Dermatology Practical & Conceptual

Chondrodermatitis Nodularis Helicis: Association with Higher Risk of Multimorbidity and Mortality in Middle-Aged Individuals and Implications for Prevention. An Observational Multicenter Retrospective Case-Control Investigation in Northern Spain

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Key Message: In this study, chondrodermatitis nodularis lesions in middle-aged patients (46–61 years) were associated with multimorbidity, leading to higher mortality compared to controls. Prospective studies are necessary to confirm these findings.

Key words: Chondrodermatitis nodularis, Mortality, Survival, Comorbidities, Multimorbidity

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ABSTRACT

Introduction: Previous studies have independently linked chondrodermatitis nodularis (CN) with vascular injury, tobacco smoking, and diabetes, particularly in adult patients with early onset lesions.

Objectives: To build on previous research by investigating survival and frequency of comorbidities in adult patients diagnosed with premature CN lesions (<61 years).

Methods: We conducted a retrospective multicenter case-control observational study focused on individuals diagnosed with CN before the age of 61. Participants were further categorized into those diagnosed before 46 years and those diagnosed between ages 46 and 60 years. We evaluated the frequency of cancer, chronic obstructive lung disease, severe liver disease, diabetes mellitus, HIV infection, arterial disease, hypertension, dyslipidemia, multimorbidity, and tobacco smoking as well as survival rates. Statistical analysis included univariate analysis (including Holm-Bonferroni test), Kaplan-Meier plot estimation with log-rank test, and multivariate Cox analysis.

Results: Patients diagnosed with CN between ages 46 and <61 years showed significantly greater multimorbidity (Holm-Bonferroni test, P=0.00007 < 0.00122) and higher mortality rates compared to controls (log-rank test, P=0.006). Multivariate Cox analysis revealed an adjusted HR of 2.75 (95% CI: 1.36–5.54, P=0.005).

Conclusions: The novel finding of this retrospective multicenter study is that a diagnosis of CN in middle-aged patients could be a marker of elevated risk of systemic comorbidity and mortality. These results highlight the need for prospective studies to confirm these associations. Meanwhile, clinicians should be aware that emphasizing healthy lifestyle choices of patients with CN may have an important preventive value.

Introduction

Chondrodermatitis nodularis chronica helicis (CN), or Winkler disease, is a localized ischemic, degenerative skin disorder of the external ear [1-7]. Appearance of CN lesions depend on both external triggers (mainly repeated minor trauma) and predisposing factors (mainly aging, male sex, and sun damage). CN is a curable, benign disease, and its clinical relevance has been based only on the pain it causes and on the need for differentiation with skin carcinoma. It is assumed to occur as an isolated disease limited to the skin, but a few case reports initially reported sporadic associations with diseases with microvascular injury [8], scleroderma [9], and atopy [10], and the hypothesis that CN could be a cutaneous sign of systemic diseases with microvascular injury in younger patients was suggested in a small, uncontrolled case series [8]. Epidemiologic research of comorbidities is important in dermatology to develop individualized, patient-oriented, interdisciplinary methods of care and to reinforce prevention measures. According to this, despite a limited theoretical background, we considered it of value to initiate a line of investigation focused on patients with CN. First, we performed a pilot empirical hypothesis-driven, single-center studies that separately investigated the burden of comorbid autoimmune diseases [11] and the survival of patients with CN (Table S1).This study included an age subanalysis differentiating between adult patients with early onset (< 61 years) (EO) and patients with late onset (61 years) (LO) of lesions. Comorbidities were not investigated. Briefly, we found that the mortality rate was higher in patients with EO CN (9.7%) than in controls (1.7%) (P=0.02). This was supported with a lower Kaplan-Meier survival test (log-rank test, P=0.02) for CN patients. On the contrary, significant differences in survival were not found in the LO subsample (27.5% in CN patients and 22.1% in controls) (P=0.29). Based on these interesting preliminary results, we limited the investigation of CN patients to the EO age subset (<61 years), and we reported later the possible association between CN and tobacco smoking and with diabetes mellitus (DM) in univariate analysis of single-center, case-control studies of CN patients in this age subset (<61 years) [11-13].

Considering the potential preventive importance of these preliminary results for patients, we built on our previous single-center research and constructed this larger multicenter retrospective case-control study with the aim of investigating for the first time the survival rate in conjunction with the frequency of eight systemic chronic comorbidities in patients with premature CN lesions (<61 years).

Objectives

In this multicenter retrospective case-control observational investigation, we compare the burden of eight systemic comorbidities (cancer, chronic obstructive lung disease (COPD)/asthma, severe liver disease (SLD), diabetes mellitus (DM), human immunodeficiency virus (HIV) infection and arterial disease (AD), hypertension (HT), and dyslipidemia (DL), the frequency of multimorbidity and the survival rates

of patients with EO CN (< 61 years) compared to a matched control population.

Methods

This multicenter case-control epidemiologic, histopathology registry-based study was carried out in two hospitals in Spain (Hospital Universitario Central de Asturias, Oviedo, Asturias; and Hospital Universitario Marqués de Valdecilla, Santander, Cantabria). Patients with a histopathological diagnosis of CN (between 1 January 2000 and 31 December 2022) were compared with matched individuals randomly selected from the histopathological register of seborrheic keratosis (SK) of the same hospitals and period, in a ratio of 1:2. Their investigation was performed in two independent phases: a) blind recruitment of controls according to matching demographic criteria (sex, age at diagnosis ±2 years) and year of histopathology diagnosis (±2 years), to avoid differences in the length of observation before diagnosis; b) the access to clinical histories of SK patients was carefully performed only after their inclusion in the study. It is to be noted that a comparison of cases with a sample of individuals with a diagnosis of SK as controls has previously been performed [14].

The study was approved by the Hospital Ethics Committee (ref 111/18 and 2021.340). According to our preliminary results (Table S1), the study was restricted to adults with a diagnosis before the age of 61 years who were further classified by differentiating between those receiving a diagnosis before the age of 46 years and those in the age range 46 to <61 years.

We investigated the number of non-traumatic deaths of eight comorbidities (defined by the presence of a specific diagnosis by a physician and the use of specific medications):

a. Six systemic comorbidities included in the Charlson Comorbidity Index (CCI) [14]: systemic (non-cutaneous) cancer, chronic obstructive lung disease (COPD)/asthma, severe liver disease (SLD), diabetes mellitus (DM), human immunodeficiency virus (HIV) infection, and arterial disease (AD). AD included coronary artery disease, cerebrovascular disease, aortic aneurysm, peripheral artery disease and carotid artery stenosis, peripheral lower limb artery disease, and multifocal artery disease.
b. CCI-based multimorbidity: diagnosis of more than one of of the six above-mentioned CCI-based diseases (DM, AD, cancer, SLD, COPD / asthma, and HIV infection).
c. Hypertension (HT) and dyslipidemia (DL) (not included in the CCI).
d. History of tobacco smoking (dichotomously categorized as lifetime non-smoker or as former or current smoker).

The data investigated were recorded for patients and controls until death, the last available visit, or the end of the study (31 December 2022). Patients with organ transplantation or cancer-prone syndromes before diagnosis were excluded.

Statistical Analyses

Results are expressed as numbers (percentage) or as median and interquartile range (IQR), as appropriate. Differences in survival time were calculated using a Kaplan-Meier plot estimator with a log-rank test. A multivariate analysis of survival time was fitted using a Cox proportional hazards regression model. The results are presented as the hazard ratio (HR) with 95% confidence intervals (CI). Mann-Whitney U-test and chi-squared or Fisher tests were used to compare continuous and categorial variables, respectively. The Holm-Bonferroni test for multiple comparisons was performed to control for the family-wise error rate. All p-values less than 0.05 were considered statistically significant.

Results

Comorbidities and Multimorbidity

Table 1 shows demographics and the significant associations between EO CN and 5/6 evaluated comorbidities in the univariate analysis as well as with CCI-based MB. AD were the most frequently observed comorbidities. The Holm-Bonferroni test confirmed the significance of the association with CCI- based multimorbidity (P=0.00003 < 0.00119).

Survival

The excess of non-traumatic deaths in patients with EO CN was also significant in the univariate analysis (Table 1). The causes of death in deceased patients with EO CN were AD (9/19; 47.4%), cancer (9/19; 47.4%), or sepsis (1/19; 5.3%, in a patient with HIV infection). On the other hand, cancer was the main cause of death in most control individuals who died (13.18; 72.2%), with only one dying from AD (1/18; 5.6%). The mean age at the time of diagnosis of skin lesions for individuals who died was 56.0 years (range 46.1–60.8 years) for patients with CN and 55.9 years (range 36.9–60.6 years) for individuals in the control group.

The Kaplan-Meier survival curve was significantly lower in patients with EO CN than in controls (log rank test, P=0.016) (Figure 1). The increase in the risk of death was independent of a CN diagnosis. CCI-based MB accounted for the excess mortality of CN patients in the Cox proportional risk multivariate analysis model (HR 2.68; 95% CI: 1.33–5.40; P=0.006), adjusted for diagnosis, age, sex, and tobacco smoking history (Table 2).

Table 1. Demography and Univariate Analysis in Patients with Early Onset CN and Matched Controls (<61 Years at Histopathological Diagnosis)*

		Total Sample (<61 Years)		P-value	OR	95% CI
1.	Demographics	CN	Controls			
	Number of individuals	N=154	N=306			
	Female (n, %)	40 (26.0%)	79 (25.8%)			
	Male (n, %)	114 (74.0%)	277 (74.2%)	P=1.000		
	Age (years) (median [IQR])	52.9 [44.5-57.0]	52.6 [44.4-57.0]	P=0.813		
	Follow-up (years) (median [IQR])	11.1 [5.4-16.7]	11.2 [6.4-16.8]	P=0.681		
2.	CCI-based comorbidities					
	COPD/asthma	19 (12.3%)	20 (6.5%)	P=0.049	2.01	1.01-4.06
	Severe liver diseases	8 (5.2%)	2 (0.7%)	P=0.003	8.29	1.75-54.91
	Artery diseases	30 (19.5%)	24 (7.8%)	P<0.001	2.84	1.55-5.12
	HIV	4 (2.6%)	1 (0.3%)	P=0.045	8.10	1.04-197.80
	Diabetes mellitus	27 (17.5%)	29 (9.5%)	P=0.016	2.03	1.11-3.66
	Cancer	24 (15.6%)	38 (12.4%)	P=0.386		
3.	CCI-based multimorbidity (6 diseases)	33 (21.4%)	22 (7.2%)	P<0.001	3.51	1.94-6.49
4.	Other associations					
	Tobacco	115/148 (77.7%)	184/290 (63.4%)	P=0.002	2.00	1.27-3.19
	Hypertension	60 (39.0%)	100 (32.7%)	P=0.213		
	Dyslipidemia	60 (39.0%)	100 (32.7%)	P=0.213		
5.	Survival					
	Deceased patients	19 (12.3%)	18 (5.9%)	P=0.028	2.25	1.13-4.45

*Including human immunodeficiency virus (HIV) infection results. Abbreviations: CCI: Charlson Comorbidity Index; CI: confidence interval; CN: chondrodermatitis nodularis; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; OR: odds ratio.

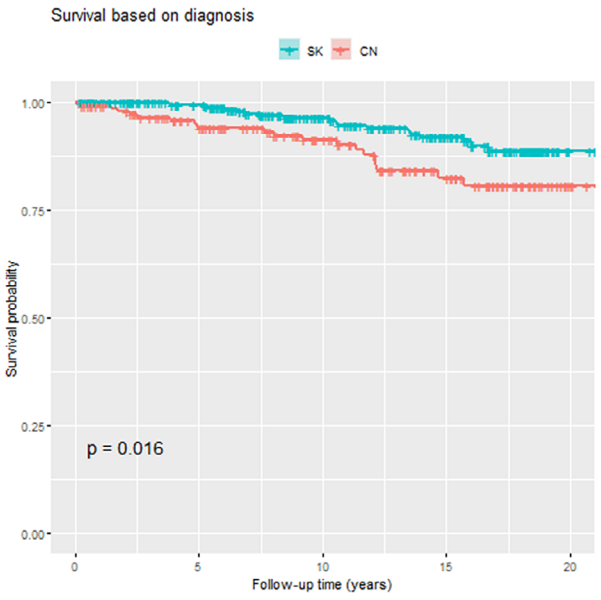

Figure 1. Kaplan-Meier survival probability for early onset patients, by chondrodermatitis (red) and controls (blue); 95% confidence bands were included (patients <61 years at histopathological diagnosis). CN = chondrodermatitis nodularis; SK = seborrheic keratosis.

Table 2. Results of the Cox Regression Model Analysis (Patients <61 Years at Histopathological Diagnosis).

Variable	Hazard Ratio (95 % CI)	P-value
Multimorbidity	2.68 (1.33-5.40)	**P=0.006**
Diagnosis (seborrheic keratosis)	1.77 (0.90-3.46)	P=0.096
Age (years)	1.09 (1.03-1.16)	**P=0.004**
Sex	0.70 (0.32-1.54)	P=0.376
Tobacco smoking	2.35 (0.88-6.24)	P=0.087

Age and Risk Stratification

Demographics and results of a further age subanalysis are shown in Table 3. The risks were restricted to middle-aged patients with a CN diagnosis in the age range 46–<61 years: association with MB based on CCI (Holm-Bonferroni test, p-value= 0.00007< 0.00122) and the decrease in survival (Figure 2) (log rank test, p=0.0063 were attributable to the association with CCI-based MB in the Cox multivariate

Table 3. Demography and Univariate Analysis in Patients With CN and Matched Controls in a Further Age Subanalysis.

	Further Age Subanalysis					
	[46-61) years			<46 years		
	CN	Controls	P-value, OR, 95% CI	CN	Controls	P-value, OR, 95% CI
1. Demographics						
Number of individuals	N=108	N=215		N=46	N=91	
Female (n, %)	33 (30.56%)	65 (30.23%)	P=1.000	7 (15.22%)	14 (15.38%)	P=1.000
Male (n, %)	75 (69.44%)	150 (69.77%)		39 (84.78%)	77 (84.62%)	
Age (years) (median [IQR])	55.6 [51.9-58.1]	55.6 [52.3-58.2]	P=0.813	37.9 [30.8-41.9]	39.1 [31.0-42.5]	P= 0.649
Follow-up (years) (mean [IQR])	11.1 [5.1-15.6]	11.9 [6.6-16.7]	P=0.312	11.6 [6.2-17.7]	10.0 [6.1-17.3]	P=0.433
2. Six CCI-based comorbidities						
Artery diseases	28/108 (25.93%)	23/215 (10.70%)	P=0.001; OR=1.15; CI=0.71-1.86	2/46 (4.35%)	1/91 (1.10%)	P=0.261
Severe liver diseases	7/108 (6.48%)	2/215 (0.93%)	P=0.008; OR=7.33; CI=1.60-49.78	1/46 (2.17%)	0/91 (0.00%)	P=0.336
Diabetes mellitus	23/108 (21.30%)	25/215 (11.63%)	P=0.030 OR=2.05; CI=1.10-3.99	4/46 (8.70%)	4/91 (4.40%)	P=0.442
COPD/asthma	14/108 (12.96%)	18/215 (8.37%)	P=0.236	5/46 (10.87%)	2/91 (2.20%)	P=0.042 OR=5.35 CI=1.06-39.41
HIV infection	3/108 (2.78%)	0/215 (0.00%)	P=0.037	1/46 (2.17%)	1/91 (1.10%)	P=1.000
Cancer	23/108 (21.30%)	36/215 (16.74%)	P=0.360	1/46 (2.17%)	2/91 (2.20%)	P=1.000
3. CCI-multimorbidity*	30/108 (27.78%)	21/215 (9.77%)	P<0.001; OR=3.54 CI=1.89-6.66	3/46 (6.52%)	1/91 (1.10%)	P=0.110
4. Other associations						
Tobacco	85/107 (79.44%)	136/210 (64.76%)	P=0.009 OR=2.10 CI=1.21-3.68	30/41 (73.17%)	48/80 (60.00%)	P=0.166
Hypertension	49/108 (45.37%)	90/215 (41.86%)	P=0.554	11/46 (23.91%)	10/91 (10.99%)	P=0.076
Dyslipidemia	49/108 (45.37%)	87/215 (40.47%)	P=0.406	11/46 (23.91%)	13/91 (14.29%)	P=0.233
5. Survival						
Deceased patients	19/108 (17.59%)	17/215 (7.91%)	P=0.014; OR=2.48 CI=1.22-5.21	0/46 (0.00%)	1/91 (1.10%)	P=1.000

Abbreviations: CCI: Charlson Comorbidity Index; CI: confidence interval; CN: chondrodermatitis nodularis; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; OR: odds ratio.

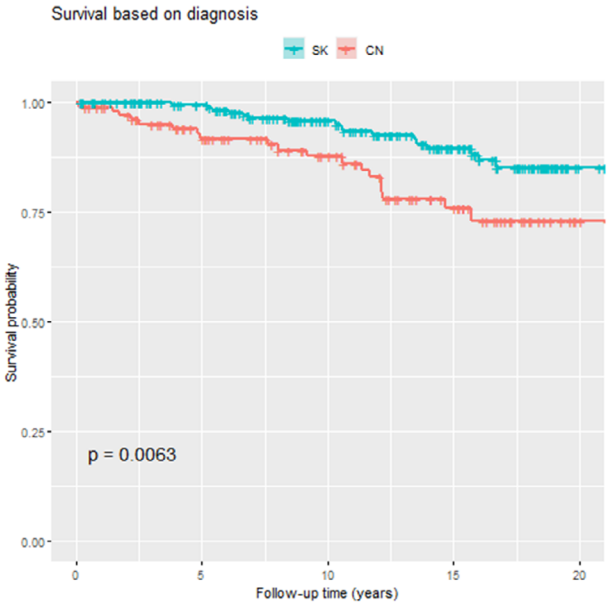

Figure 2. Kaplan-Meier survival probability for patients with diagnosis between ages 46–61 years, by chondrodermatitis (red) and controls (blue); 95% confidence bands were included. CN = chondrodermatitis nodularis; SK = seborrheic keratosis.

analysis (HR 2.75;95% CI: 1.36–5.54; *P*= 0.005) (Table 4) and were restricted to this age range. On the other hand, the differences between patients and controls with a diagnosis before 46 years were significant only for COPD/asthma (Table 3).

Discussion

CN clinically manifests as painful, round, centrally eroded papules on the most protruding areas of the helix or antihelix of the ear [1-7]. CN lesion pain is related to nerve hyperplasia [16]. The anatomy of the ear facilitates its development because of the lack of subcutaneous tissue and the scarce vascular supply derived only from small arterioles. Anatomic protuberant variants of the ear can also favor its appearance. The main known predisposing factor is age, and CN is considered an aging-related disease. Most patients (70%) are older than 60 years at the time of diagnosis, and most of them are males (65%), although the frequency in older females has increased in the last few decades [7]. It is exceptional in children [3,4].

CN is idiopathic but, nosologically, it is considered a secondary form of acquired perforating dermatosis (APD) [1,2,17] or a localized variant of prurigo nodularis (PN) [6]. CN is an ischemic, degenerative, inflammatory necrobiotic disease, with a complex interplay of trauma, altered wound healing, tissue hypoxia, and microangiopathy [8]. Vasculopathy has been related to vasculitis or to systemic diseases with vascular damage [8] in uncontrolled case reports. The vasculitis theory, first suggested by Halter in 1936, suggests

Table 4. Results of the Cox Regression Model (Patients With Chondrodermatitis Nodularis and Controls in Age Range 46 – < 61 Years at Histopathological Diagnosis).

	Hazard Ratio (95 % CI)	P-value
Multimorbidity	2.75 (1.36-5.54)	**0.005**
Diagnosis (seborrheic keratosis)	1.89 (0.96-3.71)	0.066
Gender (ref: Female)	1.05 (0.96-1.14)	0.320
Age, years	0.71 (0.32-1.58)	0.397
Tobacco (ref: Non-Smoker)	2.30 (0.86-6.16)	0.098

the appearance of specific perichondrial arteriolar changes in CN lesions [18]. Some histological findings of CN present similarities with ischemic syndromes, such as Degos' disease [8]. The involvement of cartilage is not a constant.

Regarding the results of the present study, it is worth highlighting first that five out of six CCI- related diseases (AD, SLD, CPOD/asthma, HIV infection, and DM) and CCI- based MB (more than one of these six diseases: HIV, AD, SLD, COPD, DM, and cancer) were higher in adult patients with EO CN than in controls in the univariate analysis. The Holm-Bonferroni test confirmed the significance of multimorbidity based on CCI. Secondly, the long-term survival of EO CN patients was significantly decreased compared to controls; this was attributable to the association with CCI-based multimorbidity in the Cox multivariate. Thirdly, these risks were limited to middle-aged CN patients (diagnosis in the age range 46 to–61 years), both in the association with CCI-multimorbidity and in the decreased survival, which was also related to the association with CCI-multimorbidity.

To comment our results, it must first be noted that CN is generally accepted as an isolated dermatosis limited to the skin. Nevertheless, it is an under-investigated disease, with a theoretical background limited to a small number of case series, apart from our own investigation. A comparison of our findings with other controlled studies was not possible. To interpret this study, we also highlight that this was an epidemiological study, not designed to assess causality, and we can only speculate different plausible, although not necessarily exclusive, hypotheses to comment our observations. One possible explanation is that these findings may merely reflect an increase in external triggers, such as the nocturnal external pressure on the ear, particularly in patients with declining health or reduced physical activity. Conversely, the potential link between the premature onset of CN, comorbidities, and survival also warrants consideration.

Different pathomechanisms are plausible: a) First, comorbidities, synergistically or not, could damage the skin and

additionally increase the susceptibility of the ear to development of CN lesions; b) secondly, CN, comorbid diseases, and decreased survival could be pleiotropic consequences of the same shared underlying risk factors; c) the predisposing effects of risk factors and comorbidities can be linked and summative, favoring CN development in different ways, such as increasing skin aging through vascular damage, by delaying healing, modifying the inflammatory response, or through deposition of advanced glycosylation end-products (AGEs) [19]. AGEs are extremely oxidant compounds that have been demonstrated in CN lesions, and they could play a role on its development [20]. Different additional dermal injuries related to comorbidities could precipitate ischemic degeneration over an already deficient vascular supply [8]. Finally, it is also to be noted that most of the comorbidities reported here in CN patients are typically associated with aging and a suboptimal lifestyle. According to geroscience, aging and chronic diseases are interconnected consequences of the same basic processes, which depend on genetics and lifestyle [21,22]. As an integrative hypothesis, it could be speculated as biologically plausible that the greater divergence between biological and chronological age in middle-aged patients with CN could be interpreted as a sign of premature health decline and premature aging phenotype, which could be related to lifestyle. The skin is a useful mirror reflecting internal aging, and different skin biomarkers of the risk of aging-related diseases have been suggested [23-28]. Thus, the premature appearance of a diagonal skin crease (DEC) in the skin of the earlobe (Frank´s sign) has been related to accelerated aging and artery diseases [27, 28]. In addition, skin aging parallels lung and arterial aging in different studies.

Furthermore, perceived age (PA), i.e., looking older than one´s chronological age, has also been reported as a biomarker of aging in association with a higher mortality rate and age-related systemic morbidities [29]. On the other hand, and from a qualitative point of view, it is also worth commenting on the accumulation of rare smoking-dependent inflammatory diseases (particularly, Buerger disease and pulmonary Langerhans cell histiocytosis), which reinforces the hypothesis of tobacco as a risk factor for CN lesions but also could suggest an interaction with genetic factors in patients with premature CN [11]. On the other hand, one of the deceased patients with premature CN in this study had a possible diagnosis of progeroid Werner syndrome and DM, supporting the hypothesis of a possible premature aging phenotype in some of these patients.

Limitations

The strengths of this study are that all diagnoses were histopathologically confirmed, its multicenter design, and the long duration of the study period (22 years). This is the largest sample of patients with CN investigated; information regarding immunosuppression and cancer-prone syndromes was recorded. The Holm-Bonferroni test controlled for the family-wise error rate. On the other hand, the limitations of this study are those inherent to an observational, retrospective investigation. These results achieved statistical significance, but their interpretation cannot be based only on p-values, and the possibility of chance, bias, or missing events cannot be excluded. Extrapolation to other countries cannot be adequately performed, thus limiting the generalizability of these findings. On the other hand, all patients were treated surgically/biopsied, and this could represent a worse subgroup of patients with a greater number of comorbidities, but a comparison with studies in other countries was not possible. In addition, data regarding tobacco smoking should be interpreted considering the high frequency of smoking among the controls, which made it convenient to obtain larger samples to detect differences with greater precision. Furthermore, the discrimination we used was simple (ever versus never smokers) and lacked the identification of active smokers as well as of the intensity and duration of the smoking habit. Additionally, it was difficult to separate the influence of risk factors and comorbidities, as they can be linked. The influence of sociodemographic and socioeconomic factors was not investigated.

It is accepted that CN is a homogenous disorder where the initial damage of CN lesions occurs in the dermis, and that the basically poor blood supply of the ear, in conjunction with aging, solar elastosis, and repeated minor traumas, could cause the dermal degeneration and transepidermal elimination of the degenerated dermal collagen [1-7]. The importance of this study is primarily that, for the first time, it is suggested that CN could be a heterogeneous syndrome in a spectrum including patients with an isolated disease limited to the skin and patients with an increased risk of systemic comorbidity and mortality. Our results raise significant concern about these patients and gives support for the design of future investigations, but the limitations of this study necessitate a cautious interpretation of the findings, and future investigations must overcome them. Thus, it is necessary to perform larger prospective, multicenter validation studies involving cohorts from different countries and adjusting for known risk factors of chronic diseases (smoking, alcohol, diabetes, body mass index, education, social class, physical activity, hormone therapy, and other). It would also be of value to apply more precision to the study of smoking habits, distinguishing active smokers from ever smokers and measuring smoking intensity and duration, and to consider prognosis in subsamples according to the type of treatment (chirurgical treatment/biopsy versus conservative measures). From a practical point of view, our findings may also serve to stimulate research on an under-investigated disease and may contribute to a better

understanding of its pathophysiology. Further studies should also focus on the pathogenic pathways and molecular mechanisms potentially linking CN and multimorbidity. To investigate potential histological differences between CN patients with or without chronic comorbid diseases could be another interesting line of investigation. Besides, further larger multicenter studies to confirm our preliminary, single-center results on patients with late onset CN (61 years) should also be considered. We did not observe any significant differences in this age subsample, but this was a pilot study and must also be interpreted with caution. The greater burden of comorbidities i older individuals could require larger samples to detect differences with greater accuracy.

Despite the limitations of this study, the potential clinical significance of the observed multimorbidity and decrease in survival among adult patients with EO CN lesions should not be underestimated, as it seems possible that it could be preventable. Rejecting our concerning results prematurely as radically contrasting with our traditional understanding of CN could imply a loss of benefit for affected patients. Prospective studies are necessary to confirm this investigation, but their feasibility is limited by the fact that the probability of developing an early CN lesion is low in the general population, and most individuals potentially exposed to external risk factors will not develop this disease. In our opinion, therefore, in the meantime, we can bear in mind what has been said for patients with psoriasis and comorbid diseases, for example: an ounce of prevention is worth a pound of cure.

Conclusion

The importance and novelty of this retrospective multicenter study is first and foremost that it proposes for the first time that a diagnosis of CN in middle-aged patients could be a biomarker of elevated risk of systemic comorbidities, multimorbidity, and lower survival rate. These results present clinical relevance but highlight the need for prospective studies to confirm these associations. Meanwhile, it seems possible that attention should be paid to prevention or multidisciplinary treatment of comorbidities as well as to the skin lesion itself in the management of middle-aged patients with CN. Clinicians should be aware that emphasizing healthy lifestyle choices in these patients may have an important preventive value for them, without the need for risks or additional costs. Further studies must also assess whether CN could represent a sign of premature aging and an accessible research model to identify commonalities in aging pathways across organ systems.

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