Introduction
Cryptococcosis as an opportunistic infection is a rare complication of sarcoidosis, when the latter is being treated with immunosuppressive agents, especially corticosteroid.1 As is reported that quite a few non-HIV pulmonary cryptococcosis are symptomless. 2,3 Pulmonary nodules are the most common radiographic presentation of pulmonary cryptococcosis4 which may mimic sarcoidosis. The gold standard of diagnosis for those patients is positive histopathological, direct microscopic examination or cytopathological results of sterile specimens. However, lung biopsy is invasive and the sensitivity of culture is very low3 which makes the diagnosis of cryptococcosis challenging. Thus, the clinicians need to analyze those patients comprehensively based on risk factors and laboratory findings and diagnose cryptococcosis clinically. Here, we reported a case of cryptococcosis secondary to sarcoidosis due to the application of corticosteroid to treat the latter.

Case presentation
A previously healthy 55-year-old woman had a chest computed tomography (CT) scan showing mediastinal lymph node enlargement in September 2015. She denied any symptom of cough, hemoptysis, dyspnea, nasal congestion, wheezing, gastroesophageal reflux, fever and headache. Besides, she also denied being a smoker or drug user, bird or mold exposure, recent travel, or contact with tuberculosis or contagious water. Her family and psycho-social history are not specific. She had not been hospitalized in the past year. Six months later, without pharmacotherapy, she had an enhanced chest CT scan which revealed multiple mediastinal lymphadenopathy, the largest one being 17 mm × 14 mm (Figure 1(a)). Then, she was admitted into the Department of Thoracic Surgery in our hospital. On admission, her physical examination did not reveal any positive sign. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed to evaluate the mediastinal lymph node size. Furthermore, the biopsy result (Figure 2) revealed the enlarged lymph node was benign but contained non-caseating granulomas. Her brain CT scan was normal. Serological tests for human immunodeficiency

Abstract
Cryptococcosis is a rare complication of sarcoidosis, especially when it grows in lungs. It may escape from being diagnosed because of low prevalence and non-specific radiological presentation. Hereby, we reported an unusual case of pulmonary cryptococcosis secondary to the long-term use of glucocorticoids to treat sarcoidosis which can be misdiagnosed as progression of sarcoidosis due to the similar radiological presentation. After targeted therapy with fluconazole for 5 months, her chest computed tomography rescan revealed resolution of the pulmonary lesions.
virus, viral hepatitis, T cells enzyme-linked immunospot (T-SPOT) and purified protein derivative (PPD) for tuberculosis were all negative. Angiotensin-converting enzyme was 24 U/L. Mediastinoscopy was ordered to fetch biopsy of enlarged lymph nodes, and she was finally diagnosed with sarcoidosis by pathology (Figure 3). Then, she was treated with oral methylprednisolone 24 mg/d from 20 June 2016 to 1 March 2017. On 31 August 2016, another chest CT scan was performed which demonstrated multiple enlarged mediastinal lymph nodes were significantly smaller than before (the largest one was 7 mm × 10 mm). Six months later, she had a third chest CT scan which showed the lymph nodes had totally shrunk. However, multiple small nodules were found in the right upper lobe (Figure 1(b)). Given that she had been treated with glucocorticoid for over 7 months, we ordered a series of tests for opportunistic infections, among which the serum cryptococcal antigen was positive (the titer was 1:5) while her blood culture was negative and her lymphocyte subsets were normal. Since the diagnosis of cryptococcosis was probable which was the most likely cause of her pulmonary nodules, we suggested a lumbar puncture to rule out intracranial infection. However, she rejected it. Then, her corticosteroid was tapered off, and she was treated with oral fluconazole 400 mg/d according to the Chinese expert consensus. The whole clinical course was summarized in Table 1.

During the follow-up, she underwent a fourth chest CT scan on 2 August 2017, which revealed that multiple nodules in the right upper lobe and the lymph nodes were both obviously shrunken. Due to the imaging improvement, she stopped fluconazole on her own terms which was against our recommendation of 6-month course. Since then, she had visited our hospital yearly with annual chest CT scans which indicated the original lesions turned to chronic inflammatory lesions gradually. Besides, she had never complained of any discomfort such as fever, headache, cough and so on during the follow-up.

Discussion
We presented a rare case of pulmonary cryptococcosis secondary to sarcoidosis after being treated with glucocorticoid. The intercurrent cryptococcosis maybe misdiagnosed as the
newly developed lesion of sarcoidosis. Moreover, the therapeutic strategies of cryptococcosis and sarcoidosis can contradict each other.

Immunosuppressive therapy for sarcoidosis can place patients at risk for opportunistic infections, such as mycobacterial infection, cryptococcosis, progressive multifocal leukoencephalopathy and aspergillosis. However, the incidence of opportunistic cryptococcal infection with sarcoidosis was relatively low. There were only 72 such cases published from 1950 to 2011. The main risk factor for non-HIV-associated cryptococcosis is corticosteroids therapy. Bernard et al. analyzed 18 patients of sarcoidosis with secondary cryptococcosis, among which 12 cases were treated with steroids. Baughman and Lower reviewed 753 patients with sarcoidosis over an 18-month period and found just one patient diagnosed with cryptococcosis. A retrospective cohort study of sarcoidosis reported that after a median follow-up of 8 years, only two cases were diagnosed with cryptococcosis. Here, we described an immunocompetent case who suffered from sarcoidosis and later on acquired cryptococcosis due to the prolonged use of glucocorticoids. As reported by others, glucocorticoids can reduce chemotaxis, phagocytosis, and the release of some cytokine such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α, and so on leading to dysfunction of monocyte-macrophage. As a result, the anergic macrophages can hardly phagocytize any cryptococcus. What’s more, glucocorticoids can interfere with cellular immune processes, reducing T cell activation and proliferation, breaking the balance between T-helper (Th)1 and Th2 cells, diminishing cooperation with B cells and suppressing phagocyte effector cell functions, resulting in poor outcomes of battle against cryptococcosis. More importantly, extensive clinical practice provides evidence that glucocorticoids can increase the risk of opportunistic infections in patients. Leaving aside sarcoidosis, it is believed glucocorticoids therapy is the main risk factor for non-HIV-associated cryptococcosis. And the dosage of corticosteroids more than 20 mg/d might place the patients at a higher risk for opportunistic infection. Thus, corticosteroids maybe a vital risk factor for cryptococcosis in sarcoidosis especially in extra-thoracic sarcoidosis. However, some experts held opposite opinions as some untreated sarcoidosis could complicate cryptococcosis as well, which maybe accounted for by lymphocytopenia and dysfunction of cytokine secretion in sarcoidosis. It was reported that sequestering of cluster of differentiation 4 (CD4) T cells in granulomas and suppression of T cells proliferation by regulatory CD4 T cells might cause anergy. The median count of CD4 cells showed 145/mm³ in cryptococcosis with sarcoidosis, independent from the application of corticosteroids. However, compared with CD4 lymphocytopenia in other conditions of cryptococcosis, they believed CD4 was not an independent risk factor of cryptococcosis.

Most cryptococcosis in sarcoidosis was presented as meningitis while lung involvement was rare, which did not match with the high occurrence of pulmonary cryptococcosis in non-HIV patients. The underlying mechanism is still unclear. Possible publication or reporting bias should be concerned of. Meanwhile, cryptococcal meningitis secondary to sarcoidosis is recognizable due to the typical clinical manifestations such as headache, fever and vomiting. However, pulmonary cryptococcosis is hard to be distinguished from sarcoidosis whose imaging features were alike. And a considerable number of pulmonary cryptococcosis patients were symptomless.

According to the guideline, fluconazole 400 mg/d for 6–12 months is recommended for immunosuppressed patients and immunocompetent patients with mild-to-moderate pulmonary cryptococcosis. However, Chinese expert’s consensus for pulmonary cryptococcosis management suggests oral fluconazole 200–400 mg is enough to non-immunosuppressed, asymptomatic pulmonary cryptococcosis while fluconazole 400 mg/d for 6–12 months is suitable for asymptomatic immunosuppressed hosts. We treated the patient based on these guidelines, although the course was shortened due to her poor drug adherence. Fortunately, her imaging improved significantly during follow-up. Cryptococcosis in this case was not pathologically confirmed which maybe our biggest limitation. However, pulmonary cryptococcosis was diagnosed clinically in this case based on following aspects: first, the patient was treated with high-dose steroids for quite a long time which may cause acquired immunosuppression; second, in the course of hormone therapy, multiple small nodules were found in her lung with positive serum cryptococcal antigen; third, after fluconazole treatment with steroids tapered off, the pulmonary

### Table 1. Timeline.

| Time       | Events                                                                 |
|------------|------------------------------------------------------------------------|
| 2015.9     | A chest CT scan showed mediastinal lymph node enlargement.             |
| 2016.3–2016.6 | An enhanced chest CT scan revealed mediastinal multiple lymphadenopathy, the largest being 17 mm × 14 mm. |
|            | The biopsy result of EBUS-TBNA revealed the enlarged lymph node was benign but contained non-caseating granulomas. Her angiotensin-converting enzyme was 24 U/L. She underwent mediastinoscopy to fetch biopsy of enlarged lymph nodes whose pathology showed sarcoidosis. So, she was diagnosed as having sarcoidosis. |
| 2016.6–2017.3 | She was treated with oral methylprednisolone 24 mg/d.                  |
| 2017.3     | Chest CT showed that her lymph node had totally shrunk; however, multiple small nodules were found in the upper right lobe and she was tested positive for serum cryptococcal antigen, she was diagnosed as having cryptococcosis. |
| 2017.3–2017.8 | She was treated with oral fluconazole 400 mg/d and recovered after 5 months. |

CT: computed tomography; EBUS-TBNA: endobronchial ultrasound-guided transthoracic needle aspiration.
lesions subsided significantly which supported cryptococcosis diagnosis as well.

**Conclusion**

Chronic corticosteroid therapy and cell-mediated immunodeficiency of sarcoidosis maybe risk factors for the onset of opportunistic infections in patients with sarcoidosis. Here, we presented a rare case of a cryptococcosis in the setting of sarcoidosis, due to long-term use of steroids which highlights that clinicians should watch out for pulmonary cryptococcosis while treating patients for sarcoidosis since it maybe misdiagnosed as relapse or aggravation of original disease.

**Author contributions**

J.S. drafted the manuscript. N.Y. and L.C. collected the related literature for discussion. A.H.Y.M., G.Q. and L.Z. revised the manuscript. All authors were involved in the care of the patient except A.H.Y.M. All authors made important contributions and have read and approved the final version of the manuscript.

**Availability of data and materials**

The data that support the findings of this study are available from outpatient and inpatient electronic medical record system of Ningbo First Hospital, but restrictions apply to the availability of these data, which were used under license for this study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with the permission of Ningbo First Hospital.

**CARE Checklist (2016) statement**

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

**Consent for publication**

Written informed consent was obtained from the patient for publication of this case report and the accompanying images. A copy of the written consent is available for review.

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

**Ethical approval and consent to participate**

Our institution does not require ethical approval for reporting individual case or case series. Written informed consent was obtained from the patient for publication of this case report and the accompanying images. A copy of the written consent is available for review.

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