Cyclooxygenase-2 expression in ependymoma of the spinal cord

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Object. Cyclooxygenase-2 (COX-2), also known as prostaglandin endoperoxide synthase, has been reported to play an important role in the tumorigenicity of many types of tumors. The expression of COX-2 in spinal ependymomas, however, has not been studied. The authors evaluated COX-2 expression in ependymoma of the spinal cord.

Methods. Sixteen ependymoma samples obtained in patients undergoing surgery between 1995 and 2004 were utilized for immunohistochemical studies to evaluate COX-2 and vascular endothelial growth factor (VEGF) expression. Intratumoral microvessels were also stained immunohistochemically using anti–human von Willebrand factor antibody and were quantified to determine the microvessel density (MVD). The clinical features were reviewed and recorded and the association with COX-2 expression was assessed.

Seven (43.8%) of the 16 ependymoma specimens expressed COX-2. All three of the myxopapillary-type ependymomas exhibited COX-2–positive staining. Excluding the three myxopapillary-type cases, COX-2 expression was identified in four (30.8%) of 13 cellular-type ependymomas. The COX-2–positive samples exhibited a significant increase in VEGF-positive staining cells and MVD compared with COX-2-negative samples. The clinical features were not associated with COX-2 expression.

Conclusions. The results of the present study indicate that COX-2 expression may promote angiogenesis through VEGF expression in ependymomas of the spinal cord. It is suggested that the use of selective COX-2 inhibitors may provide a new therapeutic strategy for spinal cord ependymomas due to their inhibition of the COX-2-mediated angiogenesis.

KEY WORDS • ependymoma • spinal cord tumor • cyclooxygenase-2 • prostaglandin endoperoxide synthase • vascular endothelial growth factor

Abbreviations used in this paper: COX = cyclooxygenase; MVD = microvessel density; SD = standard deviation; VEGF = vascular endothelial growth factor.

Cyclooxygenase exists as two isoforms, COX-1 and COX-2. Cyclooxygenase-1 is a housekeeping enzyme that is expressed constitutively in many tissues. Cyclooxygenase-2 is an inducible enzyme that is usually associated with inflammation. Recently, COX-2 has been shown to be constitutively expressed in malignant tumors.

An overexpression of COX-2 has been demonstrated in many types of malignant tumors, such as colorectal, prostate, breast, and lung carcinoma, and various types of COX-2 inhibitors have exhibited anticancer properties. We have reported on the overexpression of COX-2 in an osteosarcoma cell line and the inhibitory effect of a pre-
Expression of COX-2 in spinal cord ependymoma

Although a few authors have demonstrated COX-2 overexpression in intracranial ependymomas,\textsuperscript{1,11} we were unable to find any previous reports of COX-2 expression in spinal cord ependymoma. Therefore, the goal of the present study was to evaluate COX-2 expression in spinal cord ependymoma and investigate the role of COX-2 in tumor activity.

Materials and Methods

Tissue Specimens and Clinical Records

We studied formalin-fixed and paraffin-embedded spinal cord ependymoma tissue samples that had been obtained in consecutive patients who had undergone tumor resection at our institution between February 1995 and July 2004. Cases in which there was no definitive histopathological diagnosis were excluded; 16 samples were available for this study. There were eight male and eight female patients whose mean age was 45.6 years (range 6–71 years). There were 13 cases of cellular-type ependymoma (obtained in six male and seven female patients [mean age 50.2 years, range 30–71 years]) that were intramedullary spinal cord tumors, and there were three cases of myxopapillary-type tumors (obtained in two male and one female patients [mean age 25.7 years, range 6–54 years]). One of the three myxopapillary-type lesions originated in the conus medullaris (Case 8), whereas the other two originated in the terminal filum (Cases 1 and 9). Because myxopapillary-type ependymomas are a clinicopathologically and genetically unique variant of ependymomas,\textsuperscript{1,10} we performed data analysis using two distinct categories: Group A consisted of all 16 cases, including the myxopapillary types, and Group B consisted of the 13 cellular-type ependymomas, excluding the myxopapillary-type lesion. Other clinical features such as age, sex, primary symptom(s), location and length of the tumor (identified by Gd-diethylenetriamine pentaacetic acid–enhanced magnetic resonance imaging; length was indicated as the number of vertebrae), extent of surgery (total resection, 100% tumor removal; subtotal resection, ≥ 90%; partial resection, < 90%), and neurological status were also reviewed and evaluated with respect to the expression of COX-2.

Immunohistochemical Studies

The paraffin-embedded tissue samples were cut into 4-μm-thick serial sections. The paraffin-embedded tissues were deparaffinized, rehydrated, and washed three times in phosphate-buffered saline. Endogenous peroxidase activity was blocked by incubation with 0.3% hydrogen peroxidase for 30 minutes. The slides were then soaked in normal rabbit (COX-2) or goat (VEGF and von Willebrand factor rabbit polyclonal antibody, which has been shown to cross-react with human VEGF, and von Willebrand factor) serum (HISTFINE Kit, Nichirei Corp.) for 10 minutes at room temperature. The primary specific anti-rat COX-2 goat polyclonal antibody, which has been shown to cross-react with human COX-2 (Santa Cruz Biotechnology), anti-human VEGF rabbit polyclonal antibody (Santa Cruz Biotechnology) or anti-human von Willebrand factor rabbit polyclonal antibody (DakoCytomation) was applied at dilutions of 1:500, 1:500, and 1:1000, respectively, and incubated for 1 hour at room temperature. After rinsing in phosphate-buffered saline, the sections were processed using the HISTFINE Kit and a diaminobenzidine-containing substrate solution. Granular brown cytoplasmic staining was considered positive. Cyclooxygenase-2 has been reported to localize in both nucleus and cytoplasm.\textsuperscript{20} In regard to COX-2 and VEGF, five different high-power fields were selected randomly, and positively stained cells were counted under a light microscope at a magnification of 400. The percentage of positively stained cells was calculated. In the same way intratumoral microvessels that were identified by positive staining for von Willebrand factor were counted in five different high-power fields selected randomly at a magnification of 100, and the average of number of microvessels/high-power field was calculated as the MVD. All evaluations of tumor staining were performed in a blinded manner by two pathologists.

Statistical Analysis

The differences between two data samples were analyzed using the Mann–Whitney U-test or chi-square test. Correlation was evaluated using the Spearman rank correlation coefficient. A probability value less than 0.05 was considered statistically significant. Values are presented as the means ± the SDs.

Results

Expression of COX-2 in Spinal Cord Ependymomas

A summary of COX-2 expression is provided in Table 1 and Fig. 1. Immunohistochemical staining demonstrated COX-2 expression in seven (43.8%) of the 16 ependymomas (Group A) (Fig. 1A). Excluding the myxopapillary-type cases (Group B), COX-2 expression was identified in four (30.8%) of 13 cellular-type ependymomas (Fig. 1B). All three of the myxopapillary-type cases exhibited COX-2-positive staining (Figs. 1A and 2 [see Fig. 2G]). In all positive cases, all tumor cells exhibited positive staining and diffuse cytoplasmic staining (Fig. 2A). Therefore, the tissue could be classified into COX-2–positive and –negative samples (Fig. 2A and B).

Expression of VEGF and Association With COX-2 Expression

A summary of VEGF expression is shown in Table 1. The expression of VEGF was observed in nine cases (56.3%) in Group A and six cases (46.2%) in Group B. All of the COX-2–positive samples exhibited VEGF expression (Fig. 2C). The mean percentage of VEGF-positive cells was 17.9 ± 36.3% in COX-2–positive samples and 0.1 ± 0.1% in COX-2–negative samples in Group A (Fig. 3A). All three of the myxopapillary-type lesions expressed VEGF, and the percentages of VEGF-positive cells were 100 ± 0% (Case 1) (Fig. 2H), 7.7 ± 5.8% (Case 8), and 4.4 ± 3.5% (Case 9), respectively. In Group B, the percentages of VEGF-positive cells were 3.1 ± 1.1% in the

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<th>Case Number</th>
<th>Lesion Type</th>
<th>Age (yrs.)</th>
<th>Sex</th>
<th>Location of Tumor</th>
<th>COX-2 Expression</th>
<th>VEGF-Positive Cells (%)</th>
<th>MVD</th>
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Table 1: Clinical features of all 16 cases

* Conus medullaris origin.
† Terminal filum origin.
COX-2–positive samples and 0.1 ± 0.1% in the COX-2 negative samples (Fig. 3B). In both Groups A and B, the percentages of VEGF-positive cells were significantly increased in COX-2–positive samples compared with COX-2–negative samples (p = 0.0008 and 0.0025, Groups A and B, respectively). Almost all of the COX-2–negative samples exhibited negative staining for VEGF (Fig. 2D) except in two cases. Interestingly, the specimens in these two cases that exhibited VEGF-positive and COX-2–negative expression were revealed to express low percentages of VEGF-positive cells (0.3 ± 0.3% [Case 3] and 0.2 ± 0.2% [Case 10]) compared with COX-2–positive samples.

**Intratumoral MVD**

Intratumoral microvessels were identified by positive immunohistochemical staining for von Willebrand factor, and the MVD was calculated. The MVD values are summarized in Table 1. As shown in Fig. 4A and B, the percentages of VEGF-positive cells correlated significantly with MVDs in both Groups A and B (p = 0.0021 and correlation coefficient 0.706 in Group A; p = 0.0043 and correlation coefficient 0.611 in Group B). The mean MVD in the VEGF-positive samples was 18.1 ± 6.4/hpf and that in the VEGF-negative staining samples was 5.5 ± 6.2/hpf in Group A. In Group B, the mean MVD in the VEGF-positive samples was 14.9 ± 7.4/hpf and that in the VEGF-negative samples was 3.0 ± 1.0/hpf. In both Groups A and B, the MVDs increased significantly in the VEGF-positive samples compared with the VEGF-negative samples (p = 0.0012, Group A; p = 0.0027, group B). As already mentioned, all the COX-2–positive samples exhibited VEGF expression, whereas almost all of the COX-2–negative samples were VEGF-negative, excluding two cases. The MVDs in the two cases that exhibited COX-2–negative and VEGF-positive staining were relatively greater than the VEGF-negative samples (6.8 ± 3.3/hpf [Case 3] and 21.6 ± 2.4/hpf [Case 10]). With regard to the association between COX-2 expression and MVD, the MVD was increased significantly in the COX-2–positive samples compared with the COX-2–negative samples in Groups A and B. Representative photomicrographs are shown in Fig. 2E and F. In Group A, the MVD in the COX-2–positive samples was 18.1 ± 6.4/hpf, whereas in the COX-2–negative samples the MVD was 5.5 ± 6.2/hpf (p = 0.0095) (Fig. 4C). The MVDs in the three myxopapillary samples were 24.0 ± 1.4/hpf (Case 1), 21.0 ± 7.8/hpf (Case 8), and 20.8 ± 5.3/hpf (Case 9), respectively. In Group B, the MVD was 15.2 ± 7.4/hpf in the COX-2–positive samples and 5.5 ± 6.2/hpf in the COX-2–negative samples (p = 0.0206) (Fig. 4D).

**Clinical Features**

The clinical features of the patients in all 16 cases of spinal cord ependymoma are reviewed and summarized in Table 1. No significant differences in clinical features were detected between the COX-2–positive and –negative samples in Groups A and B. Preoperative neurological status was not associated significantly with COX-2 expression (data not shown). No relapse was evident, as identified by diagnostic imaging studies obtained in patients in whom total or subtotal tumor resection was achieved.

**Discussion**

There is ample evidence that COX-2 is involved in carcinogenesis in various types of malignant tumors. Therefore it has been suggested that selective COX-2 inhibitors may provide a new therapeutic tool for COX-2–expressing tumors. There have been very few studies of COX-2 expression in ependymoma. In one detailed investigation, the authors reported COX-2 overexpression in pediatric intracranial posterior fossa ependymomas via immunohistochemical staining and Western blot analysis. The authors found COX-2 immunopositivity in 15 (79%) of 19 intracranial ependymomas. They also cultured ependymoma cells in vitro and demonstrated COX-2 expression in cultured intracranial ependymoma cell lines by Western blot analysis. Furthermore, they demonstrated an inhibitory effect and proapoptotic effect of NS-398, a selective COX-2 inhibitor, on cultured brain ependymoma cells. These antitumoral effects were demonstrated to result from the downregulation of Bcl-2 and P-gp (permeable glycoprotein). To our knowledge, there have been no previous reports of COX-2 expression in ependymoma of the spinal cord. Therefore, our study is the first to examine COX-2 expression and its role in spinal cord ependymomas.

Cyclooxygenase-2 has been demonstrated to promote tu-
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Fig. 2. Representative photomicrographs in Case 5 (A, C, and E [representative of a cellular-type COX-2–positive lesion]), Case 11 (B, D, and F [representative of a cellular-type COX-2–negative lesion]), and Case 1 (G and H [representative of a myxopapillary-type lesion]). A, B, and G: Immunohistochemical staining for COX-2. C, D, and H: Immunohistochemical staining for VEGF. E and F: Immunohistochemical staining for von Willebrand factor. Arrows in C indicate VEGF-positive cells; arrows in E and F indicate intratumoral microvessels. Original magnifications × 400 (A–D, G, and H), × 100 (E and F).

Tumor growth via many pathways, including upregulation of growth factors, such as VEGF. Cyclooxygenase-2–derived prostaglandin E2 has been shown to dominantly regulate angiogenesis in tumors. Furthermore, a selective COX-2 inhibitor has been demonstrated to suppress tumor activity not only through the induction of apoptosis but also the downregulation of VEGF. The authors of another study demonstrated that the vascular density in tumors grown in COX-2−/− mice decreased significantly compared with wild-type mice. We have also previously demonstrated the inhibitory effect of meloxicam, a preferential COX-2 inhibitor, on murine osteosarcoma cell growth and metastasis in vivo through the inhibition of VEGF expression. Therefore, we aimed to evaluate COX-2 expression and the association between COX-2 expression and VEGF expression or MVD in ependymomas of the spinal cord.

In the present study, we detected COX-2 expression in 43.8% in Group A and 30.8% in Group B (excluding the myxopapillary type) of spinal cord ependymomas. These incidences were relatively low compared with the results of intracranial ependymomas reported previously. Intracranial ependymomas are often life threatening in childhood, and 5-year survival rates have been reported to range from 45 to 64%. On the other hand, ependymomas of the spinal cord essentially represent a benign tumor, and their clinicopathological characteristics differ from those of in-
tracranial ependymoma. Therefore, we considered that COX-2 may play somewhat different roles in the tumor activity of spinal cord ependymomas compared with intracranial ependymomas or other malignant tumors.

We also found a significant association between COX-2 expression and VEGF expression or MVD. Furthermore, we also confirmed a correlation between VEGF expression and MVD. In COX-2–positive samples, the percentages of VEGF-positive cells and MVD were significantly increased compared with COX-2–negative samples in both Groups A and B. These results suggested an important role of COX-2 expression in the angiogenesis of spinal cord ependymomas and were consistent with previous studies regarding the association between COX-2 expression and angiogenesis. With regard to VEGF expression in ependymomas, the authors of a previous report have shown that the expression of VEGF and hypoxia-related factor carbonic anhydrase IX in intracranial ependymomas were associated with angiogenic pattern. The authors of another study have reported an elevation of VEGF levels in the cystic portion of a brain ependymoma. Although no detailed investigations of VEGF expression in ependymomas of the spinal cord have been reported, these findings of intracranial ependymomas may lend support to an association between VEGF and angiogenesis in spinal cord ependymoma. In our study, most of the COX-2–negative samples did not express VEGF and were revealed to exhibit significantly lower MVD than the COX-2–positive samples; however, the two specimens that exhibited COX-2–negative staining expressed relatively low levels of VEGF and relatively high MVD compared with other COX-2–negative cases. The existence of these two exceptional cases was significant and suggested that angiogenesis in spinal cord ependymomas was not modulated solely by the COX-2–VEGF pathway. Because the tumor activity in each of these cases might be regulated by COX-2 and many

**Fig. 3.** Bar graphs showing an association between COX-2 and VEGF expression in spinal cord ependymomas. The expression level of VEGF is indicated as a percentage of the VEGF-positive staining cells in Group A (A) and Group B (B). Bars represent the mean ± SD. **p < 0.01, statistically significant difference between COX-2–positive and –negative samples.

**Fig. 4.** Graphs demonstrating an association between MVD and VEGF or COX-2 expression.  A and B: Correlation between the expression of VEGF-positive cells and MVD in Group A and in Group B.  C and D: Correlation between COX-2 expression and MVD in Group A and in Group B. Bars represent the mean ± SD. *p < 0.05, statistically significant difference between COX-2–positive and –negative samples; **p < 0.01, statistically significant difference between COX-2–positive and –negative samples.
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other modulators, these findings were not completely inconsistent with our hypothesis. In this investigation, because only paraffin-embedded tissues were available, we were not able to perform reverse transcriptase polymerase chain reaction or Western blot analysis. If real-time reverse transcriptase polymerase chain reaction or Western blot analysis were conducted, more precise quantification of the levels of COX-2 and VEGF expression could be evaluated and more detailed and mechanistic findings would be achieved.

The myxopapillary-type lesion is a unique variant of ependymoma.\textsuperscript{1,2,7,10} We performed data analysis by two methods—including or excluding the myxopapillary-type lesion. Considering the rich vascular proliferation that is a typical pathological characteristic of the myxopapillary-type ependymoma, the upregulation of VEGF expression and the increase of MVD in the three myxopapillary cases were considered to be reasonable findings. The expression of COX-2 was detected in all three of the myxopapillary-type lesions in our study. Therefore, the association between COX-2 expression and VEGF expression/MVD in the COX-2–positive myxopapillary cases could not be compared with that of the COX-2–negative myxopapillary cases. Conversely, the possibility was suggested that the myxopapillary-type ependymoma might be characterized by a high incidence of COX-2 expression. With regard to VEGF expression, the lesion in Case 1 expressed an excessively high level of VEGF (percentage of VEGF-positive cells 100 ± 0%). The reason this sample alone exhibited such excessive VEGF expression is difficult to explain. Furthermore, regardless of such an excessively high level of VEGF expression, this exceptional case did not exhibit an excessive increase of MVD compared with the other two myxopapillary-type lesions. An analysis of a larger number of myxopapillary samples is warranted and might provide a better understanding of the roles of COX-2 expression and the modulation of VEGF expression in myxopapillary-type ependymomas. Myxopapillary ependymoma is often difficult to treat. Therefore, it is worthwhile to determine more precisely the association between COX-2 expression and tumor activity, including angiogenesis, in these tumors.

In our study, there were no significant differences in clinical features between the COX-2–positive and –negative samples. Several investigators have examined the association between COX-2 expression and the clinical features or outcome in various malignant tumors. In one report, the authors demonstrated that COX-2 expression in pediatric sarcomas did not correlate with the clinical features and outcome.\textsuperscript{8} In another study the clinical features and COX-2 expression in cholangiocarcinoma were not significantly associated.\textsuperscript{12} Brain ependymomas have also been shown not to exhibit a significant association between vascular proliferation and patient survival.\textsuperscript{21} Brain ependymomas have been demonstrated to have no association between COX-2 expression and the clinical features.\textsuperscript{13} In contrast, glioma and carcinoma of the ampulla of Vater exhibited a significant correlation between COX-2 expression and clinical outcome.\textsuperscript{5,12,27} This argument remains controversial. Because the clinical outcome of spinal cord ependymoma, such as postoperative neurological status and surgical technique,\textsuperscript{5,22} we did not evaluate any association between postoperative neurological status and COX-2 expression. Furthermore, the most important factor in the clinical outcome of patients with malignant tumors is survival time, whereas that of patients with spinal cord ependymoma is postoperative neurological status. Hence, comparison between other malignant tumors and spinal cord ependymoma was considered to be invalid.

In the present study we found that COX-2–positive ependymomas exhibited significantly upregulated VEGF expression and angiogenesis that might promote tumor growth, although no significant correlation between COX-2 expression and tumor length was detected. Initially, these two results appeared to contradict each other, but the lesion length in each case was the result of tumor growth after various time spans and could not directly reflect the speed of tumor growth. Furthermore, the preoperative duration of symptoms was not significant when COX-2–positive and –negative samples were compared (data not shown) and it was not able to precisely identify the moment of tumor generation. Therefore, we believe that an association between COX-2–mediated tumor growth and angiogenesis could not be completely refuted.

Conclusions

In the present study we demonstrated COX-2 expression in spinal cord ependymomas, including the myxopapillary type, and evidence that COX-2 expression in spinal cord ependymoma may induce VEGF (via prostaglandin E\textsubscript{2} production) and result in intratumoral angiogenesis. The efficacy of adjuvant therapy after incomplete resection or in cases of myxopapillary-type spinal cord ependymoma remains debated. Therefore, new therapeutic tools are required. The findings in our study suggest the possibility that selective COX-2 inhibitors may provide a new strategy for some, but not all, COX-2–expressing spinal cord ependymomas through inhibition of intratumoral angiogenesis; however, COX-2 may modulate angiogenesis as well as many other different aspects of tumor activities. Therefore, the various interpretations of COX-2 expression in ependymomas of the spinal cord should be investigated.

References


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