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Original Article

Comparative study of primary pulmonary cryptococcosis with solitary nodule by CT and pathological findings

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Abstract: Primary pulmonary cryptococcosis with solitary nodule used to mimic lung cancer. Distinguishing this disease from lung cancer remains a formidable challenge. By comparing high resolution computer tomography (HRCT) and pathological findings, the aim of present study was to improve the diagnostic accuracy for this disease and to explain some possible imaging presentation by pathological findings. The medical records of 15 patients of this disease were analyzed retrospectively from 2009 to 2014. High resolution CT demonstrated 11 patients with solitary nodule were misdiagnosed as lung cancer. Most of those lesions displayed suspected malignant signs, including irregular margin, spicules, lobulation, pleural indentation, blood vessel convergency, ground glass opacity. However, some benign signs such as air bronchogram, halo sign, and calcification were also found. Pathological findings showed some important signs which may be used to explain CT presentation. Most solitary nodule is granuloma lesions, in which cryptococcus were found in macrophage. Special staining of these lesions presented pas (+) and acid fast stain (-). It was suggested some imaging signs may be explained by pathological findings. Together, a high index of awareness of this suspected CT signs is required for early diagnosis of this disease.

Keywords: Pulmonary cryptococcosis, lung cancer, high resolution computer tomography (HRCT), pathological findings

Introduction

Pulmonary Cryptococcosis is a life-threatening disease. It is mainly caused by cryptococcus neoformans which affected not only immunocompromised patients, but also immunocompetent individuals [1, 2]. Primary pulmonary cryptococcosis with solitary nodule, a special form, is encountered on occasion in clinic [3-5]. It is usually misleading, giving a false sense of malignant lesion, and resulting in operation [4-6]. Here, we investigated the clinical, radiologic and histologic features of 15 patients in order to improve the accuracy of diagnosing and explain some imaging signs by comparing pathological findings.

The imaging signs of lung cancer include irregular margin, spicules, lobulation, pleural indentation, blood vessel convergency, ground glass opacity. However, primary pulmonary cryptococcosis, especially for that with solitary nodule, mimics radiologic features of lung cancer. Despite of development of radiology and laboratory examination, accurate diagnosis of this disease remains a formidable challenge. Clinical misdiagnosis used to make patient operated and delay the initiation of suitable treatment. Therefore, when solitary nodule is suspected as primary pulmonary cryptococcosis, a paracentesis biopsy is required to identify nature of the lesions before operation. Additionally, Cryptococcal antigen (CrAg) titre of blood may be helpful for diagnosis of this disease.

Patients and methods

From January 2009 to December 2014 in clinic (Chinese PLA General Hospital and Beijing Shijitan Hospital), out of 40 patients with primary pulmonary cryptococcosis, 15 patients present imaging sign with solitary nodule. The

Table 1. The clinical characteristics of 15 patients with primary pulmonary cryptococcosis presented solitary nodule

No./ Gender/Age	History	Symptoms	Location	Size (cm)	CT presentations	CT primary diagnosis	Biopsy style	Pathology	Treatment	Prognosis
1/m/32	Not	Cough, fever	Ril-anterior basal segment	1.3×1.9	Irregular margin, spicules, air bronchogram	Benign lesions	Operation	Granuloma lesions with necrosis, cryptococcus in necrosis tissue pas (+), acid fast stain (-)	Not antifungal threatment	No recurrence
2/f/54	Hypophsma surgery, take hormone for 2 years	Not	Rml-lateral segment	1.8×2.0	Irregular margin, spicules, lobulation, pleural indentation, air bronchogram	Suspicious lung cancer	Operation	Granuloma lesions with necrosis, cryptococcus in necrosis tissue pas (+), acid fast stain (-)	Not antifungal threatment	No recurrence
3/m/36	Not	Not	Ril-back segment	2.0×2.5	Spicules, lobulation, pleural indentation, air bronchogram, Asymmetry intensify, suv 15.1 in pet-ct	Suspicious lung cancer	Operation	Granuloma lesions with necrosis, cryptococcus in necrosis tissue, pas (+), acid fast stain (-)	Not antifungal threatment	No recurrence
4/m /57	Hypertension	Not	Ril-back segment	1.3×1.4	Irregular margin, short spicules, lobulation, pleural indentation, air bronchogram, blood vessel convergency, obvious intensify	Suspicious lung cancer	Operation	Granuloma lesions, cryptococcus in macrophage, pas (+), acid fast stain (-)	Fluconazole for 6 months	No recurrence
5/m/41	Not	Chest pain	Rul-tip segment	2.0×1.8	Long spicules, lobulation, punctuate calcification, pleural indentation, satelitic lesion	Tuberculoma	Operation	Granuloma lesions with cheesy necrosis and calcium salt mineralization cryptococcus in necrosis tissue, pas (+), acid fast stain (-)	Fluconazole for 6 months	No recurrence
6/m/53	Not	Not	Lul-lingual segment	1.5×1.2	Irregular margin, suv 5.047 in pet-ct	Suspicious lung cancer	Operation	Organized lesions with fibration, no foam cell in alveolar space, pas (+), acid fast stain (-)	Fluconazole for 3 months	No recurrence
7/m/49	Not	Cough	Rml-lateral segment	1.1×1.2	Irregular margin, spicules, blood vessel convergency, asymmetrical obvious intensify	Unknown origin	Operation	Granuloma lesions without necrosis, cryptococcus in macrophage, pas (+), acid fast stain (-)	Fluconazole for 3 months	No recurrence
8/m/52	Not	Not	Lil-back segment	1.1×0.9	Short spicules, shallow lobulation, blood vessel convergency, obvious marginal intensify, suv 1.1 in pet-ct	Benign nodule	Operation	Granuloma lesions, cryptococcus in macrophage, pas (+), acid fast stain (-)	Fluconazole for 6 months	No reexamination
9/f/73	Diabetes, liver cancer surgery	Short of breath, cheset pain	Ril-back segment	0.9×0.7	Irregular margin, shallow lobulation, halo sign around nodule	Suspicious lung cancer	Operation	Granuloma lesions, foam cell in alveolar space, cryptococcus in macrophage, pas (+), Acid fast stain (-)	Fluconazole for 3 months	No recurrence
10/m/54	Diabetes	Not	Lil-back segment	1.8×1.1	Irregular margin, short spicules, lobulation, pleural indentation, air bronchogram, halo sign around nodule	Lung cancer	Operation	Granuloma lesions, cryptococcus in macrophage, methenamine silver stain (++), pas (+)	Fluconazole for 6 months	No recurrence
11/m/52	Not	Not	Lil-posterior basal segment	0.9×0.6	Ground glass shadow, irregular margin, air bronchogram	Early lung cancer	Operation	Cryptococcus in macrophage, pas (+), acid fast stain (-)	Not antifungal threatment	No recurrence
12/f/54	Hypertension	Cough	Rul-anterior segment	1.7×1.9	Irregular margin, short spicules, lobulation, air bronchogram, halo sign around nodule	Lung cancer	Operation	Granuloma lesions, organized lesions, cryptococcus in macrophage, pas (+), Acid fast stain (-)	Not antifungal threatment	No recurrence

13/m/54	Not	Not	Rul-tip segment	2.6×1.8	Irregular margin, long spicules, lobulation, air bronchogram	Lung cancer	Operation	Cryptococcus in macrophage, pas (+), Acid fast stain (-), alcian blue (+)	Fluconazole for 3 months	No recurrence
14/m/40	Opticneuritis, hormone for 3 months	Cough	Ril-posterior basal segment	2.3×1.4	Irregular margin, long spicules, air bronchogram, suv 6.2 in pet-ct	Organized pneumonia or lung cancer	Paracentesis	Granuloma lesions without necrosis, cryptococcus in macrophage, pas (+), acid fast stain (-)	Fluconazole for 6 months	Significantly small
15/m/42	Not	Fever, headach	Lul-tip segment	2.2×1.7	Irregular margin, spicules, lobulation	Lung cancer	Operation	Granuloma lesions without necrosis, cryptococcus in macrophage, pas (+), acid fast stain (-)	Amphotericin-b and 5-fc for 1 month, then fluconazole for 6 months	No recurrence

Not: not any symptom or not any disease history or not any complication.

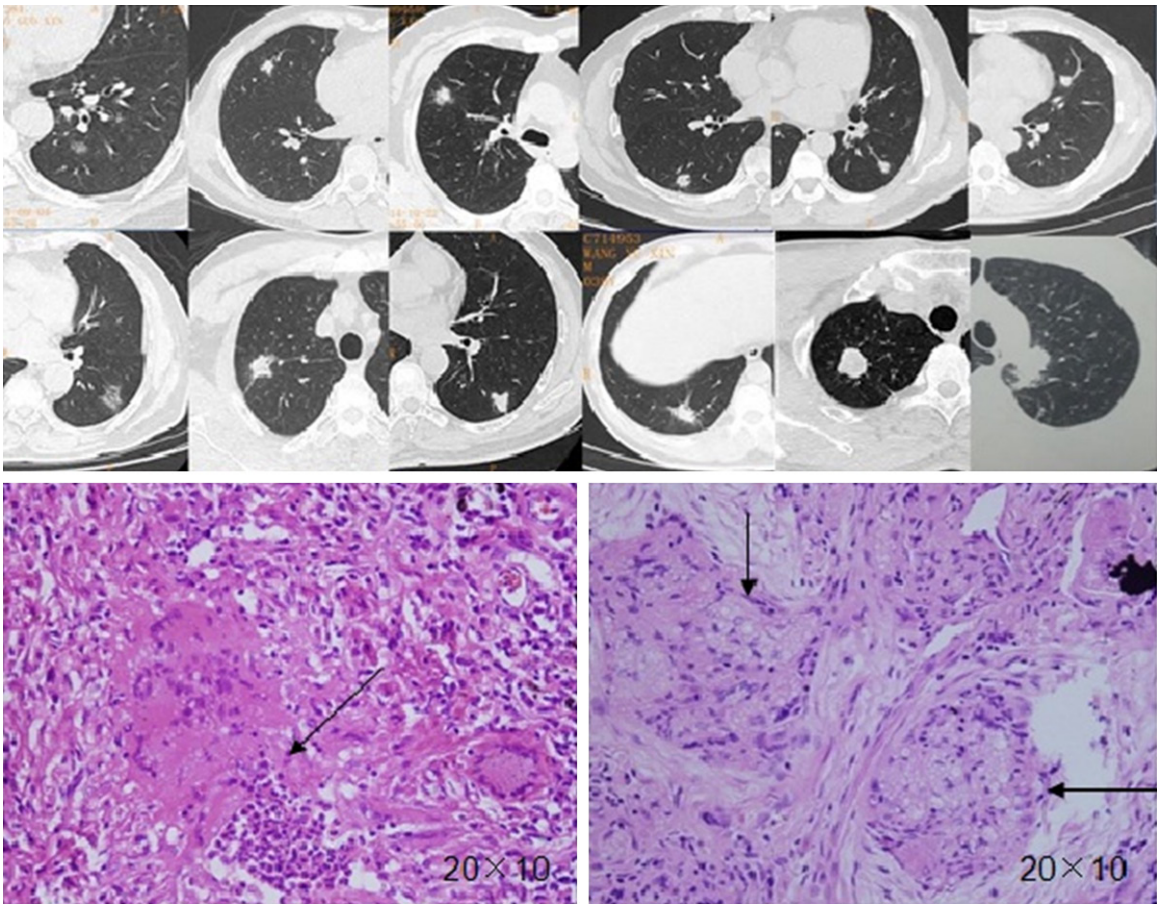

Figure 1. CT findings presented solitary nodule located at pulmonary periphery. Pathological findings presented many granuloma lesions, in which cryptococcus were found in macrophage.

diagnosis of this disease was based on imaging findings and pathological biopsy after pulmonary lobectomy or wedge excision. All patients underwent HRCT examination. 14 patients underwent pulmonary lobectomy or wedge excision and 1 patient underwent paracentesis. We retrospectively analyzed 15 patient's medical records, imaging signs, pathological changes, therapeutical strategies and time of recovery after operation and paracentesis. The Ethics Board in two hospitals made the decision that there was no need to gain informed consents from the patients since this study was a retrospective investigation.

Results

In the five-year period, 12 male and 3 female patients were included in this study (**Table 1**). Their mean age was about 49.53 years with a range from 32 to 73 years. Three patients were immunocompromised, and twelve patients were apparently immunocompetent. There were seven patients with symptoms of fever, cough, chest pain, short of breath and headache, and eight patients without any symptom.

CT findings presented these solitary nodules located at pulmonary periphery (**Figure 1**) except one patient. The lesions occurred at right upper lobe in three patients, right middle lobe in two patients, right lower lobe in five patients, left upper lobe in two patients, left lower in three patients. The biggest lesion was 2.6×1.8 cm and the smallest was 0.9×0.6 cm. Patients with solitary nodule mimicking lung cancer displayed suspected malignant signs, including irregular margin (12/15), spicules (12/15), lobulation (10/15), pleural indentation (5/15), obvious intensify (4/15), blood vessel convergence signs (3/15) and ground-glass opacity (3/15) respectively. However, some benign signs such as yielding air bronchogram (9/15), halo sign around nodule (3/15) and calcification (1/15) were also found.

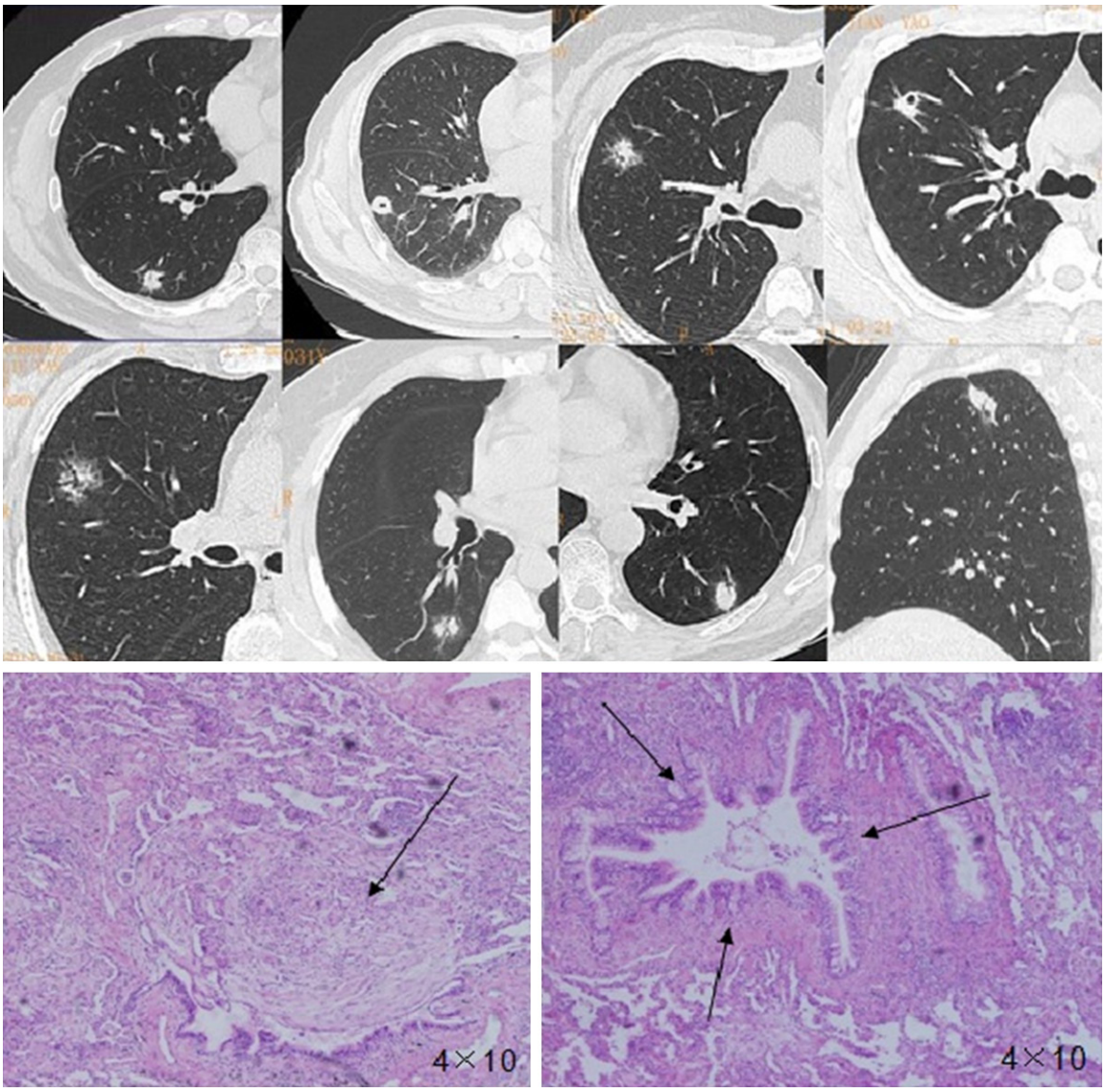

Figure 2. CT findings presented air bronchogram. Pathological finding (left) presented airway was pressed by granuloma. Pathological finding (right) presented airway was draged by granuloma around.

Given suspected malignant imaging signs and patent's request, the surgeries of pulmonary lobectomy or wedge resection were performed in fourteen patients except one patient. Pathological findings confirmed these lesions were granuloma lesions, in which cryptococcus were found in macrophage (**Figure 1**). Special staining of these lessions presented pas (+) and acid fast stain (-). Following the prognosis of all patients, ten patients with surgery and one patient without surgery were given antifungal threatment, and four patients with surgery were not given antifungal threatment. There are no signs of recurrence in all patients except one without reexamination.

Comparing the CT presentation and microscopic findings, we found that some of CT presentations can be explained by microscopic findings, such as the following signs (**Figures 2**-**5**).

Discussion and conclusion

In recent years, the incidence of primary pulmonary crytococcosis has increased with the progression of diagnostic technique, especially the HRCT [7-12]. Inconsistent with the known epidemiology of pulmonary crytococcosis, the majority (80%, 12/15) of patients with solitary nodule in this study had normal immune function. Primary pulmonary crytococcosis with soli-

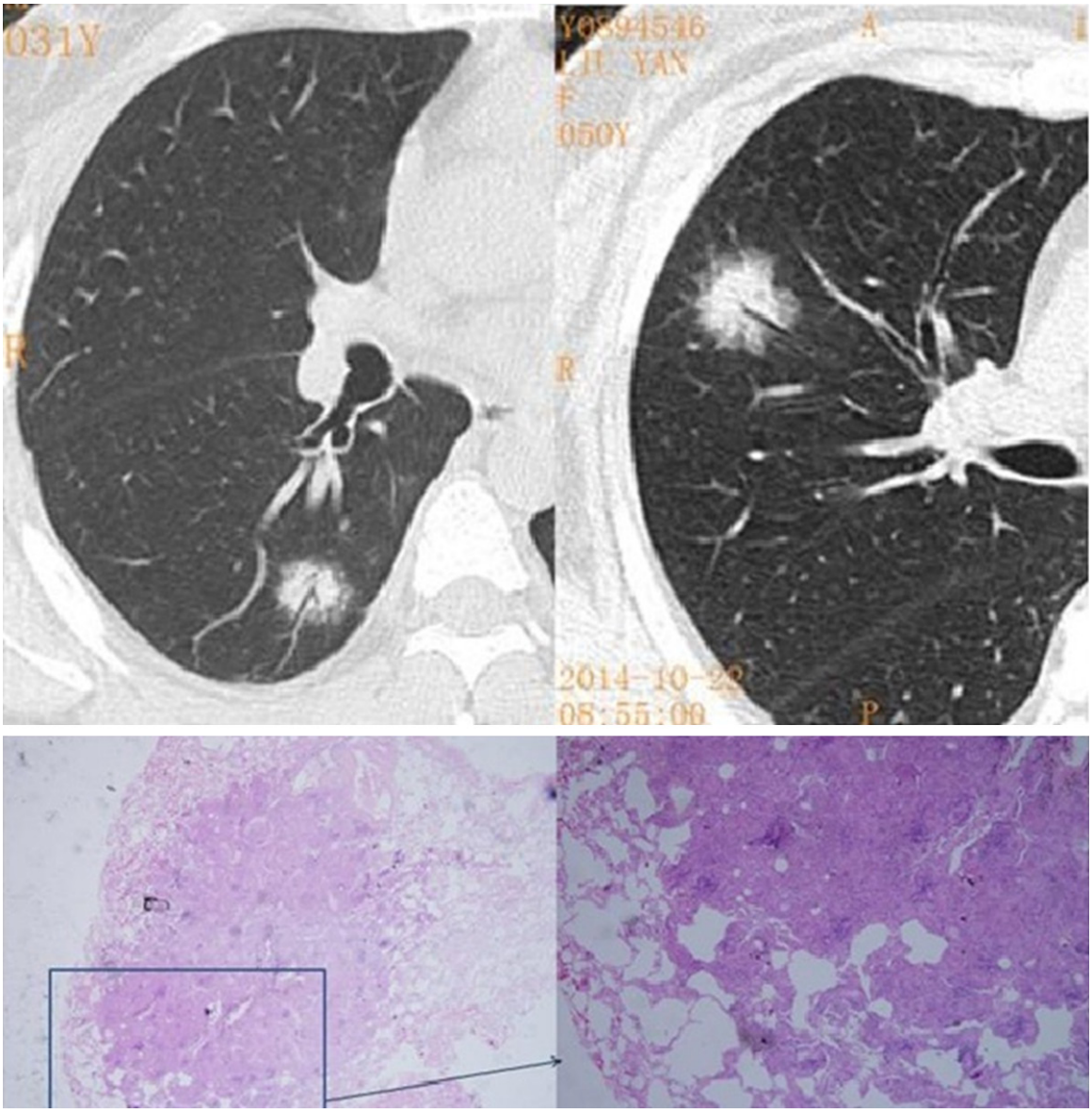

Figure 3. CT findings presented halo sign around nodule. Pathological finding presented unclear bound between lesion tissue and normal tissue. There were foam cells and unconsolidated granuloma in alveolar space.

tary nodule is a special form of fungal disease which used to mimic lung cancer. Distinguishing between primary pulmonary crytpcoccosis and lung cancer remains difficult. Clinical physician should be highly aware of the radiologic features and microscopic findings of this disease.

Comparing the CT presentation and microscopic findings, clinical physician should understand some possible forming mechanism of CT signings. Irregular margin, spicules and lobulation may be induced by irregular granuloma. Ground glass opacity may be formed with foam cells or erythrocyte in alveolar space. Air bronchogram may be induced by direct drag of granuloma or indirect pression of granuloma. Halo sign around nodule may be formed by unconsolidated granuloma or inflammatory cells in alveolar space. All the above forming mechanism may be considered as potential clues for diagnosis of this disease.

In conclusion, to the best of our knowledge, the number of patients of pulmonary crytococcosis with solitary nodule studied here is the largest in the English language literature. Primary pulmonary crytococcosis with solitary nodule might be delayed or mistakenly diagnosed as

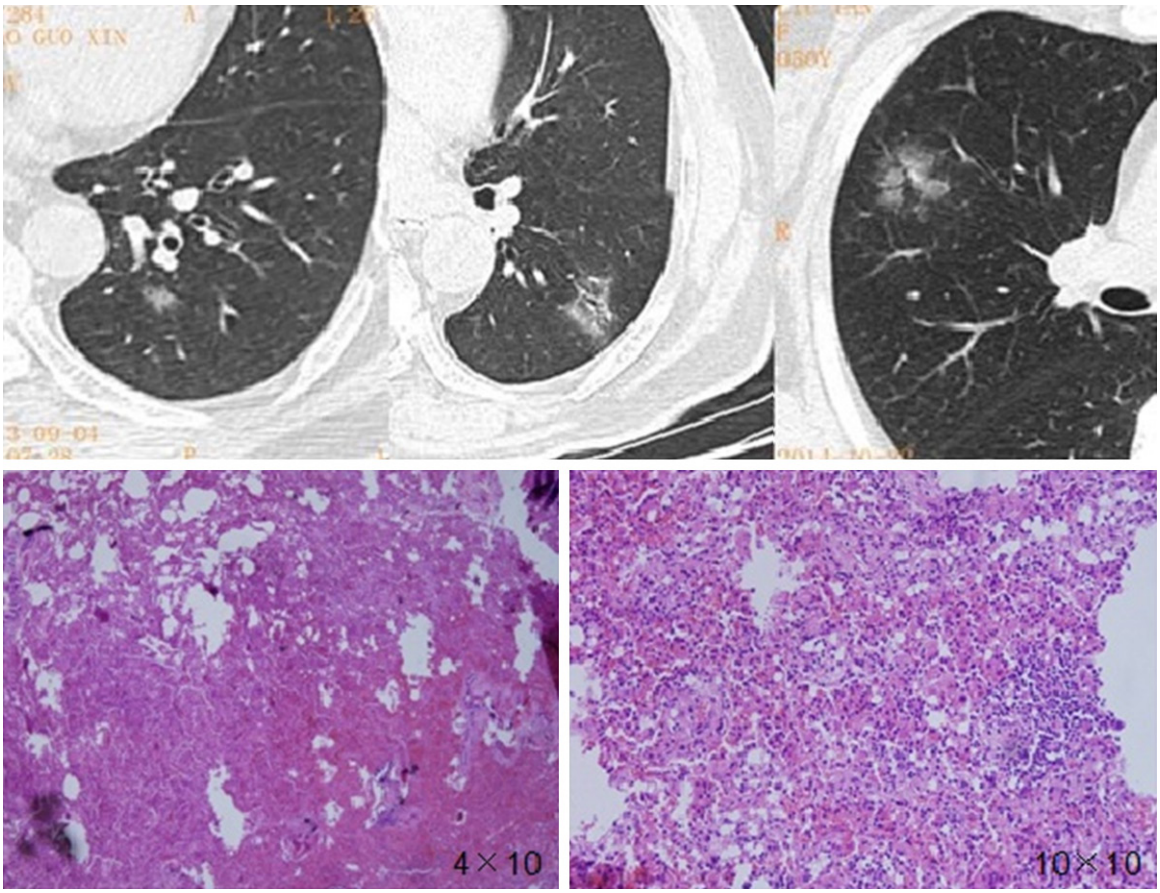

Figure 4. CT findings presented the lesion with ground-glass opacity. Pathological finding presented lots of foam cells and erythrocyte aggregation in alveolar space.

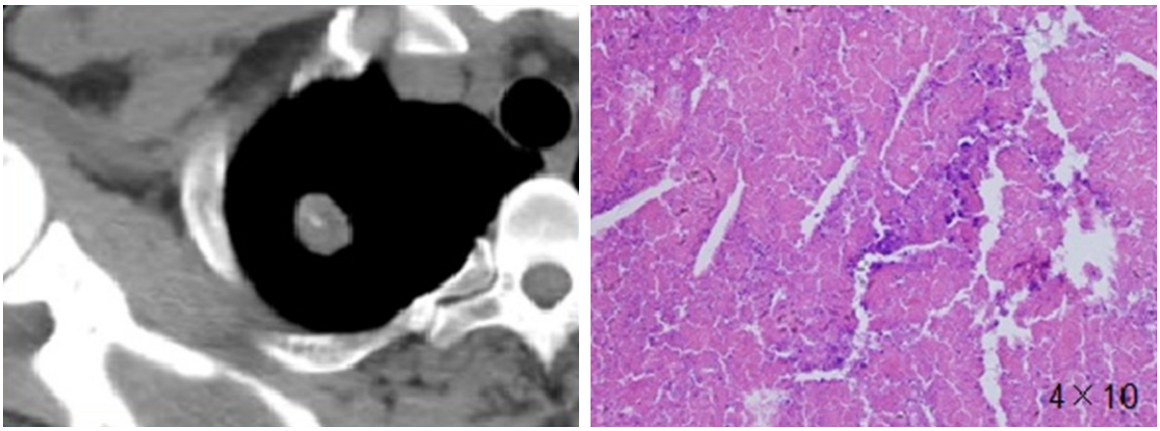

Figure 5. CT findings presented the lesion with calcification. Pathological finding presented lots of calcium salt mineralization in alveolar space.

malignant disease. Therefore, a high index of awareness is required for the early diagnosis of this disease.

Disclosure of conflict of interest

None.

Authors' contribution

Xinying Xue, Sheng Zhao, Chongchong Wu, Shaohong Zhao, Jie Gao participated all the process of projection, configuration, experiments and results analysis as well as the composition and reversion.

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