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# Cryptogenic Organizing Pneumonia Presenting as a Solitary Mass: Clinical, Imaging, and Pathologic Features

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**Background:** Cryptogenic organizing pneumonia (COP), with a variety of radiologic findings, is a clinical pathological entity characterized by the presence of granulation tissue composed of fibroblasts/myofibroblasts and loose connective tissue in the alveoli and/or the distal bronchioles. Nevertheless, the presence of a solitary mass in COP is relatively rare. This study investigated the clinical, imaging, and pathologic features of COP with solitary mass form.

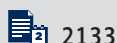
**Material/Methods:** This retrospective analysis included 12 patients (9 men and 3 women; age range 36–78 years; mean age  $60 \pm 9$  years) with surgery- or biopsy-proven COP with a solitary lung mass, diagnosed between June 2012 and December 2017 at the Department of Radiology in our hospital.

**Results:** All patients experienced cough with expectoration and 8 patients had hemoptysis. All lesions were adjacent to the pleura. Mean size of the lesions was  $4.2 \pm 0.9$  cm (range, 3.2–6.1 cm). The upper left lobe was the site of the lesion in 4 patients. Six masses had heterogeneous density; among these, 4 had cavities and distal obstructive inflammation. The mass caused pleural indentation in 4 patients. Lymphadenopathy was seen in 7 patients. All specimens showed buds of granulation tissue within the lumen of the distal pulmonary airspaces, with significant increase in interstitial lymphocytes in 4 specimens.

**Conclusions:** Patients with COP with solitary mass form are more susceptible to hemoptysis and the mass is prone to necrosis. Vascular bundles, exudation around the mass, interstitial lymphocyte infiltration, and mediastinal lymph node enlargement are common features.

**MeSH Keywords:** **Cryptogenic Organizing Pneumonia • Hemoptysis • Tomography Scanners, X-Ray Computed**

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## Background

Organizing pneumonia (OP) was originally described as a pathological term, but it has gradually become recognized as a clinicopathologic entity. OP is characterized by the presence of granulation tissue – composed of fibroblasts/myofibroblasts and loose connective tissue – in the alveoli and/or the distal bronchioles [1]. In 1983, Davison et al. introduced the concept of cryptogenic pathogenic pneumonia through case reports of patients who suffered from organizing pneumonia but without a definite pathogenic cause [2]. Cryptogenic organizing pneumonia (COP) – a class of idiopathic interstitial pneumonia – is a clinicopathologic entity of unknown etiology [3]. The disease lacks specific clinical manifestations, and radiologic findings vary. Histologically, it is characterized by granulation tissue within the lumen of the distal pulmonary airspaces [4]. The prognosis of COP is good and patients can be easily treated with glucocorticoids but are also subject to frequent relapses when the treatment is tapered or stopped.

The radiologic manifestation of COP varies, and it can be divided into 3 main categories: multiple alveolar opacities (typical COP), solitary opacity (focal COP), and infiltrative opacities (infiltrative COP) [5].

Previous reports show that about 10–15% of patients present with focal lesions. Nevertheless, besides a very general description referring to size, shape, and density, there are no more details regarding COP with a solitary mass [6]. Most of the relevant articles have only focused on morphology [7] and few articles have described the radio-pathologic correlation of focal COP [8]. There is also a lack of details about the clinic-radio-pathology correlation of COP with solitary mass form.

The purpose of this study was to summarize the clinical, imaging, and pathological features of COP presenting as a solitary mass, which is a relatively rare form.

## Material and Methods

### Patients

The study was approved by the hospital Ethics Committee. COP was diagnosed according to requirements of clinical-radiologic-pathology. We enrolled 67 patients whose histopathological data were in line with organizing pneumonia (OP) in our hospital from June 2012 to December 2017. Among them, there were 35 patients with unknown etiology. Radiologically, 12 patients had a solitary mass (diameter  $\geq 3$  cm). Inclusion criteria were: 1) OP confirmed by pathological examination, 2) unknown etiology, and 3) imaging showed a solitary mass  $\geq 3$  cm in diameter. The exclusion criterion was: definite etiology is known.

Data collected from the case records were: 1) clinical symptoms and signs; 2) results of laboratory investigations (before the surgery or biopsy), including white blood cell counts and differential count, erythrocyte sedimentation rate (ESR), serum oncology indicators, antinuclear antibody, antineutrophil cytoplasmic antibody, and rheumatoid arthritis-related antibody; 3) results of bacterial sputum culture (for bacteria, fungi, and *Mycobacterium tuberculosis*); 4) findings from imaging studies (all 12 patients underwent spiral CT scan, 9 patients underwent enhanced CT scan, and 3 patients underwent PET/CT scan). In addition, all examinations were done before the pathological diagnosis.

### Imaging protocol

All 12 patients had at least 1 multi-detector CT (MDCT) scan before puncture or surgery, and 9 patients received an enhanced CT examination. Scanning was performed with either a Philips 256 iCT (Philips Healthcare, Best, The Netherlands) with the following scan parameters: tube voltage, 120 kVp; automatic tube current control; slice thickness, 1.0 mm; beam pitch, 0.980; or with a GE LightSpeed VCT (GE Healthcare, Waukesha, WI, USA) with the following scan parameters: tube voltage, 120 kV; tube current, 150 mAs; slice thickness, 1.0 mm; beam pitch, 0.516. For enhanced CT scan, a double-cylinder high-pressure syringe pump was used to inject 80 mL iodine volts alcohol (containing iodine 350 mg/mL) contrast agent + 10 mL normal saline into the elbow vein at a flow rate of 3 mL/s. Arterial phase and venous phase images were acquired 28 and 58 seconds, respectively, after drug infusion. The scanning range covered the entire area from the apex to the base of the lung and included the chest wall and axilla of both sides; a matrix of 512 $\times$ 512 and field of view (FOV) of 350 $\times$ 350 mm was used, with standard algorithm reconstruction. The image was uploaded to a Philips Intellispace portal for multi-planar reconstruction (MPR) and volume rendering (VR). PET/CT were performed by Siemens Biography sensation 64 PET/CT with the following scan parameters: tube voltage, 140 kV; tube current, 120 mAs. Before the PET/CT examination, all patients were fasted for at least 6 h, and they had rested for 1 h after the 4.4-MB/Kg of 18F-FDG injection.

### Image analysis

The images were blindly and retrospectively analyzed by 2 experienced radiologists (>5 years of experience in thoracic imaging). When there was disagreement, it was settled by a senior radiologist (a third person). All images were viewed with lung window settings (window width, 1500 HU; window level, -450 HU) and with mediastinal window settings (window width, 360 HU; window level, 40 HU). The following features of the mass were analyzed: location; size; shape (round/ovoid/irregular/lobulated); edge (smooth/well defined/fuzzy); inner

**Table 1.** Glossary of terms used for describing imaging findings in this study. Most were based on the Glossary of Terms for Thoracic Imaging [1].

Term	Definition
Mass	A solid or partly solid opacity, greater than 3 cm in diameter (without regard to contour, border, or density characteristics)
Air bronchogram	A pattern of air-filled (low-attenuation) bronchi on a background of an opaque (high-attenuation) airless lung
Cavity	A gas-filled space, seen as a lucency or low-attenuation area, within a pulmonary consolidation, a mass, or a nodule
Fibrous band	Linear 1–3-mm-wide high-density shadow within the lung parenchyma
Halo sign	Ground-glass opacity surrounding a nodule or mass
Pulmonary emphysema	Permanently enlarged airspaces distal to the terminal bronchiole, with destruction of alveolar walls, focal areas or regions of low attenuation, usually without visible walls
Lymph node enlargement	Mediastinal and hilar lymph nodes ranging in size from sub-CT resolution greater than 10 mm
Broncholith	A small calcific focus in or immediately adjacent to an airway
Pleural plaque	A fibrohyaline, which is a relatively acellular lesion arising from the pleura; it is usually seen in the parietal pleura, particularly that overlying the diaphragm and the lower ribs; calcification may be present
Vascular bundles (Figure 2C)	Multiple ( $\geq 3$ ) blood vessels gathered together close to the mass
Pleural indentation	The visceral pleura is indented toward the lesion, and shaped like a bell; the cavity is liquid; the pleural itself has no thickening or adhesion
Burr	The edge of the mass stretch to the surrounding, radial, fine, and short line shadow
Lobulation	The edge of the mass forms multiple arcs
Enhancement degree	The net added value of enhancement – I: mild (0–20 HU); II: moderate (20–40 HU); III: marked ( $\geq 40$ HU)

structure (density, enhancement changes, air bronchogram, cavity); surrounding structures (pleural indentation, distal obstructive inflammation, vascular bundles, fibrous band, halo sign); and accompanying signs (lymph node enlargement, pleural effusion). Background lung features and other signs were also recorded. Most descriptions of CT images were based on the Glossary of Terms for Thoracic Imaging published by the Fleischner Association in 2008 (Table 1) [9].

### Pathological analysis

Specimens of 12 patients were obtained by surgery (n=6) or CT-guided biopsy (n=6). Specimens were then fixed, embedded, sectioned, stained with H&E, and analyzed blindly under a light microscope by 2 experienced pathologists. If there were disagreements, the decision was made by another experienced pathologist (a third person).

## Results

### Clinical features

The clinical findings of 12 patients (9 men and 3 women), mean age  $60 \pm 9$  years (range, 36–78 years) with COP presenting as solitary mass are summarized in Table 2. All patients experienced cough with expectoration; 8 had varying degrees of hemoptysis; 2 had fever with maximum body temperatures of  $38.5^\circ\text{C}$  and  $39.6^\circ\text{C}$ ; 3 had ipsilateral chest pain; 4 had weight loss (1.5–5 kg) since disease onset; 6 had elevated ESR (30–116 mm/h); and 2 had a slight increase in neutrophil: granulocyte ratio. In addition, none of the patients had Velcro rales (fine, dry, inspiratory crackles) or finger clubbing. No patient had previous history of pneumonia. All patients have no common history or exposure. The mean time from disease onset to treatment was  $53 \pm 51$  days (range, 3–180 days). Data are expressed as mean  $\pm$  standard deviation.

**Table 2.** Clinical findings in the 12 patients with COP of the solitary mass form.

Patient	1	2	3	4	5	6	7	8	9	10	11	12	Total
Age, years/Sex	67/F	58/M	63/M	62/M	57/F	65/M	58/M	78/M	52/M	62/M	36/M	64/F	
Symptoms													
Cough	+	+	+	+	+	+	+	+	+	+	+	+	12
Sputum	+	+	+	+	+	+	+	+	+	+	+	+	12
Hemoptysis	+		+	+	+		+	+		+		+	8
Chest pain				+		+				+			3
Fever				+						+			2
Weight loss, kg	+	+		+						+			4
History of smoking		+		+		+		+	+	+			6
Erythrocyte sedimentation rate increased (>15 mm/h)		+	+	+	+			+		+			6
Neutrophil: granulocyte ratio increased				+						+			2
Time from onset to treatment, days	90	120	30	30	3	60	30	10	30	180	30	30	
treatment	Glucocorticoids				Surgery				Glucocorticoids		Surgery		

### Imaging characteristics

We analyzed the imaging features of the solitary mass and details are shown in Table 3. The masses were adjacent to the pleura and their mean diameter was  $4.2 \pm 0.9$  cm (range, 3.2–6.1 cm). In addition, masses were with round or ovoid, and 6 masses were lobulated (Figure 1).

The inner density of 6 masses was uneven. An eccentric thick-walled cavity was present in 4 masses. A smooth inner wall of the cavity was found in all cases. As shown in Figure 2, endobronchial mucous plug with obstructive inflammation distally was seen in all cases with cavitation, air bronchogram was seen in 7 cases, pleural indentation in 4 cases, and vascular bundles were seen around 7 masses. Furthermore, fibrous bands were observed around the masses in 12 cases, and the halo sign was present in 4 cases. Lymph node enlargement was present in 7 patients and pleural effusion was found in 2 patients (Figure 3).

All 6 nonsurgical patients received glucocorticoid drugs, which relieved their symptoms. Among the 6 nonsurgical patients who were treated with glucocorticoids, the lesions showed resolution on CT but did not fully disappear; fibrotic lesions

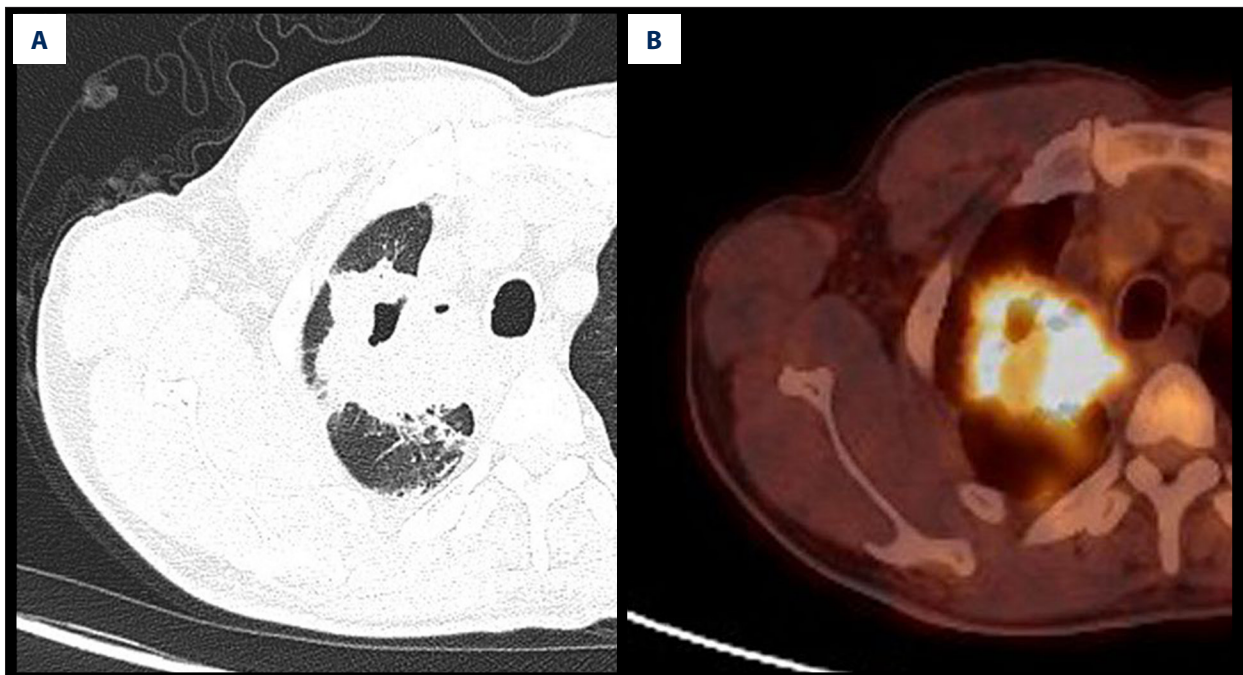
persisted in the lung (Figure 3). In the 6 patients who underwent surgery, the lesion was successfully removed. No recurrence was observed.

### Pathologic features

Based on gross examination, the cut surface of the mass was gray-white in color, and the mass was clearly demarcated from surrounding tissue. Adjacent pleura was slightly thickened. Light microscopy of H&E-stained specimen showed no obvious damage to alveolar structure. Alveolar type II epithelial hyperplasia was present. There was widening of the alveolar interval, and a small amount of plasma cells and tissue cells was seen in the interstitial part. An obvious increase in interstitial lymphocytes was present in 4 cases. The rounded or long strip of granulation tissue – composed of connective tissue mixed with fibroblasts/myofibroblasts – was seen occluding the alveoli, alveolar ducts, and distal bronchioles. Granulation tissue was seen within the distal bronchioles in all 5 resected masses (Figure 4).

**Table 3.** CT scans the 12 patients with COP of solitary mass form.

Patient	1	2	3	4	5	6	7	8	9	10	11	12	Total
Distribution	Middle Right	Upper Left	Upper Right	Upper Right	Lower Left	Upper Left	Lower Right	Lower Left	Upper Left	Upper Left	Lower Right	Lower Right	
Diameter, cm	4.3	3.2	4.5	5.5	3.2	3.8	3.8	3.3	4.1	6.1	5.6	3.5	
Shape													
Round		+			+	+		+		+	+		6
Ovoid			+						+			+	3
Irregular	+			+			+						3
Lobulated		+		+	+		+		+			+	6
Edge													
Smooth		+											1
Well defined				+	+		+	+	+	+			6
Coarse							+	+	+	+	+		5
Burr				+	+							+	3
Fuzzy	+		+			+						+	4
Inner structure													
Uneven density	+	+	+	+	+	+							6
Cavity	+	+	+	+									4
Thickness of cavity wall, cm	1.5	1.0	0.9	1.6									
Air bronchogram	+	+				+	+	+	+	+			7
Enhancement degree	II	II	II	-	II	II	II	II	II	-	-	III	
Surrounding structure													
Pleural indentation	+						+	+	+				4
Distal obstructive exudation	+	+	+	+									4
Vascular bundles	+	+				+	+	+	+	+			7
Fibrous band	+	+	+	+	+	+	+	+	+	+	+	+	12
Halo sign	+		+			+						+	4
Accompanying signs													
Lymph node enlargement	+		+	+	+	+	+		+				7
Pleural effusion							+			+			2
Other signs				Broncholith			Broncholith		Pleural plaque				
Background lung		Pulmonary emphysema					Pulmonary emphysema					Pulmonary emphysema	



**Figure 1.** Imaging data of 62-year-old man (Patient 4) who experienced cough and sputum with fever for 1 month. PET/CT image (A) shows a cavitated mass in the upper right lung. The edge is well defined, with a burr. PET fusion image (B) shows the high intake of the mass. The SUVmax is 8.8.

### Correlations between clinical, imaging, and pathologic findings

Enhanced CT examination was performed in 5 out of the 8 patients with hemoptysis, and revealed vascular bundles in 4 patients. An obvious increase in interstitial lymphocytes was found in 4 out of 7 patients with lymph node enlargement. Among 4 of the 6 patients who underwent surgery, the lesion was confirmed to be a solid mass, and granulation tissue was identified in the distal bronchioles.

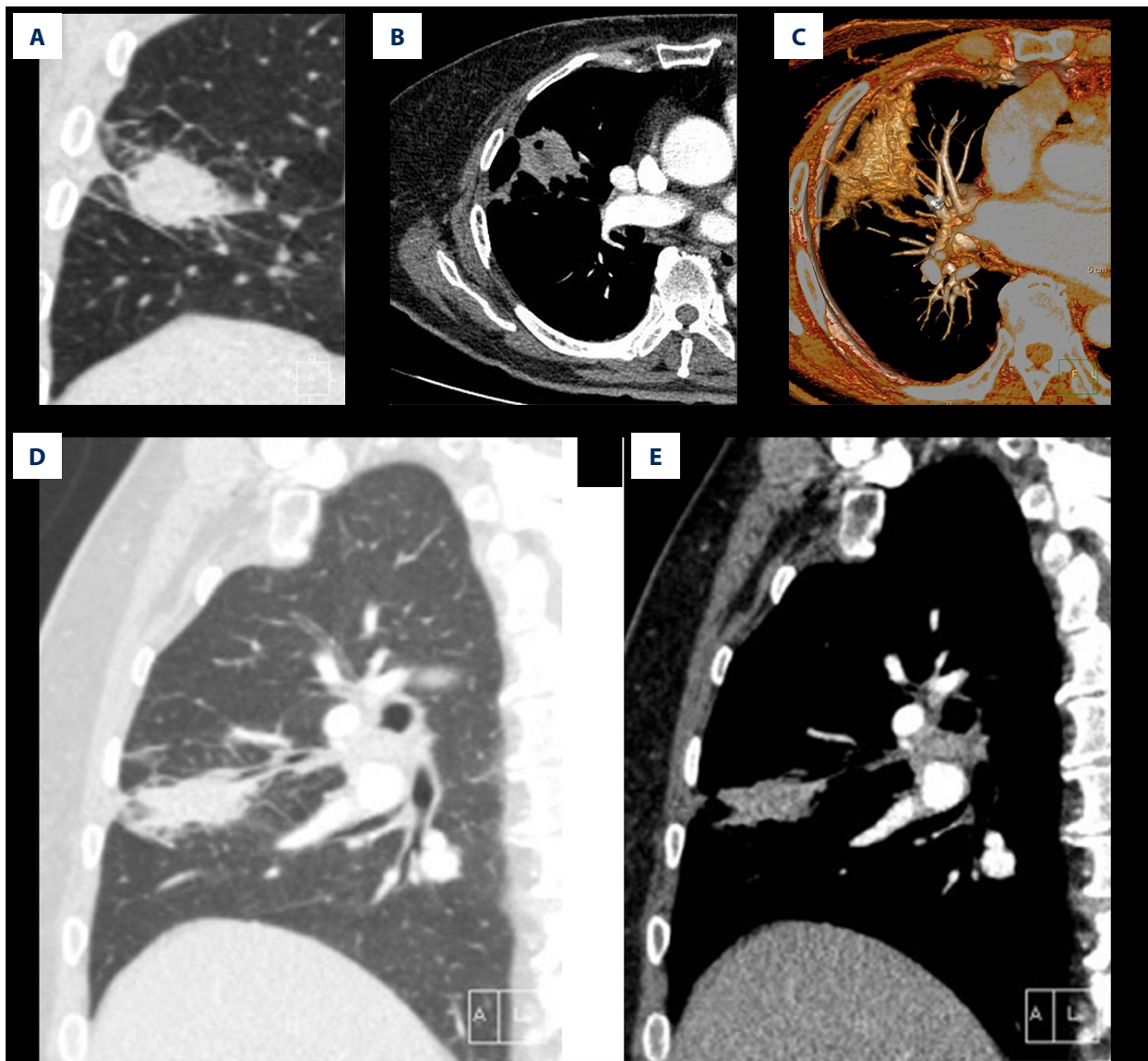
### Discussion

OP is regarded as a pattern of lung injury response, similar to the process of recovery from skin injury [9]. If the basic structure of the lung is not damaged, lesions can be absorbed after glucocorticoid treatment [10]. Because of its unclear etiology, patients with COP are often misdiagnosed and receive antibiotic therapy or undergo surgery. Our study examined a special form of COP – with solitary mass – which is most likely to be misdiagnosed. Clinical, imaging, and pathological data and their correlations were examined in each patient.

According to a previous report, COP affects both sexes equally; is most common among 40–50-year-old age group and has no obvious correlation with smoking [10]. In our sample, however, more men were affected (9: 3 male: female ratio). Furthermore,

patients were relatively older (age range 36–78), and most patients (6/12) had a smoking history. These differences may be due to the small sample size and the inclusion of only COP with a solitary mass. In our study, 6 of our patients had increased ESR, and previous reports also indicate that ESR is elevated in most COP patients [11]. Furthermore, 8 out of 12 patients had hemoptysis, but this is not concordant with earlier reports suggesting that hemoptysis is uncommon in patients diagnosed with COP [12]. Moreover, in our sample, 4 of the 8 patients with hemoptysis had vascular bundles. We believe that the vascular bundles are partly due to contraction of the fibrous band around the mass and partly due to inflammatory hyperemia. The evidence from the present study suggests that the mass type of COP is more likely to present with hemoptysis, caused by damage to pulmonary blood vessel walls.

There was no obvious pattern in the location of the masses. Four of the masses were in the left upper lobe, while the remaining were evenly distributed in the other lobes of the lung. In previous reports on focal organizing pneumonia, the lesions have been predominately located in the periphery of the lungs [13]. Necrotic cavities were present in 4 of our patients. In our study, the inner wall of cavities was smooth in 4 cases, and was consistent with the characteristics of a benign cavity. The endobronchial mucous plug with the distal mass and the accumulated necrotic matter within the cavity can mimic a malignant tumor. Image reconstruction and careful examination is necessary to differentiate the appearance from



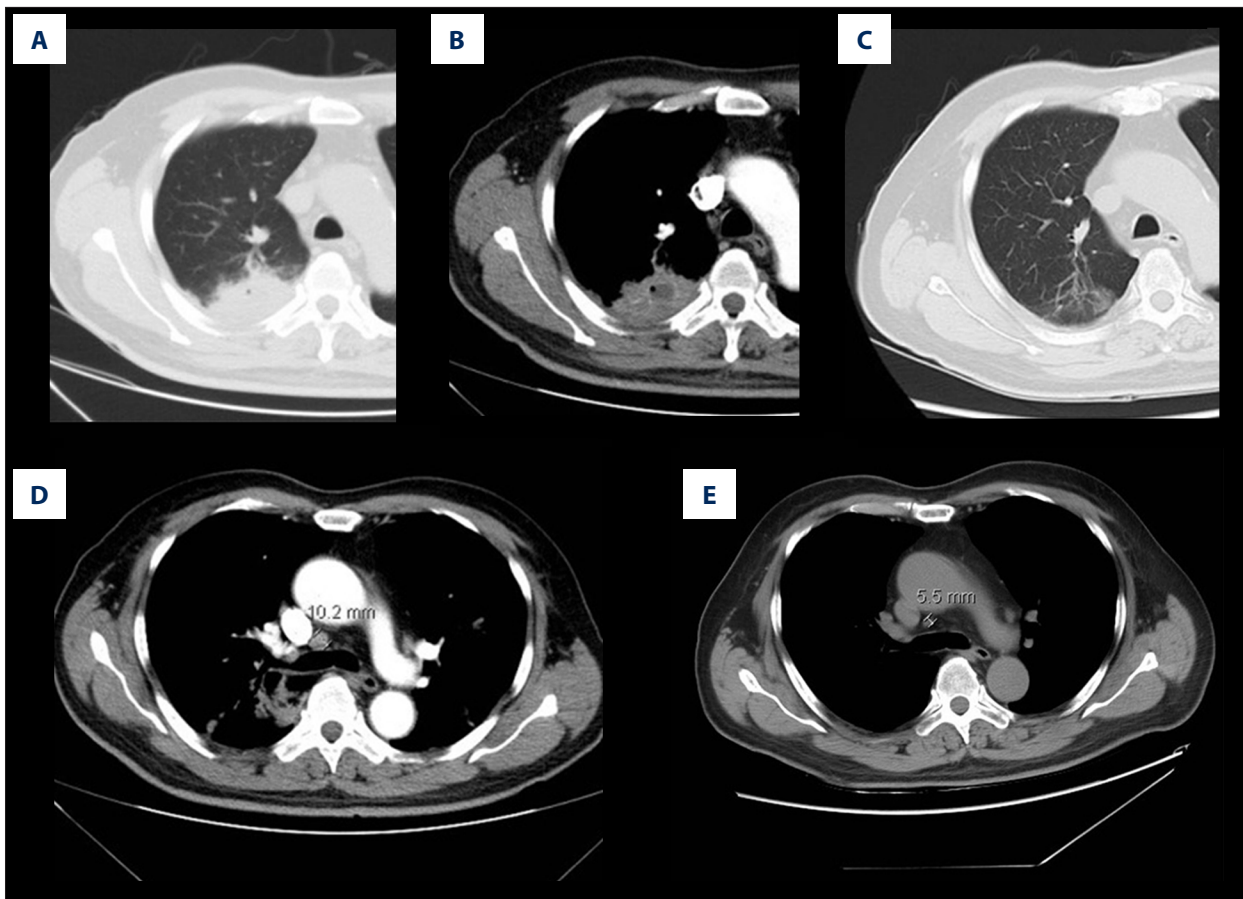
**Figure 2.** Imaging data of a 67-year-old woman (Patient 1) who experienced cough and sputum with hemoptysis for 3 months. CT scan MPR sagittal plane (**A**) and CT arterial enhancement (**B**) show a cavitated mass in the middle of the right lung. The mass is adjacent to the pleura, and the pleural indentation sign is visible. The edge of the mass is not clear. Around the mass, ground-glass opacity and fibrous lesions are visible. Arterial VR images (**C**) shows multiple blood vessels close to the mass (vascular bundles). MPR (**D**, **E**) shows the connection between the mass and bronchi. Image (**E**) shows bronchus truncation by the mucous plug.

the bronchus cut-off sign seen in malignant tumors (Figure 1). Six of the masses in our study showed multiple focal necrosis, which is characteristic of inflammatory masses [14].

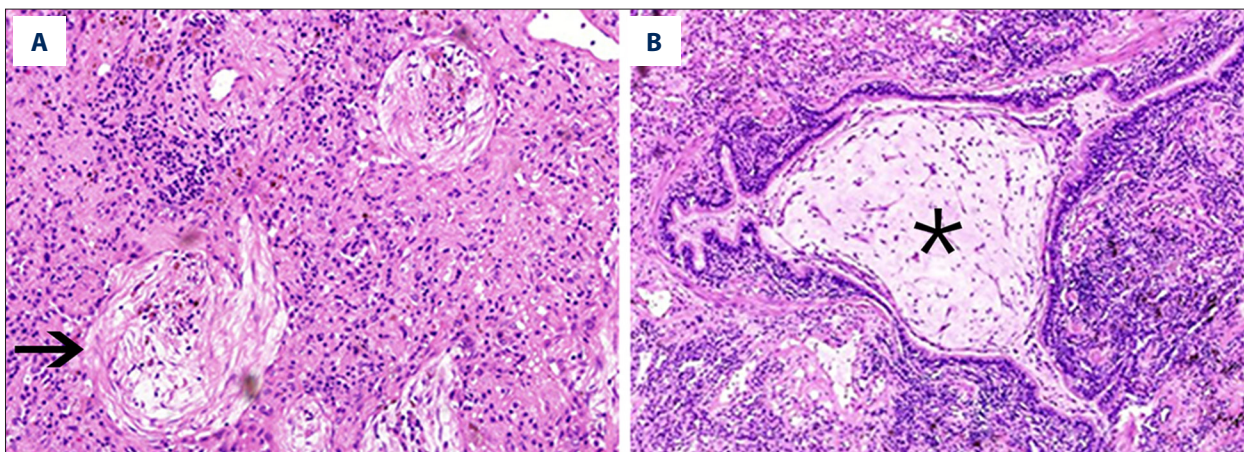
Mediastinal lymph nodes were enlarged in 7 out of 12 patients in this study. The nodes in 4 of these 7 patients showed obvious increase in lymphocytes on microscopic examination. Mild mediastinal lymph node enlargement was also reported by Greenberg-Wolff et al., who examined 8 COP cases [15]. We believe that mediastinal lymph node enlargement is a

characteristic feature of COP that occurs due to lymphadenitis as a result of interstitial lymphocytic infiltration.

Previous articles showed that imaging features of focal COP can mimic the characteristics of malignant tumors [16]. In our study, 3 patients were initially misdiagnosed as having lung cancer. However, due to the small number of cases and lack of diagnostic accuracy, we plan to further investigate the association between tumors and COP diagnosis.



**Figure 3.** Imaging data of a 63-year-old man (Patient 3) who experienced cough with hemoptysis for more than 1 month, with increased symptoms over the last 5 days. CT scan (A) and enhanced CT, arterial phase (B), shows a cavitated mass in the right upper lobe. The edge of the mass is fuzzy; the halo sign and a fibrous line around the lesion can be seen. (C) After 5 months of glucocorticoid treatment, the lesion almost disappeared; while a few ground-glass opacities and fibrous lesions remained. Enhanced CT, arterial phase (D), shows enlarged mediastinal lymph nodes with diameter >1 cm, and CT scan (E) shows decreased in size of the enlarged lymph nodes after treatment.



**Figure 4.** (A) H&E stained specimen ( $\times 200$ ) shows granulation tissue in the alveolar space (arrows). No obvious damage can be seen in the alveolar structure; alveolar type II epithelial hyperplasia is present. The alveolar interval is widened, and a small amount of plasma cells and tissue cells can be seen in the interstitium. Marked lymphocytic infiltration is present. (B) H&E stained specimen ( $\times 200$ ) shows granulation tissue (\*) can be seen in the distal bronchioles.



This study has certain limitations. First, this was a retrospective analysis of a small number of cases at a single center at a single geographic location, and selection bias cannot be ruled out. Second, some clinical examinations were not performed, including lung function testing and bronchoalveolar lavage fluid examination. Third, some of the glucocorticoid-treated patients were not followed up.

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## Conclusions

To sum up, hemoptysis was commonly found in patients with isolated mass-type COP. The mass was more likely to be round in shape. Necrotic cavitation, obstructive inflammation in the distal mass, vascular bundles and exudation around the mass, and lymph node enlargement with interstitial lymphocytic infiltrates were the most frequently observed features.

## Conflict of interest

None.