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SHORT COMMUNICATION

The incidence rate and histological characteristics of intimal hyperplasia in elastase-induced experimental abdominal aortic aneurysms in mice

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Abstract

Intimal hyperplasia (IH) is a negative vascular remodeling after arterial injury. IH occasionally occurs in elastase-induced abdominal aortic aneurysm (AAA) mouse models. This study aims to clarify the incidence and histological characteristics of IH in aneurysmal mice. A retrospective study was conducted by including 42 male elastase-induced mouse AAA models. The IH incidence, aortic diameters with or without IH, and hyperplasia lesional features of mice were analyzed. Among 42 elastase-induced AAA mouse models, 10 mice developed mild IH (24%) and severe IH was found in only 2 mice (5%). The outer diameters of the AAA segments in mice with and without IH did not show significant difference. Both mild and severe IH lesions show strong smooth muscle cell positive staining, but endothelial cells were occasionally observed in severe IH lesions. There was obvious macrophage infiltration in the IH lesions of the AAA mouse models, especially in mice with severe IH. However, only a lower numbers of T cells and B cells were found in the IH lesion. Local cell-secreted matrix metalloproteinases (MMP) 2 was highly expressed in all IH lesions, but MMP9 was only overexpressed in severe lesions. In conclusion, this study is the first to demonstrate the occurrence of aneurysmal IH and its histological characteristics in an elastase-induced mouse AAA model. This will help researchers better understand this model, and optimize it for use in AAA-related research.

KEYWORDS
abdominal aortic aneurysms, animal model, histology, intimal hyperplasia

1 | INTRODUCTION

Intimal hyperplasia (IH) is a pathological process of negative vascular remodeling after arterial injury. IH of large or medium arteries generally occurs after injury, percutaneous coronary intervention, atherosclerotic plaque removal and endovascular repair of abdominal aortic aneurysms (AAAs).[1–3] IH is histologically characterized by as excessive proliferation of vascular smooth muscle cells (SMCs)

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and endothelial cells, and excessive production of extracellular matrix.[4,5]

Since the elasticity of the arteries gradually decreases with age, a physiological thickening of the intima may occur. Some scholars also believe that coronary atherosclerosis begins with pathological aortic dilation and IH, leading to intimal hypoxia and adventitial neovascularization, and promoting accumulation of oxidized lipoproteins under the intima and phagocytosis by macrophages.[6,7] AAAs mainly caused by tunica media injury and atherosclerosis originating from intimal dysfunction are the two most common vascular diseases, and their pathogenesis also shares some similarities, such as vascular inflammation.[8–10] Since AAAs often occur in elderly smoking men, and these patients usually have atherosclerotic diseases at the same time, how IH occurs in AAA patients or animal aneurysmal models, and whether it is involved in the pathogenesis of AAAs currently remains unclear due to a lack of clinical and laboratory data.

Mouse is one of the most commonly used animals for AAA modeling. The AAA modeling methods in mice mainly include elastase infusion, angiotensin II infusion and perivascular application of calcium chloride calcium, with the first two methods being more commonly used.[11–14] Although the surgery for elastase infusion is complicated, the histological characteristics of the elastase-induced AAAs in mice well represent the inflammatory process in aneurysm progression, which has led to the wide use of this model.[13] Our laboratory has carried out elastase-induced AAAs modeling in mice for many years and we have also found that IH occurs at the lesion site of some mice with aneurysms. The purpose of this study is to clarify the incidence and histological characteristics of IH in aneurysmal mice by reviewing and analyzing the aneurysmal mice data obtained over the past 2 years, and to accumulate basic laboratory data to elucidate the relationship between IH and AAAs.

2 | METHODS

2.1 | Mice

In this retrospective study, 42 male C57BL/6J mice aged 10–14 weeks were obtained and kept at Laboratory Animal Center of Xi'an Jiaotong University. During the experiment, all mice had free access to water and diet. The animal experimental protocols were approved by the Laboratory Animal Administration Committee of Xi'an Jiaotong University (No. 2019–1178) and performed according to the Guidelines for Animal Experimentation of Xi'an Jiaotong University and the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH Publication No. 85–23, revised 2011).

2.2 | The creation of AAAs

Porcine pancreatic elastase (PPE) was used to induce AAAs in mice according to a previously described method.[15–20] After anesthesia with 2% isoflurane, the abdominal hair of the mouse was removed with depilatory cream, the surgical area was disinfected with iodine, and an approximately 2–3 cm long incision was made along the midline of the abdomen to fully expose the segment of infrarenal abdominal aorta, and branch arteries were separated and ligated. A PE-10 tube was inserted into the abdominal aorta to continuously infuse PPE solution for 5 minutes under the control of a syringe pump. After recovery from surgery, all mice were returned to animal facility and housed in individual cages. After 14 days of PPE infusion, all mice were sacrificed by carbon dioxide inhalation for aorta sample harvesting.

2.3 | Aortic diameter measure

In mice infused with PPE, abdominal aortic photography and outer diameter measurement were performed using a microscope camera during surgery (recorded as day 0 for baseline diameter) and 14 days after surgery.[21–23] If the diameter of the abdominal aorta dilated by more than 50% on day 14 after surgery, we assumed that AAA was successfully induced.[24]

2.4 | Histological and immunohistochemical (IHC) analysis

Aortic aneurysmal segments were embedded in OCT compound and continuous sectioning for histological analysis was performed. Hematoxylin–eosin (H&E) staining and elastic van Gieson (EVG) staining were conducted according to commercial kit instructions. The standard streptavidin-biotin-peroxidase complex method was used for IHC staining. Staining of SMCs (α-actin) and endothelial cells (CD31) was mainly used to evaluate the cellular composition of the proliferative intima. IHC staining of inflammatory cells, including macrophages (CD68), T cells (CD4 and CD8, respectively), and B cells (B220), showed infiltration of inflammatory cells in hypertrophic intima. Expression of intimal-infiltrated inflammatory cell-secreted matrix metalloproteinases (MMP) 2 and 9 was also detected by IHC staining, and can be used to analyze their possible role in AAA progression. Macrophages and MMP2 and 9 expression levels were quantified as a positively stained areas in the IH lesion using imaging software (WinRood 6.5, Mitani Co. Ltd., Tokyo, Japan). The densities of $CD4^+$ T cells, $CD8^+$ T cells and $B220^+$ B cells in IH lesions were quantified as the number of positively stained cells per aortic cross-section (ACS). All the main chemicals and antibodies used in the study are summarized in Table S1.

2.5 | Incidence of IH in aneurysmal aortas

H&E and EVG stained sections of all aneurysmal aortas were observed under a microscope, and the number of samples with IH was counted and the incidence rate calculated. All samples were divided into two groups – those with and without IH – and the increase

in aortic outer diameter between the two groups was compared. Among the samples with IH, the lesions were graded as mild or severe hyperplasia according to whether the neointima constituted more than 50% of size of the lumen.

2.6 | Statistical analysis

GraphPad Prism 9.0 was used for statistical analysis and quantitative data were showed as means ± standard deviation (SD). The comparative data from the two groups were first tested for normal distribution. For normal distributed data, Student's *t* test was performed; otherwise, the non-parametric Mann–Whitney test was used. For two time point data, two-way ANOVA followed by a multiple comparisons test was used to determine significance between different groups, and $p < 0.05$ was assumed to indicate a statistically significant difference.

3 | RESULTS

3.1 | Incidence of IH in PPE-induced AAA mouse models

We analyzed the IH prevalence in 42 PPE-induced AAA mouse models that were included in this retrospective study. Among them, 12 AAA mouse models with IH were found, while 30 mice had no similar intimal lesions. In our laboratory, the incidence of IH in mice after PPE modeling was 29% (12/42) (Figure 1A). Of the 12 samples, only two could be graded as 'severe'. Statistical analysis of the outer diameters of AAA segments in mice with and without IH revealed that the average diameter of aneurysmal aortas in the group with IH (1.27 mm) was slightly larger than that in the group without IH (1.23 mm), but the statistical difference was not significant (Figure 1B). The aorta diameter over baseline between the two groups was also similar on day 14 after PPE infusion (Figure 1C).

3.2 | The histological characteristics of IH in aneurysmal aorta

Under the microscope, a clear vascular wall structure, neatly arranged SMCs, and continuous elastic lamina can be seen in normal non-aneurysmal abdominal aorta (Figure 1D). After PPE infusion, the abdominal aortic lumen was significantly dilated on day 14, the vascular structure was disordered, the medial SMCs were depleted, the elastin was broken/degraded, and obvious inflammatory cell diffuse infiltration was observed (Figure 1D). In 12 of 42 mice, the aneurysmal lesion was accompanied by IH, and a thickened intima with inflammatory cell components arranged in a disorderly and dispersed manner was observed, especially in samples with severe IH. Accumulation of leucocytes was also more obvious (Figure 1D).

3.3 | SMCs, not endothelial cells, are the main cellular components of IH

In a general model of IH, proliferating and migrating SMCs and endothelial cells are the main cellular components of the lesions.[25] IHC staining of SMCs and endothelial cells showed that the number of proliferating endothelial cells was rare in AAA combined with a mild IH lesion, and endothelial cells were occasionally seen in severe IH lesions (Figure 2). However, the SMC-positive staining area was larger than that of endothelial cells and morphologically an irregular arrangement of the positive staining cells was seen (Figure 2). In severe IH lesions, many diffuse infiltrating inflammatory cells were also seen.

3.4 | Macrophages are the main infiltrated leucocyte subset in IH lesions

Inflammatory cells are involved in the progression of aortic injury-induced IH. IHC staining of the main leucocyte subtypes was conducted. The results showed that there was obvious macrophage infiltration in the IH lesions of the AAA mouse models, especially in mice with severe IH (Figure 3A). Other leucocyte subsets, including $CD4^+$ T cells, $CD8^+$ T cells and B cells, showed only a lower number of positively staining cells in the IH lesions (Figure 3A). Quantitative analysis also showed that leucocytes accumulated significantly more in severe IH lesions than in mild IH lesions in aneurysmal aortas of mice (Figure 3B–D).

3.5 | The expression of MMP2 and MMP9 in IH lesions

MMPs secreted by inflammatory cells contribute to the progression of injury-induced vascular remodeling. IHC staining analysis showed high expression of MMP2 in the area of the IH lesions (Figure 4). However, MMP9 was only overexpressed in severe IH lesions but not in mild lesions, which may be related to the different numbers of leucocytes infiltrating the lesional segments of the aorta (Figure 4).

4 | DISCUSSION

AAA and atherosclerosis are two common aortic diseases and are typical cases of systemic metabolic disorders and inflammatory reactions leading to local vascular lesions.[26,27] AAA is an aortic medial disease, common in the elderly and sometimes associated with atherosclerosis.[27,28] In both human and large animal models, IH may be a risk factor for atherosclerosis, especially in coronary artery.[6] Increasing evidence indicates that IH caused by various injuries is not only an important vascular remodeling event after endovascular repair, but may also be involved in the regulation of atherosclerotic diseases.[29–32] However, there are few laboratory and clinical

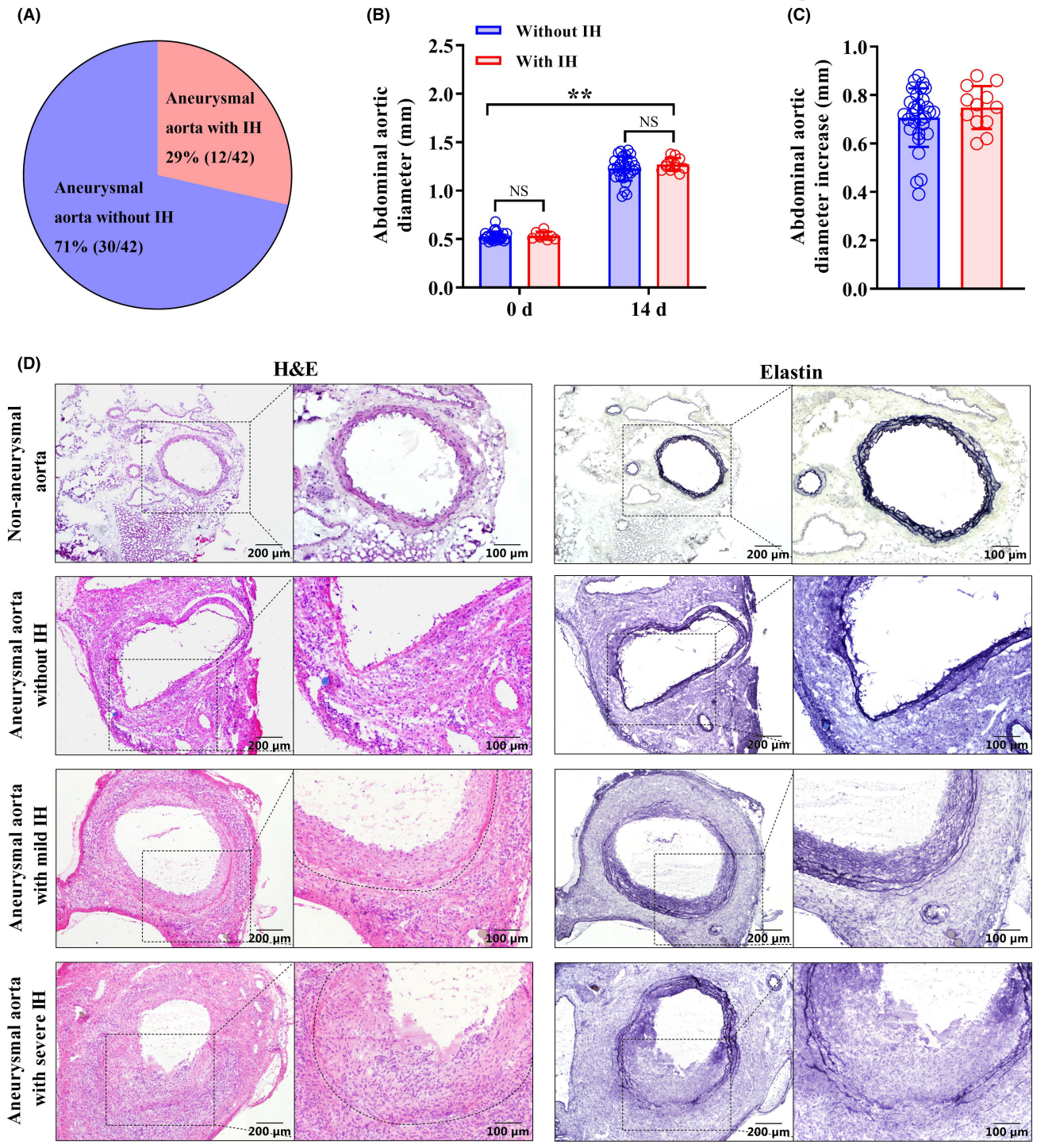

FIGURE 1 Incidence of IH in aneurysmal mouse aortas and its histological characteristics. (A) Incidence of IH in PPE-induced AAA mouse models. (B) Aortic outer diameters on day 0 (baseline level) and day 14 after PPE infusion in mice with or without IH. NS, not significant; IH, intimal hyperplasia. Two-way ANOVA followed by two group comparison was performed, $^{**}p < 0.01$. (C) The aortic outer diameters increase in mice with or without IH. Student's *t* test for two group comparison was performed. (D) Representative micrographs of H&E and EVG staining of non-aneurysmal abdominal aorta and aneurysmal aorta with or without IH (mild or severe) in mice on day 14 after PPE infusion. The IH appears to reduce the lumen of the aneurysm aorta.

studies that clarify whether IH is involved in the occurrence and development of aneurysms. During the creation of PPE-induced AAA mouse models in our laboratory, it was found that some mice also developed IH and formed aneurysms at the same time. This study describes the histopathological characteristics of this type of IH and discusses its possible impact on AAAs.

This retrospective study found that the incidence rate of IH in the PPE-induced AAA models was less than 30%, and most of

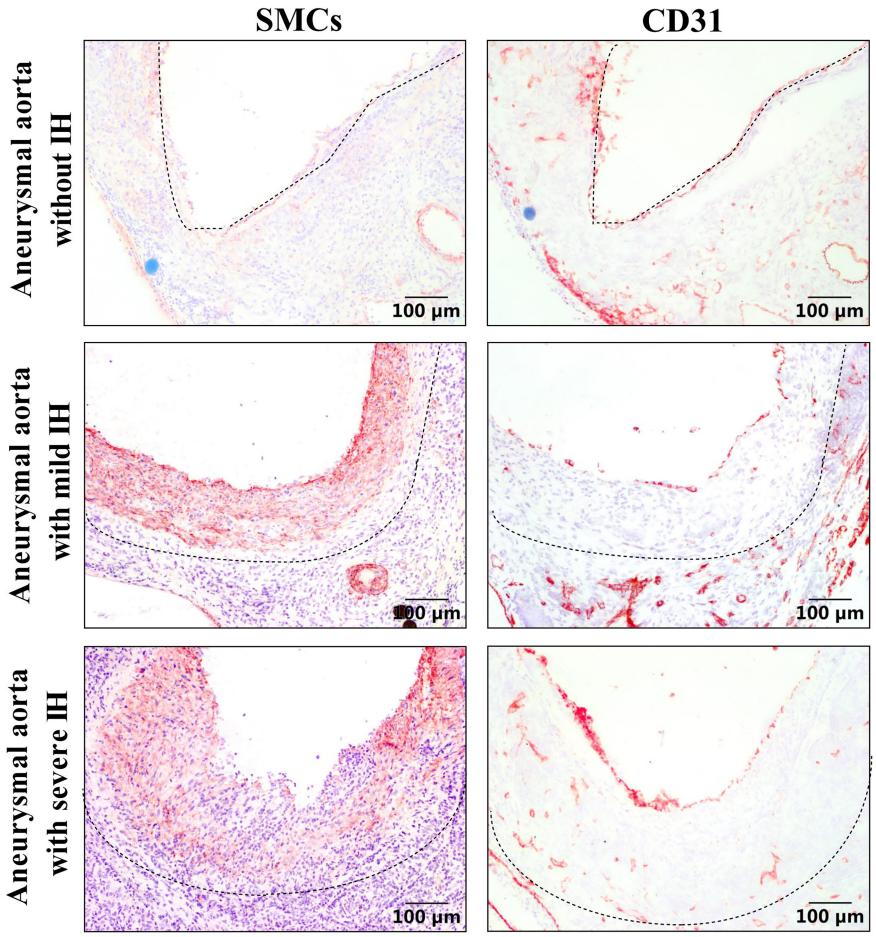

FIGURE 2 Representative immunohistochemical (IHC) micrographs of smooth muscle cells (SMCs) and endothelial cells. IHC analysis of vascular SMCs (α-actin) and endothelial cells (CD31 labeled) was performed to show the cell components of IH in aneurysmal aortas. IH, intimal hyperplasia.

lesions were mild, with only about 5% (2/42) showing severe hyperplasia. We analyzed the histological characteristics of IH in mice with aneurysms and found that it was not completely consistent with arterial ligation-induced IH.[25,33] Excessive SMC and endothelial cell proliferation and migration are key events in the development of IH,[25,34,35] although SMCs are the main cellular components of aneurysmal IH, while endothelial cells are rare in the lesion. Regardless of whether the IH lesion is mild or severe, massive macrophage infiltration can be observed. In severe hyperplasia lesions, scattered distribution of other subtypes of leucocytes can also be observed. The expression of MMP2 secreted by leucocytes was increased in all IH lesions; however, the expression of MMP9 was significantly increased only in severe hyperplasia lesions. The hyperplasia lesion exhibited inflammatory characteristics in histology, which may affect the development of media aneurysmal lesions and contribute to the progression of AAAs.

We compared and analyzed the aortic outer diameters in mice with and without IH, and found that the diameters were slightly larger in mice with IH than in mice without IH, but the statistical difference was not significant. These results suggest that the abundance of inflammatory macrophages in hyperplasia lesions may enhance local inflammation and promote aortic expansion, and locally overexpressed MMPs may be one of the contributors.

It should be pointed out that, in this study, we directly measured the aortic 'outer' diameter, and its size was not affected by IH lesions.[12,13,19] However, in clinical and laboratory research, one of the most commonly used methods of measuring the aortic 'inner' diameter is with ultrasound equipment.[36,37] IH may affect the measurement of the aortic 'inner' diameter due to occlusive narrowing of the lumen. This study also provided a reasonable explanation for the discovery in experimental studies that ultrasound measurement of diameters showed no significant dilation, but after aorta sample collection, the aneurysm lesion was found to be more severe than estimated based on ultrasound data. In a severe IH mouse aneurysm model, measurement of both the inner and outer diameters of aorta at the time of euthanasia can help accurately evaluate the condition of aneurysm lesions.

In this study, it was found that in a PPE-induced AAA model, the incidence of IH, especially severe hyperplasia, is not high and generally does not affect the evaluation of aneurysms in this model. Even so, researchers do not want IH to occur in aneurysm models to avoid affecting the main research aims. The occurrence of IH in a PPE-induced mouse aneurysm model may be the result of mechanical dilation during PPE infusion causing intimal damage, since IH is normally a response of the arteries to injury stimuli. IH may also be due to a technical problem. The tip of the PE infusion tube, when inserted into the lumen, can injure the intima or even the media, resulting in reactive vascular remodeling. Therefore, the incidence of IH can be reduced by strengthening surgical practice and improving surgical skills to avoid direct injury to the aorta during surgery.

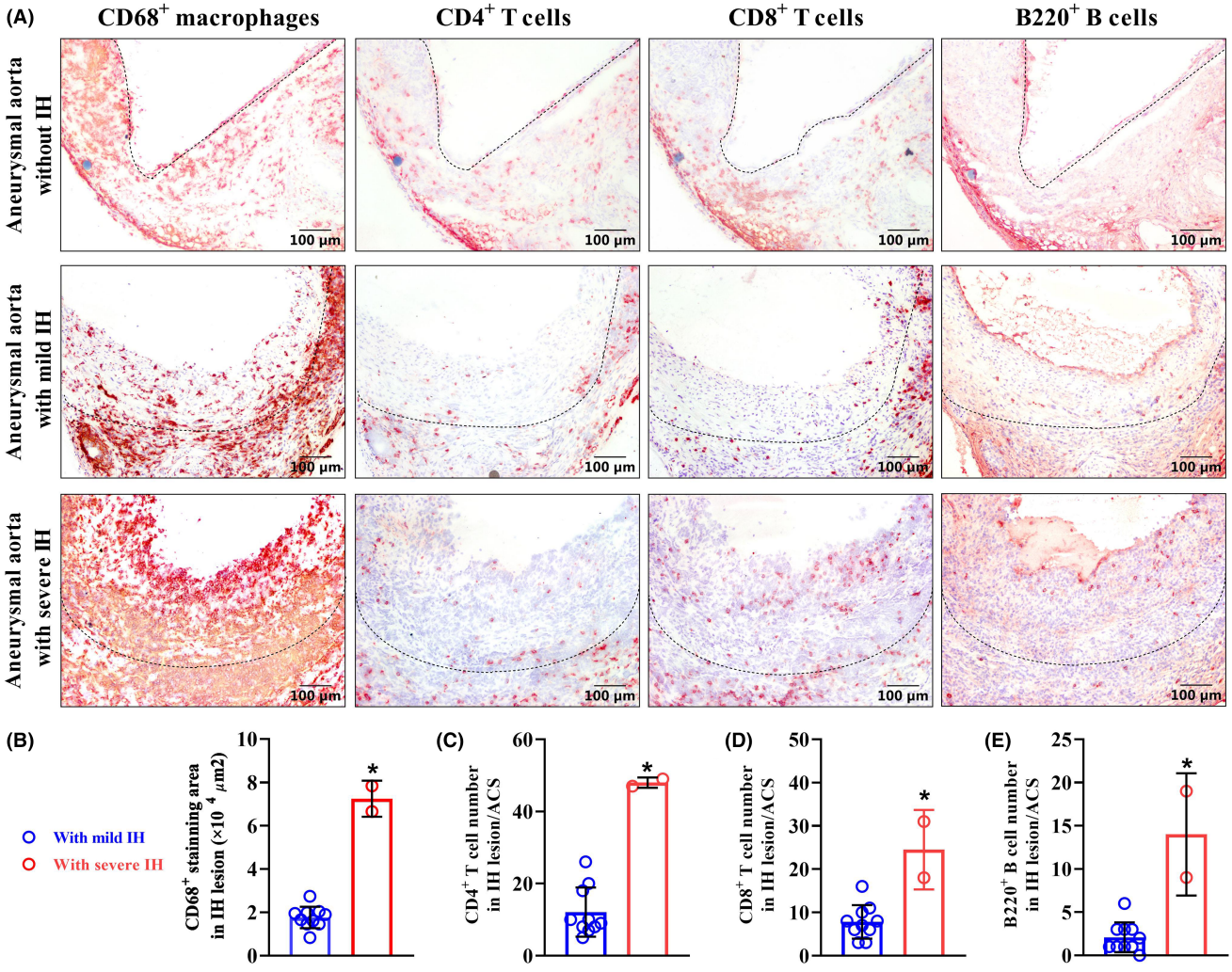

FIGURE 3 Infiltrated leucocyte subsets in IH lesions. (A) IHC staining of macrophages, $CD4^+$ T cells, $CD8^+$ T cells and B cells was performed in aneurysmal aorta samples with or without IH lesion. (B–E) Quantification of infiltrated leucocyte subsets in IH lesions. The non-parametric Mann–Whitney test was was performed, $^*p < 0.05$. IH, intimal hyperplasia.

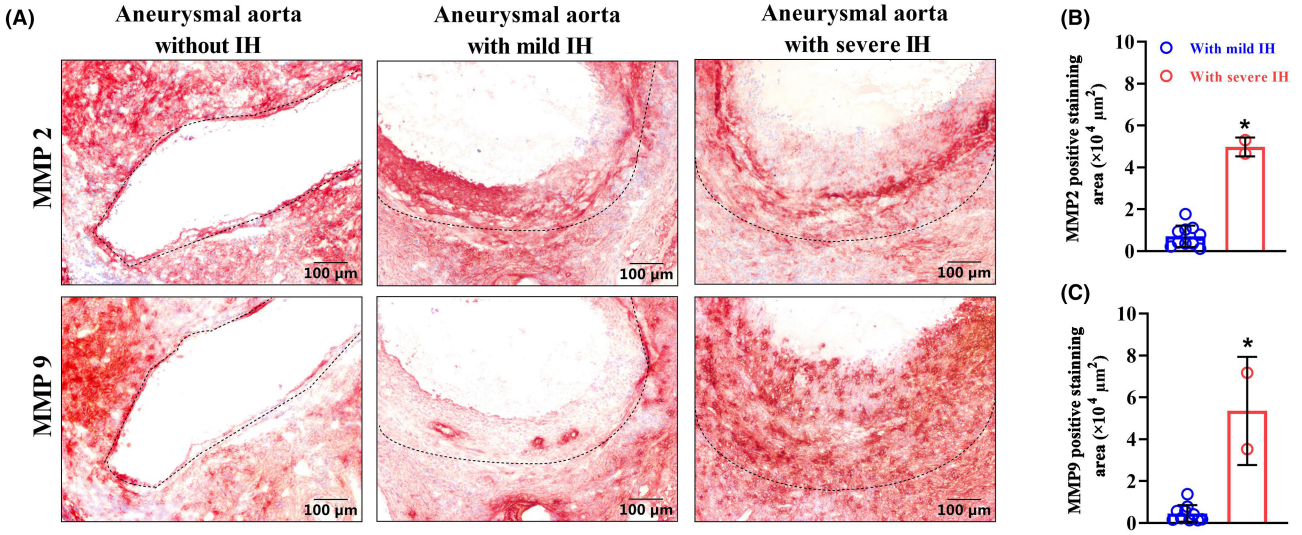

FIGURE 4 The expression of MMP2 and MMP9 in IH lesions. (A) IHC staining of lesional local cell-secreted MMP2 and MMP9. (B, C) Quantitative analysis of MMP2 and MMP9 expression in mild or severe IH lesions. The non-parametric Mann–Whitney test was performed, $^*p < 0.05$. IH, intimal hyperplasia.

In summary, in this study we first describe the occurrence of IH and its histological characteristics in a PPE-induced mouse AAA model, and analyze the potential causes and the impact on AAA progression. This study also suggests that in future clinical and laboratory research, in addition to studying IH after endovascular repair, there is a need for greater observation of whether IH is present during the occurrence and progression of aneurysms and its possible effects.

AUTHOR CONTRIBUTIONS

Sihai Zhao, Yankui Li, Baohui Xu and Enqi Liu designed and supervised this experiment. Meng Li, Panpam Wei, Haole Liu, Kexin Li, Naqash Alam and Haiwen Hou performed animal experiments. Meng Li, Panpam Wei, Haole Liu and Kexin Li conducted the histological analysis. Jie Deng and Sihai Zhao analyzed and interpreted the data. Sihai Zhao and Yankui Li wrote the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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