Peer Review File
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First Round Peer Review

Reviewer A

In this retrospective study, the authors try to identify factors associated with relapse in 36 CEP treated with corticosteroids. The findings suggest that presence of centrilobular consolidations and higher SP-D levels were predictive of relapse. Although the subject is of interest for the community, the study suffers from several flaws that need to be addressed to improve its overall quality:

Comment 1: The authors use uneven criteria for inclusion: 6% eosinophilia in blood and 10% in BALF are below the usual cut-off values. Could the authors explain their point and provide values for patients including the range?
Reply 1: Thank you very much for your very important remarks.
The criteria included cases which fulfil two of the following three situations: eosinophilia in BALF ≥10%, eosinophilia in peripheral blood ≥ 6%, and eosinophil infiltration in the TBLB specimens. The percentages of eosinophilia in BALF and peripheral blood in the criteria were consistent with the previous reports (16, 9).〔 Meyer KC, Raghu G, Baughman RP, et al. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. Am J Respir Crit Care Med 2012;185:1004-14. Jederlinic PJ, Sicilian L, Gaensler EA. Chronic eosinophilic pneumonia. A report of 19 cases and a review of the literature. Medicine (Baltimore) 1988; 67:154-62.〕.
Changes in the text: We revised our paper (see Page 6, line 16-21) .

Comment 2: Why did the author decide not to include untreated patients? What is the relapse rate in this population?
Reply 2: For untreated cases, it is sometimes difficult to determine relapse because of spontaneous remission and shadow wonderings. If we include relapse cases after spontaneous remission, the definition of relapse becomes complicated, so we enrolled the CS-treated cases of CEP in this study. We defined a relapse as a case in which the patient resumed or increased the dose of systemic corticosteroid therapy when their shadows worsened during tapering or after discontinuation of corticosteroid therapy, based on the assumption that the shadow would improve once corticosteroid therapy was started. The relapse rate in untreated patients was 22.6%.
Changes in the text: none (see Page 6, line 22-23)".

Comment 3: The use of KL-6 and SP-D as biomarkers for the study should be justified in the introduction; there is no literature supporting the relevance of KL-6 in these settings, please clarify.
Reply 3: Thank you for pointing this out. Transbronchial lung biopsy in EP shows findings that indicate an OP pattern, which can be problematic to dissimilar to organizing pneumonia.
KL-6 was measured because of OP with elevated KL-6.
Changes in the text: none.

Comment 4: Centrilobular opacities were associated with relapse, but at this point a comparator is missing: do patients that did not require a treatment display centrilobular opacities?
Reply 4: Thank you for your important remarks. Centrilobular opacities were observed in 12 of 31 patients who did not require steroid treatment.
Changes in the text: none.

Comment 5: In the discussion, the authors should discuss the interest of biologicals (anti-IL-5) as rescue therapy (see for instance Brenard et al. Lung 2020).
Reply 5: Thank you for your constructive comment. We discussed the interest of biologicals (anti-IL-5) as rescue therapy .
Changes in the text: We have modified our text as advised (see Page 12, line 4-10)".

Comment 6: Language editing is advised.
Reply 6: Thank you for your useful comment. We requested English editing before submitting our paper.
Changes in the text: none.

Reviewer B

Comment 1: Please provide a reference for introduction line 59-60.
Reply 1: Thank you for your useful comment. We provided a reference for introduction line 59-60.
Changes in the text: We revised our paper as you indicated (see Page 5, line 10).

Comment 2: What was the avg. duration and dose of corticosteroids used in the 36 patients?
Reply 2: As for initial dose of corticosteroids, 12 patients received corticosteroid pulse therapy and the other 14 patients received about 0.5 mg/kg/day of corticosteroid. The average duration of initial administration was 309 days, except for 6 patients who were still on corticosteroid therapy. The median duration of the 6 patients was 2185 (range: 1590-4527) days.

Changes in the text: We have modified our text as advised (see Page 8, line 23-25)".

Comment 3: Were any of the patients treated with corticosteroid sparing agents?
Reply 3: No other immunosuppressive drugs were used.
Changes in the text: We have added our text as advised (see Page 8, line 25 -Page 9, line 1)".

Comment 4: Did any of the patients undergo lung biopsy?
Reply 4: All patients underwent transbronchial lung biopsy.
No one performed a surgical lung biopsy.
Changes in the text: We have added our text as advised (see Page 8, line 22-23)".

Comment 5: Did any of the patients undergo repeat chest radiography that showed increase in centrilobular nodules compared to their previous scans during the time of relapse?
Reply 5: Thank you for your constructive comment. Chest X-rays were performed in all cases, however chest CT was not taken in all cases at the time of relapse. In some cases, centrilobular nodules were identified. Unfortunately, we do not have detailed data. Our apologies.
Changes in the text: none.

Comment 6: How was the diagnosis of "relapse" made--? Repeat BAL that showed >25% eos that had previously resolved, or increase in chest radiographic findings. The authors have not clarified how the initial diagnosis of CEP made? Whether it was by biopsy or by BAL or by peripheral eosinophilia or by radiological findings. Please refer "https://erj.ersjournals.com/content/41/2/402" to clarify how the initial diagnosis was made and a relapse of CEP was reached. Per the ATS guidelines, an infectious etiology, pulmonary edema have to be ruled out and acute exacerbation of interstitial lung disease remains a diagnosis of exclusion. Simply an increased requirement or an increased requirement cannot be used to define a relapse.
Reply 6: Thank you for your informative comment. We defined a relapse as a case in which the patient resumed or increased the dose of systemic corticosteroid therapy when their shadows worsened during tapering or after discontinuation of corticosteroid therapy, while clinically ruling out infection or pulmonary edema.
Changes in the text: We have added our text as advised (see Page 7, line 23, and Page 8, line 1-3)".

Comment 7: There have been case reports where CEP has been associated with drugs. This should be mentioned in the introduction. Even though there are no toxic/ infectious etiologies known to cause CEP, certain drugs such as NSAIDS, nitrofurantoin, Ustekinumab. Etc.
Reply 7: Thank you very much for your very important remarks. We define CEP as idiopathic CEP

of unknown cause, excluding drugs whenever possible (Cordier JF, Cottin V. Eosinophilic pneumonias. In: Schwarz MI, King Jr TE, editors. Interstitial lung disease. 5th ed. Shelton: People's Medical Publishing House-USA; 2011. p.833–93.) . We have added that drugs are also ruled out as a diagnosis of CEP.
Changes in the text: We have added our text (see Page 5, line 4)".

Comment 8: Introduction line "65" is incorrect. Peripheral distribution of consolidation or radiographic negative of pulmonary edema is see in only about 25% of the cases.
Reply 8: Thank you for pointing this out.
Changes in the text: We have modified our text as advised (see Page 5, line 15-16)".

Comment 9: A prediction score based on "presence or absence" of centrilobular nodules does not provide any information about the initial severity of the illness. Having a predictive model that could assess how many lobes/ segments were involved with centrilobular nodules, presence of concomitant ground glass opacities would be more relevant clinically.
Reply 9: Thank you for pointing out this very important point. We have not been able to determine how many lobule-centered granular shadows were present in each lobes/segments in this study. I would like to make this an issue for the future. Thank you very much.
Changes in the text: none.

Comment 10: Table 2- 23 patients had centrilobular nodules and 13 did not (n=36). However, 35 out of 36 had consolidation, ground glass along with centrilobular nodules. Please do a multivariate analysis of combined "centrilobular nodules, consolidation and ground glass".
Reply 10: Thank you very much for your suggestion. One case without ground-glass opacity showed consolidation and centrilobular opacity, and one case without consolidation showed ground-glass opacity and no centrilobular opacity. We performed a multivariate analysis combining centrilobular opacity, consolidation, and ground-glass opacity, and the results were almost the same as those obtained in the variate analysis using centrilobular opacity, alone, so we have included the analysis focusing on the centrilobular opacity.
Changes in the text: none.

Second Round Peer Review

Comment 1: There still remains some major flaws with the study. Those flaws could simply be attributed to the retrospective nature of the study. This research involved patient for over 20 years which is a long time for a retrospective study and definition, diagnostic criteria and etiology of CEP

have certainly changed.
Reply 1: Thank you very much for your very valuable input.
As you have pointed out, this study is more than 20 years long, but the CEP criteria for the included studies are conventional and have not changed. We will also note this in our limitations.
Changes in the text: We revised our paper as you indicated (see Page 12, line 13-17).

Comment 2: It is unclear still, how the definition of an exacerbation was met. In our clinical practice, ILD exacerbation remains a diagnosis of exclusion after ruling out an embolism, infection and volume overload and trial of antibiotics, diuresis and then proceeding with pulse dose steroids. Simply increase in the radiographic opacities on CXR does not qualify for defining an exacerbation.
Reply 2: Thank you for your informative comment. We understood what you said. As you say, we diagnose relapse of CEP after clinically ruling out embolism, infection, volume overload, etc. to the extent clinically possible.
Changes in the text: We have added our text as advised (see Page 7, line 23, and Page 8, line 1-3)".

Comment 3: The authors describe that the patients with CEP were on an avg treated with corticosteroids alone for 309 days and 2185 days for other 6 patients and no corticosteroid sparing agents were tried/initiated??
Reply 3: I apologize for the confusion. I have corrected the error. As for the CS treatment, 12 patients were treated with 500-1000 mg/day of methylprednisolone for three successive days (8 patients received maintenance prednisolone therapy of 0.5-1.0 mg/kg/day and 4 patients receive no maintenance therapy) and the remaining **24 patients** received prednisolone therapy dosing approximately 0.5 mg/kg/day. The average duration of initial administration was 309 days, except for 6 patients who were still on corticosteroid therapy.
Changes in the text: We have corrected a numbering error (see Page 8, line 21-25)".