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# Phenotyping chronic pulmonary aspergillosis by cluster analysis

*To the Editor:*

Chronic pulmonary aspergillosis (CPA) is a complex disorder involving various underlying conditions and risk factors, clinical and radiological features, and natural histories or responses to treatment [1]. Untreated, patients with CPA have  $\geq 50\%$  5-year mortality [2, 3]. Recently, it was proposed that CPA includes simple aspergilloma, chronic cavitary pulmonary aspergillosis (CCPA) and chronic necrotising pulmonary aspergillosis (CNPA) [1].

However, aside from simple aspergilloma, the presentation and treatment of which is distinct from that of CCPA and CNPA, considerable overlap seems to exist between the various clinical, radiological and histological presentations of CCPA and CNPA [1, 4]. Improving the classification of CCPA and CNPA by integrating the multiple aspects of the disease is critical for future clinical trials. Here, we used a subject-centred multivariate clustering approach without *a priori* assumptions to identify phenotypes among patients with CPA (excluding simple aspergilloma) based on integrated clinical, biological and radiological features.

This study was based on a retrospective analysis of 127 patients with CPA (simple aspergilloma excluded) seen between January 2002 and December 2011 in eight chest departments at French university hospitals. The study was approved by the local research Ethics Committee (DR-2012-304) of Poitiers, France.

CPA was diagnosed according to the following criteria (all criteria were required) [1]. 1) Pulmonary cavitation(s) with a wall and possible pleural thickening on imaging with or without intracavitary mass or other radiological patterns compatible with CPA, such as progressive consolidation with or without secondary cavitation. 2) Serological or microbiological evidence implicating *Aspergillus* spp. 3) The presence of persistently elevated inflammatory markers. 4) Exclusion of all other causes with a similar disease presentation (e.g. active tuberculosis, nontuberculous mycobacterial infection and other bacterial infections). Subjects were required to have had a whole chest computed tomography (CT) at the time of diagnosis. Exclusion criteria were simple aspergilloma, invasive aspergillosis, allergic bronchopulmonary aspergillosis and significant immunosuppression (uncontrolled HIV, haematological malignancy, chronic granulomatous disease or glucocorticoid dose >7.5 mg of prednisolone per day).

Demographic, clinical and radiological data were collected at the time of diagnosis. CT images were reviewed by two chest radiologists blinded to the clinical data (F. Laurent and C. Beigelman-Aubry), who reached a final decision by consensus. The following features were collected in each lung: number/volume of cavities, maximal cavity wall thickness, number/volume of fungus balls, and maximal pleural thickness. Alveolar consolidation, lobar collapse(s), tree-in-bud and nodules >5 mm were visually quantified. The presence, severity and extent of bronchiectasis, and bronchial wall thickening were assessed [5].

A hierarchical ascendant classification [6] was used to identify relevant subgroups without prior assumptions [7]. Importantly, the classical subtypes of CCPA and CNPA used in previous classifications were not included in the analysis. The following characteristics were included [1]: age; body mass index (BMI); sex; chronic obstructive pulmonary disease; prior tuberculosis, nontuberculous mycobacterial infection, sarcoidosis, interstitial pneumonia or thoracic surgery; prior glucocorticoid and antifungal treatments; alcoholism; diabetes; smoking habit; the presence of fever, chest pain, haemoptysis or weight loss; the time frame of the evolution of symptoms (1–3 months *versus* >3 months); the presence of cough, dyspnoea and expectoration; precipitating (IgG) antibodies to *Aspergillus* (Microgen Bioproduct Ltd, Camberley, UK) in serum; *Aspergillus* cultures; C-reactive-protein; serum galactomannan antigen; the presence of cavity, fungus balls, collapse, tree-in-bud, nodules >5 mm and areas of consolidation; bronchiectasis CT score; and the maximum thickness of the cavity wall and pleura. All quantitative and qualitative variables were discretized using a multiple correspondence analysis for standardisation before cluster analysis.

Out of the 127 patients, 106 were assessed for the cluster analysis (14 patients had non-usable CT and seven were excluded due to missing clinical data). 70 (66.0%) were male, with a median age of 58 years (range: 46–66 years), and a median BMI of 20.0 kg·m<sup>-2</sup> (range: 17.5–22.5 kg·m<sup>-2</sup>). The most common underlying conditions were previous history of tuberculosis (49.1%) and chronic obstructive pulmonary disease (34%). More than two thirds of the patients had underlying risk factors, mainly smoking (44.3%), glucocorticoid use (36.8%) and alcoholism (21.7%). The commonest presenting symptoms were cough (86.8%), sputum (75.5%), haemoptysis (48.1%) and weight loss (51%). Direct examination of sputum revealed *Aspergillus* hyphae in 38 (35.8%) cases. Sputum cultures were positive in 62.3% of cases, with positive serum galactomannan antigen in eight (18%) out of 45 cases. *Aspergillus fumigatus* precipitins were positive in 85% of cases. The most common CT abnormalities were the presence of cavities (86.8%) with thick walls (85%), adjacent pleural thickening (81.6%) and fungus balls (56.6%). Additional features were predominantly areas of consolidation (68%), lobar collapse (64.1%) and nodules >5 mm (37.7%). Bronchiectasis was present in 78% of cases, and was mild in 27% of cases, moderate in 46% and severe in 19%.

No significant differences were found between radiological and clinical variables of the patients included in the cluster analysis and those of patients not eligible for the analysis. Only one phenotype was identified according to the clustering approach. The dendrogram (fig. 1) showed the distances between groups to be small, expressing little dissimilarity between them. According to the level of clustering, we nevertheless considered two and three potential subgroups, with very few patients (six *versus* 100 patients and four *versus* two *versus* 100 patients, respectively), and explored their relevance. Secondary analysis of these groups did not show relevant clinical or imaging characteristics. Hence, the 106 patients with CPA were considered relatively homogenous with regard to the epidemiological, clinical, and radiological features at diagnosis. Notably, the classical subtypes of CPA, *i.e.* CNPA or CCPA, were not identified by the cluster analysis.

The CNPA criteria originally defined by BINDER *et al.* [8] and then by GEFTER *et al.* [9] are not strictly equivalent to those proposed by DENNING *et al.* [1] more recently. BINDER *et al.* [8] suggested a definition of CNPA involving histological evidence. While GEFTER *et al.* [9] proposed a radiological definition based on the presence of a pre-existing cavity to distinguish the invasive and noninvasive forms. The criteria they used to distinguish CCPA and CNPA are neither specific nor based on a large prospective series with supporting histological evidence. All three definitions include the notion of baseline imaging before more invasive investigations are considered, and histological data are rarely available. Recently, IZUMIKAWA *et al.* [10] retrospectively studied 27 cases of CPA, and divided them into four groups according to the presence of

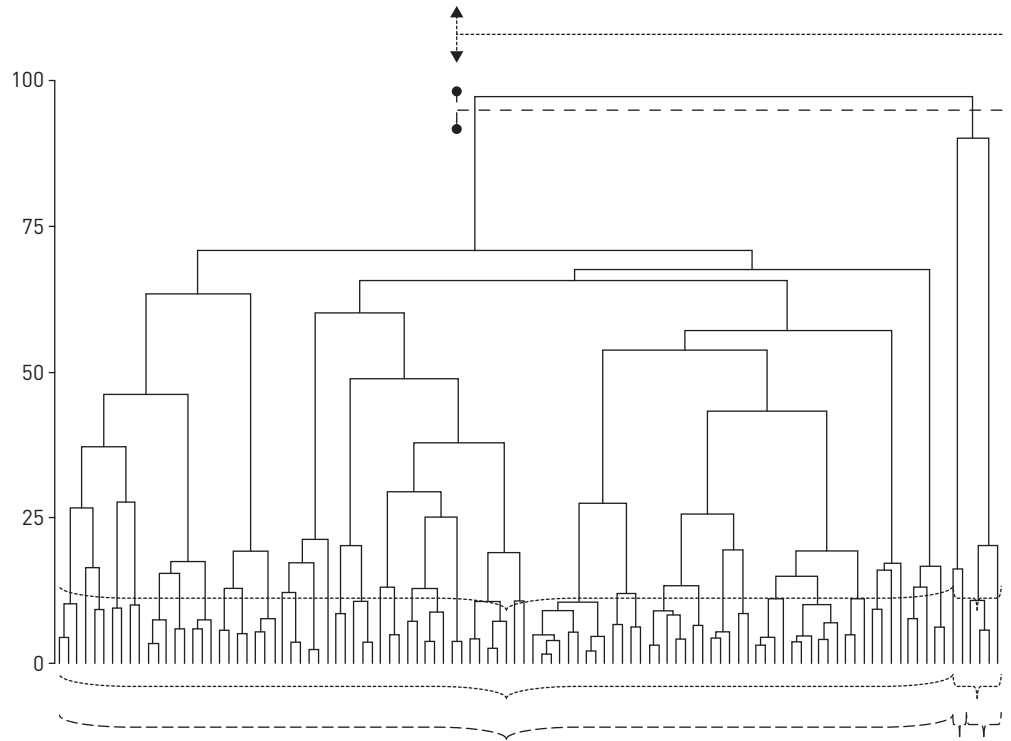


FIGURE 1. Dendrogram based on the characteristics of patients at the time of diagnosis (n=106). The dotted line, arrows and curly brackets show the results of clustering after the first division, while the dashed symbols show the results of clustering after two divisions. The x-axis represents patients classified according to the clusters to which they belong and the y-axis represents distance reflecting the dissimilarity between the two clusters.

histological lung invasion, in order to determine whether clinical or radiological parameters could discern between CCPA and CNPA. Being unable to distinguish CCPA from CNPA based on clinical and radiological settings, these authors have proposed the term “chronic progressive pulmonary aspergillosis” for a broad clinical syndrome including both CCPA and CNPA. Our study in a large series of CPA patients was consistent with the findings of IZUMIKAWA *et al.* [10]. Furthermore, the two classical subtypes of CCPA and CNPA did not emerge as two separate clusters. Limitations of our study included the retrospective design and the absence of histological data, as they are rarely available in clinical practice. The hierarchical ascendant classification [6] is, by nature, exploratory and aims at revealing patterns without any *a priori* assumptions; however, it does not allow estimation of the study power. The main strength of the study is to provide, in the largest published series, to date, of a still poorly known pulmonary disease, a rigorous CT assessment with a thorough clinical and biological evaluation.

In conclusion, our data demonstrate that patients with CPA (excluding simple aspergilloma) have relatively homogeneous characteristics, and support the notion of a continuum in the clinical and radiological features of CPA rather than identifying somewhat artificial subtypes as classically proposed.



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**Cluster analysis based on clinical and radiological settings does not distinguish any specific phenotype of CPA** <http://ow.ly/QZq7V>

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