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CLINICAL FORUM

Spontaneous pneumomediastinum in patients with severe acute respiratory syndrome

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ABSTRACT: Spontaneous pneumomediastinum (SP) unrelated to assisted ventilation is a newly recognised complication of severe acute respiratory syndrome (SARS). The objective of the present study was to examine the incidence, risk factors and the outcomes of SP in a cohort of SARS victims from a community outbreak.

Data were retrieved from a prospectively collected database of virologically confirmed SARS patients. One hundred and twelve cases were analysable, with 13 patients developing SP (11.6%) at a mean±SD of 19.6±4.6 days from symptom onset.

Peak lactate dehydrogenase level was associated with the development of SP. SP was associated with increased intubation and a trend towards death. Drainage was required in five cases. For patients who survived, the SP and/or the associated pneumothoraces took a median of 28 days (interquartile range: 15–45 days) to resolve completely.

In conclusion, spontaneous pneumomediastinum appeared to be a frequent complication of severe acute respiratory syndrome. Further research is needed to investigate its pathogenesis.

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Severe acute respiratory syndrome (SARS) has been documented to be caused by a novel coronavirus (SARS-CoV) [1–3], which satisfied the Koch's postulations for causation [4, 5]. At the time of writing, the numbers of probable SARS cases has reached 8,422 globally [6]. Two previous studies have noted the occurrence of spontaneous pneumomediastinum (SP) occasionally in patients with SARS, unrelated to assisted ventilation [7, 8]. However, SP in SARS has not been systematically studied. In the present study the incidence, risk factors and the implications of the development of SP in SARS sufferers were examined.

Methods

The present study examined SP in SARS patients by retrospective analysis of a prospectively collected SARS database. Patients included in the study were consecutive SARS patients admitted to the United Christian Hospital (Hong Kong, SAR, China) during a community outbreak from March 24 to April 28, 2003. Patients met a modified WHO definition of SARS, which included fever ($\geqslant$38°C), cough or shortness of breath, new pulmonary infiltrates on radiological examination, in the absence of an alternative diagnosis, together with virological documentation of SARS-CoV infection (paired serology and/or positive RT-PCR for SARS-CoV from clinical specimens). All patients were treated with a standard protocol of broad spectrum antibiotics, ribavirin and a tailing regimen of corticosteroids [9]. The clinical, haematological, biochemical, radiological and virological findings were prospectively entered into a preset database, according to previous publications [1, 7].

Chest radiographs were taken at intervals of 1 to 3 days, depending on clinical need. SP was defined as the presence of gas in the mediastinum, occurring before assisted ventilation. For equivocal cases, high resolution computed tomography (HRCT) of the thorax would be utilised to detect this complication. All chest radiographs and HRCT were interpreted by thoracic radiologists.

Results were expressed as mean±SD unless otherwise specified. Univariate analyses of potential factors associated with the occurrence of SP were performed with the unpaired t-test, Mann-Whitney U-test or Fisher's exact test where appropriate. A two-tailed p-value of <0.05 was considered statistically significant.

Results

There were 123 virologically confirmed SARS patients admitted to hospital during the study period. Altogether, there were 24 patients with pneumomediastinum: 13 had SP and 11 developed pneumomediastinum with or without pneumothorax after the commencement of assisted ventilation. The baseline characteristics were not significantly different between those with SP and those with ventilator-associated barotraumas (VAB) (table 1). However, the cumulative dose of methylprednisolone received by the SP group prior to the onset of pneumomediastinum was significantly lower than that received by the VAB group (median: 2.0 *versus* 3.0 g, respectively, p=0.003).

Eleven cases of VAB were excluded from further analysis. This left 112 cases for analysis, including 13 cases complicated by SP. The mean age of the 112 cases was 38.8±12.7 yrs. There were 46 males (41.1%) and 66 females (58.9%). The initial chest radiographs appeared normal in 28 (25%)

Table 1. – Comparisons of initial clinical, radiological and laboratory features between severe acute respiratory syndrome (SARS) patients with spontaneous pneumomediastinum (SP) and ventilator-associated barotraumas (VAB)

Parameters	SP	VAB	p-value
Subjects n	13	11	
Fever	13 (100)	11 (100)	1.0
Chills	8 (61.5)	6 (54.5)	1.0
Rigors	6 (46.2)	6 (54.5)	1.0
Myalgia	8 (61.5)	10 (90.9)	0.166
Cough	8 (61.5)	7 (63.6)	1.0
Dyspnoea	9 (69.2)	5 (45.8)	0.408
Diarrhoea	7 (53.8)	7 (63.6)	0.697
Ever-smoker	0 (0)	0 (0)	1.0
Normal chest radiograph	2 (15.4)	4 (36.4)	0.357
Multilobar involvement	3 (23.1)	1 (9.1)	0.596
Haemoglobin $g \cdot dL^{-1}$	13.5 (12.7–14.9)	14.1 (13.5–14.7)	0.531
Lymphocyte $\times 10^9 \cdot L^{-1}$	0.8 (0.6–1.4)	0.7 (0.6–0.8)	0.424
Platelet $\times 10^9 \cdot L^{-1}$	191 (144–232)	162 (146–197)	0.569
Initial LDH $IU \cdot L^{-1}$	412 (357–505)	344 (293–523)	0.207

Data are presented as n (%) or median (interquartile range) unless otherwise stated. SP: spontaneous pneumomediastinum; VAB: ventilator-associated barotraumas.

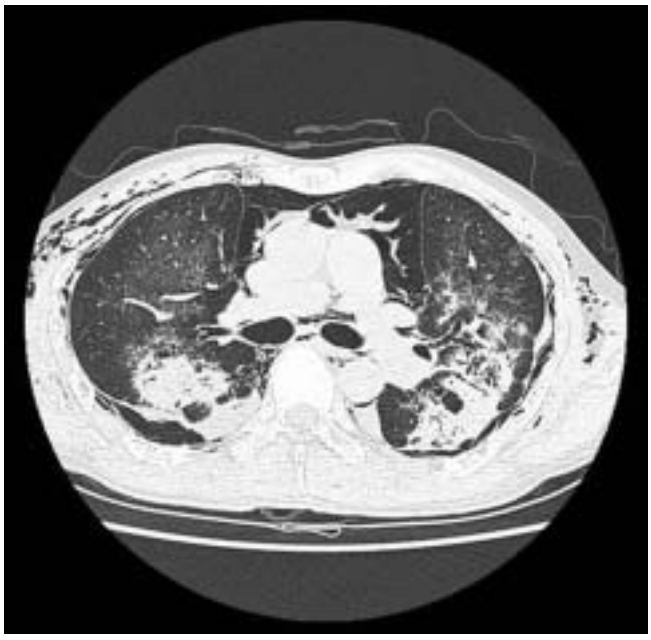

Fig. 1. – High-resolution computed tomography (HRCT) thorax of a patient with severe acute respiratory syndrome (SARS) complicated by spontaneous pneumomediastinum, subcutaneous emphysema and rims of bilateral pneumothoraces.

patients, who had HRCT findings compatible with SARS. Multilobar involvement was evident on presentation in 21 (18.8%) cases.

Thirteen patients developed SP (11.6%) during the course of SARS, at a mean of 19.6±4.6 days from symptom onset. Of these 13 cases, one had concomitant subcutaneous emphysema, three had simultaneous spontaneous bilateral pneumothoraces, and two had subsequent progression into subcutaneous emphysema and bilateral pneumothoraces. One patient had pneumomediastinum, bilateral pneumothoraces and subcutaneous emphysema (fig. 1). Bilateral tube thoracostomies were necessary in the five cases complicated by bilateral pneumothoraces, of whom one case received chemical pleurodesis; the rest of the SP was managed conservatively. No patient in this series had isolated pneumothorax and all pneumothoraces occurred concomitantly with, or were preceded by, SP.

Univariate analysis showed that only peak serum lactate dehydrogenase (LDH) was associated with the development of SP (p=0.001). Other factors, including viral load in the nasopharynx, cumulative dose of corticosteroids, initial radiographical findings and other laboratory parameters were not associated with the development of SP (table 2).

Of the 13 patients with SP, five were intubated and two of the intubated patients died; two additional patients with SP died without intubation on surrogates' requests, giving a total of four deaths in SP patients. Patients who developed SP had a statistically higher chance of intubation (p=0.015) and showed more of a trend towards death (p=0.057) (table 1). For patients who survived, the SP and/or the associated pneumothoraces took a median of 28 days (interquartile range: 15–45 days) to resolve completely.

Discussion

SP developed in 11.6% of the present study SARS cohort at 19.6±4.6 days from symptom onset. High peak LDH level was associated with its development. Development of SP was associated with significant intubation rate and mortality. In survivors, resolution of SP was slow.

Pneumomediastinum is the presence of extra-alveolar air in the mediastinum. Free air leaks from ruptured alveoli, dissecting along the bronchovascular sheaths towards the mediastinum [10]. The incidence of SP was reported to be one in 32,896 in the general population [11]. In immunocompetent hosts with pulmonary infections, air leak as a complication is uncommon, but it has been reported in staphylococcal pneumonia [12] and fungal pneumonia [13]. It has also been reported to complicate interstitial pneumonitis secondary to systemic lupus erythematosus [14] and bronchiolitis obliterans organising pneumonia [15]. In HIV infection, SP is reported in association with *Pneumocystis carinii* pneumonia in 9.5% and with tuberculosis in 6.8% of cases [16]. SP is also reported to complicate cytomegalovirus pneumonitis in patients with haematological malignancies [17] and idiopathic pneumonia syndrome after bone marrow transplantation [18].

It was interesting to note that isolated pneumothorax, without a preceding or concomitant pneumomediastinum, was not observed in the current series of patients. One possible explanation is that the current study examined the patients regularly by chest radiographs and/or HRCT. This might have given the authors an opportunity to witness a sequence of events that took place in these severely lung-damaged patients. The current authors postulate that alveolar rupture may occur in SARS as a result of severe diffuse alveolar damage [19] and cause interstitial emphysema. Air may then dissect along the bronchovascular sheaths into the mediastinum to manifest as SP initially, which may further progress to pneumothoraces and subcutaneous emphysema in some patients.

VAB in the current study was, by definition, not spontaneous and, therefore, could not be classified as SP. However, their clinical, laboratory and radiological features did not seem to be fundamentally different from those of SP. The higher dose of methylprednisolone received in patients with VAB *versus* those with SP was probably an indicator of the need for more intensive treatment in sicker patients. It is possible that both SP and VAP in SARS share similar pathogenic mechanisms, although mechanical ventilation may further aggravate barotraumas and air leak.

High peak LDH level, which might signify cellular damage,

Table 2. – Comparisons of potential risk factors and the outcomes of severe acute respiratory syndrome (SARS) patients with and without spontaneous pneumomediastinum (SP)

Parameter	No SP	SP	p-value
Subjects n	99	13	
Mean±SD age yrs	39.4±12.9	34.1±9.6	0.153
Male	38 (38.4)	8 (61.55)	0.138
Smoking status: nonsmoker, exsmoker, current smoker	92, 4, 3 (93, 4, 3)	13, 0, 0 (100, 0, 0)	0.612
Active comorbidity	13 (13.1)	3 (23.1)	0.394
Apparently normal chest radiograph on admission	23 (23.2)	5 (38.5)	0.305
Multilobar involvement on initial chest radiograph	20 (20.2)	1 (7.7)	0.456
Haemoglobin $g \cdot dL^{-1}$	13.5±1.6	14.2±0.8	0.052
Initial total peripheral WBC count $\times 10^9 \cdot L^{-1}$	6.3±2.1	7.5±2.7	0.055
Initial lymphocyte count $\times 10^9 \cdot L^{-1}$	0.9±0.5	0.8±0.3	0.458
Initial platelet count $\times 10^9 \cdot L^{-1}$	170±49	172±37	0.910
Initial urea $mmol \cdot L^{-1}$	4.1±1.2	4.4±1.1	0.475
Initial creatinine $\mu mol \cdot L^{-1}$	85.5±16.0	90.7±14.3	0.266
Initial LDH $IU \cdot L^{-1}$	379 (313–449)	344 (296–518)	0.663
peak LDH $IU \cdot L^{-1}$	583 (471–746)	863 (702–1485)	0.001
Cumulative methylprednisolone dose g	2.3±1.1	2.4±0.5	0.741
Viral load in NP specimen on presentation $\log_{10}$ RNA copies$\cdot mL^{-1}$	0 (0–5.0)	0 (0–4.6)	0.493
Viral load in NP specimen peak $\log_{10}$ RNA copies$\cdot mL^{-1}$	0 (0–5.3)	4.5 (0–6.6)	0.169
Intubation	10 (10.1)	5 (38.5)	0.015
Death	10 (10.1)	4 (30.8)	0.057

Data are presented as mean±SD, n (%) or median (interquartile range) unless otherwise stated; WBC: white blood cell; NP: nasopharyngeal; LDH: lactate dehydrogenase.

was associated with the development of SP. In contrast, viral load was not related to the development of SP, suggesting processes other than viral-induced cytolysis might be important in the pathogenesis of alveolar damage (*e.g.* immunopathological damage). In this connection, it is interesting to note that the onset of SP (mean: 19 days) occurs after the phase of viral replication (day 10), at a time when immunopathological damage is thought to be important [7].

In conclusion, spontaneous pneumomediastinum appeared to be a characteristic and frequent complication of severe acute respiratory syndrome. It portends a poor outcome. Further research is needed to investigate the pathogenesis of spontaneous pneumomediastinum in severe acute respiratory syndrome.

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