Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-23-1160

Reviewer A

This is a nice observation paper, although it does not have any clinical impact. You can compare the histology aspects of these both groups of COPD patients, but their physiology is completely different.

Reply: Thank you for your review and comment. We agree that the pathophysiology of the two groups is different, but we believe that it can contribute to improving knowledge of the disease.

Reviewer B

Overall Comments on Paper
The authors do a fantastic job highlighting coexistent histologic findings in explants after lung transplantation. However, comparing them with lobectomy resection specimens is fraught with significant limitations. Most importantly, the discrepancy between available specimen sizes when comparing explanted lungs with a lobectomy specimen is profound, a fact that the authors highlight under the limitations.
I do not see any significant value in comparing the explant pathology with lobectomy specimen pathology for this study. The comparison does not add to the scientific merit and dilutes the message about the transplant cohort. It may be worth considering 2 separate descriptive reports for lung transplant recipients and lung cancer patients rather than clubbing them together.

Reply: Thank you for your comment and review of the document. We completely agree with your statement, and in fact, that idea is reflected in the discussion. However, unlike interstitial diseases (in which case they often have a biopsy before transplantation and the histology can be compared before and after), there are hardly any histological samples from patients with emphysema. Therefore, the only opportunity to have a large control group were patients undergoing surgery for lung cancer.

We thought that making a report only with the histology data of transplant recipients could be interesting, but it is not known how frequently other histological findings are added to emphysema (there is hardly any literature on it), and therefore the importance of taking a control group with emphysema without the need for transplantation.

Specific comments
Lines 153-154. Tobacco consumption was higher in the cancer group, with 50 (40 – 70) packs-year, 154 as compared to LTR, with a median of 40 (30 – 60) packs-year ($P < 0.001$).
Comment: Literature suggests that the duration of smoking may be more strongly associated with both risk of COPD and lung cancer. if available, it will be helpful to study the duration of

tobacco consumption in addition to cumulative tobacco consumption. (Bhatt SP, Kim Y, Harrington KF On behalf of the COPDGene Investigators, et al Smoking duration alone provides stronger risk estimates of chronic obstructive pulmonary disease than pack-years Thorax 2018;73:414-421.)

Reply: Thank you very much for this comment. It's a good appreciation. However, we do not have this information on the duration of smoking. We have added a comment in the manuscript indicating this limitation (lines 221-223 from the revised version highlighted in yellow)

Lines 216-18: The fact that the LTR group had a worse respiratory outcome does not rely on tobacco use or α1-antitrypsin deficiency but on the potential concurrence of other unknown risk factors or lung diseases that may exacerbate the primary lung disease.
Comment: There is significant selection bias in this study. Patients with emphysema who end up on LT waitlist or receive a lung transplant typically have more advanced disease. It is hard to reconcile that explant-proven coexistent non-emphysematous lung disease potentially drives worse respiratory function. Similarly, with the wide spectrum of smoking-associated lung pathology clinically, radiologically, and physiologically, it seems a stretch to glean, based on this study, that worse respiratory function does not rely on tobacco use. It gives a somewhat misleading message to the audience that smoking may not have culminated in the end-stage lung disease necessitating transplant.

Reply: We totally agree with your comment. We have made a modification to the text to clarify this (lines 233-240 from the revised version highlighted in yellow)

Additional comments:
It's unclear to me how the LT cohort was obtained. Was it obtained from a CXR/CT review listing diagnosis?
This is important as patients are not infrequently noted to have an element of non-emphysematous disease or CT- be it atelectasis/subtle scarring/small nodules/occasional cysts/bronchiectasis. However, with the limited options available for UNOS listing groups and diagnoses, most teams list patients with the dominant clinical/radiologic/physiologic abnormality even if a subtle co-existent process is visualized on imaging.
It may add strength to the study to have a radiologist look at the CT scans in a blinded fashion. At a bare minimum, a radiologic review of patients with an additional histologic diagnosis would add weight to the authors' discussion and arguments.

Reply: Thank you for your comment. It is a very good assessment. It is not uncommon for patients with obstructive ventilatory syndrome to be referred to the transplant center with a diagnosis of COPD and who suffer from other different diseases that also cause obstruction (such as silicosis, bronchiolitis obliterans, etc...)

In Spain we do not use UNOS, and our national registry system does allow many other entities with obstructive ventilatory syndrome.

We have clarified in the text how the diagnosis of COPD was established (all patients must have, according to our hospital protocol, at least an annual chest CT before transplant, and all of them had to have signs of emphysema described in the radiologist's report). (Lines 106-110 from the revised version highlighted in yellow)

Reviewer C

It is not possible to compare the pathology of patients who will undergo transplantation vs. lung resection due to cancer. They are very different groups, the group that goes to the transplant has an end-stage lung disease and those who resect the lung for cancer must have a lung condition that allows the surgery.

Reply: Thank you for your comment and review of the document. We completely agree with your statement, and in fact, that idea is reflected in the discussion. However, unlike interstitial diseases (in which case they often have a biopsy before transplantation and the histology can be compared before and after), there are hardly any histological samples from patients with emphysema. Therefore, the only opportunity to have a large control group were patients undergoing surgery for lung cancer.

Reviewer D

Dr. Mora-Cuesta and colleagues are presenting an interesting study on additional findings on explanted lungs after transplantation.
Although I believe this study is potentially very intriguing and may start filling a gap in the understanding of diffuse respiratory diseases, several areas require clarification to increase its clarity and overall impact.

- I don't understand the point of collecting data regarding post-transplant variable, like use of induction, incidence of PDG etc. (lines 123-126; 184-189); this is a study focusing on explanted lungs, which are, by definition, influenced by what comes before and not after lung transplant. That is the same reason why I don't really understand the usefulness of table 6 and Figure 1: why should we expect any difference in terms of post-variable outcomes in case of add-on diagnosis? Emphysema was certainly the main parenchymal abnormality in these patients and this is why we should expect more and less the same course after the transplant procedure.

Reply: Thank you for your comment. It is true that induction with basiliximab does not provide relevant information, since it is part of the center's immunosuppression protocol (we have withdrawn it from the manuscript). The idea of adding a few immediate postoperative variables was to compare whether patients with added diagnoses (and potentially a different pathophysiological substrate, with potentially greater baseline inflammation), could have a somewhat different post-transplant course.

- Lines 146-147: what kind of parenchyma did the 22 patients with A1AT deficiency had before transplantation? It is well known that A1AT deficiency may cause bronchiectasis as well as emphysema. On the other hand, how many patients, among those who were found with additional bronchiectasis, had A1AT?

Reply: Thanks for the appreciation. In accordance with another reviewer's comments, we have clarified in the methods that all patients included as COPD had emphysema on chest CT (lines 101-105). Therefore, all 22 patients with alpha-1 deficiency had emphysema on chest CT.

Regarding bronchiectasis in these patients, 8 of them had bronchiectasis in the explant (36.4%). We have added this information to the results. (Lines 184-185 from the revised version highlighted in yellow)

- Lines 158-160: I presume these results were to be expected.

Reply: Yes. This result was expected. In fact, that's where the idea of doing the study came from. In accordance with the classic scheme of the scientific method, everything started from the observation of seeing that many lung transplant patients had other histological findings in the explant pieces.

- Lines 170-171: I don't understand the meaning of this sentence

Reply: This means that of the 93 patients with an added histological diagnosis, 14 of them had other alterations other than emphysema in the chest CT before transplantation that could suggest other added entities. We have modified it in the text to try to make it better understood. (Lines 181-183 from the revised version highlighted in yellow)

- Lines 172-173: what did the authors do with these patients? Did these patients undergo different examinations/screening after lung transplantation and/or any change in their immunosuppressive therapy?

Reply: Thank you for your comment. It is an excellent appreciation. We have added a few lines in the discussion in this regard. (Lines 241-253 from the revised version highlighted in yellow)

- Discussion: I am not sure the current discussion truly gets the point of this paper. The authors are not discussing the possible implication of such findings, especially in the cohort of lung transplant recipients. Comparisons should probably be made between those who had previously undetected neoplasm and those who did not.

Reply: We have made many changes to the discussion from the original version. Although expanding the discussion on neoplasms in explants is possible, it was not the main

objective of our study, which was to focus on added histological diagnoses. The implications of this are still unknown because it is a single report from a single center with a retrospective methodology. We have only been able to give a little information about what happens in the follow-up after the transplant.

- Finally, I don't really see the additional value of a control group, especially given the conclusions. What is the point? Is it a matter of incidence? I think it was to be expected that these two groups were very different and could not be considered comparable.

Reply: As we mentioned to another reviewer, we completely agree with your statement. However, unlike interstitial diseases (in which case they often have a biopsy before transplantation and the histology can be compared before and after), there are hardly any histological samples from patients with emphysema. Therefore, the only opportunity to have a large control group were patients undergoing surgery for lung cancer. We thought that making a report only with the histology data of transplant recipients could be interesting, but it is not known how frequently other histological findings are added to emphysema (there is hardly any literature on it), and therefore the importance of taking a control group with emphysema without the need for transplantation. So, yes, it is a matter of incidence.