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ORIGINAL ARTICLE

Skin manifestations and dermatological diseases in COPD: a cross-sectional study and brief narrative review

Manifestações cutâneas e doenças dermatológicas na DPOC: um estudo transversal e breve revisão narrativa

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Abstract

Objectives: This study aims to pinpoint dermatological disorders or cutaneous manifestations that correlate with chronic obstructive pulmonary disease (COPD), determining whether these associations persist independently of respiratory insufficiency or neoplastic disease. **Methods:** A cross-sectional cohort study was conducted, with prospective data collection of patients admitted to the internal medicine ward of a tertiary hospital, over a 6-month period. Participants included patients diagnosed with cigarette smoke-induced COPD and a control group without COPD. Collected data included demographics and medical history (tobacco use, dermatological diseases, malignancy, respiratory insufficiency, etc.). All patients underwent a dermatological examination to detect the following skin manifestations: xerosis, malar exanthema, Thinker's sign, tobacco stains, nail clubbing, Beau's lines, Muehrcke's lines, koilonychia, longitudinal melanonychia, onycholysis, onychomycosis, onychorrexis, and paronychia. **Results:** Of the 187 patients analyzed, 94 (50.3%) had COPD. The most common skin findings were xerosis, onychomycosis, and clubbing. Statistical analysis revealed significant associations of xerosis, nicotine stains, and clubbing with COPD. The presence of neoplastic disease was identified as a confounder of the association between xerosis and COPD. The presence of chronic respiratory insufficiency was not a confounding factor. **Conclusions:** This study underscores the prevalence of xerosis and clubbing in patients with cigarette smoke-induced COPD. These findings advocate for heightened clinical awareness and prompt treatment of symptomatic xerosis in COPD patients and that the presence of clubbing does not require an alternative diagnosis to be sought.

Keywords: Chronic obstructive pulmonary disease. Skin. Nails. Respiratory insufficiency. Neoplasms. Digital clubbing.

Resumo

Objetivos: Este estudo visa identificar doenças dermatológicas e alterações cutâneas que se correlacionem com a DPOC, determinando se estas associações persistem independentemente de insuficiência respiratória ou doença oncológica. **Métodos:** Foi realizado um estudo de coorte transversal, com colheita prospetiva de dados de pacientes internados na enfermaria de Medicina Interna de um hospital terciário, ao longo de um período de 6 meses. Os participantes incluíram pacientes diagnosticados com DPOC induzida pelo tabaco e um grupo de controlo sem DPOC. Os dados coletados incluíram informação demográfica e antecedentes pessoais (uso de tabaco, doenças dermatológicas, doença oncológica, insuficiência respiratória, etc.). Todos os pacientes foram submetidos a um exame dermatológico para detetar as seguintes manifestações

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cutâneas: xerose, exantema malar, sinal de *Thinker*, manchas de nicotina, hipocratismo digital, linhas de *Beau*, linhas de *Muehrcke*, coiloniquia, melanoniquia, onicólise, onicomicose, onicorrexia e paroníquia. **Resultados:** Dos 187 pacientes analisados, 94 (50,3%) tinham DPOC. As manifestações cutâneas mais comuns foram xerose, onicomicose e hipocratismo digital. A análise estatística revelou associações significativas de xerose, manchas de nicotina e hipocratismo digital com a DPOC. A presença de doença oncológica foi identificada como um fator de confusão na associação entre xerose e DPOC. A presença de insuficiência respiratória crónica não se revelou fator confundidor. **Conclusões**: Este estudo destaca a prevalência de xerose e hipocratismo digital em pacientes com DPOC induzida pelo tabagismo. Esses achados defendem uma maior conscientização clínica e tratamento precoce da xerose sintomática em pacientes com DPOC, assim como que a presença de hipocratismo digital não obriga à procura de um diagnóstico alternativo.

Palavras-chave: DPOC. Pele. Unhas. Insuficiência respiratória. Neoplasias. Hipocratismo digital.

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, accounting for 6% of all deaths, according to the World Health Organization's Global Health Estimates. This condition is increasingly recognized as a critical public health issue[1].

COPD is a complex, multi-component disease characterized by persistent respiratory symptoms and airflow limitation that is not fully reversible[1]. However, there is increasing evidence that COPD encompasses more than just airflow obstruction, with systemic inflammation observed in patients that extends beyond the effects of cigarette smoke alone. It's still unclear whether this systemic inflammation is the result of spillover from inflammation in the peripheral lung, leading to the release of inflammatory mediators into the circulation (meaning the central process is still in the lung) or whether it's related to a comorbid condition that creates a pro-inflammatory state that affects the lung (meaning the main process here is the systemic inflammation itself). It is now known that this systemic inflammation leads to extrapulmonary manifestations and can also cause or exacerbate comorbid conditions[2].

COPD has a significant impact on health status at all stages, even in milder diseases, and its extrapulmonary effects and comorbidities contribute to its burden[2,3]. More than 70% of patients have an additional chronic conditions and a further 40% have two or more, with prevalence increasing with age[3-5].

Comorbidities have a major impact on healthcare costs, symptom burden, and quality of life and may contribute to reduced life expectancy. Some of these (such as cardiovascular disease, malnutrition, anemia, osteoporosis, and depression) are well recognised[2-4]. However, less known conditions associated with COPD also exist. Milkowska-Dymanowska et al., in their article published in 2015, discuss these under-recognized comorbidities of COPD and include "skin changes" as one of them[5].

The skin is the largest organ in the human body and is a multifunctional unit that acts as a protective physical barrier, absorbing UV radiation, preventing the penetration of microorganisms and chemicals, and controlling the passage of water and electrolytes; it also has thermoregulatory, immunological, sensory and autonomic functions[3].

Smokers are known to have accelerated skin aging with characteristic facial features such as prominent wrinkles, gaunt face, grey appearance of the skin, and a puffy complexion[5,6]. It can be postulated that the pathophysiology of both COPD and accelerated skin aging lies in the systemic inflammation caused by tobacco exposure. Interestingly, one study showed that facial wrinkling was not only associated with COPD risk, but its severity was also congruent with the extent of emphysema on CT scans[6].

Majewski et al. compared the biophysical properties of the skin in non-smokers, healthy smokers, and COPD patients and found that there were significant differences in skin temperature, melanin index, sebum content, and hydration levels between COPD patients and healthy non-smokers. These differences correlated with the BODE index (a marker of COPD severity), showing that skin condition in COPD patients worsens as the disease progresses[3].

Evidence on skin and/or nail changes in COPD are lacking and the available evidence is outdated. Data on the link between clubbing and COPD are also inconsistent, with some authors saying it's a sign of COPD[7] and others saying it should prompt a search for another diagnosis, such as lung cancer[1].

An association between psoriasis or rosacea and COPD has also been described[8,9] but further research is needed to confirm this.

The aim of this study is to investigate skin and nail changes in COPD and associated dermatological

conditions, and whether these associations are independent of the presence of respiratory insufficiency and/or neoplastic disease.

Methods

Cross-sectional cohort study with prospective data collection of all patients admitted to the Internal Medicine ward of a tertiary hospital in Lisbon from January 2023 to June 2023, defining cases as patients with a diagnosis of cigarette smoke-induced COPD (ICD-10 criteria J40 to J44) and controls as patients without a diagnosis of COPD. Controls were selected by consecutive sampling until the number of controls matched the number of cases.

The following inclusion criteria were defined to establish a diagnosis of cigarette smoke-induced COPD:

- History of tobacco use (mandatory)
- Symptoms consistent with chronic bronchitis, such as chronic cough and/or chronic sputum production and/or dyspnea odds ratio (OR)
- Imaging evidence of emphysema in the absence of another most likely cause OR
- Spirometry showing a non-reversible obstructive pattern OR
- A well-established diagnosis of COPD, documented in medical records, with appropriate medication and follow-up.

All patients' electronic medical records were reviewed and the following data were collected: sex, age, and medical history (tobacco use, dermatological diseases, malignancy, home oxygen therapy [HOT], home non-invasive ventilation [NIV]).

Patients were defined as having chronic respiratory insufficiency (CRI) if HOT was prescribed OR NIV was prescribed, excluding prescription due to diagnosis of obstructive sleep apnea OR they had an arterial blood gas sample consistent with CRI after stabilization.

After obtaining informed consent, all patients underwent a thorough dermatological examination by a dermatology resident to detect skin manifestations such as xerosis, malar exanthema, Thinker's sign, tobacco stains, nail clubbing, Beau's lines, Muehrcke's lines, koilonychia, longitudinal melanonychia, onycholysis, onychomycosis, onychorrexis and paronychia. These were recorded as present or absent.

Descriptive statistical analysis was performed for numerical variables using measures of central tendency and dispersion, while frequencies and percentages were used for qualitative variables. Chi-square and Fisher's exact tests were used to compare variables between cases and controls, as appropriate. For statistically significant variables identified in the first analysis, their OR were calculated and compared in a stratified analysis according to the presence of CRI and the presence of a neoplastic diagnosis, using the Mantel-Haenszel test where appropriate. Statistical significance was defined as a two-tailed $p < 0.05$. Statistical Package for the Social Sciences version 20.0 was used.

The study protocol was approved by the CHULN Ethics Committee, aligning with the Declaration of Helsinki.

Results

Demographic data

A total of 187 patients were included, of whom 94 were diagnosed with COPD (Table 1), 60 (63.8%) men and 34 (36.2%) women, with a mean age of 76.3 ± 12.2 years. The remaining 93 patients without a diagnosis of COPD, consisted of 59 men (63.4%) and 34 women (36.6%), with a mean age of 80.9 ± 10.3 years.

Clinical data

The most common skin lesions were xerosis, onychomycosis, and clubbing (Table 2). Xerosis, nicotine stains, and clubbing were statistically significantly associated with COPD. Onycholysis on the other hand was associated with the absence of a COPD diagnosis.

In terms of diseases (Table 3), the most common were CRI and neoplasms, with both HOT and NIV reaching statistical significance and being associated with COPD.

Stratified analysis

In the stratified analysis, the Mantel-Haenszel test showed that the association between clubbing and COPD is independent of the presence of respiratory insufficiency or neoplastic disease. On the other hand, the association between xerosis and COPD is dependent on the presence of a neoplastic disease. This test was not carried out on the variable "nicotine stains" because this nail sign is known to be associated with chronic tobacco smoking.

Discussion

In our study, out of the 94 patients with COPD, 63.8% were men, which is consistent with the current

Table 1. Demographic data

Patients	Male	Female	Total	Age (years)
With COPD	60 (63.8)	34 (36.2)	94	76.3 ± 12.2
Without COPD	59 (63.4)	34 (36.6)	93	80.9 ± 10.3

COPD: chronic obstructive pulmonary disease.

Table 2. Skin and nail signs in patients with and without COPD

Skin signs	Without COPD (n = 93) (%)	With COPD (n = 94) (%)	p
Xerosis (n = 69)	27 (29)	42 (44.7)	0.027†
Malar exanthema (n = 15)	4 (4.3)	11 (11.7)	0.06†
Onychomycosis* (n = 47)	24 (25.8)	23 (24.5)	0.833†
Onycholysis (n = 6)	6 (6.5)	0 (0)	0.014‡
Clubbing (n = 35)	9 (9.7)	26 (27.7)	0.002†
Nicotine stains (n = 25)	0 (0)	25 (26.6)	0.000†
Onychorrhexis (n = 33)	15 (16.1)	18 (19.1)	0.702†
Koilonychia (n = 6)	2 (2.2)	4 (4.3)	0.682‡

*Of toe nails.
†Qui-squared test.
‡Fisher's exact test.
COPD: chronic obstructive pulmonary disease.

Table 3. Other diseases found in inpatients with or without COPD

Disease	Without COPD (n = 93) (%)	With COPD (n = 94) (%)	p
Psoriasis (n = 3)	0 (0)	3 (3.2)	0.246 (Fisher)
Rosacea (n = 6)	4 (4.3)	2 (2.1)	0.444 (Fisher)
Skin cancer (n = 1)	1 (1.1)	0 (0)	0.497 (Fisher)
Eczema (n = 3)	0 (0)	3 (3.2)	0.246 (Fisher)
Lung cancer (n = 12)	5 (5.4)	7 (7.4)	0.577 (QQ)
Other cancers (n = 46)	23 (24.7)	23 (24.5)	0.966 (QQ)
NIV (n = 15)	3 (3.2)	12 (12.8)	0.016 (QQ)
HOT (n = 34)	8 (8.6)	26 (27.7)	0.001 (QQ)
CRI (n = 43)	11 (25.6)	32 (74.4)	0.000 (QQ)

COPD: chronic obstructive pulmonary disease; NIV: non-invasive ventilation; HOT: home oxygen therapy; CRI: chronic respiratory insufficiency.

evidence of a 3:2 male-to-female ratio in the diagnosis of COPD[10]. The mean age of the COPD patients was 76.3 ± 12.2 years, whereas the mean age of the non-COPD patients was 80.9 ± 10.3 years, which may indicate that COPD patients have a slight tendency to require hospitalization at a younger age or may reflect a bias in the selection of control patients.

The present study found that xerosis (44.7%), clubbing (27.7%), and nicotine nail stains (26.6%) were common manifestations in patients with COPD and were statistically significantly associated with this disease. Xerosis has been previously described as being more prevalent in people with chronic lung disease, particularly emphysema[11,12] Xerosis can be symptomatic and quite bothersome, manifesting primarily as pruritus. It is important for clinicians to be aware of this so that they can diagnose and manage it more effectively, advising skin moisturization, emollients, short showers with lukewarm water, and avoidance of skin irritants[13].

As mentioned in the Introduction, clubbing has been described by some as being associated with COPD and by others as an alert for another diagnosis. This study found evidence to support clubbing as a common manifestation of cigarette smoke-induced COPD, independent of the presence of neoplastic disease.

We didn't consider the association found between nicotine nail stains and cigarette smoke-induced COPD because these nail sign is known to be associated with chronic tobacco smoking[14].

Onychorrexis was not found to be associated with COPD, although it has been described as such in other studies[11].

Regarding skin and nail signs, there were some with significantly low numbers, such as onycholysis (3%) and koilonychia (3%), and some that were not observed in any patient such as the Thinker's sign[15], Beau's lines, Muehrcke's lines, longitudinal melanonychia and paronychia.

Table 4. Stratified analysis of xerosis and clubbing by CRI

Skin findings	OR	OR (with CRI)	OR (without CRI)	Mantel-haenszel
Xerosis	1.97 (1.09-3.62), p = 0.027	1.20 (0.29-4.94), p = 1.000	2.25 (1.13-4.51), p = 0.032	1.99 (1.07-3.71), p = 0.043
Clubbing	3.57 (1.57-8.12), p = 0.002	1.50 (0.27-8.45), p = 1.000	4.38 (1.70-11.32), p = 0.002	3.39 (1.48-7.81), p = 0.005

OR: odds ratio; CRI: chronic respiratory insufficiency.

Table 5. Stratified analysis of xerosis and clubbing by the coexistence of neoplasia

Skin findings	OR	OR (with ND)	OR (without ND)	Mantel-haenszel
Xerosis	1.97 (1.08-3.62), p = 0.027	5.08 (1.50-17.24), p = 0.007	1.39 (0.68-2.81), p = 0.471	1.95 (1.07-3.56), p = 0.029
Clubbing	3.57 (1.57-8.12), p = 0.002	1.50 (0.23-9.76), p = 1.000	4.51 (1.77-11.46), p = 0.002	3.65 (1.60-8.33), p = 0.002

OR: odds ratio; ND: neoplastic disease.

In concern to onycholysis and koilonychia, these low findings probably reflect an overall low prevalence of these nail changes in the population. There is currently no information on the prevalence of onycholysis or koilonychia in different age groups and sexes. This also means that the association found between onycholysis and lack of COPD diagnosis is probably spurious and should not be considered given the biological implausibility and the small sample size.

As for the other skin signs mentioned that were not found (Thinker's sign, Beau's lines, Muehrcke's lines, longitudinal melanonychia, and paronychia), this may also reflect an overall low prevalence in the population. There is little to no evidence of the true prevalence of these conditions.

t was difficult to identify previous diagnoses of dermatological conditions (psoriasis, rosacea, eczema, skin cancer) from medical records, as most doctors don't consider dermatological history to be worth mentioning on their records, especially if the patient is old. Patients were asked about a previous dermatological diagnosis, but due to their age, the information was not completely reliable. This may be a possible explanation for the low number of patients found with a previous diagnosis of chronic dermatological disease or skin cancer. However, our numbers are in line with the reported prevalence of psoriasis (0.5-1%)[16], although a recently published article suggests that the prevalence of psoriasis in Portugal is much higher, about 4%[17]. Our numbers are also in line with the reported prevalence of rosacea (5%)[18]. This small sample size does not allow us to carry out credible statistical studies.

In this study, we aimed to clarify whether the skin and nail changes that were statistically significantly associated with COPD were related with CRI, to clarify whether this was something specific to COPD or a possible common finding in chronic respiratory diseases in general. Due to the above-mentioned conflicting evidence regarding clubbing and COPD, this study also aimed to clarify whether those skin changes were associated with the presence of a diagnosis of lung cancer and/or other cancer diagnoses. Stratified analysis using the Mantel-Haenszel test showed that the association between clubbing and COPD was independent of the presence of respiratory insufficiency or neoplastic disease. On the other hand, the association between xerosis and COPD was dependent on the presence of neoplastic disease (Tables 4 and 5). The pathophysiology behind COPD and skin or nail changes could be related to the previously mentioned systemic inflammation, which is known to be present in COPD patients. Whether this systemic inflammation is due to spillover from inflammation in the peripheral lung (caused by tobacco smoke), a parallel abnormality, or related to a comorbid disease that also affects the lung, the truth is that the presence of increased circulating cytokines, chemokines, and acute phase proteins may eventually trigger these skin and nail changes[2]. Further research is needed to clarify this issue.

Limitations

The present study has a few limitations.

One significant issue is that patients were seen in the hospital in an acute or decompensated phase (whether

from COPD or another disease), which means that some findings need to be considered with caution, and others could not be assessed in this setting (such as the presence of central cyanosis).

Another important aspect concerns the study's small sample size, which is always a limitation, but even more so when we wanted to evaluate the relationship between certain dermatological diseases with a low prevalence in the population and COPD.

To explore this issue further, another study should be designed in a Primary Care setting, which would probably allow a larger sample size and easier access to previously known diseases, while assessing patients in a stable phase.

Conclusion

The present study was carried out in a tertiary hospital in Lisbon, Portugal. Bearing in mind previously mentioned limitations; it still allows us to conclude that clubbing is a manifestation of COPD, independent of the presence of CRI or neoplastic disease. This means that clubbing in a COPD patient should not prompt suspicion of another diagnosis, as previously reported.

Xerosis is also a common manifestation of COPD, although the diagnosis of neoplastic disease seems to be a confounder in this association.

These skin and nail signs should be at the forefront of the clinicians' minds when dealing with these patients and should be treated promptly if necessary.

The relationship between certain chronic dermatological conditions and COPD warrants further investigation.

Data availability statement

The data that support the findings of this study are available from the corresponding author, Inês Abreu, upon request.

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None.

Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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