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ORIGINAL ARTICLE

Association of MMP-2 and MMP-9 expression with recurrences in primary spontaneous pneumothorax

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Abstract Primary spontaneous pneumothorax (PSP) is a common benign problem. However, PSP recurrence is still a troublesome complication for most patients. This study intended to determine the role of matrix metalloproteinase-2 (MMP-2) and MMP-9 in type II pneumocytes of patients with PSP and its relation with recurrence. Ninety-one patients who had undergone needlescopic video-assisted thoracoscopic surgery wedge resection of lung with identifiable blebs for PSP were included in this study. Immunohistochemical (IHC) staining was used to measure the expression of MMP-2 and MMP-9 in lung tissues of PSP patients. The results were further correlated with clinicopathological parameters and recurrence rates using chi-square or Fisher's exact test. The value of MMP-2 and MMP-9 for overall recurrence was analyzed

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by univariate and multivariable Cox regression model. IHC data revealed that MMP-2 and MMP-9 staining was predominantly observed in type II pneumocytes of patients with PSP. We found that MMP-2 and MMP-9 expression in PSP, especially male PSP patients, was significantly correlated with recurrence. In the univariate and multivariate analyses, MMP-2 and MMP-9 were statistically significant risk factors for overall recurrence in PSP patients. Therefore, high expression levels of MMP-2 and MMP-9 in type II pneumocytes show a positive correlation with PSP recurrence risk. Further studies are needed to validate whether reduction of MMP-2 and MMP-9 expression may be a promising way for decreasing the risk of PSP recurrence in the future.

Introduction

Primary spontaneous pneumothorax (PSP) is an important health problem, mostly occurs in young males, and is encountered in clinical practice [1]. It has an annual incidence of 18—28/100,000 in males and 1.2—6/100,000 in females [2]. PSP occurs without trauma or obvious precipitating cause and arises in persons without clinically apparent lung diseases. The average rate of ipsilateral recurrence of PSP is 30%, with a range of 16—52%, and the incidence of contralateral recurrence is around 15% after first episode of PSP [3,4].

PSP is caused by chronic destruction of subpleural alveolar structures because of hypoxia, oxidative stress, and chronic inflammation [5,6]. PSP is associated with the degradation of elastic fibers and is mediated through infiltration of proinflammatory mediators secreted by type II pneumocytes [7]. The elastolysis in lung disease is caused by an imbalance of proteases and antiproteases [8,9].

Matrix metalloproteinases (MMPs) comprise a family of zinc-dependent enzymes and are classified into several subgroups: collagenases, gelatinases, stromelysins, elastases, and membrane-type MMPs [10,11]. Although MMPs play a crucial physiological role in wound healing, tissue remodeling, and angiogenesis, their overexpression is connected to some pulmonary diseases [12,13]. PSP is caused by the fracture of the pulmonary parenchyma or visceral pleura, which is related to the weakening of subpleural lung tissue. Recently, MMP-2 and MMP-9 have been marked as being critical for the clinical pathology of lung diseases [14—16].

Type II pneumocyte hyperplasia was reported to be associated with reactive epithelial change in pneumothorax [17]. However, the expression of MMP-2 and MMP-9 in type II pneumocytes of PSP patients and their relationship to PSP recurrence remain unknown. In the current study, we examined MMP-2 and MMP-9 expression levels in type II pneumocytes of both lung tissue resections and surrounding normal tissue resections by immunohistochemical (IHC) staining. Their association with the clinical variables was assessed as to whether MMP-2 and MMP-9 expression levels may be clinical factors involved in PSP recurrence.

Materials and methods

Participant samples

From January 2012 to December 2013, we retrospectively reviewed the clinical data of 91 PSP patients who underwent surgery at the Division of Thoracic Surgery, Department of Surgery, Kaohsiung Medical University Hospital (Kaohsiung, Taiwan). They received surgical treatment owing to recurrence, persistent air leak (for $\geq$5 days), or patient preference. PSP patients included in this study were diagnosed by chest radiography and computed tomography (CT) scan as well as their age ($\leq$40 years). Some patients were excluded because of secondary pneumothorax, traumatic or iatrogenic pneumothorax, lung disease (i.e., asthma, pneumonia, chronic obstructive pulmonary disease, tumor), or lung surgery (i.e., wedge resection of the lung, lobectomy). The recurrence group consisted of patients with radiological proof of relapse of pneumothorax after the first episode of PSP, and their specimens and adjacent normal lung tissues were collected while they were undergoing surgery. The nonrecurrence group consisted of persons who underwent surgery during their first admittance with PSP and had no recurrence during a 2-year follow-up period. All resections were carried out for IHC staining. The age, sex, body mass index (BMI, kg/m^2), smoking status, and side of pneumothorax were recorded. The study was approved by the Kaohsiung Medical University Hospital Institutional Review Board (KMUH-IRB-20130268), and informed consent was obtained from all patients.

Operative technique

The operative technique for needlescopic video-assisted thoracoscopic surgery blebectomy has been described previously [18].

IHC staining

IHC staining for MMP-2 and MMP-9 was performed on a Bond-Max autostainer (Leica Microsystems, Bannockburn, IL, USA) as described previously [19]. In brief, resections were incubated with MMP-2 (1:200; Abgent, San Diego, CA,