MAPKs is a common event in many signal transduction pathways. At least six important pathways have been identified to utilize different MAPK for signal transduction. Numerous studies have shown that MAPK1/ERK2 and MAPK3/ERK1 play an important role in the MAPK/ERK signaling cascade. Mitogen-activated protein kinase (MAPK) pathway dysregulation is implicated in >30% of all cancers, rationalizing the development of RAF, MEK and ERK inhibitors.

There were few studies that already support the association of HER2 and aggressive form of Meningioma. In a study conducted by Loussouran et al., HER2 immunostaining was detected in 10 (28.5%) out of 35 meningiomas. They also reported a significantly higher rate of tumor recurrence in HER2-positive, compared to HER2-negative meningiomas. Torp et al. reported a higher ratio (63%) of HER2-positive meningiomas, but their study has some limitations: 1) they applied immunostaining on frozen sections, 2) they investigated a small number of meningiomas. Other studies by Andersson et al. also demonstrated a high rate of HER2 expression in meningiomas. However, there was a conflicting result from Potti et al. that suggested HER2 overexpression has no role as a prognostic factor in meningiomas based on their finding that HER2 was found in a very low rate.

A study conducted by Wang, et al. in 2016 reported that overexpression of HER2 might promote human meningioma cell proliferation and invasion in vivo and in vitro, which may affect the meningioma development and progression. Furthermore, those study recorded the correlation between HER2 signaling and the activity of MAPK (ERK) in cell proliferation and invasion. Another study demonstrated that high expression of HER2 was associated with an increase of tumor grades and recurrence rate. These results may explain, in part, the association between increased HER2 in human meningioma cells with the high recurrence potential and poor prognosis.

Determination by using MTT, colony formation, and Edu labeling assays found that when gene expression of HER2 was downregulated, the proliferative ability of the cells declined. In terms of the cell cycle, these cells were arrested at the G0/G1-phase, and apoptosis was increased. When the gene expression of HER2 was upregulated, the proliferation ability of the cells increased, and the invasive and migration abilities increased significantly. The cell cycle was promoted at the G1/S-phase, and apoptosis was decreased. Therefore, those study demonstrated that HER2 promoted cell proliferation and invasion and inhibited apoptosis in the human malignant meningioma cells.

Previous studies show over-expression of HER2 may promote human meningioma cell proliferation and invasion, both in vivo and in vitro. Therefore, expression of HER2 affects meningioma development and progression. These findings may explain, in part, the association between increased HER2 in human meningioma cells with the high recurrence potential and poor prognosis. Furthermore, the present report showed support for the hypothesis that HER2 signaling and the activity of MAPK3 (ERK) involved cell proliferation and invasion of meningioma. These data indicated that the HER2-RAS-MAPK pathway to a certain extent might be a potential for the development of novel therapeutic approaches.

At present, for the majority of cases, surgical resection remains the most reliable choice in treating meningioma. Total resection gives the best result for the cure of the tumor and has the least chance of recurrence while subtotal resection may significantly increase the postoperative recurrence rate. Although total resection is the preferred choice, it may not always feasible due to some factors such as extent, location, and bony or dural infiltration.

Possible alternative nonsurgical treatments of recurrent meningiomas have been explored. The most frequently used of nonsurgical managements are radiotherapy and chemotherapy. At present, there is no single consensus that states the role of radiotherapy and chemotherapy in therapeutic management. Nevertheless, radiotherapy is considered important in WHO grade III meningiomas, due to its potential for recurrence and aggressive characteristic. Chemotherapy has not shown any convincing effect on atypical and anaplastic meningiomas and should be reserved for a recurrent case which shows no response to all standard therapies.

**CONCLUSION**

The mechanisms and factor related to recurrence of meningiomas are still poorly understood. The recurrence of intracranial meningiomas might indicate unfavorable prognosis, and multiple surgical resections are required for the treatment. The results of our case report support the role of HER2 and MAPK3 in recurrent meningioma. A better understanding of this pathway is required to explain the pathology and develop a novel therapeutic approach.

**CONFLICT OF INTEREST**

All authors declare no conflict of interest.
**AUTHORS CONTRIBUTIONS**

All of the authors read and approved the final version of the manuscript.

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**REFERENCES**