

Prof. Jin-Lei Wang

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Title: Combined silicosis and mixed dust pneumoconiosis with rapid progression

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We thank the reviewers for their thoughtful and constructive reviews on 24/10/2018. Based on the comments from the reviewers, we have revised the manuscript as detailed below. Some parts of the manuscript have been modified as we received English editing service again. Changes made in the manuscript are marked in red color. We hope that the revised manuscript will be acceptable for publication in *World Journal of Clinical Cases*.

Reviewer Comments:

Reviewer 1

Your case report is well written. I have no additional comments

→A1. Thank you for your constructive opinion.

Reviewer 2

We'd appreciate the invitation to review this manuscript. This article reported a case who were diagnosed with RPP of mixed dust pneumoconiosis combined with silicosis after an extended period of discontinuation of silica exposure. We appreciate detailed total history record and suitable examination of the patient. However we believe this article is too simple, neither informative nor innovative, due to lack of information regarding differential diagnosis and treatment

→A1. Thank you for the good suggestion. Unfortunately, our patient was not able to be diagnosed with pneumoconiosis when visiting for multiple lung nodules five years ago because we did not investigate his occupational history. At the current presentation, we performed a histologic examination for differential diagnosis between tuberculosis and tumor. In addition, he showed dramatic improvement in symptoms after he quit his job. Therefore, our intent is to emphasize the importance of investigating a patient's occupational history to distinguish lung nodules.

Reviewer 3

I have reviewed the manuscript entitled "Combined silicosis and mixed dust pneumoconiosis with rapid progression" by Dr. Yoon, et al. Briefly, this is a case report of a 64 year old man who was

employed in a stone processing factory as a young man and then worked in his own grist mill for the past 25 years. His chest radiograph had aggressively progressed in the past 5 years in a manner that is not consistent with silicosis. Mycobacterial infection was not shown. A percutaneous needle biopsy showed macrophages and birefringent crystals by polarizing microscopy. A diagnosis of mixed dust pneumoconiosis with rapid progression was made. The authors concluded that the rapid progression with silicosis may be attributable to the grist mill exposure. I offer the following comments.

Q1. The abstract reports that Rapidly progressive pneumoconiosis (RPP) frequently occurs in coal workers,... Indeed, this can occur, but to report that this is a frequent occurrence is not clear. Authors have often reported these rapidly occurring cases as case reports and case series, implying that they are out of the ordinary.

→A1: As suggested by the reviewer, the word “frequently” was replaced with the word “occasionally.” We changed the sentence in the abstract as follows:

“Rapidly progressive pneumoconiosis (RPP) occasionally occurs in coal workers, particularly those with high exposure to silica.”

Q2. This worker had been employed in a stone processing factory for 17 years prior to his work as a grain grinder. The authors report that he "processed granite... without protective equipment." No further information is provided. Please describe this job in more detail. Certainly if he was grinding, or working in a way that generates dust from stone (particularly in a dry environment), this is important to note

→A2: Per the suggestion by the reviewer, we added the relevant context in the manuscript as follows:

“His gristmill was in a poorly-ventilated small room located underground. He poured the grains directly into the funnel-shaped grinder entrance, then put the grained grains into the bag by connecting the grinder outlet.”

Q3. The silica content of granite is variable – and frequently reported as ranging from 10% to 50%. As cited in references 7 and 8, silica exposure during grain grinding over a period of time in a relatively enclosed space, could play a role in the development of silicosis. Under similar circumstances, this could be associated with silica progression, as in this case. During his work as a grinder, was he in grinding room when the grinding was performed?

→A3: We agree with the opinion of the reviewer. Our patient continued his work in an almost-unventilated underground grinding room, so we also considered the progression of silicosis. However, his histopathological findings suggested that mixed dust pneumoconiosis was more favorable considering his clinical course. Silicosis of the cellular phase is mainly observed in acute heavy silica exposure, which is not consistent with the findings seen in chronic and long-term silica exposure as in our patient. We further described his work environment in the text below.

“...he operated his own gristmill and worked seven days a week grinding rice, beans, red beans, and peppers using a granite roller grinder in a poorly ventilated underground mall without protective equipment for 25 years.”

Q4. I have reviewed the pathology report. This showed diffuse infiltration of phagocytic

macrophages with focal sclerosis and a few multi-nucleated giant cells. Macrophages contained anthracotic pigment, and lightly birefringent crystals were observed with polarized light microscopy. The histopathologic diagnoses were pneumoconiosis, cellular phase of silicosis, and/or mixed dust pneumoconiosis. I recognize features of pneumoconiosis (although the presence of anthracotic pigment may be a non-specific finding) and silicosis. Although he could have a diagnosis of mixed grain pneumoconiosis by history, how was the pathologic diagnosis of mixed dust pneumoconiosis made? Perhaps the authors may comment on the pathologic criteria of "mixed dust pneumoconiosis." What does the "and/or" aspect of this statement refer to? Is the pathologist suggesting that there is no diagnosis of silicosis but rather this is pneumoconiosis attributable solely to grain dust? ? I ask that you review this diagnosis and explain this further.

→A4: The pathologic findings of mixed dust pneumoconiosis are dust macules or mixed-dust fibrotic nodules with or without silicotic nodules in patients exposed to mixed dust (Hum Pathol. 2004 Dec;35(12):1515-23.). The diagnosis of mixed dust pneumoconiosis requires exclusion of other pneumoconiosis and cellular phase silicosis; mixed dust pneumoconiosis cannot be clearly distinguished by biopsy specimen alone. Therefore, it is not easy to suspect mixed dust pneumoconiosis because silica is once seen in biopsy without knowing its past history. However, we considered that the time of exposure to silica and grain dust and the lack of findings typical of silicosis (i.e., concentric patterns, fibrosis) were more likely to be associated with mixed dust pneumoconiosis. Thus, we used the term "and/or." We also added the following context to manuscript:

Result section

"Without detailed knowledge of the patient's history, the initial histopathologic diagnosis was silicosis with rapid progression."

Final diagnosis

"After consideration of the patient's occupational history of chronic exposure to silica and cellular proliferation in histopathology, the final diagnosis was mixed dust pneumoconiosis with rapid progression. We suggest that the silica-containing grain dusts in the gristmill environment may have caused rapid progression of pneumoconiosis over five years and provoked the development of chronic obstructive pulmonary disease (COPD)."

Discussion

"In this case, silica, which is weakly birefringent under the usual polarized light, was identified in a lung biopsy specimen, and silicosis was first considered in histopathologic diagnosis. However, the lung lesions in our case were highly cellular rather than fibrotic. In silicosis, cellular proliferation is usually seen in the acute stage after heavy exposure to silica, and the lesion is replaced by fibrosis and ischemic changes in the chronic stage [10]. Since cellular infiltration occurred long after cessation of stone processing, contaminated grain dust during recent gristmill work may have played a role in the rapid progression of this case. Mixed dust pneumoconiosis refers to the changes caused by inhalation of a mixture of silica (less than 10% in proportion) and other less fibrogenic substances. Surgically resected specimens typically show a stellate margin in histologic section [10]. Although discrimination between silicosis and mixed dust pneumoconiosis was not possible with needle biopsy specimen only, we concluded that the presenting case was rapidly progressing mixed (grain) dust pneumoconiosis after comprehensive correlation of occupational history and pathologic features."

Q5. Please note, reference 1 is incomplete

→A5: Thank you. We added a page to complete reference 1.