

Peer Review File

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Reviewer A

General comment: My primary criticism of the work concerns the observed recurrence rate of ~17%. Generally, the incidence of recurrent spontaneous pneumomediastinum is approximately 1%, as noted in the manuscript and other review articles. Some elaboration on possible reasons for the high observed rate of recurrence would strengthen the study. Does the age range (6-18 years) differ from the demographics of other studies citing a ~1% rate of recurrence? Are there different incidences of co-morbidities (e.g. congenital pulmonary atresia) that may explain the 17 fold difference in recurrence rates observed?

Reply to the General comment: We appreciate the reviewer's suggestion, which has helped us to strengthen this study, as the reviewer mentioned. According to a published literature review of spontaneous pneumomediastinum, the mean age range is generally between 18 and 27 years (Takada et al. Ther Adv Respir Dis 2009). In a report with the largest cohort (n=62), the reported median age was 30 years (range, 18-84 years). In comparison, the age range of our patient cohort (median, 16 years; range, 12–26 years) is relatively lower. Additionally, despite their young age, 17% of the patients had a medical history of respiratory-related illness and 30% of patients had radiological findings of bulla or bleb on CT scan (Table 1). The characteristics of our cohort might have affected the higher recurrence in our study cohort compared with that of previously published studies. This was described in the Discussion section.

Changes in the text:

Discussion (page 13, lines 258-266)

Fourth, according to a published literature review of spontaneous pneumomediastinum, the mean age range is generally between 18 and 27 years (4). In a report with the largest number of cohort (n=62), the reported median age was 30 years (range, 18-84 years) years old. In comparison, the range of age of our patient cohort (median, 16 years; and range, 12 – 26 years) is relatively lower. Additionally, despite their young ages, 17 % of the patients had a medical history of respiratory-related illness and 30% of patients had radiological findings of bulla or bleb on CT scan (Table 1). Patient characteristics in our cohort mentioned above might have affected the higher recurrence rate in our study cohort compared with previously published studies.

Comment 1: Page 5, line 125: "Most of these patients were men (87%)" implies that the patients are adult men 18 years of age or older. This is particularly important given the age range of 13-18 years that presumably includes multiple male children rather than men. Replace "men" with "males" for clarity.

Reply to comment 1: We appreciate and agree with the reviewer's suggestion. We replaced "men" with "males" accordingly throughout.

Comment 2: Page 5, lines 125-126 and Table I: The text states an age range of 13-18 years, but a range of 13-19 years is given in Table I column 4 row 1. This is likely a typo, but worth correcting.

Reply to comment 2: We appreciate the reviewer's point. However, 13-19 was not a typo but a range (interquartile range) for 25 patients without recurrent SPM. The difference between cohorts was the reason why the ranges were different.

Comment 3: Page 16, Figure 1 legend. The final sentence explaining what the Macklin effect is would be more appropriate in the Introduction section of the manuscript.

Reply to comment 3: We appreciate the reviewer's suggestions. We agree. The explanation of the Macklin effect was removed from the legend of Figure 1, and the following sentence is added to the Introduction section:

Changes in the text:

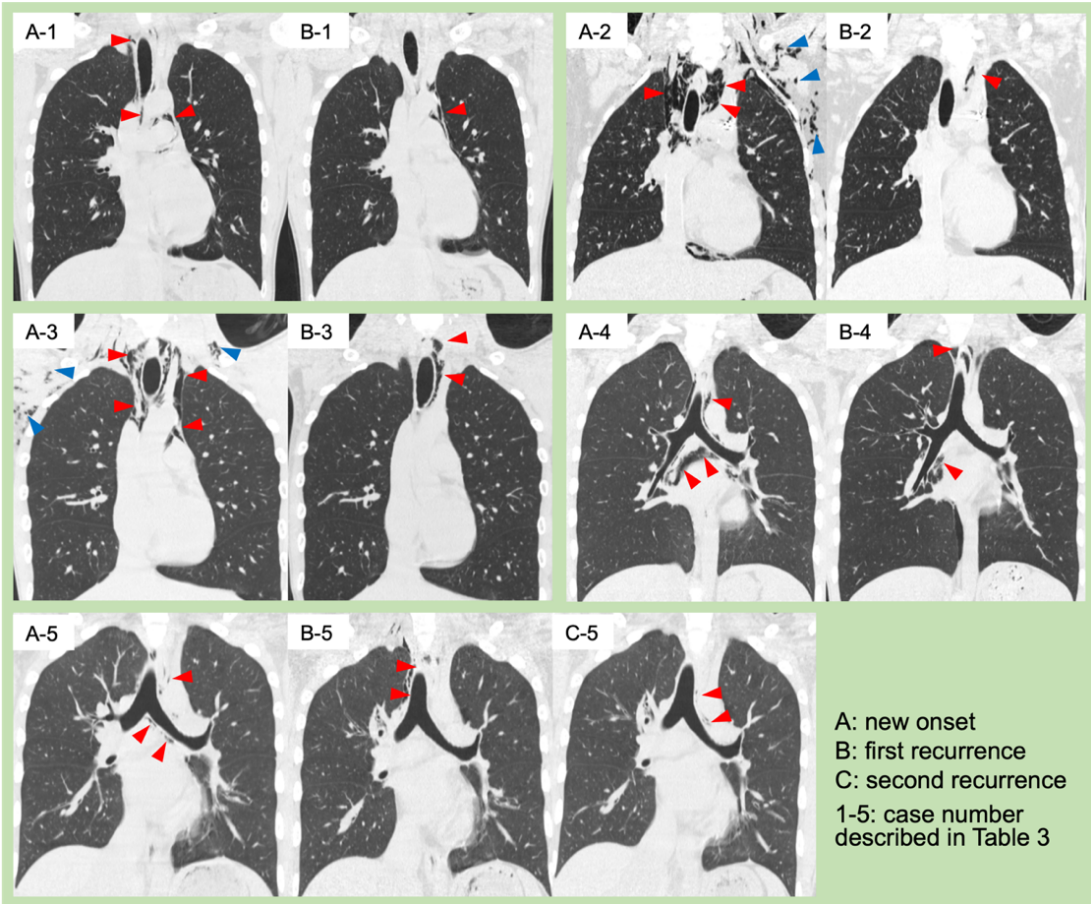
Introduction (page 5, lines 67-77)

Spontaneous pneumomediastinum (SPM) is a rare entity defined as the presence of free air in the mediastinum that is not associated with any noticeable cause such as chest trauma. It has been proposed that the pathophysiology of SPM involves rupture of the alveoli caused by a rapid increase in alveolar pressure, which has been referred to as the Macklin effect [1]. The Macklin effect refers to the phenomenon of a large pressure gradient between the alveoli and lung interstitium inducing alveolar rupture and the subsequent release of free air along the pulmonary vessels and bronchus in the limited area of the lungs coursing toward the mediastinum. Studies have suggested that SPM frequently presents with the sudden onset of symptoms, such as chest pain, in young adults with or without events, such as physical exercise, that can trigger a rapid increase in intrathoracic pressure [2, 3].

Comment 4: Page 17, Figure 2 legend is confusing because it does not follow the standard JTD figure formatting of Figure 2A, 2B, 2C, ect.

Reply to comment 4: We thank the reviewer for this comment. We have modified Figure 2 to avoid the confusion.

Figure 2



Reviewer B

Abstract

1-Most patients were men (87%). The median 35 age of the patients was 16 years (range, 12-26 years). This should be in the results section.

Reply: We thank the reviewer for this comment. We moved the sentences accordingly.

Introduction

This needs to be stronger.

Reply: We thank the reviewer for this comment. We additionally described the pathophysiology of spontaneous pneumomediastinum in Introduction.

Changes in the text:

Introduction (page 5, lines 67-77)

Spontaneous pneumomediastinum (SPM) is a rare entity defined as the presence of free air in the mediastinum that is not associated with any noticeable cause such as chest trauma. It has been proposed that the pathophysiology of SPM involves rupture of the alveoli caused by a rapid increase in alveolar pressure, which has been referred to as the Macklin effect [1]. The Macklin effect refers to the phenomenon of a large pressure gradient between the alveoli and lung interstitium inducing alveolar rupture and the subsequent release of free air along the pulmonary vessels and bronchus in the limited area of the lungs coursing toward the mediastinum. Studies have suggested that SPM frequently presents with the sudden onset of symptoms, such as chest pain, in young adults with or without events, such as physical exercise, that can trigger a rapid increase in intrathoracic pressure [2, 3].

Materials and Methods

1- The PSM grading system should be explained better for the benefit of a general reader.

Reply: We thank the reviewer for the suggestion, which we agree with. We have added a new figure demonstrating the SPM grading system.

Figure 1

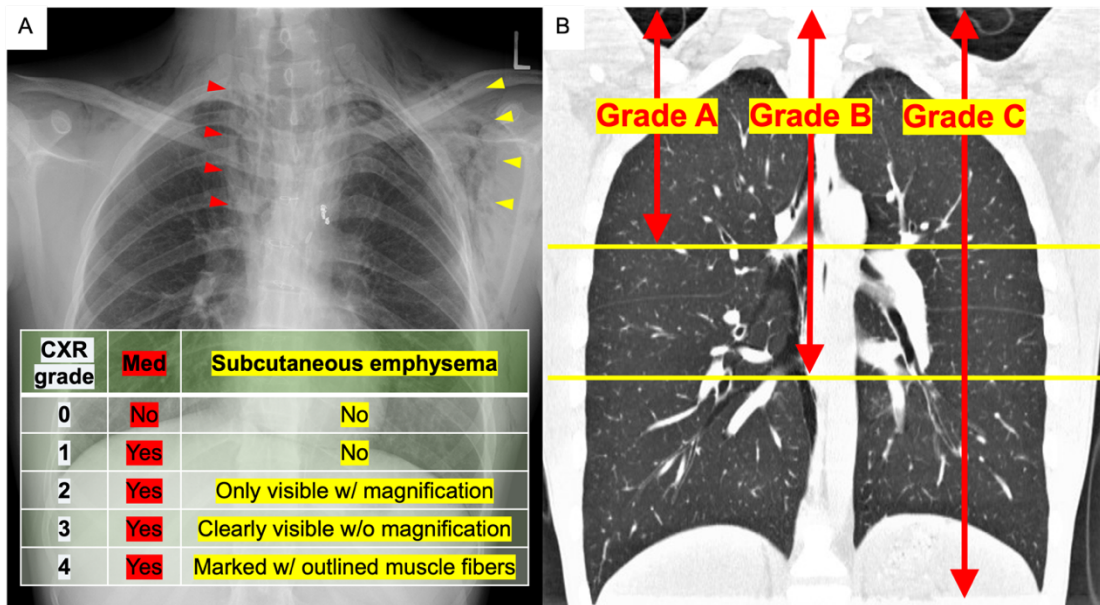


Figure legend

Figure 1.

The radiological grading system of spontaneous pneumomediastinum (SPM). (A) Representative case of grade 3 in the grading system based on chest radiography (CXR) grading of SPM showing air space in the mediastinum (red arrowheads) plus subcutaneous emphysema (yellow arrowheads) clearly. The table in the figure demonstrates each CXR grade with radiological findings of the mediastinum and subcutaneous emphysema. (B) Schema of computed tomography-based grading system of SPM. Grade A: free air confined to the mediastinum superior to the level of the tracheal carina. Grade B: free air confined to the mediastinum superior to the caudal end of the inferior pulmonary vein. Grade C: free air extending from the superior to the inferior mediastinum.

CXR grade, grade based on chest radiography; Med, mediastinum emphysema.

2- If the general condition was stable, then the blood test showed acceptable results. What does this mean?

Reply: We thank the reviewer for this comment. We rewrote this sentence as follows:

Methods (page 7, lines 124-126)

If the general condition of a patient was stable, the blood test showed acceptable results, and the CXR did not show worsening of the pneumomediastinum, then the patient was discharged.

Results

1- This needs a major revision. Figures and tables should supplement the discussion

Reply: We thank the reviewer for this comment. Our major study focus was recurrence of SPM; therefore, we showed a comparison between no recurrence and recurrence in the total cohort (Tables 1 and 2) and between initial SPM and recurrent SPM in patients with recurrent SPM (Figure 2 and Table 3). Figure 3 [previous Figure 1] showed representative radiological findings with the Macklin effect, but not the main results. Therefore, we modified the order of paragraphs in the Results section; specifically, the first paragraph was moved to the last in the Results section. In addition, we added references of figures and tables in the Discussion section to clarify supportive data in each discussion.

Changes in the text:

Discussion (page 11, lines 210-219):

In this study, we examined the clinical features of 30 patients with SPM, including five patients with SPM recurrence. This novel study had some strengths. For example, this is the first study to provide comparative data and radiological images of the initial SPM and SPM recurrence (Figure 2, Table 3), thereby demonstrating that the clinical presentation during recurrence is similar to or less aggressive than that at the time of the initial onset. Furthermore, this is the first study to statistically analyze the predisposing factors for SPM recurrence by using various factors, including the radiologic extent of SPM and laboratory data, suggesting that the presence of preexisting lung diseases, such as bronchial asthma, is a potential predisposing factor for recurrence (Table 1, 2).

2- In terms of trigger factors, 16 patients (53%) had performed physical activity that could have increased the intrathoracic pressure at the initiation of SPM. The most common trigger was a ball game exercise (9 patients), followed by swimming/diving (2 patients) and vomiting (2 patients). Numbers do not add up!

Reply: We thank the reviewer for this comment. We have changed the statement according to the reviewer's suggestion.

Results (page 8, lines 151-153)

The most common trigger was a ball game exercise (9 patients), followed by swimming/diving (2 patients), other exercise (2 patients), vomiting (2 patients), and using a loud voice (1 patient).

3- The median duration of hospitalization was 8 days (range, 6-9 days). Could the authors explain the reason for the long stay of 8 days?

Reply: We thank the reviewer for this comment. During this study period, we treated patients in the hospital setting until we confirmed their emphysema was mostly disappeared, which might have contributed to our relatively longer hospital stay. Additionally, the relatively

lower medical care costs in Japan compared with that in other developed countries might also have contributed to it.

Changes in the text:

Discussion (page 12, lines 236-243)

In this study, the median length of the hospital stay was 8 days, which was relatively longer than that reported by other studies. During the study period, we treated patients in the hospital setting until we confirmed that their emphysema mostly disappeared, which might have contributed to the relatively longer hospital stay. Additionally, the relatively lower medical care costs in Japan compared with those in other developed countries might have contributed to the relatively longer hospital stay. However, none of the patients had any exacerbating conditions, including emphysema, during hospitalization.

4- What is BT?

Reply: We thank the reviewer for this valuable comment. BT refers to body temperature. We replaced “BT” with “ body temperature” throughout.

Discussion-

1- The authors should explain why Asthma is a risk factor. There is evidence for this and this is an important discussion point.

Reply: We thank the reviewer for this comment. Several literatures suggested an association between asthma and SPM. We have discussed this point in the Discussion section as follows.

Changes in the text:

Discussion (page 11, lines 220-226)

SPM was first described by Hamman in 1939 [7]. Since then, many case reports and literature have been published, and the potential causes of SPM have been discussed. Childhood asthma is one of the known predisposing conditions for SPM [8-10]. Among patients with childhood asthma visiting emergency departments, the reported incidence of SPM was 0.3% [8], which was higher than the general incidence of SPM of 0.001% to 0.01% [11]. However, many reports suggest that SPM recurrence is rare.