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Corpora amylacea in sputum smears: Incidence and clinical significance

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Abstract

Objective: To examine conventional sputum smears for the presence of corpora amylacea (CA), determining their incidence and clinical significance.

Methods: A retrospective 4-year cohort study was undertaken of sputum samples from 1176 consecutive patients for the presence of CA. Variables such as age, sex, smoking status, and the presence or absence of haemoptysis were extracted from the medical record. A random group of 50 patients was selected as a control group, and a random group of 50 patients whose ages were below 49 years was also included as an age-based control.

Results: A total of 1075 of the initial cohort of consecutive patients were included in the study. from these, there were 6898 sputum smears, of which 1.91% (132 smears) contained CA, corresponding to 9.86% of the cohort of patients (106 patients). There was a strong, positive, statistically significant correlation between age and CA presence ($\tau_b = .402$, $P < .001$), which supports that CA are associated with older patients. The results of a binary logistic regression indicated that there was a significant association between age, diagnosis of chronic obstructive pulmonary disease and CA presence ($\chi^2 = 49.051$, $df = 2$, $P < .001$).

Conclusions: The presence of CA in sputum smears is related to age, being much more frequent in older people. Moreover, CA are related to non-neoplastic lung diseases.

KEYWORDS

clinical significance, corpora amylacea, incidence, sputum smears

1 | INTRODUCTION

Corpora amylacea (CA) were first reported in the brains of elderly patients by J.E. Purkinje in 1837.[1] Later, their first description in the lung was made by Friedreich in 1856.[2] CA are non-calcified concentric lamellated structures with a round-oval shape and of different sizes (from 30-45 to 300-400 μm in diameter), sometimes showing a glass-like appearance. They have been observed in different organs such as the prostate, brain and lungs, among others.[3] Chemically they are composed of glycoproteins. In the lungs, by means of immunochemistry analysis, CA are composed principally of surfactant apoprotein[4] and surfactant proteins type A, which are deposited in concentric layers, while periodic acid-Schiff (PAS)-positive glycoproteins comprise their interior.[5] Histochemical studies demonstrate that CA show an affinity for Congo red staining and exhibit strong positivity for the PAS reaction.[6]

Regarding the respiratory apparatus, CA may be observed both in histological sections and cytological samples. In 1957, Michaels and Levene reported that pulmonary CA were found in 41 out of 1070 (3.83%) post-mortem lung sections in increasing frequency

with advancing age.[7] Hollander and Hutchins also observed that pulmonary CA were seen in 37 out of 6500 (0.6%) of their autopsy cases.[8] In addition, by means of open lung biopsy, CA within alveolar spaces have been also reported.[9] The presence of CA in sputum smears has been noted in textbooks and selected monographs on pulmonary cytopathology.[10-13] However, to the best of our knowledge, there are no published studies regarding CA in sputum samples of large patient series.

The aim of this work was to examine conventional sputum smears for the presence of CA, to determine their incidence and relationship with clinical characteristics.[1]

2 | MATERIALS AND METHODS

A retrospective 4-year cohort study (January 2012 to December 2015) was undertaken of samples from 1176 consecutive patients, who provided 2940 samples as a result of spontaneous expectorations with a total of 7060 conventional sputum smears. All of the samples were submitted to the INCLÍNICA Foundation laboratory. Individual patient consent was not sought, as these data are routinely collected by the first author's laboratory and all analyses were undertaken using fully anonymised data. The study was undertaken in compliance with the principles laid out in the Declaration of Helsinki.

The samples were assessed using a *pick-up-smear* technique. A small quantity of sputum expectorate was selected and placed on a glass slide. With the help of another glass slide, a smear was made by displacing the glass slides in opposite directions. The smears were fixed in 96% ethanol, stained by the Papanicolaou method, and examined for the presence of CA. The following variables were extracted from the medical records of these patients: age, sex, smoking status, and the presence or absence of haemoptysis. Clinical and histopathological diagnoses were also recorded, based on information recorded in the medical records.

All patients with CA present in the sputum were included in the analysis (n = 106 patients). As it was impractical to include all other sputum cases in the control group, a random number generator was used to identify 50 cases among the full sample of sputum cases to serve as the control group. One of the 50 cases identified corresponded to a patient with CA present (2%) and was therefore excluded from the control group, resulting in a total of 49 control cases. Since CA appeared to be associated with older patients, a separate group of age-based controls (patients younger than 49 years) was randomly selected among the full sample of sputum cases. None of these cases randomly selected among patients younger than 49 years had CA present. Due to the selection criteria of age, the age-based control group was included in the descriptive analysis only.

Statistical analysis was performed comparing patients in the general control group with those who had CA. The normality of the distribution of patient age in years was examined using the Shapiro-Wilk normality test. As the data were not normally distributed, Kendall τ_b correlation was used to correlate age with the presence/absence of CA. The Pearson χ^2 test was used to determine if the proportion of cases with/without CA was different among the categorical data variables (sex, smoking history, haemoptysis and diagnostic categories). A univariate binary logistic regression was used to determine the variables most strongly associated with CA presence. The results included odds ratios, 95% confidence intervals, Wald χ^2 statistics, and corresponding *P*-values, with significance assumed at $P \leq .05$. Collinearity was ruled out using a tolerance >.2 and a variance inflation factor <5. Once multicollinearity was ruled out, a multiple binary logistic regression analysis was used with the

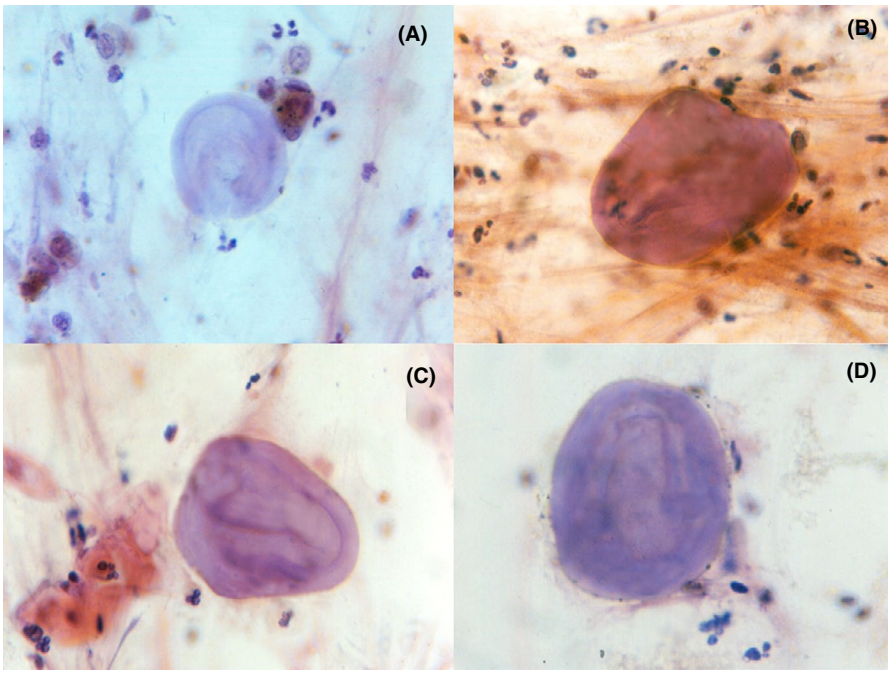

FIGURE 1 Corpora amylacea in sputum smears. (A) round structure about 80 μm in diameter with a bluish-purple hue. Note the concentric lamellar pattern. Several dust laden macrophages appear in the background (Papanicolaou stain, ×400). (B) Oval structure about 160 μm in diameter with a magenta hue and admixed with strands of mucus, leucocytes and histiocytes (Papanicolaou stain, ×400). (C) round to oval structure about 130 μm in diameter with a purple hue. A concentric lamellar pattern is observed (Papanicolaou stain, ×400). (D) oval structure about 120 μm in diameter with a purple hue. Note the concentric lamellar pattern (Papanicolaou stain, ×400)

variables identified in the univariate analysis as having the strongest relationship with CA. Statistical significance was assumed at $P \leq .05$. Analyses were performed using IBM SPSS Statistics 22.

3 | RESULTS

A total of 1075 of the initial cohort of 1176 consecutive patients were included in the study (101 patients were excluded because their samples were classified as not valid or insufficient due to the absence of alveolar macrophages and abundance of squamous cells, indicating that the samples were primarily made up of saliva). This excluded 162 sputum smears. Of the remaining 6898 sputum smears, 1.91% (132 smears) contained CA, corresponding to 9.86% of the cohort of patients (106 patients). The number of CA-compatible structures that were observed ranged from a minimum of two elements to a maximum of six in each of the sputum smears examined. With the Papanicolaou method, CA were identified as round to oval structures, ranging from 80 to 160 μm in diameter, with a concentric lamellar pattern, and of different colours from purple-magenta to various blue hues (Figure 1A-D).

A descriptive summary of patient age among the three groups is shown in Table 1. A Kendall τ_b correlation was run to determine the relationship between age and CA presence/absence (using the general control group for CA absence). There was a strong, positive, statistically significant correlation between age and CA presence ($\tau_b = .402$, $P < .001$), which supports that CA presence is associated with older patients. Table 2 shows the distribution of categorical variables among the three groups. The majority of the patients in each group were male (93% CA, 92% general control group, 92% age-based control group), and had no haemoptysis present (61% CA, 53% general control group, 74% age-based control group). Most of the CA group and the general control group were smokers (62% CA group, 76% general control group), whereas the majority of the age-based control group were non-smokers (66%). Chronic obstructive pulmonary disease (COPD) was the most common diagnosis among the CA patients (42%) and the general control group (67%), and cough was the most common clinical diagnosis among the age-based control group.

Table 3 shows the results of the Pearson χ^2 test, which identifies statistically significant associations between CA presence and sex, smoking history, haemoptysis and clinical diagnosis. Dichotomous variables (sex and haemoptysis) have the same statistical results for each variable and therefore are presented as males and haemoptysis present. A congestive heart failure diagnosis was more likely to have CA present than absent ($\chi^2 = 4.941$, $P = .026$), while a diagnosis of COPD was less likely to have CA present than absent ($\chi^2 = 8.307$, $P = .004$). There is no significant association between CA presence/absence and sex, smoking history, haemoptysis or other diagnoses shown.

A univariate logistic regression analysis was performed for CA presence with age (in years), sex, smoking history, haemoptysis and clinical diagnosis to identify which variables to include in a multiple regression model. The clinical diagnosis variable was coded as cases with COPD or no COPD since COPD was the most prominent diagnostic category. For dichotomous variables, the absence of the variable (code of 0) was the reference for comparison when applicable (males were used as the reference for sex). Smoking history was treated as an ordinal variable, and the reference variable was non-smokers. Table 4 shows the univariate logistic regression results for the variables included in each univariate regression. Age and diagnosis (COPD vs no COPD) were each significantly associated with CA presence. These variables were tested for multicollinearity to determine if they could be included in the multiple regression model. Multicollinearity was not a factor between age and diagnosis (tolerance = .995, variance inflation factor = 1.005), and therefore a multiple binary logistic regression was performed with the two independent variables and CA presence. The results of the multiple logistic regression are shown in Table 5, with the classification accuracy shown in Table 6.

The logistic regression model was statistically significant ($\chi^2 = 49.051$, $df = 2$, $P < .001$). The model explained 38.1% (Nagelkerke R^2) of the variance in CA presence, and correctly classified 75.5% of the cases. Since the *y*-intercept was negative (−11.955), when COPD is absent or the age is low, CA presence is less likely. COPD has a larger absolute value coefficient than age, and therefore the presence/absence of COPD has a larger impact on the equation. Since the actual coefficient was negative, the odds of CA presence in the test group (COPD) were lower than the reference group (no COPD). The coefficient for age was positive, suggesting that CA presence increases with age. Based on this model, if a 65-year-old patient has COPD, the following equation could be applied:

$$\text{Predicted logit} = -11.955 + (0.205 \times (\text{age}) + (-1.119 \times (\text{COPD})).$$

TABLE 1 Age and CA presence

		CA present	No CA present (general control group)	No CA present (age-based control group)
Age (years)	Min	58	38	39
	Max	79	70	49
	Median	68	63	46
	Average	68.3	61.1	45.7
Total		106	49	50

Abbreviation: CA, corpora amylacea.

TABLE 2 Summary of sex, smoking history, haemoptysis and diagnosis among the CA groups (CA present, general control, age-based control)

	CA present		No CA present (general control group)		No CA present (age-based control group)	
	n	% (out of n = 106)	n	% (out of n = 49)	n	% (out of n = 50)
Gender						
Male	99	93%	45	92%	46	92%
Female	7	7%	4	8%	4	8%
Smoking history						
Non-smoker	31	29%	10	20%	33	66%
Former smoker	9	8%	2	4%	0	0%
Current smoker	66	62%	37	76%	17	34%
Haemoptysis						
No	65	61%	26	53%	37	74%
Yes	41	39%	23	47%	13	26%
Diagnosis						
Acute bronchitis	6	6%	1	2%	7	14%
Adenocarcinoma	2	2%	0	0%	0	0%
ARDS	0	0%	0	0%	2	4%
Alveolitis	0	0%	0	0%	1	2%
Aspergillosis	0	0%	0	0%	1	2%
Asthma	12	11%	5	10%	10	20%
CHF	10	9%	0	0%	0	0%
COPD	45	42%	33	67%	0	0%
COPD/ Bronchiectasis	6	6%	2	4%	0	0%
Cough	12	11%	5	10%	22	44%
Pneumonia	6	6%	2	4%	4	8%
PTE	3	3%	0	0%	0	0%
Silicosis	4	4%	1	2%	2	4%
Tuberculosis	0	0%	0	0%	1	2%

Abbreviations: ARDS, acute respiratory distress syndrome; CA, corpora amylacea; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PTE, pulmonary thromboembolism.

$$Z = -11.955 + (0.205 \times 65) + (-1.119 \times 1) = 0.251.$$

To determine the probability of CA presence, the following equation could be applied:

$$\text{Predicted probability} = e^{0.251} / \left(1 + e^{0.251}\right).$$

$$\text{Predicted probability} = 2.718282^{0.251} / \left(1 + 2.718282^{0.251}\right) = 56.24\%.$$

In other words, the patient would have a 56.24% probability of CA presence. By changing the diagnosis to no COPD, the result changes as follows:

$$Z = -11.955 + (0.205 \times 65) + (-1.119 \times 0) = 1.37.$$

$$\text{Predicted probability} = 2.718282^{1.37} / \left(1 + 2.718282^{1.37}\right) = 79.74\%.$$

In other words, the probably of CA presence increased to 79.74%.

4 | DISCUSSION

To the best of our knowledge, this is the first study to analyse the presence of CA in conventional sputum smears in a large group of patients (n = 106), studying its incidence and clinical significance. CA were found in 132 sputum smears with a percentage of 1.91%. It has not been possible to compare this result with other series as we could not find similar studies in the medical literature. Nevertheless, if we compare this result with pulmonary histopathological studies from autopsies, obviously with a much higher number of samples, the percentage is slightly higher than that shown by Hollander and Hutchins[8] (0.6% of unselected autopsies), and lower than that shown by Michaels and Levene[7] (3.83% from 1070 consecutive necropsies).

TABLE 3 Comparison of CA presence or absence (general control group) by sex, smoking history, haemoptysis, and diagnostic category

	CA present	No CA present (general control group)			
	% (out of n = 106)	% (out of n = 49)	CA higher rate	χ^2	*P*-value
Sex					
Male	93.4%	91.8%	Yes	0.124	.725
Smoking history					
Non-smoker	29.2%	20.4%	Yes	1.345	.246
Former smoker	8.5%	4.1%	Yes	0.988	.320
Current smoker	62.3%	75.5%	No	2.637	.104
Haemoptysis					
Yes	38.7%	46.9%	No	0.943	.332
Diagnosis					
Acute bronchitis	5.7%	2.0%	Yes	1.018	.313
Adenocarcinoma	1.9%	0.0%	Yes	0.937	.333
ARDS	0.0%	0.0%	—	—	—
Alveolitis	0.0%	0.0%	—	—	—
Aspergillosis	0.0%	0.0%	—	—	—
Asthma	11.3%	10.2%	Yes	0.043	.836
CHF	9.4%	0.0%	Yes	4.941	**.026**
COPD	42.5%	67.3%	No	8.307	**.004**
COPD/ Bronchiectasis	5.7%	4.1%	Yes	0.171	.680
Cough	11.3%	10.2%	Yes	0.043	.836
Pneumonia	5.7%	4.1%	Yes	0.171	.680
PTE	2.8%	0.0%	Yes	1.414	.234
Silicosis	3.8%	2.0%	Yes	0.322	.570
Tuberculosis	0.0%	0.0%	—	—	—

Abbreviations: ARDS, acute respiratory distress syndrome; CA, corpora amylacea; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PTE, pulmonary thromboembolism.

TABLE 4 Binary logistic regression analysis of CA presence with each variable, sorted by Wald χ^2

Predictor	*B*	Wald χ^2	*P*	Odds Ratio exp(B)	95% CI for exp(B)	
					Lower	Upper
Age (years)	0.219	24.112	**<.001**	1.245	1.141	1.359
Diagnosis—COPD	−1.028	8.043	**.005**	0.358	0.176	0.728
Smoking history						
Non-smoker (B0)		2.726	.256			
Former smoker (B1)	0.373	0.187	.666	1.452	0.268	7.866
Current smoker (B2)	−0.553	1.751	.186	0.575	0.254	1.305
Hemoptysis	−0.338	0.940	.332	0.713	0.360	1.413
Gender	−0.229	0.123	.726	0.795	0.222	2.855

Abbreviations: CA, corpora amylacea; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

In this study, it has been demonstrated that the presence of CA in sputum smears is related to age and it is much more frequent in older people. This fact is also true in lung autopsies of individuals over 84 years, which showed a percentage of 17.27%.[14] In other human organs such as the prostate and brain, CA are also related with ageing and dementia.[15-17] Moreover, CA were associated with

TABLE 5 Binary logistic multiple regression analysis

Predictor	*B*	Wald χ^2	*P*	Odds Ratio exp(B)	95% CI for exp(B)	
					Lower	Upper
Age (years)	0.205	23.600	<.001	1.228	1.130	1.334
Diagnosis—COPD	−1.119	6.599	.010	0.327	0.139	0.767
Constant	−11.955	18.663	<.001	0.000		

Abbreviations: CA, corpora amylacea; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

TABLE 6 Classification table

		Predicted			
		No CA present	CA present	Total	Percentage correct
Observed	No CA present	23	26	49	46.9%
	CA present	12	94	106	88.7%
	Total	35	120	155	75.5%

Abbreviation: CA, corpora amylacea.

benign lung diseases, which coincides with the textbooks consulted that mentioned CA have no known clinical significance. COPD was the most frequently observed disease in the group of patients with CA in their sputum smears (45.28%), followed by asthma (11.32%) and congestive heart failure (9.43%). This was also observed in the control group where COPD was noted in 62% of the patients, followed by cough (10%) and asthma (8%). In both groups of patients, there was also a higher proportion of smokers than non-smokers (62.26% and 64%, respectively). On the contrary, the relationship of CA with lung cancer was low, with only two cases detected (both adenocarcinoma) in 106 patients (1.88%). No malignancy was observed in the patients from the control group. Other studies examining the presence of CA in prostatic needle core biopsies indicated their incidence in association with adenocarcinoma was low.[18]

In human brains, CA were found to contain glycoprotein deposits with a complex tri-dimensional structure.[19] However, an interesting study about their formation in lungs, based on electron microscopy analysis, reported that amyloid-like fibrils were found in the cytoplasm of macrophages and that CA might be formed by the sequential aggregation, fusion, coalescence and compaction of degenerated alveolar macrophages.[6]

In bronchial washings and lung aspirates, CA must be distinguished from amyloid, mucus and chondroid material. Although both CA and amyloid are positive for Congo red stain, other stains and markers such as haematoxylin-eosin, DiffQuik®, CD45 and CD20 may be useful in selected cases.[20] Although CA usually are observed with a concentric lamellar patter these structures are not calcified, unlike other non-cellular elements with a similar pattern that may be also observed in sputum smears such as calcareous concretions, which, unlike CA, present a characteristic dark reddish hue due to their high content of calcium salts.[21] By contrast, the lineal radiating pattern seen with some CA should not be misinterpreted with fungal organisms.[22] In pulmonary alveolar proteinosis, a rare disease of the lungs characterised by the accumulation in the alveolar spaces of acellular material probably due to pulmonary surfactant, the presence of PAS-positive lamellar bodies with a globular hyaline appearance, which stains positively for surfactant apoprotein, may also be very similar to CA.[23] Apart from sputum smears, CA have been described in exfoliative cytology in other types of cytological samples such as cerebrospinal fluid,[24] cervicovaginal smears[25] and voided urine.[26]

This study has some limitations due to its retrospective design. Further work to investigate the clinical significance of CA in sputum smears warrants an increased follow-up period.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest with this manuscript.

AUTHOR CONTRIBUTIONS

Both authors have contributed equally to the preparation of this manuscript.

ETHICAL APPROVAL

This study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

INFORMED CONSENT

Informed consent was not obtained from all participants included in this study due to retrospective study design.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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