Cardiac septic pulmonary embolism

A retrospective analysis of 20 cases in a Chinese population

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Abstract

Based on the source of the embolus, septic pulmonary embolism (SPE) can be classified as cardiac, peripheral endogenous, or exogenous. Cardiac SPEs are the most common.

We conducted a retrospective analysis of 20 patients with cardiac SPE hospitalized between 1991 and 2013 at a Chinese tertiary referral hospital.

The study included 14 males and 6 females with a median age of 38.1 years. Fever (100%), cough (95%), hemoptysis (80%), pleuritic chest pain (80%), heart murmur (80%), and moist rales (75%) were common clinical manifestations. Most patients had a predisposing condition: congenital heart disease (8 patients) and an immunocompromised state (5 patients) were the most common. Staphylococcal (8 patients) and Streptococcal species (4 patients) were the most common causative pathogens. Parenchymal opacities, nodules, cavitations, and pleural effusions were the most common manifestations observed via computed tomography (CT). All patients exhibited significant abnormalities by echocardiography, including 15 patients with right-sided vegetations and 4 with double-sided vegetations. All patients received parenteral antimicrobial therapy as an initial treatment. Fourteen patients received cardiac surgery, and all survived.

Among the 6 patients who did not undergo surgery, only 1 survived. Most patients in our cardiac SPE cohort had predisposing conditions. Although most exhibited typical clinical manifestations and radiography, they were nonspecific. For suspected cases of SPE, blood culture, echocardiography, and CT pulmonary angiography (CTPA) are important measures to confirm an early diagnosis. Vigorous early therapy, including appropriate antibiotic treatment and timely cardiac surgery to eradicate the infective source, is critical.

Abbreviations: ATG = antithymocyte globulin, CT = computed tomography, CTPA = CT pulmonary angiography, CTV = computed tomographic venography, IE = infective endocarditis, IV = intravenous, LMWH = low-molecular-weight heparin, MRSA = methicillin-resistant Staphylococcus aureus, PICC = peripherally inserted central catheter, SPE = septic pulmonary embolism, TEE = transesophageal echocardiography, TTE = transthoracic echocardiography, UC = ulcerative colitis, V/Q = ventilation-perfusion, VSD = ventricular septal defect.

Keywords: echocardiography, heart, septic pulmonary embolism, surgery, vegetations

1. Introduction

Septic pulmonary embolism (SPE) is a rare disorder that usually presents with fever, cough, and hemoptysis.1–5 Depending on the embolic source, SPE can be classified as cardiac, peripheral endogenous, or exogenous,6 each manifest in different epidemiological and clinical spectra. Of these subtypes, cardiac embolic SPE is the most common.1,2,4–6

A severe complication of infective endocarditis (IE) is organ embolization.5,9 The characteristics of SPE at presentation are nonspecific and usually go unrecognized by clinicians. The initial clinical features vary from a low-grade fever and respiratory symptoms, including cough, hemoptysis, chest pain, purulent sputum, and dyspnea. Most SPE patients have similar presentations with pneumonia. An SPE diagnosis is therefore, frequently delayed, which consequently influences prognosis. On the other hand, the chest computed tomography (CT) of more than half of the reported SPE cases show multiple, bilateral peripheral pulmonary nodules/cavitations. In light of these factors, we sought to review the epidemiologic, clinical, radiologic, and microbiological features of SPE as well as treatment outcomes in 20 Chinese patients with cardiac SPE to facilitate the recognition, diagnosis, and prognosis of this uncommon disease.

2. Materials and methods

We identified 348 cases of IE using a computer-assisted search for patients hospitalized with IE at Peking Union Medical College Hospital between January 1, 1991, and January 1, 2013. After reviewing these patients’ medical records and radiologic images, 20 cases of cardiac SPE were identified. The following data were recorded for analysis: age, sex, probable risk factors and
symptoms at presentation, physical examination and laboratory findings (including microbiologic culture results, radiologic findings, and echocardiography results), treatment (including antibiotic regimens, anticoagulation, and surgery), comorbid medical conditions, and outcomes. All patients and/or their relatives provided written informed consent to publish their clinical details. The study was approved by the ethics committee of Peking Union Medical College Hospital.

The diagnostic criteria for SPE were modified from Cook’s definition,[1] as follows: (1) focal or multifocal lung infiltrates compatible with septic embolism in the lung according to a ventilation-perfusion (V/Q) scan plus chest CT and/or CT pulmonary angiography (CTPA), (2) the presence of active extrapulmonary infection as a potential embolic source, (3) the exclusion of other potential explanations for lung infiltrates, and (4) the resolution of lung infiltrates with appropriate antimicrobial therapy. The data are expressed as the mean ± standard deviation (SD) for continuous variables and as percentages for categorical variables.

3. Results

3.1. Demographics and clinical manifestations

There were 20 subjects in this study, and their clinical characteristics are summarized in Table 1. The study group included 14 male and 6 female patients, with a median age of 38.1 years (range, 19–71 years; mean 38.1 ± 15.2 years). One patient was <20 years of age, and 4 were ≥50 years of age (only 2 patients were >60 years of age).

Presenting symptoms included fever (100%, including 8 patients with a high-grade fever), cough (95%), sputum (80%), hemoptysis (80%, most of which manifested as blood in the sputum, and no patients exhibited massive hemoptysis), pleuritic chest pain (80%), and dyspnea (60%). A moist rale was observed in 13 cases (65%), and heart murmurs were present in 16 cases (80%).

Predisposing conditions for SPE were identified in 17 patients, including congenital heart disease in 8 patients (40%), 4 cases had a membranous ventricular septal defect, 3 cases had bicuspid aortic valves, and 2 cases had previously undergone aortic sinus aneurysm repair surgery; skin injury in 3 patients (15%, 7–28 days before the SPE), anaplastic anemia in 2 patients (10%), the implantation of a pacemaker due to arrhythmia in 2 patients (10%, 1–3 years prior), Behcet disease in 1 patient (5%), thymic carcinoma in 1 patient (5%), ulcerative colitis (UC) in 1 patient, and intravenous (IV) drug use in 1 patient (5%) (Table 1).

Both of the patients with anaplastic anemia had been given high doses of methylprednisolone and/or cyclosporine plus antithymocyte globulin (ATG), and one of them had a peripherally inserted central catheter (PICC). The patient with Behcet disease received long-term corticosteroids. The patient with ulcerative colitis was given sulfasalazine and methotrexate.

3.2. Microbiologic features

Microbiological testing revealed putative causative pathogens in 14 patients (70%). All these 14 patients had positive blood culture results, and 1 also produced a positive vegetation culture result. The most common pathogens were staphylococcal species and methicillin-resistant Staphylococcus aureus.

Table 1: Demography, clinical, microbial features of the 20 patients.

| Case No | Age, yr/sex | Underlying conditions | Foci of infection | Pathogens | Culture sample | Surgery | Hospital duration (d) | Outcome |
|---------|-------------|-----------------------|------------------|-----------|----------------|---------|----------------------|---------|
| 1       | 33/M        | IV drug user          | RA               | MSSA      | Blood          | Yes     | 18                   | Recovered |
| 2       | 21/F        | AA                    | TV               | MSSA      | Blood          | No      | 55                   | Died     |
| 3       | 57/M        | AV malformation       | AV               | Staphylococcus | Blood  | No      | 19                   | Died     |
| 4       | 22/M        | Skin injury           | TV               | MSSA      | Blood          | Yes     | 73                   | Recovered |
| 5       | 33/M        | Skin injury           | AV               | MSSA      | Blood          | No      | 4                    | Died     |
| 6       | 29/M        | Ventricular septal defect | TV              | Streptococcus haemolyticus | Blood | Yes*  | 29                   | Recovered |
| 7       | 30/F        | AV malformation       | TV               | MSSA      | Blood          | No      | 3                    | Died     |
| 8       | 47/M        | Pacemaker             | TV, Lead wire in RA | NA      | NA            | Yes     | 16                   | Died     |
| 9       | 49/M        | Skin injury Thymic carcinoma | RA              | Bacteroides fragilis | Blood | Yes*  | 36                   | Recovered |
| 10      | 35/M        | AV malformation       | RA               | MSSA      | Blood          | No      | 3                    | Died     |
| 11      | 20/M        | Behcet’s disease      | RV               | Streptococcus haemolyticus | Blood | No      | 30                   | Recovered |
| 12      | 65/F        | Pacemaker             | Lead wire in RA | MSSA      | Blood          | No      | 8                    | Recovered |
| 13      | 58/F        | AV malformation       | AV, RA           | NA        | NA            | Yes     | 49                   | Recovered |
| 14      | 71/M        | None                  | TV               | NA        | NA            | Yes     | 44                   | Recovered |
| 15      | 19/F        | Ventricular septal defect | RVOT PA, PV    | MSSA      | Blood          | Yes     | 158                  | Recovered |
| 16      | 31/M        | Ventricular septal defect | RVOT, MV       | Streptococcus ventricularis | Blood | Yes    | 75                   | Recovered |
| 17      | 20/M        | None                  | TV               | MSSA      | Blood          | Yes     | 10                   | Recovered |
| 18      | 41/M        | Ulcerative colitis    | TV               | MSSA      | Blood          | No      | 53                   | Recovered |
| 19      | 31/F        | Aortic sinus aneurysm | TV               | MSSA      | Blood          | Yes     | 100                  | Recovered |
| 20      | 41/M        | None                  | TV               | MSSA      | Blood          | Yes     | 37                   | Recovered |

AA = anaplastic anemia, AV = aortic valve, F = female, IV = intravenous, M = male, MRSA = methicillin-resistant Staphylococcus aureus, MSSA = methicillin-susceptible Staphylococcus aureus, MV = mitral valve, NA = not applicable, PA = pulmonary artery, PICC = peripherally inserted central catheter, PV = pulmonary artery valve, RA = right atrium, RV = right ventricle, RVOT = right ventricular outflow tract, TV = tricuspid valve.

* Yes surgery in another heart specialist hospital.
(8 patients), whereas streptococcal species were cultured in 4 patients. *Bacteroides fragilis* was cultured in 1 patient with thymic carcinoma, and *Mycobacterium fortuitum* was cultured in 1 patient with anaplastic anemia who had been given a high dosage of methylprednisolone, cyclosporine, and ATG (Table 1).

### 3.3. Characterization of chest imaging

All patients underwent chest CTs, and all scans were abnormal (HRCT; Figs. 1 and 2) (informed written consent was obtained for the publication of individual personal information from these 2 patients). Ten patients were diagnosed as PE by CTPA plus computed tomographic venography (CTV). Seven cases were diagnosed as having a PE by V/Q scan. Three patients, all of whom suffered sudden death, were diagnosed with a PE by multidisciplinary discussion between experienced PE experts in respiratory, cardiological, hematological, and radiological departments based on the combination of clinical manifestations in the context of cardiovascular vegetations.

Eighteen patients (90%) exhibited bilateral abnormalities. According to the CTPA and V/Q scan results, 17 patients had multiple pulmonary emboli. Two patients had deep vein emboli at the same time (1 had Behcet disease and 1 had ulcerative colitis). Parenchymal opacities were observed in 19 patients (95%), 2 of whom had migratory pulmonary shadows. Nodular infiltrates were observed in the chest CT scans of 16 patients (80%), and cavitations were observed in 5 patients (25%). Pleural effusion was detected in 7 patients (35%) and was unilateral in 2 cases. The CT imaging of 5 patients (25%) revealed hilar and/or mediastinal lymphadenopathy.

### 3.4. Echocardiography

Transthoracic echocardiography (TTE) was performed in all 20 patients, and all exhibited significant abnormalities. Three patients had undergone transesophageal echocardiography (TEE) before cardiac surgery. All the patients who underwent cardiac surgery received a TEE during the surgery. Eleven patients had pulmonary hypertension, as determined by the tricuspid valve regurgitation velocity (41–67 mm Hg).

All 20 patients had at least 1 vegetation, including tricuspid valve vegetations in 9 patients, right atrium vegetations in 6 patients (2 also had vegetations around the lead wire), aortic valve vegetations in 4 patients, right ventricular outflow tract vegetation in 3 patients (all had a membranous ventricular septal defect), pulmonary valve or pulmonary artery vegetations in 2 patients, and mitral valve vegetation in 1 patient.
patients, mitral valve vegetations in 1 patient, and right ventricle vegetations in 1 patient. Four patients (20%) had a membranous ventricular septal defect. Three had a bicuspid aortic valve defect, 2 of whom also had a perianricular abscess (Table 1).

### 3.5. Treatment and clinical outcomes

All 20 patients had taken antibiotics for at least 1 week prior to arrival at our hospital. All received parenteral antimicrobial therapy as an initial treatment in the hospital, and all were prescribed with at least 2 different types of antibiotics. The duration of total antimicrobial therapy ranged from 3 days up to 16 weeks. Patients who required cardiac surgery received antimicrobial therapy for 4 days to 3 months prior to the surgery.

Ten patients (50%) received cardiac surgery in our hospital, including valvuloplasty or valve replacement surgery, right ventricular outflow tract reconstruction, and ventricular septal defect repair surgery. All the vegetations were removed and sent for pathology and microbial culturing. Among these 10 patients, 4 patients had a fever before surgery. None of the 10 patients who received cardiac surgery in our hospital experienced significant complications. Four other patients received cardiac surgery in a specialized heart hospital. Infected catheters or pacemakers (including the lead wire) were removed from all patients. Cardiac surgery was not arranged for the remaining 6 patients. None of the 20 patients underwent chest tube insertion or pneumonectomy.

Only 6 patients (30%) were medicated with heparin or low-molecular-weight heparin (LMWH) prior to cardiac surgery. Seven patients were treated with warfarin for 3 to 6 months after surgery. The hospital stay ranged from 3 to 158 days (average 42.6 days). Fifteen patients recovered from their illness. Among these 15 cases, 10 patients underwent cardiac surgery in our hospital, and only 1 patient had not received any surgery. Five patients died; their underlying conditions included anaplastic anemia (2 patients), a congenital bicuspid aortic valve (2 patients, 1 accompanied by aortic sinus aneurysm that had been surgically repaired 1 month prior), and pacemaker lead wire infection (1 patient). Sudden death occurred in 3 cases due to massive pulmonary emboli (2 cases were diagnosed by the combination of clinical manifestations and evolving pulmonary lesions in the context of cardiovascular vegetations, and 1 case exhibited positive CTPA imaging). None of the patients who died underwent cardiac surgery (Table 1).

### 4. Discussion

The predisposing conditions for cardiac SPE have shifted in recent years (Table 2). Previously, intravenous drug use was the most common cause of cardiac SPE. With the increasing use of indwelling catheters and devices, the widespread use of hygienic syringes and increasing numbers of immunocompromised patients, cardiac SPE is now generally associated with cardiac device implants, intravascular catheters, and an immunocompromised state. Occasionally, cardiac SPE can also be caused by congenital heart disease, septic abortion, and other conditions. In our study, the most common causes of cardiac SPE were various types of congenital heart disease, especially membranous ventricular septal defect (VSD), bicuspid aortic valve, and rupture of an aortic sinus aneurysm. The patient group in our study included 4 VSD cases, 3 bicuspid aortic valve cases, and 2 aortic sinus aneurysm cases. Kahveci et al suggested that patients with infective endocarditis in a bicuspid aortic valve had a higher incidence of perianricular complications. Perianricular abscess may cause right atrial vegetation, which may
be the cause of cardiac SPE in cases with aortic valve vegetations. Other common causes in our study included implanted pacemakers and an immunocompromised state. Our study included 2 anaplastic anemia patients, 1 Behcet disease patient, and 1 ulcerative colitis patient, all of whom received corticosteroids and/or immunodepressants. Cardiac device endocarditis associated with SPE is not rare.\textsuperscript{1,3,6,7} In our study, 2 patients with pacemakers presented with lead wire vegetations and SPE. The predisposing conditions observed in our cohort differed from those of Cook et al.\textsuperscript{3,11} Lee et al.\textsuperscript{2} and Goswami’s studies,\textsuperscript{4} and also differed from another Chinese study of SPE in a hospital specializing in cardiac disease\textsuperscript{[5]} (Table 2).

In our study, the presentation of fever, cough, hemoptysis, and chest pain were the most common clinical manifestations of SPE, similar to other SPE studies.\textsuperscript{1–6} In most of the patients, a heart murmur was detectable by stethoscope. Skin injury was also prevalent in our study group, as was reported in Goswami’s study.\textsuperscript{14} The typical radiographic features of SPE include patchy air space lesions, multiple nodules, and cavitations, and all shadows are typically multiple and peripheral.\textsuperscript{11,5,18–20} In this study, we were able to identify the features associated with pleural effusion, and hilar and/or mediastinal lymphadenopathy. For febrile patients with multiple patches, nodules, and cavitations detected by CT imaging, careful inquiry and heart auscultation should be administered. If the patient suffers from skin injuries and presents with the typical manifestations of SPE, a diagnosis of cardiac SPE should be considered.\textsuperscript{4} Because CTPA is the first-line imaging choice for suspected cases of PE,\textsuperscript{21,22} it should be initiated to confirm the diagnosis as quickly as possible.

In patients with IE, bacteremia is nearly always present, and the blood culture is always positive, which facilitates the diagnosis and prognosis of IE patients through bacterial susceptibility testing.\textsuperscript{13} The reported incidence of positive blood culture ranged from 35.2% to 92.9%\textsuperscript{[1–2,4,5]} (Table 2). However, blood culture-negative IE can also occur in 2.5% to 31% of IE cases\textsuperscript{23} most often arising due to prior antibiotic administration and occasionally due to specific microorganisms in immunocompromised patients. In our study, most cases were transferred from other hospitals, and all were previously medicated with at least 2 different types of antibiotics. The positive blood culture rate was 70% for our patients and the most common causative organism was staphylococcus, which is coincident with the microbiology of infective endocarditis.\textsuperscript{7} However, 3 patients were infected with methicillin-resistant \textit{Staphylococcus aureus} (MRSA), which may be the result of prior antibiotic administration. One patient with coincident anaplastic anemia harbored \textit{Mycobacterium fortuitum}, which is a rare micro-organism. Therefore, the repeated testing of blood cultures as early as possible prior to the first dose of antibiotics as well as early consultation with infectious disease specialists are both recommended.

Transesophageal and transthoracic echocardiography (TTE and TEE) are the fundamental and most important methods used to diagnose, manage, and follow-up cases of IE. TTE must be performed rapidly and as soon as IE is suspected.\textsuperscript{[6]} The sensitivity of TTE ranges from 40% to 63%, but that of TEE ranges from 90% to 100%.\textsuperscript{[24]} If the result of TTE is negative and the clinicians highly suspect a diagnosis of IE, then a TEE should be performed. If vegetations are very small (<2 mm), not yet present, or have already broken off and embolized, then diagnosis may be challenging.\textsuperscript{[6]} If the level of suspicion remains high, TTE and/or TEE should be repeated 7 to 10 days later. In our study, 1 patient who presented with isolated aortic valve vegetation suffered from sudden death and did not undergo a TEE, and therefore we were unable to exclude perianular abscesses and some complications of cardiovascular vegetations. In our study, 3 out of 4 cases with aortic valve vegetations exhibited bicuspid aortic valve malformations. Between 10% and 30% of bicuspid aortic valves develop infective endocarditis, and 25% of cases of infective endocarditis develop on a bicuspid aortic valve.\textsuperscript{[25,26]} Although infective endocarditis in a bicuspid aortic valve resulted in a high incidence of perianular complications,\textsuperscript{[16]} we suggest that patients with bicuspid aortic valve malformation suffering from a fever, and lung shadows should be monitored for perianular abscesses, complicated right-sided vegetations, and cardiac SPE. According to the echocardiography results, although most cardiac SPE was caused by right-sided IE, several cases also exhibited left-sided IE. Thus, a technician or cardiologist should perform echocardiography carefully and should not stop upon finding left-sided vegetations.

In contrast to previously reported studies, all of our enrolled cases underwent chest CT during their hospitalization. Parenchymal opacities and nodules were the most common radiological manifestation in our study. As listed in Table 2, pulmonary nodules were the most common feature reported by all 4 previous studies, followed by cavitations.\textsuperscript{[11–5]} The diagnosis of SPE should be strongly suspected in febrile patients whose chest CT showed multiple pulmonary nodules/patches, with or without cavitations.

The successful treatment of IE and cardiac SPE depends on the eradication of microbes by antimicrobial drugs (Table 2). Antibiotics are the principal and most important mode of therapy in all forms of septic pulmonary infarction.\textsuperscript{[2–7,9,10]} Pulmonary involvement such as septic emboli or cavitation is one of the key indications for surgery in right-sided IE.\textsuperscript{9,11,12,27,28} In our study, all patients who underwent cardiac surgery survived. The survival rate was not directly related to whether the patient’s body temperature had stabilized before the surgery. Only 1 of 6 patients who did not receive surgery survived, and the other 5 who received antibiotics without surgery died. Therefore, we suggest that patients with cardiac SPE receive cardiac surgery to eradicate the source of the septic emboli.

Although anticoagulation therapy is important for treating noninfective pulmonary embolism, it is not typically used in cases of septic embolization due to the increased risk of bleeding in the area of the infected embolus.\textsuperscript{[15]} In our study, short-term anticoagulation therapy was given to many patients who underwent valvuloplasty or valve replacement surgery both before and after surgery.

Our retrospective study has several limitations. First, the 2 following factors might have resulted in a selection bias: (1) all enrolled cases had at least 1 vegetation detected by TTE/TEE, and (2) all enrolled cases had a definite diagnosis of SPE; for those patients who had a missed diagnosis of SPE were therefore not included in our study. Second, our hospital is a tertiary transfer hospital that specializes in treating rare and difficult cases in China. All enrolled cases in our study had been prescribed antibiotics before they were admitted to our hospital, which could have influenced the microbiological testing results. Third, CTPA was not performed for all enrolled cases. Some patients were diagnosed as having a PE following a multidisciplinary discussion between experienced PE specialists. However, our study appears to be the largest analysis of SPE cases that includes chest CT results, which better indicates radiological manifestations. This study may help clinicians to better understand the risk factors and clinical characteristics of cardiac SPE patients, thereby improving their prognosis.
5. Conclusions
Cardiac SPE remains a diagnostic challenge for clinicians. Our study demonstrated that congenital heart disease, cardiac device implants, and an immunocompromised state are underlying factors for cardiac SPE. Although right-sided vegetations are the main source of cardiac SPE, this condition can also be caused by double-sided vegetations. Most patients exhibited typical clinical manifestations and radiography results, but they were nonspecific. For suspected cases, blood culture, TTE/TEE, and CTPA are important measures for early diagnosis and treatment. Vigorous early therapy, including treatment with appropriate antibiotics and timely cardiac surgery to eradicate the infective source, is extremely critical. Moreover, the administration of an anti-coagulant depends on the requirements of cardiac surgery and whether the infection is controlled.

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