## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | An Observational Study of Giant Cell Interstitial Pneumonia and Lung Fibrosis in Hard Metal Lung Disease |
| **AUTHORS** | Takada, Toshinori; Tanaka, Junichi; Moriyama, Hiroshi; Terada, Masaki; Suzuki, Eiichi; Narita, Ichiei; Kawabata, Yoshinori; Yamaguchi, Tetsuo; Hebisawa, Akira; Sakai, Fumikazu; Arakawa, Hiroaki |

## VERSION 1 - REVIEW

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| **REVIEWER** | Jerrold L. Abraham, MD<br>Dept of Pathology<br>SUNY Upstate Medical University<br>Syracuse, NY |
| **REVIEW RETURNED** | 26-Dec-2013 |

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| **GENERAL COMMENTS** | This is another in a series of elegant studies by the authors' group investigating the morphology and microanalytical results in Hard Metal Disease. It is not clear exactly which of the 19 cases were previously reported by them or others, and this could be clarified further. How were the analyses previously reported different from any of the analyses done in the same cases reported in this study? Some authors on previous publications were not included in this study which includes some of the same cases?<br><br>Specific Comments:<br><br>Abstract:<br>Is there any ability or attempt to correlate the pathology with the radiologic findings? The origin (site -- upper, middle or lower lobe?) of the biopsies is not stated.<br><br>Introduction<br>It is not completely clear how the authors are separating GIP from UIP, since some of the illustrated cases show features of GIP and UIP but case 10, for example, is classified as UIP. ??<br><br>Radiology.. HRCT<br>It would be helpful if a description of the distribution of changes were included so as to allow correlation with the actual biopsy site(s) in each case.<br><br>EPMA<br>The methods previously described by the authors are understood, and the lack of true individual particle analysis is recognized, but the description of the 'qualitative element analysis' vs the mapping is not clearly described.<br>Are there results for the qualitative analyses? If the authors meant the areas mapped varied from 5x5 um to 10x10 um this is not |

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| | correct. From the one figure which is labled, the area mapped is approximately 1.55 mm x 1.55 mm. The other maps have no scale on them, so it is not possible to know what the dimensions are.<br>A minor typo in the 2nd to last sentence says 'legion' when the authors probably meant 'lesion'.<br><br>RESULTS<br><br>Subject characterization<br>It is not clear why the patch testing was done only in those with allergic history? Would it not have been of interest to determine if there were sensitization to cobalt in the others? Could a lymphocyte proliferation test be done as in Beryllium disease?<br>It is also of interest that most of the cases are never-smokers, as has been seen in Beryllium disease and hypersensitivity pneumonitis (HP). This has also been seen in hard metal disease series of cases.<br><br>Table 1. From looking at this table the years of exposure varied from 1 year to 37 years. It would be very informative and interesting to include Year of first exposure and Year of Biopsy or autopsy in the table. One could wonder how industrial practices changed over that period of many years. Could materials be different as well as industrial hygiene practices? Some thought and discussion about this would be of interest, especially as the cases classified as UIP (although case 10 really shows features of GIP in the figures) had longer exposure and consequently exposure during an earlier decade (1980s or 1970s). Did case 10 also have exposure in an earlier decade? [Hence the interest in the actual calendar years of exposure for each case].<br><br>Page 10, in the last sentence before Table 3, it needs clarification /explanation of what the authors mean by the statement that 'although centrilobular micronidular opacities were noted in these patients, they were unremarkable' [emphasis added].<br><br>Table 3. Radiologic findings<br>This table could be a logical and useful place to put in the comparison of zonal differences with biopsy site(s) information.<br><br>Pathological findings and elemental analysis<br>In the 2nd paragraph, it refers to Figure 4, which is only presenting results from case 10, but there is no EPMA mapping shown for the areas of case 10 which showed centrilobular pattern or the cannibalistic giant cells in Figure 3. Could this be included and discussed perhaps?<br><br>Table 4<br>There is one case (#16) with both VATS and autopsy. What was the time interval between biopsy and autopsy? and what if any differences were seen in the histopathology? There are some cases in the literature (including one of Liebow's original cases) which had more that one lung tissue sampling showing different histopathologic findings over time. This could be discussed as well.<br><br>Table 5<br>Were other potential causes of pulmonary fibrosis searched for, such as asbestos or silica? This could be added to the methods (and results, if, for example, iron stained sections from each case were prepared and searched for asbestos bodies; and if polarized light |

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| | examination for birefringent particles such as silica were done).?<br><br>Discussion<br>The last sentence of the first paragraph is a bit confusing. ..<br>...'suggesting allergic inflammation should be different between hard metal lung disease and berylliosis.' Perhaps this could be clarified, in the light of knowledge of similarities between HMD, chronic Be disease (CBD) and HP? Some HMD cases do show features of HP with small interstitial granulomas, although well formed granulomas as in CBD are very rarely seen in HMD or HP.<br><br>page 15. paragraph starting with "UIP pattern is the pathological abnormality essential to the diagnosis of IPF." It is not specific for IPF, however, since if a cause is identified it is no longer idiopathic PF, of course.<br>If there were 3 cases diagnosed as UIP pattern who also had centrilobular [note typo 'centriolobular'] micronodular opaciteis by HRCT, this again points to the desirability (if not necessity) of correlating the biopsy site(s) with the HRCT findings.<br>Why was the one with both UIP and centrilobular classified as UIP rather than GIP? Why not HMD with both UIP and GIP patterns?<br>The conclusion (or really, speculation) that 'inhaled hard metal elements in UIP pattern may not trigger as much inflammation as in GIP' is not supported or refuted by the observations made at a time of biopsy or autopsy. To answer this a prospective or animal model study would be needed. One could easily speculate that the inhaled elements in some cases lead to MORE inflammation and fibrosis in some cases and to more of a hypersensitivity, small airway centered, reaction in other cases. Individual immune susceptibility/response may be the more important factor, no?<br><br>Page 16, last paragraph.<br>The sentence 'However, the pathological findings of UIP pattern demonstrated no microscopic connection between centrilobular fibrosis and the UIP area, .." is not fully supported, unless additional exposures were excluded by specifically searching for them, as noted above re asbestos, silica, etc..<br><br>Figures. see comments, above.<br>The scales for the magnification are present only in one of the EPMA figures. |

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| **REVIEWER** | Nemery, Benoit<br>KU Leuven, Belgium |
| **REVIEW RETURNED** | 12-Jan-2014 |

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| **GENERAL COMMENTS** | 2. Abstract: should not just give p-values, but actual figures<br>3. Study design: only a longitudinal design could answer the research question, but this cross-sectional evaluation does nevertheless provide interesting clues<br>4. Methods: the method of the selection of subjects for inclusion in the study is very unclear: nationwide survey? what was the response rate? how was the presence of W, Co or Ta known in the first place? what was the period of inclusion (from ... to ...)?<br>10. The results are generally presented clearly, but the histopathological images are difficult to assess in the pdf documents that I got<br>11. see item 3 |

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| | 15. the English is generally quite good, but see some corrections below<br><br>This is a nice retrospective analysis of the pathology of a relatively large number of subjects (considering the rarity of the condition) with hard-metal lung disease (GIP or UIP with W in their lungs). As indicated above, the main shortcoming of the analysis (acknowledged by the authors) is the absence of longitudinal data to answer the main question of the article, i.e. does GIP evolve to UIP? The authors suggest that the answer to this relevant question is NO, but does this then also imply that subjects who worked in the hard-metal industry and develop UIP/fibrosis with W and Ta in the biopsies do not have hard-metal lung disease? In their discussion page 16-17, it is not clear what they conclude.<br><br>Specific and Minor comments<br>- It is unclear to what extent the patients described here overlap with those described in the authors' previous publication, even though it is stated that 8 patients were common to this study and those of ref 7 (please specify in table 1).<br>- It would be interesting to have the authors' background data on element analysis (for W, Ta, ...) in other cases of UIP.<br>- page 4, line 13: replace "and " by "or"; line 18: replace "is" by "are"; line 37: delete "the" before UIP; line 45: thought by whom? (please provide reference, if any).<br>- page 5, patient population: please provide more details about period of inclusion, number of pathologists included, etc<br>- page 6, line 6: replace "underwent" by "had undergone"<br>- page 6, line 35: "each tissue sample": did you obtain paraffin-embedded tissue from various pathologists?<br>- page 7, lines 10-13: the representativeness of the element analysis for the whole tissue should be addressed<br>- page 7, line 47: how long was the delay between cessation of exposure and biopsy in the 5 patients who were no longer exposed?<br>- page 8, line 11: "no bizarre multinucleated giant cells in BAL": did you analyze the cytology slides or was this feature not reported in the patient notes (my experience is that cytologists may overlook this)<br>- page 10, description of HRCT : this could be elaborated on slightly more, and I suggest a final radiological "diagnosis" could be mentioned in table 3 (e.g. "compatible with UIP/IPF, compatible with HP, ...) [note: "curvillnear", not "curvilnear"]<br>- page 13, table 5: please clarify the meanings of %VC, FEV1% (%) and %DLco in a legend; do not show 4 decimals for p-values<br><br>Although I have nothing against BMJ Open, I am not sure this journal is the best choice for the publication of such specialized findings in a rare (though fascinating) disease ... |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer Name Jerrold L. Abraham, MD
Institution and Country Dept of Pathology
SUNY Upstate Medical University
Syracuse, NY

COMMENT:
It is not clear exactly which of the 19 cases were previously reported by them or others, and this could be clarified further.

RESPONSE:
Page 9, line 8 to 10.
At first we thought that 8 cases were already reported in our previous paper, but found 6 of 19 cases; case 2, 5, 7, 8, 10, and 16 corresponding to case 1, 3, 5, 6, 14, and 16 in 2007 report respectively, were in it. When we enrolled the 6 patients in this paper, we noticed some errors in the previous paper, which were that case 10 (14 in 2007) was non-smoker and Ta was detected in case 16 (also 16 in 2007). We added corrected information of those 6 cases in Results.

COMMENT:
How were the analyses previously reported different from any of the analyses done in the same cases reported in this study?

RESPONSE:
Element analyses were not different from the previous report, but we included clinical data and CT findings of the 6 cases reported in the present study.

COMMENT:
Some authors on previous publications were not included in this study which includes some of the same cases?

RESPONSE:
They left the institutes they belonged to in the previous study and did not participate in the Tokyo ILD Meeting. Last time we focused on pathology and immnohistochemistry of lung tissue of the disease, while in this study we evaluated clinical features and CT findings which were not analyzed before. That is a reason why we excluded them from the present study.

COMMENT:
Is there any ability or attempt to correlate the pathology with the radiologic findings?
The origin (site -- upper, middle or lower lobe?) of the biopsies is not stated.

RESPONSE:
Page 13, table 3 and page 15, table 4.
In order to correlate the pathology with the radiologic findings, we added information of biopsy sites and radiological diagnosis of every patient in Table 3 and 4.

COMMENT:
It is not completely clear how the authors are separating GIP from UIP, since some of the illustrated cases show features of GIP and UIP but case 10, for example, is classified as UIP. ??

RESPONSE:
Page 15, table 4.
Pathological diagnosis of UIP is sometimes controversial because each pathologist has his/her own

diagnostic criteria of UIP consisting of heterogeneous appearance honeycomb change and fibroblast foci. We attach greater importance to patchy appearance at low magnification than to any other components. Since centrilobular involvement and giant cell are apparent, we changed the diagnosis of case 10 as predominant UIP with GIP. Actually the same case was pathologically diagnosed as atypical GIP in the previous report. Diagnosis of UIP with GIP should be much appropriate to describe the actual pathological findings of the case. We changed the diagnosis of case 10 to UIP with GIP.

COMMENT:
It would be helpful if a description of the distribution of changes were included so as to allow correlation with the actual biopsy site(s) in each case.

RESPONSE:
Page 13, table 3 and page 15, table 4.
We had not evaluated the distribution of changes, but added radiological diagnosis in Table 3 in connection with biopsy site(s) in Table 4 to help readers correlate the pathology with the radiologic findings.

COMMENT:
..but the description of the 'qualitative element analysis' vs the mapping is not clearly described.

RESPONSE:
Page 8, line 6 to 11.
In fact, our technique can simultaneously reveal presence of elements and draw maps. Each pixel in the focused areas of 5 x 5 to 10 x 10 μm in the tissue was scanned by three wavelength dispersive crystals; RAP, PET, and LiF for screening elements of Al, K, RAP; Si, K, PET; Ti, K, LiF; Cr, K, LiF; Fe, K, LiF; Co, K, LiF; Ta, M, PET; W, M, PET, and Zn, L, RAP. Since generated X-ray signals from each pixel were the smallest part of a distribution map, we can obtain element maps by scanning all pixels in the focused area. We revised the methods section.

COMMENT:
Are there results for the qualitative analyses?

RESPONSE:
Yes, we have results of qualitative analysis by the screening describe above, but did not show them in the study because they may give little information about the issue discussed in the article.

COMMENT:
If the authors meant the areas mapped varied from 5x5 μm to 10x10 μm this is not correct. From the one figure which is labeled, the area mapped is approximately 1.55 mm x 1.55 mm.

RESPONSE:
Page 8, line 3 to 7.
We at first screen wider areas raging about 1.5 mm x 1.5 mm at largest when we decide interested areas for fine mapping. Then we focused in three areas of 5 x 5 μm to 10 x 10 μm at smallest in the centrilobular legion of GIP which cover most of the affected areas in a specimen to obtain fine images of EPMA analysis. We revised the sentences to describe exact procedures of element mapping.

COMMENT:
A minor typo in the 2nd to last sentence says 'legion' when the authors probably meant 'lesion'.

RESPONSE:
Page 8, line 4.

We corrected the typo.

COMMENT:
Subject characterization
It is not clear why the patch testing was done only in those with allergic history? Would it not have been of interest to determine if there were sensitization to cobalt in the others? Could a lymphocyte proliferation test be done as in Beryllium disease?

RESPONSE:
We understand the reviewer's comment and the patch testing would be useful and informative to realize disease etiology, but it requires specialists in dermatology and not much popular in Japan. A lymphocyte proliferation test is available to help make diagnoses of drug-induced diseases, but is not performed to any other diseases in Japan.

COMMENT:
Table 1. It would be very informative and interesting to include Year of first exposure and Year of Biopsy or autopsy in the table.
Could materials be different as well as industrial hygiene practices?
Did case 10 also have exposure in an earlier decade?

RESPONSE:
Page 10, table 1.
We added year of first exposure and year of biopsy in the table 1. All of the patients in GIP group had exposure history later than 1980, whereas exposure of the others in fibrosis group started before 1975. We did not have any information on differences in materials or industrial hygiene practices between these periods.

COMMENT:
Page 10, in the last sentence before Table 3, it needs clarification /explanation of what the authors mean by the statement that 'although centrilobular micronodular opacities were noted in these patients, they were unremarkable' [emphasis added].

RESPONSE:
Page 12, line 6 to 8.
We mean that centrilobular micronodular opacities were recognized on HRCT, but they were minor findings. We corrected the sentence.

COMMENT:
Table 3. Radiologic findings
This table could be a logical and useful place to put in the comparison of zonal differences with biopsy site(s) information.

RESPONSE:
Page 13, table 3 and page 15, table 4.
We had not evaluated zonal distribution of changes in chest CT, but added information of biopsy sites and radiological diagnosis of every patient in Table 3 and 4 to help readers correlate the pathology with the radiologic findings.

COMMENT:
Pathological findings and elemental analysis
..centrilobular pattern or the cannibalistic giant cells in Figure 3. Could this be included and discussed perhaps?

RESPONSE:
Page 29, legend for figure 4.
When we analyzed the specimen for the first time, we found W and Ta in the periarteriolar area and subpleural fibrosis, which was shown in Figure 4, and made a diagnosis hard metal lung disease. Since further analysis would not change the diagnosis, we did not elementally analyze the centrilobular pattern or the cannibalistic giant cells shown in Fig 3. We added a sentence in the legend for Figure 4.

COMMENT:
There is one case (#16) with both VATS and autopsy. What was the time interval between biopsy and autopsy? and what if any differences were seen in the histopathology?

RESPONSE:
Page 14, line 6 to 10.
A report of the case was published (Inter Med 49: 2143-2145, 2010). The patient underwent VATS biopsy in 2001. In spite of corticosteroid therapy, his respiratory condition progressed to be fatal in 2005. Biopsy specimen contained apical cap-like subpleural dense fibrosis which was composed of airspace fibrosis (intraluminar organization) with collapse and increased elastic framework. The pleura showed fibrous thickening. In autopsy, we noticed remarkable subpleural elastosis with a few of cannibalistic giant cells. We added the information in the results.

COMMENT:
Were other potential causes of pulmonary fibrosis searched for, such as asbestos or silica? and if polarized light examination for birefringent particles such as silica were done).?

RESPONSE:
When we pathologically examine lung tissue, we make notes if asbestos bodies were observed, but did not find in any cases. We did not search other materials by polarized light examination.

COMMENT:
Perhaps this could be clarified, in the light of knowledge of similarities between HMD, chronic Be disease (CBD) and HP?

RESPONSE:
Page 17, line 1 to 5 from the bottom.
According to the reviewer’s suggestion, we revised the sentences.

COMMENT:
page 15. paragraph starting with "UIP pattern is the pathological abnormality essential to the diagnosis of IPF." It is not specific for IPF, however, since if a cause is identified it is no longer idiopathic PF, of course.

RESPONSE:
Page 18, line 12 to 13.
As the reviewer indicated, the sentence is not correct in this context. We revised the sentence.

COMMENT:
If there were 3 cases diagnosed as UIP pattern who also had centrilobular [note typo 'centriolobular'] micronodular opaciteis by HRCT, this again points to the desirability (if not necessity) of correlating the biopsy site(s) with the HRCT findings.

RESPONSE:
Page 13, table 3 and page 15, table 4.
These patients had radiological diagnoses of UIP or chronic IP because IP was predominant with minor findings of centrilobular micronodular opacities. Since VATS biopsy cuts out peripheral tissue from lung lobes, most of specimens should have contained interstitial pneumonia with small part of centrilobular lesions.

COMMENT:
Why was the one with both UIP and centrilobular classified as UIP rather than GIP? Why not HMD with both UIP and GIP patterns?

RESPONSE:
Page 15, table 4.
When we make a diagnosis of the patient, we at first noticed patchy appearance at low magnification. Higher magnification then revealed other findings of honeycombing and fibroblastic foci with centrilobular lesions and giant cells. That is a reason why we rather made a pathological diagnosis of UIP for the patient. We changed the diagnosis of case 10 as UIP with GIP.

COMMENT:
The conclusion (or really, speculation) that 'inhaled hard metal elements in UIP pattern may not trigger as much inflammation as in GIP' is not supported or refuted by the observations made at a time of biopsy or autopsy.
Individual immune susceptibility/response may be the more important factor, no?

RESPONSE:
Page 18, line 1 from the bottom to page 19, line 2.
We agree with the reviewer’s comment and revised the sentence.

COMMENT:
The sentence 'However, the pathological findings of UIP pattern demonstrated no microscopic connection between centrilobular fibrosis and the UIP area, .." is not fully supported, unless were excluded by specifically searching for them, as noted above re asbestos, silica, etc..

RESPONSE:
Page 19, line 4 from the bottom to page 20, line 1.
We mean here that centrilobular fibrosis does not have physical connection to subpleural fibrosing area in microscopic view. Since centrilobular fibrosis is usually irreversible, if GIP induced by W evolved to UIP, sequel of centrilobular fibrosis would be somewhat linked to peripheral UIP lesions. We revised the sentence so as not to lead to misunderstanding.

COMMENT:
The scales for the magnification are present only in one of the EPMA figures.

RESPONSE:
Figure 4 and its legend on page 29.
Scale bars for the magnification were inserted to representatives of the EPMA images.

Reviewer Name B. NEMERY
Institution and Country KU Leuven, Belgium

COMMENT

Abstract: should not just give p-values, but actual figures

RESPONSE
Page 3, line 4 to 6 from the bottom.
We added actual figures of these values.

COMMENT
Methods: the method of the selection of subjects for inclusion in the study is very unclear: nationwide survey? what was the response rate? how was the presence of W, Co or Ta known in the first place? what was the period of inclusion (from ... to ...)?

RESPONSE
Page 6, line 6 to 8, page 8, line 1 from the bottom to page 9, line1 to 6, and page 10, Table 1.
It was not a nationwide survey, but announcement of the meeting with request for submission of suspected cases. Because the announcement was distributed to the major medical institutes and hospitals which treat interstitial lung diseases and usually rare lung diseases such as hard metal lung diseases would be consulted to the physician's affiliated hospitals in Japan, we believe that the surveillance was fairly comprehensive.
When we held the Tokyo ILD Meeting, 22 cases were collected and suspected to be hard metal lung diseases due to occupational history and pathological findings, but 3 cases were excluded because W/Co were not detected in the lung tissue. In 4 of 19 patients, the presence of W, Co or Ta was not known in the first place and proved by the element analysis for the first time at the meeting. More than 5 pulmonary pathologists participated in the meeting, but actually 2 of them, YK and AH involved in decision of the final diagnosis as observers. Exposure period and biopsy/autopsy time of the patients were indicated in revised Table 1. We revised sentences in the methods and results section added occupational data in Table 1.

COMMENT
The authors suggest that the answer to this relevant question is NO, but does this then also imply that subjects who worked in the hard-metal industry and develop UIP/fibrosis with W and Ta in the biopsies do not have hard-metal lung disease?

RESPONSE
Page 20, line 13 to 19.
We conclude that GIP does not evolve to UIP because of differences in distribution of fibrosis, hard metal elements, and clinical features. If we find W or Co in the biopsies of UIP/fibrosis from the subjects who worked in the hard-metal industry, we cannot help making a diagnosis of hard-metal lung disease. Given present information, we have to say that the UIP/fibrosis may be induced by W/Co or Ta, or just a coincidence. As the reviewer comments only longitudinal data should allow us to answer the question if GIP evolves to UIP or not.

COMMENT
Specific and Minor comments
- It is unclear to what extent the patients described here overlap with those described in the authors' previous publication.

RESPONSE
Page 9, line 8 to 10.
At first we thought that 8 cases were already reported in our previous paper, but found 6 of 19 cases; case 2, 5, 7, 8, 10, and 16 corresponding to case 1, 3, 5, 6, 14, and 16 in 2007 report respectively, were as such. When we introduce the 6 patients in this paper, we noticed some errors in the previous paper, which were that case 10 (14 in 2007) was non-smoker and Ta was detected in case 16 (also

16 in 2007). We added corrected information of those 6 cases in Results. By comparing two papers, the readers will be able to know what extent the patients described this time overlap with those described in the previous publication.

COMMENT
- It would be interesting to have the authors' background data on element analysis (for W, Ta, ...) in other cases of UIP.

RESPONSE
Page 18, line 4 to 6 from the bottom.
Element analysis of the deposition in lung tissues from patients with IPF/UIP usually demonstrates following elements; Si, Al, Fe, and Ti with various degrees. We found these four elements in UIP without exception. We added these data as unpublished data in Discussion.

COMMENT
- page 4, line 13: replace "and " by "or"; line 18: replace "is" by "are"; line 37: delete "the" before UIP; line 45: thought by whom? (please provide reference, if any).

RESPONSE
Page 5.
We changed the above-mentioned words and added a reference for the sentence.

COMMENT
- page 5, patient population: please provide more details about period of inclusion, number of pathologists included, etc

RESPONSE
Page 6, line 6 to 8, page 8, line 1 from the bottom to page 9, line1 to 6, and page 10, Table 1.
Response is mentioned above under general comments.

COMMENT
- page 6, line 6: replace "underwent" by "had undergone"

RESPONSE
Page 6, line 3 from the bottom.
We corrected the word.

COMMENT
- page 6, line 35: "each tissue sample": did you obtain paraffin-embedded tissue from various pathologists?

RESPONSE
We borrowed paraffin-embedded tissue through treating physicians for each identified case. We gave it back to the hospital or institution after we cut out 3 to 5 serial sections out of it.

COMMENT
- page 7, lines 10-13: the representativeness of the element analysis for the whole tissue should be addressed

RESPONSE
Page 7, line 1 from the bottom to page 8, line 7.
According to our experiences, hard metal related elements, W/Co are always found around

centrilobular areas probably due to sizes of inhaled particles including those elements. In order to have representative images of EMPA analysis, we at first microscopically scan tissue specimens and look for lesions of centrilobular fibrosis with low magnification before we decide areas for EMPA analysis. We then screen wider areas raging about 1.5 mm x 1.5 mm at largest as indicated in Figure 2E. Next, we focused in three areas of 5 x 5 μm to 10 x 10 μm at smallest in the centrilobular legion of GIP which cover most of the affected areas in a specimen to obtain representative images of EPMA analysis. We revised the Method section.

COMMENT
- page 7, line 47: how long was the delay between cessation of exposure and biopsy in the 5 patients who were no longer exposed?

RESPONSE
Page 9, line 14 to 19.
We added sentences on the delay between cessation of exposure and biopsy in the 5 patients.

COMMENT
- page 8, line 11: "no bizarre multinucleated giant cells in BAL": did you analyze the cytology slides or was this feature not reported in the patient notes (my experience is that cytologists may overlook this)

RESPONSE
Page 10, line 3.
We re-checked case cards of all patients who had undergone BAL and found that giant cells were noted in 3 cases. We revised the sentence in the Results.

COMMENT
- page 10, description of HRCT : this could be elaborated on slightly more, and I suggest a final radiological "diagnosis" could be mentioned in table 3 (e.g. "compatible with UIP/IPF, compatible with HP, ...) [note: "curvilInear", not "curvilnear"]

RESPONSE
Page 13, table 3.
We added radiological diagnosis for each case in table 3. The typo was corrected.

COMMENT
- page 13, table 5: please clarify the meanings of %VC, FEV1% (%) and %DLco in a legend; do not show 4 decimals for p-values

RESPONSE
Page 16, table 5.
We added abbreviations for these words and showed only 3 digits for p-values.

## VERSION 2 – REVIEW

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| **REVIEWER** | Jerrold L. Abraham, MD<br>SUNY Upstate Medical University<br>Syracuse, NY<br>USA |
| **REVIEW RETURNED** | 24-Feb-2014 |

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| **GENERAL COMMENTS** | This reviewer has reviewed several versions of this manuscript. The authors have tried to respond in detail to the challenging comments and questions from reviewers. The only remaining issue is that each time they write some new text, there are English grammatical problems that are created. This reviewer would appreciate it greatly if the BMJ editorial staff would critically go over and fix the English usage. It does not need further scientific review. I think the authors realize that some of their conclusions are still a bit speculative, but this should be clear to most careful readers. |

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| **REVIEWER** | Ben Nemery<br>KU Leuven, Belgium |
| **REVIEW RETURNED** | 05-Mar-2014 |

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| **GENERAL COMMENTS** | The authors have responded adequately to my comments and questions.<br>I have the following minor comments:<br>- abstract, first sentence: insert "various" (or "diverse")before pathological patterns<br>- strengths and limitations, statement #3: rephrase to (something like) "since the incidences of HMLD and IPF in potentially exposed populations and in the general population are unknown, the probability that someone with hard metal exposure will develop "idiopathic" UIP/IPF is also unknown. (also to be changed in the penultimate paragraph of the discussion).<br>For practical purposes, however, it seems reasonable to consider that finding UIP in a (former) hard metal worker likely represents a form of HMLD (even if the present study does not indicate that GIP evolves to UIP/IPF).<br>Methods: please specify the year of the Tokyo meeting<br>Tables 2 and 5: please specify the units of the pulmonary function indices: presumably "% predicted" for VC and DLCO, and actual value for FEV1%, which should be better given as: FEV1/VC (%)<br>Table 3: make sure the column headings are in the right place (especially for PTx and other findings) |

## VERSION 2 – AUTHOR RESPONSE

Reviewer Name Jerrold L. Abraham, MD
Institution and Country Dept of Pathology
SUNY Upstate Medical University
Syracuse, NY
USA

COMMENT:
The only remaining issue is that each time they write some new text, there are English grammatical

problems that are created. This reviewer would appreciate it greatly if the BMJ editorial staff would critically go over and fix the English usage. It does not need further scientific review. I think the authors realize that some of their conclusions are still a bit speculative, but this should be clear to most careful readers.

RESPONSE:
We would like to show our appreciation for the reviewer's comments. We also would greatly appreciate it if the BMJ editorial staff would critically go over and fix the English usage in the manuscript.

Reviewer Name B. NEMERY
Institution and Country KU Leuven, Belgium

COMMENT
abstract, first sentence: insert "various" (or "diverse")before pathological patterns

RESPONSE
Page 3, line 2.
We inserted "various" before pathological patterns in the abstract.

COMMENT
strengths and limitations, statement #3: rephrase to (something like) "since the incidences of hard metal lung disease and IPF in potentially exposed populations and in the general population are unknown, the probability that someone with hard metal exposure will develop "idiopathic" UIP/IPF is also unknown. (also to be changed in the penultimate paragraph of the discussion).

RESPONSE
Page 4, line 9-11 and page 20, line 1-4 from the bottom.
We rephrased the statement #3 of strengths and limitations and the sentence in the penultimate paragraph of the discussion.

COMMENT
Methods: please specify the year of the Tokyo meeting

RESPONSE
Page 6, line 8.
We specified the year of the 10th annual meeting of the Tokyo Research Group for Diffuse Parenchymal Lung Diseases, which had been held in 2009.

COMMENT
Tables 2 and 5: please specify the units of the pulmonary function indices: presumably "% predicted" for and actual value for FEV1%, which should be better given as: FEV1/VC (%)

RESPONSE
Page 11, Tables 2 and page 16, Table 5.
We specified the units of the pulmonary function indices for VC and DLCO and inserted actual values of FEV1. We also changed FEV1% to FEV1/FVC.

COMMENT
Table 3: make sure the column headings are in the right place (especially for PTx and other findings)

RESPONSE
Page 13, Tables 3.
We corrected the column headings in the Table 3 to make them properly aligne