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Case report

Diffuse pulmonary micronodules related to prior VZV infection

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ABSTRACT

Background/introduction: Chickenpox is a common viral infection caused by Varicella-zoster virus (VZV). Pneumonia is an infrequent complication of chickenpox infection. Rarely, multiple calcified pulmonary nodules can be the sequela of healed VZV pneumonia.

Case presentation: A middle-aged female individual was found to have diffuse incidental pulmonary micronodules. By further history inquiry and diagnosis of exclusion, her pulmonary micronodules were determined to be likely associated with prior VZV infection.

Conclusions: VZV infection can cause calcified pulmonary nodules related to granuloma, and gold standard diagnosis is surgical lung biopsy with VZV PCR. However, diagnosis of exclusion is a reasonable approach to reach a presumptive diagnosis. Familiarity with this entity can potentially avoid invasive procedures in selected patients.

1. Introduction

Chickenpox is a common viral infection caused by Varicella-zoster Virus (VZV). It is usually self-limited and characterized with vesicular rashes in pediatric population. Pneumonia is an infrequent complication of chickenpox infection; however, it contributes to most of chickenpox associated mortality and morbidity [1]. Rarely, multiple calcified pulmonary nodules can be the sequela of healed VZV pneumonia [2]. Here, we present a case of middle-aged female individual who was found to have incidental pulmonary micronodules. By further history inquiry and diagnosis of exclusion, her pulmonary micronodules were determined most likely to be associated with VZV infection 20 years prior to this presentation.

2. Case presentation

53 years old female, with 15 pack year (half pack a day for 30 years) smoking history, presented to urgent care with dry cough and dyspnea on exertion. Two weeks prior to the presentation, she started to have dry cough associated with mild sore throat and rhinorrhea. Two days prior to the presentation, the patient developed mild gradual onset dyspnea on exertion, which prompted her to go to urgent care. A Chest X ray was done and showed diffuse pulmonary micronodules (Fig. 1). Subsequently, the patient was transferred to our institute for further evaluation for possible TB. She denied fever, night sweats, anorexia or weight loss, and her vital signs were in normal range. She did not require any oxygen supplementation. Patient was well appearing and breathing comfortably in ambient air. Chest auscultation revealed minimal bilateral expiratory wheezing. No rash, lymphadenopathy or abdominal organomegaly was appreciated.

The patient does not have chronic medical conditions and takes no daily medications. She reported that she moved into an old house 2 months ago and did not notice any molds in her house. She lives with two cats. She smokes half a pack per day for 30 years and denies alcohol or illicit substance use. She works in a pastry store. She lives in New England area and denied any recent domestic or international travel. Last long-distance travel was more than 20 years ago. She went to England and Barbados.

On further inquiry, the patient had varicella in her 30s when she was postpartum, which she contracted from her elementary-school-aged daughter. Neither of them were hospitalized.

CT pulmonary angiogram showed numerous, diffuse, subcentimeter, pulmonary nodules throughout the lungs, many of which demonstrate calcification with an associated calcified mediastinal lymph node (Fig. 2). Patient's CBC with differential, basic chemistry profile, liver functional test, inflammation markers including ESR and CRP were all

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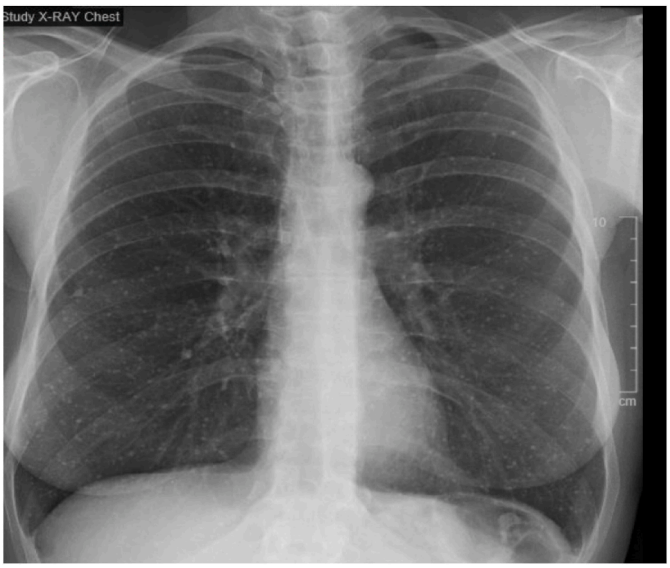

Fig. 1. Chest Xray: bilateral diffuse micronodules.

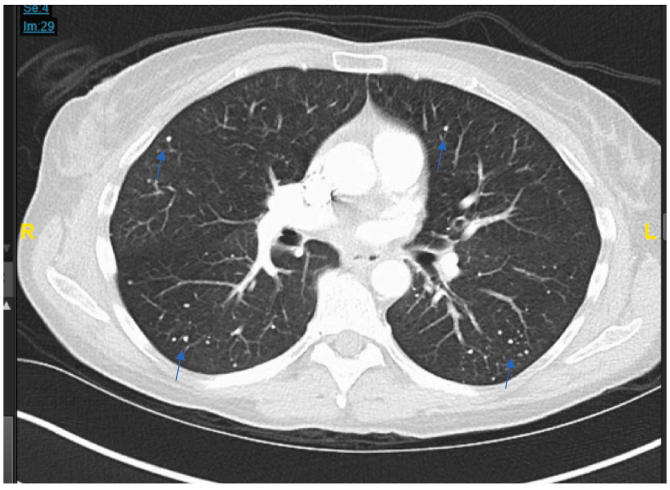

Fig. 2. CT chest showed numerous, diffuse, subcentimeter, pulmonary nodules throughout the lungs (indicated by arrows), many of which demonstrate calcification.

within normal limits. Respiratory pathogen panel was negative. Urine and serum histoplasma antigens were negative. Coccidoides antibody was negative. Patient was not able to produce sputum even with induction, hence AFB culture with smear was not performed. TB QuantiFERON was negative. VZV IgM was negative, but IgG was positive. HIV was non-reactive. CT of abdomen and pelvis showed no intraabdominal abnormalities.

A multidisciplinary discussion was held between internal medicine, pulmonary medicine, infectious disease as well as radiology. Given patient was overall well appearing, no B symptoms, fever or hypoxia, no travel history to endemic mycoses area or occupation exposure history, as well as pan-negative lab data including non-reactive fungal, TB and HIV serology. Pt was presumptively diagnosed with healed chronic granulomatous lung infection. Given she had history of varicella 20 years ago and her VZV IgG was positive, we believe her lung lesions are most likely secondary to healed VZV lung infection. After careful weighing risk and benefit, no further invasive testing such as bronchoscopy or lung biopsy was recommended.

We believe patient's respiratory symptoms, including cough and shortness of breath, were related to obstructive lung disease rather than pulmonary nodules. She was treated empirically with prednisone and albuterol/ipratropium nebulizer with significant improvement and discharged with a 5-day course of prednisone.

The patient followed up with primary care physician one month after discharge and was feeling well. Her lung nodules do not require further follow-up imaging. One year after discharge, patient self-reported feeling well in a follow up phone call by one of the authors.

3. Discussion

Pulmonary involvement of VZV infection is not common. It usually occurs in immunocompromised adults. The features of chest imaging include nodular or interstitial pneumonitis [1]. Taga et al. reported a case of adult primary varicella pneumonia (PNA) [4]. That patient had a history of anaplastic lymphoma, and her CT chest showed multiple nodules with surrounding ground-glass attenuation (GGA) and consolidation. After administration of acyclovir, the pulmonary abnormalities resolved.

However, VZV PNA can also occur in immunocompetent individuals, and it tends to be mild. This mild form of VZV infection may induce formation of pulmonary granuloma. Rossi et al. reported a series of 8 patients with bilateral small lung nodules which were evenly distributed throughout lung fields [5]. All patients underwent VATs lung biopsy because they were suspected to have metastatic lesions of unclear source. Granulomas were confirmed and positive for VZV in all 8 cases via PCR based molecular analysis on tissue pathology slides. Furthermore, the core of granuloma consists of eosinophilic acellular necrotic tissue. In retrospect, all the 8 patients had prior clinically obvious VZV infection during adulthood, and none of them had severe respiratory symptoms. This is like our patient, who had VZV infection two decades ago with mild symptoms. Lococo et al. reported a case of young female patient with incidental findings of multiple lung nodules; and there was concern of metastatic lung disease; however, biopsy confirmed varicella induced granuloma [6].

Diffuse pulmonary nodules raise diagnostic challenges for clinicians. The differential diagnosis is extremely broad including infectious (TB, fungal), inflammatory (sarcoidosis, rheumatoid nodules), neoplastic (lymphangitic carcinomatosis), environmental (silicosis) [2]. In addition, varicella lung infection can induce calcified pulmonary granuloma [3,7,8]. Golden standard of diagnosis is lung biopsy with VZV PCR. However, for some patients, multidisciplinary approach combined with diagnosis of exclusion can also reach presumptive diagnosis with reasonable confidence and avoid invasive procedures. Therefore, familiarity with this entity is important. As in our case, we ruled out military tuberculosis via lack of B symptoms and a negative TB QuantiFERON; we ruled out histoplasmosis via lack of travel history to endemic area and negative serum and urine antigen; silicosis and berylliosis were ruled out by lack of occupational exposure; diffuse lung metastasis was ruled out by CT chest and abdominal pelvis. Also, a calcified mediastinal lymph node without mediastinal or hilar lymphadenopathy makes sarcoidosis very unlikely; calcified pulmonary nodules are highly atypical for respiratory bronchiolitis associate interstitial lung disease. Considering this patient's prior varicella infection, positive varicella IgG and overall very stable clinical picture, this patient was clinically diagnosed with pulmonary nodules due to prior healed VZV infection without invasive procedures by multidisciplinary discussion among internal medicine, pulmonary medicine, infectious disease and radiology. Patient's respiratory symptoms including dry cough and dyspnea added some challenge to diagnosis. As they were not related to her chest imaging findings but likely related to long smoking history and underlying COPD.

Diffuse pulmonary nodules secondary to VZV infection is not common. Our case is one of few on literature to report a presumptive clinical diagnosis of VZV induced diffuse pulmonary nodules based on serology and radiology without lung biopsy. We suggest thorough history taking of prior VZV infection for all patients with diffuse pulmonary nodules. It

potentially can narrow differential diagnosis and avoid unnecessary invasive testing.

4. Conclusion

Diffuse pulmonary micronodules have broad differential diagnosis, including TB, fungal, non-TB mycobacteria, carcinomatosis, sarcoidosis, silicosis. VZV infection is a relatively rare cause of calcified pulmonary nodules related to healed granuloma. Although lung biopsy with VZV PCR is the gold standard for diagnosis, thorough history taking, detailed physical examination and extensive laboratory testing including serologies as well as multi-disciplinary cooperation may lead to a presumptive diagnosis with reasonable confidence and avoid painful invasive procedures for patients.

Declaration of competing interest

Regarding the publication being submitted, "Diffuse pulmonary micronodules related to prior VZV infection", this is to disclose that the authors do not have any conflict of interest to disclose. This research did not receive any funding. Kun Yang, MD.

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