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Original contribution

Differential expression of extracellular matrix–related genes in rare variants of meningioma☆

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Summary Secretory, clear cell, and rhabdoid meningiomas are rare variants of meningiomas characterized by unique histologies and behaviors. Extracellular matrix proteins provide a morphologic structure and influence the biologic behavior of tumors. However, the effects of extracellular matrix proteins on morphologies and biologic behaviors of secretory meningioma, clear cell meningioma, and rhabdoid meningioma have not been established. We evaluated the expression of matrix metalloproteinase 2, matrix metalloproteinase 9, galectin-3, fibronectin, and collagen IV in a series of those rare variants of meningioma and verified their clinicopathologic significance. A total 51 cases included 12 secretory meningiomas, 9 clear cell meningiomas, and 30 rhabdoid meningiomas. Extracellular matrix proteins showed different expression patterns according to the histologic subtypes, and messenger RNA levels were well correlated with immunoexpressions. Secretory meningiomas showed high expressions of fibronectin and galectin-3. Clear cell meningiomas showed high expression of matrix metalloproteinase 2, matrix metalloproteinase 9, and collagen IV. Rhabdoid meningiomas showed high expressions of matrix metalloproteinase 9, galectin-3, and fibronectin. Clinically, high expression of matrix metalloproteinase 9 was associated with tumor recurrence ($P < .001$) and local invasion at the time of diagnosis ($P = .018$) among the extracellular matrix–related proteins, and was also associated with shorter recurrence-free survival ($P = .025$) in the patients with rhabdoid meningioma. In conclusion, the differential expressions of extracellular matrix–related genes according to the histologic subtypes appear to be involved in biologic behavior and clinical outcome, and high matrix metalloproteinase 9 expression is associated with recurrences in rhabdoid meningiomas.

1. Introduction

Secretory, clear cell, and rhabdoid meningiomas are typical rare variants of meningioma with unique histologic features. Secretory meningiomas (SMs) are characterized by the

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formation of gland-like lumens with eosinophilic secretions and pericytic proliferation, which are associated with secretory and epithelial differentiation [1,2]. Clear cell meningiomas (CCMs) are composed of sheets of polygonal cells with a clear cytoplasm and form interstitial and perivascular hyalinization. They often lack typical histologic features of meningothelial nature such as whorl formation and psammoma bodies. Rhabdoid meningiomas (RMs) contain discohesive aggregates of rhabdoid cells with eccentric vesicular nuclei, prominent nucleoli, and densely eosinophilic cytoplasm with paranuclear globular inclusions [3,4]. In addition to their unique morphologies, their biologic behaviors are distinctive from those of common meningioma subtypes.

SMs are frequently accompanied by massive peritumoral edema. CCMs and RMs represent aggressive meningiomas, despite bland cytology and little mitotic activity [3–5]. Although CCMs have a bland cytology in most cases, they show frequent recurrence and occasional cerebrospinal fluid seeding [5]. RMs have been shown to recur frequently even after complete removal [3,4]. The histologic features of SMs, CCMs, and RMs may be related to their behaviors, which cannot simply be explained according to the criteria of atypical or malignant meningiomas. We have, therefore, focused on the varying expression of extracellular matrix (ECM) proteins, which are likely to be involved in the unusual morphology and biologic behavior of these meningiomas.

Meningiomas produce varying degrees and types of ECM proteins such as fibronectin, collagen IV, galectin-3, matrix metalloproteinase (MMP)-2, and MMP-9. The ECM proteins provide a morphologic structure and influence the biologic behavior of tumors [6]. The ECM proteins are involved in invasion, edema formation, and metastasis in various tumors [7,8]. The common meningioma subtypes have been fully studied with respect to the relationships between their pathologic characteristics and ECM protein expressions. However, very little research has been performed on SMs, CCMs, and RMs [9].

MMPs are zinc-dependent lysosomal endopeptidases for the degradation of the ECM, and they play an important role in tumor recurrence and invasion [10]. MMP-2 and MMP-9 degrade various types of collagen, especially collagen IV [10]. MMP-2 and MMP-9 expression contribute to the infiltration of meningioma cells to the dura mater and invasion to bone [11,12]. Accordingly, many investigators have reported that high expressions of MMP-2 and MMP-9 are associated with the recurrence of meningiomas and may be related to aggressive behavior and peritumoral edema of meningiomas [10,13,14].

Galectin-3 is a β-galactoside-binding lectin involved in cell proliferation, migration, neoplastic transformation, and invasive activity of various types of tumors [15–17]. Galectin- 3 expression has been described in brain tumors including spindle cell oncocytoma, pituitary adenoma, astrocytoma, and oligodendroglioma [18,19], in which the significance of galectin-3 expression seems to be limited to an ancillary aid in differential diagnoses [18,19]. Galectin-3 is also expressed in meningiomas, and previous studies showed a wide range of galectin-3 expression in meningiomas by immunohistochemical assessment [9,18,19]. Common meningioma subtypes such as fibrous, meningothelial, and transitional tend to show moderate to strong galectin-3 immunoreactivity, whereas a few cases of SM, CCM, and RM have inconsistent expression patterns varying from weak to strong [9,19]. Because SMs, CCMs, and RMs are rare variants of meningiomas, previous studies have not confirmed MMP-2, MMP-9, and galectin-3 expression and their clinical or pathologic significances on these rare variants.

The aim of the present study was to evaluate the expression of ECM genes in a series of secretory, clear cell, and rhabdoid meningiomas by means of immunohistochemical and real-time reverse transcription–polymerase chain reaction (RT-PCR) analyses and verify whether these expressions are related to clinical behaviors.

2. Materials and methods

2.1. Patients and histologic evaluation

Between 1997 and 2009, 1150 patients with meningiomas were surgically treated at Samsung Medical Center, Seoul, Korea. Of these patients, 12 (0.96%) were diagnosed with SMs; 9 (0.78%), with CCMs; and 30 (2.70%), with RMs. All the glass slides from these rare variants of meningioma were reviewed by 2 neuropathologists (Y. L. S. and M. J. K.) for diagnosis confirmation and selection of a representative section for immunohistochemical and molecular studies. The diagnostic criteria that we used were those indicated by the most recently revised World Health Organization (WHO) classification of nervous system tumors [20]. According to the current WHO classification, 12 SMs were grade I, 9 CCMs were grade II, and 30 RMs were grade III. A total of 51 patients were enrolled in this study. Medical records of each patient were reviewed for demographic information, neuroradiologic data, tumor characteristics, treatment details, tumor progression or recurrence, and local invasiveness around the tumor at the time of diagnosis. In most cases, a formal Simpson grade was not assigned or not recorded in the operative note; instead, the note contained a comment on completeness of resection such as gross total or subtotal resection. Ten patients with SM had gross total resection, and 2 had subtotal resection. All patients with SM had no further therapy. Eight patients with CCM had gross total resection, and 1 had subtotal resection. Among them, 4 had further radiotherapy. Twenty-four patients with RM had gross total resection, and 6 had subtotal resection. Fifteen patients with RM had gross total resection and further radiotherapy after surgery. Local invasion included any invasiveness to brain parenchyma, bone, orbit, sinus wall, ventricle, and cranial nerve around the tumor according to medical charts at the time of diagnosis. The peritumoral edema was determined on