Atypical presentations of pulmonary sarcoidosis: Three cases report and literature review

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Case report

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Abstract

Background: Sarcoidosis is a systematic disease with unknown etiology and lung involved predominantly and also known as a “great mimicker” in lung disease for its characteristics of various appearances in radiology images.

Case presentation: In this article, we present three sarcoidosis patients with atypical manifestation in their imaging performance, including cavitation sign, reversed-halo sign and distributed small nodules with ground glass opacities in both lungs resembled the manifestation of chronic hypersensitive pneumonia. They were diagnosed with sarcoidosis after the confirmation by pathological evidence and received relevant corticosteroid treatment. We also made a literature review from “pubmed” databases to analysis the atypical sarcoidosis performances in past five years.

Conclusions: The atypical manifestation on HRCT of sarcoidosis patients presented in different types which could be ignored by clinicians. Pathology biopsy and clinical characteristics are valuable clues for precise diagnose of sarcoidosis. Thus, clinicians should be on high alert of differential diagnosis and reasonable treatment.

Background

Sarcoidosis is a systemic granulomatous disease of unknown etiology with protean manifestations, and can affect any organ of the body[1, 2]. Notably, thoracic influence occurred in over 90% of patients with sarcoidosis. The diagnosis of sarcoidosis needs a compound of clinical manifestation, histological pathology evidence, radiological features and other auxiliary examinations[3]. High-resolution CT has predominant advantages in detecting subtle manifestation of sarcoidosis and help us to verify and exclude the differentiate disease[4, 5]. The typical appearance in chest HRCT of sarcoidosis usually described as beaded appearance of bronchovascular bundles and perihilar concentration, with lobular distortion[6]. And the other typical appearances often included hilar mediastinal, bilateral lymphadenopathy, nodules, lymphangitic spread, fibrosis, bilateral perihilar opacities, upper- and middle-zone locations of parenchymal abnormalities. However, in addition to the typical sarcoidosis appearances, atypical sarcoidosis, which contained unusual manifestations, could be generated to 25–30% of cases in all[7]. Thus, distinguishing the atypical signs in thoracic radiology and HRCT of sarcoidosis patients is pivotal to all clinicians. Mostly, atypical signs of sarcoidosis mostly contained unilateral or asymmetric lymphadenopathy, necrosis or cavitation in sarcoidosis, peripheral “pseudo-plaque” opacities, ground glass opacities with fine reticulation, airway abnormalities and pleural involvement[8, 9]. Most of the patients elder than 50 years old are more likely to present this pattern[10].

In this paper, we provided three cases of atypical sarcoidosis manifestation in radiology and reviewed previous researches.

Case Presentation

Case One

A 51-year-old male presented with cough and dyspnea for 1 months. He denied syndromes of fever, hemoptysis, dyspnea and fatigue. He declared a medical history of severe lung infection when he was young. Physic exam showed no specific results. PFTs showed obstructive pulmonary dysfunction abnormality with decline in gas transfer: The actual value of FEV1 1.89 L (53.5% of predicted). FVC 3.70 L (84.3% of predicted). FEV1/FVC 51.04% and DLCO 7.02 mL·min⁻¹·mmHg⁻¹ (70.04% of predicted). High-resolution computed tomography presented hilar and mediastinal lymphadenopathy. The enlarged lymphonodules showed in clear broader, density inside, without calcification and conglomeration. Cavitation appeared in both lungs. In left lung, the cavitation is near the division of lobar bronchus, with regular and thin wall, and a partition wall in the middle of the cavitation. In right lung, the cavitation is near the division of right superior lobar bronchus with two partition walls inside. Both cavitation was surrounded by consolidation opacities with radiation pattern of fibrosis with pleural indentation. And air bronchogram sign showed in both sides with multiple linear opacities, thickening walls and irregular narrowed of lumen were found in the bilateral bronchial. HRCT also showed uneven density of ground glass opacities in both lungs. The enlarged bronchovascular bundles were observed as well. A nodule was found in the apex of right lung. Multiple miliary nodules diffused in the inner and middle zone in both lungs. Interlobar pleural showed thicken in films (Figure 1a and 1b).

For definite diagnose, we underwent bronchoscopy tests and the vision presented the congestion of tunica mucosa bronchiorum and multiple nodules disseminated in double lung. CD4:CD8 ratio was 5.0 (higher than 3.5), total cells counting was 7.5×10^6 , phagocyte took up 97%, neutrophils were 1%. Fungi culture and drug sensitive of endotracheal aspirates showed negative of hypha and spore. Diagnosis of tuberculosis was excluded through TB-spot, immunofluorescent of acid-fast staining method in that both of them showed negative results. Culturing for acid-fast bacilli and fungi showed negative as well. ESR was 5mm/h and hsCRP was 1.07mg/L that didn't suggest the inflammation possibility. The infectious disease tests HBV, HCV, TP and HIV showed negative results. G test was normal which excluded fungus infection. ACE level in the serum was 56U/L in normal range (12.0-68.0). The regular test of blood cells didn't show clues of inflammation or infectious disease. Meanwhile, histopathology of specimen in transbronchial lung biopsy (TBLB) in the right lower lobe showed chronic inflammation in tunica mucosa bronchiorum with focal atypical epithelial proliferation. Thus, we highly suspected the diagnose of Stage III sarcoidosis. And the immunohistochemical test showed ALK-D5F3(-), CK7(+), P40(-), and TTF-1(-) that excluded the malignancy diseases. Electronic bronchoscope showed hyperaemia, multiple nodes, in bilateral lung tunica mucosa bronchiorum. The pathology of pink grew tissue from right lower lobe showed granulomatous inflammation in tunica mucosa bronchiorum with fibrous proliferation. The biopsy denied caseous necrosis. Right upper lobe mucosal biopsy indicated a focalized epithelioid granuloma in chronic inflammation without definite necrosis in bronchial mucosal (Figure 1f).

After a month with the treatment of oral prednisone (50mg per day) which was permitted by the patient, the patient's syndrome of dyspnea and cough has relieved. However, the patient described an additional fever syndrome with high temperature and the regular blood test supported a bacterial inflammation.

HRCT showed lymphadenopathy in mediastinum-bilateral hilar and paratracheal were still exist without significantly shrinkage. Cavitations in both side of lungs showed absorption in dimension. However, a brand-new sign showed up that a little volume of liquid appeared in right lung cavitation with a liquid lineage and partition of cavitation was not continuous. The radiation pattern of fibrosis showed shrinkage in area. The patchy consolidation shadow that nearby the cavitations showed shrinkage in area. However, the air bronchogram still existed. In addition, an uneven density of patchy shadow showed up in the anterior medial basal segment of lower lobe in right lung. Accompany with the new fever syndrome in this patient, we highly suspected the pathogenesis of this shadow is inflammation. HRCT showed uneven density of ground glass opacities in both lungs and enlarged bronchovascular bundles signs were not changed (Figure 1c). A year with corticosteroid treatment and the dosage maintained at 7.5mg per day for 5 months from the patient last visit. HRCT showed patchy and nodules shadow with a smaller cavitation in right lung. The uneven density ground glass opacities and fibrosis signs in both lungs were reduced (Figure 1d). Hitherto, the patient undertook 18 months corticosteroid treatment and the dosage maintained at 7.5mg per day for 6 months from last visit. The HRCT showed a significant sign of cavitations absorption in both lungs. However, the fibrosis in both lungs still remained. And lymphadenopathy in bilateral hilar and mediastinum showed shrinkage in size. The consolidation with air bronchograms signs still existed in both lungs. The treatment of corticosteroid adjusted to 10mg per day for maintaining the treatment of sarcoidosis (Figure 1e).

Case Two

A 38 year old female, maintained coughing for 1.5 months as her chief complain. Denied fever, hemoptysis syndrome. The high resolution computed-tomography showed characteristic of patchy consolidation lesions were obvious in both upper lungs and right middle lung; reverse halo signs were notable in right and left lower lungs, which confirmed to the radiology characteristics of cryptogenic organizing pneumonia (Figure 2a and Figure 2b). In mediation window, adenopathies were obvious in mediation and bilateral hilar (Figure 2c). Transbronchial lung biopsy suggested epitheloid granulomatous in lung tissue without necrosis in low magnification microscope histopathology (Figure 2d). TBNA histopathology denied cancer cells. Differential cells counting result in bronchoalveolar lavage fluid turned out to be quite normal. Total cell counts for 7.6×10^6 , alveolar macrophage percentage was 92%, lymphocyte for 7%, neutrophils for 1%, and eosnophils for 0%. The ratio of CD4⁺T lymphocytes/CD8⁺T lymphocytes was 1.3 (less than 3.5). Angiotensin converting enzyme not higher than upper limitation. Percutaneous Lung puncture result showed organizing in alveolar space and atypical epitheloid granuloma in partial range. Peripheral blood tests of autoimmune disease biomarkers, for instance, ANCA, ANA, ENA showed negative for excluding autoimmune disease, T-spot showed negative result for excluding pulmonary tuberculosis. Hyper-sensitive C-reaction protein was 28.52 mg/L (higher than normal upper limitation). Erythrocyte sedimentation rate was 92 mm/hr. In this case, the patient's histopatholgy evidence and radiology characteristic supported diagnosis of sarcoidosis (Stage III) with exclusion of other possible etiologies of tuberculosis mycobactiera infection, lymphoma, castleman's disease etc. Dealing with 45mg prednisone per day for one month treatment which was permitted by the

patient, patient declaimed a relief from coughing and dyspnea syndrome. HRCT showed an absorption of lesions in both lung and the enlarged lymphonodus were shrinked in mediation and bilateral hilar. The treatment of prednisone dosage reduced gradually to 10mg per day in 2 years. HRCT showed normal manifestation in both lungs, mediation and bilateral hilar.

Case Three

A 37 years old male came for cough with dyspnea for one year to the clinic. Notably, he declaimed a special career history of lathe processing for several years before. Physic exams didn't show any specifics, which included normal tempreature, heart rhythm and so on. However, the pulmonary High-Resolution Computed Tomography (HRCT) showed diffused micro-nodules (less than 1 mm in size) distribution in both lungs, mainly in upper-middle lobes and sub-pleura in lung window (Figure 3a and 3b). The HRCT lesion pattern is accordance with the diagnosis of both sarcoidosis and chronic hypersensitivity pneumonitis (HSP). In mediastinal window, it was clear to detect lymphadenopathy in 2R, 2L, 4R, 4L, 7, 10R, and 10L (Figure 3c). Considering his specific career history of inhaling contaminated metal working fluid (MWF), probably exposed to the iron powder for a peroid of time, and the abonormality in HRCT of small nodules throughout the both lung with ground-glass opacity, we could't denied the possibility of chronic HSP. He underwent Bronchoscopy with sampling of lung parenchyma in right lower lobe and retrieved specimens showed well-formed non-caseating epithelioid granulomas in bronchiolocentric distribution (Figure 2 d). BALF (Bronchoalveolar Lavage Fluid) with flow cytometric analysis showed 29.5% lymphocytes with 69.9% CD4⁺T cells and CD4⁺/ CD8⁺ ratio is 7.5 which is higher than normal range. These findings consistent with the diagnosis of sarcoidosis. The BALF results denied fungi or bacteria infections neither in smearing from bronchial nor in culturing aspects.

Discussion And Conclusion

The diagnose of sarcoidosis should followed three basic criteria which contained clinical features, radiography and histopathological evidence. Patients with pulmonary sarcoidosis usually presented as non-specific constitutional complaints (e.g. fever, weight loss, fatigue, anorexia, malaise) and/or symptoms directly related to the respiratory (e.g. cough, dyspnoea, particularly with exertion, chest pain and, occasionally, haemoptysis). Early in the disease, the physical findings in the chest are usually limited to dry, crackling rales, most commonly heard at the posterior base of the lung[2]. In histopathology evidence, the biopsy sample of sarcoidosis usually contained non-caseating epithelioid granulomas[11].

In radiography of sarcoidosis patients, according to ATS/ERS/WASOG statement on sarcoidosis, the typical HRCT manifestations which have been seen in 90% of patients including both hilar-mediastinal lymphadenopathy and micronodules with a perilymphatic and fissural distribution in both lungs, upper and posterior predominantly. The clinical classification of sarcoidosis based on Scadding radiographic staging: Stage 0: Corresponds to the normal sign of radiology of lymph nodes and lungs; Stage I: Bilateral hilar and mediastinum lymph node enlargement with or without paratracheal lymphadenopathy, not associated with visible lung disease; Stage II: Bilateral hilar lymph node enlargement associated with

visible lung disease; Stage III: Diffuse lung disease without lymph node enlargement; Stage IV: Lung and bronchial variation (e.g. lung fibrosis with honeycombing pattern)[12, 13].

However, The atypical patterns contained large nodules and masses, alone or associated with enlarged lymph nodes (1-4 cm in diameter, large ill-defined opacities on CT), distribution could be variable in different patterns, and small satellite nodules could also be visible at the periphery of these masses, leading to the “galaxy sign” appearance^[14]. Diletta Cozzi summarized the previous studies and concluded that 25-30% of patients develop unusual sarcoidosis with non-specific radiological patterns, which are various and in different frequencies[15].

The atypical lesion patterns in lung parenchymal included large pulmonary nodules and masses, patchy air space consolidations, patchy ground glass opacities and areas of air trapping and mosaic attenuation. Opacities represent confluent and coalescing nodules in the interstitium or the acini of the lung parenchyma and often superimposed on the background of the interstitial nodules. Mosaic attenuation occurred in the patients with small airway involvement[16]. Ma J et.al. concluded 190 patients’ chest CT manifestations and clinical characteristics from 2000 to 2015 in their hospital. The result showed that the atypical chest CT manifestations of sarcoidosis mainly included unilateral hilar lymphadenopathy with or without mediastinal lymphadenopathy (n=12, 6.3%), mediastinal lymphadenopathy without hilar lymphadenopathy (n=9, 4.7%), patchy consolidation (n=23, 12.1%), sarcoid galaxy sign (n=22, 11.6%), reversed halo sign (n=1, 0.5%), ground glass opacities (n=52, 27.4%). And 8 out of 10 patients who underwent inspiratory and expiratory CT showed air-trapping phenomenon. They re-evaluated CT images of these patients after treatment, and the majority of atypical chest CT manifestation of sarcoidosis patients showed an improvement of lesions^[17].

When the radiology showed atypical findings, clinicians should consider clinical presentation as well as histopathological testing for achieving diagnose.

1. Pulmonary nodules or Mass-like opacities

Mass-like opacities is one of the atypical manifestations in sarcoidosis patients’ imaging performance, the differential diagnosis of which based on imaging findings contained lymphoma, vasculitis, and atypical pulmonary infection. The lung consolidation that influenced alveoli and airspaces distributed in the peribronchovascular areas of the upper and middle lungs. It was reported that pulmonary nodules and masses occurred in 15%-25% of sarcoidosis patients with parenchymal opacities which usually presented in 1-4 cm in diameter that represent coalescent interstitial granulomas distributed in perihilar and bilateral, perihilar or peripheral regions commonly[18-20]. Clinicians should aware of the metastatic possibility if multiple rounded macronodules scaled out 5 mm in diameter occurred in radiographs[21].

Marie Tominna et.al. reported a 30 years old African American woman diagnosed with sarcoidosis who manifested in distributed, sharply demarcated, mass like ground glass opacities in both lungs. And CT showed right paratracheal, bilateral hilar, para-aortic, subcarinal and perivascular lymphadenopathy.

Histopathology findings revealed noncaseating granulomas, consistent with sarcoidosis diagnosis. And treatment of corticosteroids to this patient showed a good response^[22].

A. Atig et.al reported a 62 years old woman who manifested in dyspnea came into clinic and chest CT exams showed a mass consolidation in right lower lobe, coexistent with bronchovascular bundles thickening and mediastinal lymphadenopathy. However, after transbronchial lung biopsy, the histopathology result turned out to be neither malignancy disease nor granulomatous. The bronchoalveolar lavage fluid tests showed neither alveolitis nor tumor cells. They decided to give the patient diagnose of systemic sarcoidosis with pseudo-tumor pulmonary affection. After treatment with corticosteroids for 3 years, the repeat radiology image showed an improvement of lesions, which suggested previous diagnose of sarcoidosis.

Dylan W.Kelleher et.al. reported a 44-year-old African woman with a history of childhood asthma and type 2 diabetes mellitus presented with shortness of breath. Her chest radiograph revealed a mass-like opacity in the left lower lobe, and her chest CT scan showed a large, 6.7×5.4×9.9-cm left lower lobe mass and hilar lymphadenopathy. Thus, according to the existing evidence, the patient was suspected to pulmonary malignancy firstly. In order to ascertain diagnose, the patient underwent computed tomography-guided biopsy of the lung mass, and the result revealed a multifocal non-necrotizing granuloma with multinucleated giant cells. Biopsy of bronchoscopy and mediastinoscopy revealed granulomatous inflammation without evidence of malignancy or infection. According to the histopathology result, she was confirmed diagnose of sarcoidosis. Then she was treated with high-dose prednisone, and repeat imaging showed a significantly shrinking of lung mass and lymphadenopathy[23].

Kwas Hamida et.al reported a 37-year-old woman, who manifested in chest pain, cough, fever, anorexia and weight loss within the past 15 days. Chest X-ray showed diffuse and bilateral alveolar opacities with air bronchograms. Chest CT scan showed diffuse and bilateral alveolar consolidation, perilymphatic distribution of micronodules and mediastinal lymphadenopathy. Laboratory examination showed elevated serum angiotensin converting enzyme (ACE) level (140 UI/ml). BALF represented lymphocytic alveolitis but CD4+/CD8+ ratio didn't higher than normal. The histopathology of bronchial biopsy showed non-caseous epithelioid cell granuloma. Thus, diagnose of sarcoidosis could be generated. After 5 months of oral corticosteroid treatment, the patient declared a relief of her syndrome[24].

When sarcoidosis patient manifested in solitary pulmonary nodule, the clinicians ought to pay attention to the differential diagnosis of malignant disease. Han Na Lee et.al reported a 52-year-old woman who presented with uveitis, fever of unknown origin and atypical manifestation of sarcoidosis. Her chest computed tomography showed solitary pulmonary nodule, which enlarged 0.4 cm over 18 months. And the serum angiotensin converting enzyme (ACE) was 71.6U/L, higher than normal. However, the histopathology of thoracoscopic wedge resection for a nodule and excisional biopsy for a lymph node showed several small non-caseating granulomas adjacent to the bronchiolar epithelium, which confirmed the diagnosis of sarcoidosis[25].

Haykel Abdelhedi et.al reported a case of a 56 years old woman whose chest CT showed asymmetric mediastinal and bilateral hilar compressive lymphadenopathy. The chest radiography showed bilateral hilar enlargement, and pulmonary nodules, size in 5 to 10 mm diameter, were scattered in right upper lobe, right middle lobe medial segment, lateral basal segment and sub-pleural. However, these micronodules predominantly diffused in right mid-lobe and formed as tree-bud pattern in some area. FOB (Fronchofiberscope) showed granulomatous diffused along the bronchial. The histopathology of TBLB presented as epithelial and giant cell inflammation without caseous necrosis. BALF showed CD4+ T cell proliferation, and CD4+/CD8+ ratio was 4.5, higher than normal^[26]. This case indicated that when chest image manifested in multiple nodules dissemination, the differentiation diagnose of sarcoidosis should consider tumor (e.g., metastasis, lymphoma) firstly and infections (e.g., tuberculosis) secondly. When it occurred, the histological biopsy tests could be beneficial to figure out.

2. Ground glass opacities

Chunmei Ma et.al reported a case of a 40-year-old Chinese woman presented to the hospital with cough and a history of recurrent rash on the skin of the wrist and knee which resolved spontaneously. The chest CT revealed the presence of diffused ground glass opacity with minor lymphadenopathy. The histopathology of transbronchial biopsy indicated the epithelial granulomas with no caseous necrosis. Patient confirmed diagnose of sarcoidosis^[27].

3. Sarcoid cluster sign

I. Herráez Ortega et.al reported a new atypical appearance in HRCT with the description of the presence of clusters of multiple small micronodules distributed in the non-subpleural peripheral regions of the upper and middle fields of the lungs, sometimes along the lymph vessels on HRCT, and given the name “sarcoid cluster sign” (SCS)^[28].

4. Sarcoid galaxy sign

Masashi Nakatsu et.al firstly defined the “Sarcoid Galaxy” sign as an atypical manifestation of pulmonary sarcoidosis chest CT appearance. The appearance of characteristic CT pattern is that the large parenchymal nodules in pulmonary sarcoidosis appeared with some noncaseating small granulomas surrounding nearby loosely which are similar to a “galaxy”, tending to coalesce into a large nodule and usually accompany with mediastinal and hilar lymphadenopathy^[29]. Nodules in sarcoidosis mostly distributed along lymphatics in bronchovascular bundles^[30].

Alveolar or pseudoalveolar sarcoidosis present in reversible consolidations with peripheral distribution as its typical presentation in “galaxy” sign^[6]. Paul McCabe reported a case that a 27-year-old woman's HRCT presented in atypical opacities with galaxy sign with mediastinal lymphadenopathy^[31].

5. Reversed halo sign (RHS)

Edson Marchiori et.al reported that reversed halo sign, ground-glass attenuation surrounded by a partial or complete rim of consolidation, is an atypical tomographic feature of sarcoidosis. However, this description was often used to describe cryptogenic organizing pneumonia and some other diseases, including infectious (aspergillosis, blastomycosis, tuberculosis) and non-infectious conditions (drugs, hematological malignancy, granulomatosis with polyangiitis, hypersensitivity pneumonitis, inflammatory bowel disease, inhalation injury, irradiation injury, and transplantation)^[32, 33]. Thus, in this circumstance, the clinical manifestations and histopathology tests counting more. Ajmal Nazir Neelambra et.al reported a 32 years old female presented with dry cough and progressive dyspnea for 3 weeks, her chest HRCT showed peripherally based patchy, subsegmental lesions of the upper lobe and left lower lobe. After systemic treatment of steroids for 3 months and gradually tapered to stop, the lesions on chest HRCT disappeared accompanied with the relief of her syndrome, which demonstrated the good responds to steroids therapy. In this case, the patient was diagnosed with cryptogenic organizing pneumonia and sarcoidosis, in that neither single diagnose could explain her syndrome or other tests results^[34].

6. Pulmonary cavitory

A cavitory lesion was defined as an air-containing lesion of more than 1-cm diameter with either thin walls (≤ 4 mm) or thick walls (≥ 4 mm or located within an infiltrate or a mass). These lesions differed from the honeycombing feature occasionally observed in fibrotic sarcoidosis based on the heterogeneity of the size of the cysts and based on the presence of normal lung seperated rows of clustered cysts. Sandrine Hours et.al retrospectively reviewed the chest HRCT characteristics of 23 sarcoidosis patients with pulmonary cavitory lesions extracted from a large cohort of patients with pulmonary sarcoidosis in their hospital from 1988 to 2005. They concluded that about 82.6% of patients with cavitory, accompanied with granulomatous lesions around the cavitory, had high levels of SACE that suggested the active disease status. Complications of cavitory lesions including hemoptysis, aspergilloma, pneumothorax, and other infections were seen in these patients^[35].

7. Atypical pattern of Lymphadenopathy

Intrathoracic lymphadenopathy is the most common findings in sarcoidosis with bilateral hilar lymphadenopathy (BHL) alone or with mediastinal lymphadenopathy, occurs in 95% of patients. Whereas, unilateral or asymmetric lymphadenopathy and “egg-shell-like” calcifications in lymph nodes are atypical patterns of sarcoidosis^[15]. M.E. BEIN et.al reported that they analyzed 62 sarcoidosis patients’ chest radiographs, and the result turned out that approximately 95% patients had lymph nodes enlargement, 75% in the right paratracheal or aortopulmonic window regions and about 20% in the subcarinal or anterior mediastinal regions. And the most common lymphadenopathy combination features included aortopulmonic window, bilateral hilar, and right paratracheal regions^[36].

Dylan W.Kelleher et.al reported a 44-year-old African woman with a mass-like opacity in the left lower lobe, and her chest CT scan showed a large, 6.7×5.4×9.9-cm left lower lobe mass and hilar lymphadenopathy. Thus, according to the existing evidence, the patient was suspected to pulmonary

malignancy firstly. In order to ascertain diagnose, the patient underwent computed tomography-guided biopsy of the lung mass, and the result revealed a multifocal non-necrotizing granuloma with multinucleated giant cells. Then she was treated with high-dose prednisone, and repeat imaging showed a significantly shrinking of lung mass and lymphadenopathy^[23].

Andrew Meillier et.al reported a case that a 38-year-old Caucasian female, manifested in chronic cough, fatigue and a loss of appetite for 6 weeks, physic exam showed right facial droop which indicated Bell's palsy syndrome. The chest CT showed unilateral lymph node enlargement in aorto-pulmonic window. PET/CT showed multiple active lymph nodes in the mediastium. EBUS showed a mediastinal mass. The histopathology of mediastinal mass and lymph node indicated non-caseating lymphadenopathy with focal necrosis. The pathology denied malignancy. However, the clinical, radiological and pathological results suggested diagnose of sarcoidosis^[37].

8. Pleura involvement of sarcoidosis

Involvement of pleura by sarcoidosis remains a rare manifestation and varies from pleural effusion, pneumothorax, pleural thickening, hydropneumothorax, trapped lung, hemothorax, or chylothorax. Onkar Jha et.al reported a case of a 65-year-old male, presented as 4 months history of dry cough, dyspnea and intermittent fever. His chest X radiation showed right lower zone nonhomogeneous opacity. However, his sputum smear was negative for acid-fast Bacilli (AFB). Contrast enhanced computed tomography (CECT) chest showed multiple discrete and conglomerating heterogeneous mediastinal and bilateral hilar lymphadenopathy with few showing calcification and nonhomogeneous attenuation. Moreover, ill-defined right lower lobe ground glass opacities with minimal pleural effusion also presented on the image. PET/CT showed multiple fludeoxyglucose (FDG) avid lymph node revealed in prevascular, aortopulmonary window, bilateral paratracheal, sub-carinal, para-esophageal and bilateral hilar regions with FDG avid inter- and intra-lobular nodular septal thickening with multiple small nodules in perilymphatic distribution along the fissures and subpleural locations involving both lungs. EBUS showed large heterogeneous lymph nodes at stations 7, 4R, 4L, 10R and 10L. TBLB showed non-necrotizing granulomatous inflammation in the interstitium and sub-bronchial mucosal granulomas. Thus, diagnose of sarcoidosis could be made^[38]. Remi Trien et.al reported a case of a 43-year-old woman who diagnosed with sarcoidosis and probably induced by interferon-alpha-2b, which was used to treat her history disease hepatitis C. The chest radiograph showed bilateral diffuse prominence of bronchovascular markings. Chest computed tomography showed centrilobular nodules in bilateral lung parenchymal with intralobular septal thickening. Moreover, the other accompanied characteristics included central peribronchovascular interstitium, nodularity of major fissures, mediastinal lymphadenopathy. The histopathology of enlarged lymph nodes in mediastinal appeared non-caseating granulomatous inflammation, which consistent with diagnose of sarcoidosis^[39].

9. Hemoptysis

Massive hemoptysis occurred approximately less than 0.5% of the patients^[40]. Wang'ondou RW et.al reported a 45-year-old male with a history of stage IV pulmonary sarcoidosis with cardiac involvement, presented as a two months history of cough and acute non-massive hemoptysis with hypoxia. The chest CT showed ground-glass consolidation and interlobular septal thickening. The clinical manifestation and image characteristic suggested diagnose of diffuse alveolar hemorrhage (DAH)^[41]. Masoud Nazemiyeh et.al reported a rare presentation of pulmonary sarcoidosis with massive hemoptysis in early course of disease rather than lung parenchymal involvement.

10. SLS-Sarcoidosis lymphoma syndrome

Assad Oskuei et.al reported a patient had both sarcoidosis and a B-cell lymphoma with features of splenic marginal zone lymphoma (SMZL). Chest CT showed lymphadenopathy in mediastinum, hilar regions and in both axillae; in the lung parenchyma there were multiple areas of consolidation scattered diffusely, bilaterally, worse at the lung bases. The radiology manifestation was consistent with the suspicion of malignancy disease (lymphoma or bronchoalveolar cell carcinoma) or cryptogenic organizing pneumonia. After bronchoscopy and bronchoalveolar lavage result showed negative, which contained cytology, tuberculosis smear, bacterial and fungal cultures. Left axillary lymph node biopsy showed necrosis. After prednisone tapering therapy, the patient admitted an improvement of syndrome and the repeat CT image showed attenuation of opacities. The right upper, middle and lower lobes histopathological evaluation revealed multifocal well-formed non-necrotising granulomatous. SACE and hypercalcaemia levels showed elevated which supported sarcoidosis diagnose. After treatment for a year, the patient complaint left upper abdominal pain, and physic exam presented with massive splenomegaly. Then he was treated with splenomegaly and histopathological assessment showed a low-grade B-cell lymphoma consistent with marginal zone lymphoma with extensive plasmacytic differentiation reflected by the presence of component of lambda restricted plasma cells involving the spleen and perisplenic lymph nodes. Thus, the clinical features and pathology characteristic supported diagnose of sarcoidosis and lymphoma^[42].

11. Necrotizing sarcoid granulomatosis (NSG)

Te-Chih Hsiung et.al reported a case of 35-year old man who manifested in fever and night sweating with a history of pulmonary tuberculosis exposure history. His chest CT showed a 3×4 cm left paratracheal lymphadenopathy. The histopathology of EBUS guided TBNA presented as granulomatous inflammation with focal necrosis and perivascular involvement. The tests of microbiology study, septum acid-fast stain and mycobacterial cultures for tuberculosis showed negative results. Tuberculin skin test with purified protein derivative showed a positive result (induration greater than 15mm). However, after anti-tuberculosis treatment for 2 months, the repeat chest CT scan showed progression of mediastinal lesions and newly developed pulmonary infiltration in the left upper lung. In BALF, the lymphocyte ratio had increased (30%), the CD4/CD8 ratio had increased 8 times than normal. A diagnose of necrotizing subtype sarcoidosis with potential tuberculosis infection was formulated. After oral prednisone treatment for 1 month, the patient's clinical and radiological aspects showed improvement^[43].

12. Pleural plaquelike opacities

Patches of subpleural micronodules which usually occurred on the visceral pleural that referred to “pseudoplaques”, which are formed by multiple coalescent micronodules (granulomas) with well-defined irregular margins and usually detected in upper and middle zones of both lungs^[44].

13. Airway involvement

Airway involvement could be atypical manifestations in HRCT of patients with sarcoidosis. The most common appearances included mosaic attenuation pattern, air trapping, tracheobronchial abnormalities and atelectasis. Due to the small airways involvement, which may be secondary to peribronchiolar granulomas or fibrosis that could generate obstruction, air trapping and mosaic attenuation patterns on expiratory CT are common radiological features of pulmonary sarcoidosis^[45, 46].

A comparison between atypical and typical sarcoidosis in progression, recurrence, prognosis, treatment underwent by Roberta Polverosi et.al. In this research, they concluded 56 patients with pulmonary involvement of sarcoidosis. However, 39 of them showed typical patterns and the other 17 appeared with atypical patterns in chest HRCT. However, they figured out that in these untreated sarcoidosis patients, people with typical patterns showed more stable in radiologic findings than patients with atypical appearance. Recurrences occurred more often in patients with typical patterns than atypical groups^[14].

Detecting atypical sarcoidosis is still a difficulty in sarcoidosis diagnosis. We here concluded three atypical manifestations in chest HRCT images of sarcoidosis patients and reviewed articles on “pubmed” database that including ‘atypical’ and ‘sarcoidosis’ key words, and reviewed the articles of lung involvement, intending to remind clinicians to notice unfamiliar appearances of sarcoidosis. Moreover, atypical manifestations in chest radiology images of sarcoidosis sometimes resemble to the differential diagnoses, including granulomatous disorders (tuberculosis, leishmaniosis, tularaemia, fungal disease, sarcoidosis-lymphoma-syndrome), infectious disease (mycobacterial, fungal), non-infectious disease (hodgkin and non-hodgkin lymphomas, sarcomas, silicosis, berylliosis). There is a metaphor that sarcoidosis could be described as “the great pretender” since its manifestations can present as different disease manifestation^[47]. The combination of clinical history, histopathology evidence and HRCT could help to differentiate sarcoidosis.

Abbreviations

TBLB: transbronchial lung biopsy; BHL: bilateral hilar lymphadenopathy; SACE: serum angiotensin converting enzyme; TBNA: transbronchial needle aspiration; HRCT: high-resolution computed tomography; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; DLCO: diffusing capacity of carbon monoxide; HBV: hepatitis B virus; HCV: hepatitis C virus; TP: treponema pallidum; HIV: human immunodeficiency virus; ANCA: Antineutrophil Cytoplasmic Antibodies; ANA: antinuclear antibody; ENA: Extractable Nuclear Antigen Antibody; HSP: hypersensitivity pneumonitis; MWF: metal working fluid;

BALF:Bronchoalveolar Lavage Fluid; SCS:sarcoid cluster sign; RHS:Reversed halo sign; BHL:bilateral hilar lymphadenopathy; DAH:diffuse alveolar hemorrhage; SMZL:splenic marginal zone lymphoma; NSG:Necrotizing sarcoid granulomatosis;

Declarations

Ethics approval and consent to participate

Written approval was obtained from the Ethics Committee of Peking Union Medical College Hospital (No. JS-1127) to use pathology and radiology results for research purposes.

Consent for publication

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

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare no competing interests in this research.

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Authors' contributions

HH served as the respiratory expert and took the responsibility of the integrity of the work as a whole. REF served as the pathological expert of respiratory medicine and participated in recognizing and diagnosing of specimens. ZJ X contributed to the design of the paper, patients' information collection and also served as respiratory expert that contributed to the radiological analyze of the work. NW contributed to the clinical information collection. ZQ contributed to the clinical information collection, patients following-up and drafted the manuscript. All authors have read and approved the manuscript.

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Figures

Figure 1

Atypical presentations of sarcoidosis presented as cavitation. (1a) and (1b) showed the primary images in lung window and mediastinal window of the atypical manifestation of cavitation. (1c) showed liquid lineage in lung window of this patient after fever syndrome. (1d) showed lesion absorption after one year of corticosteroid treatment. (1e) the cavitation absorbed significantly after 18 months of treatment. (1f) the biopsy showed epithelioid granuloma in chronic inflammation without definite necrosis in bronchial mucosa which indicated the diagnose of sarcoidosis.

Figure 2

Atypical presentations of sarcoidosis presented as reversed halo sign. (2a) and (2b) Lung window images showed consolidation and reversed halo sign in both lungs. (2c) Mediastinal window image showed lymphadenopathy in mediastinum. (2d) showed histopathology in low magnification microscope of non-caseating granulomatous.

Figure 3

Atypical presentations of sarcoidosis resemble chronic hypersensitive pneumonia. (3a) and (3b) Images in lung window are similar to the characteristics of chronic hypersensitive pneumonia which presented as distributed small nodules in both lungs. (3c) Lymphadenopathy was obvious in mediastinal window of this sarcoidosis patient. (3d) Low magnification microscope histopathology proved non-caseating granulomatous.

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