

## Supplementary material

### Preliminary Pilot Pre-Study

#### Patients And Methods

The pre-study was conducted in a single hospital (HUCA, Oviedo, Asturias, Spain); 215 patients with a histopathological diagnosis of CN (between 1 January 2000 and 1 January 2018) were investigated and compared with matched controls randomly selected from the histopathological register of seborrheic keratosis (SK) of the same hospital (Huca) and the same period (from 2000 to 2018) [1]. Controls were matched to index CN patients by sex, age, year of diagnosis ( $\pm 2$  years), and date of birth ( $\pm 2$  years). The duration of follow-up was similar for both samples. The number of natural deaths was registered and in CN patients and controls until death, last available visit to the Asturias Community Health System, or the end of the study (1 January 2018). Traumatic deaths were not registered. Patients with organ transplantation and those with cancer-prone syndromes were excluded.

The comparison was performed in the general sample and also in a further age subanalysis, differentiating between

patients with an early onset ( $< 61$  years) (EO) and patients with a late-onset histopathological diagnosis ( $\geq 61$  years) (LO). Controls were matched in a 1:1 ratio in the overall sample; in the age subanalysis, they were also matched in a 1:1 ratio in the LO subsample and in a 1:2 case-control ratio in the EO subsample, because the latter were a minority. The study was approved by the Hospital Ethics Committee (ref 111/18).

#### Results

The characteristics of the patients and the results of the single-center pre-study are shown in Table S1 (total sample and age subanalysis). Overall, there was a small excess of mortality in the total CN sample and in both age subsamples, but this excess was only significant in the EO subsample in the univariate analysis: OR=6.3; 95% CI: 1.1–44.4; ( $P=0.02$ ) (Table S1); the long-rank test was also significant ( $P=0.02$ ); The Cox proportional hazard model disclosed a 5.93-fold increase in the adjusted HR for mortality in CN patients

**Table S1. Preliminary Single-Center Study (HUCA, Oviedo). Demographic Data and Number of Deceased Persons in the Total Sample and in the Age Subanalysis. Patients with Chondrodermatitis Nodularis (CN) versus Controls.**

	AGE SUBANALYSIS				TOTAL SAMPLE (1:1 case-control ratio)	
	<61 years (2:1 case-control ratio)		$\geq 61$ years (1:1 case-control ratio)			
	CN	Controls	CN	Controls	CN	Controls
Number of individuals	N = 62	N = 121	N = 153	N = 154	N = 215	N = 215
Female (n, %)	13 (21.0%)	26 (21.5%)	62 (40.5%)	62 (40.3%)	75 (34.9%)	75 (34.9%)
Male (n, %)	49 (79.0%)	95 (78.5%)	91 (59.5%)	92 (59.7%)	140 (65.1%)	140 (65.1%)
	P = 1.00		P = 1.00		P = 1.00	
Age (years) (Me [IQR])	54.1 [48.8-57.9]	55.1 [48.8-58.0]	74.9 [68.0-80.8]	75.6 [68.2-80.9]	69.6 [59.4-77.7]	69.7 [60.0-78.2]
	P = 0.78		P = 0.70		P = 0.72	
Follow-up (years) (Me [IQR])	10.0 [4.6-13.6]	9.8 [4.7-13.5]	5.9 [3.0-8.7]	5.7 [3.4-9.2]	6.5 [3.2-10.7]	6.5 [3.7-10.4]
	P = 0.85		P = 0.73		P = 0.80	
Deceased persons (n, %)	6 (9.7%)	2 (1.7%)	42 (27.5%)	34 (22.1%)	48 (22.3%)	35 (16.2%)
	P = 0.02		P = 0.29		P = 0.14	

Abbreviations: CN: Chondrodermatitis nodularis; Me [IQR] : Median interquartile range

compared to controls ( $P=0.03$ ; 95% CI: 1.20–29.41), after adjusting for age (HR 1.10; 95% CI: 0.22–5.46;  $P=0.23$ ), but not for sex (all deceased patients were male). The causes of death in the six patients with EO CN lesions were visceral cancer (four patients), sepsis (one patient living with HIV infection), and acute cardiovascular event (one patient with Buerger's disease). Cancer was the only cause of death in two control patients who died. None of the deceased patients or controls had an organ transplant (exclusion criterion).

## Reference

1. Vázquez-López F; Gómez-Vila B; Gómez Castro C; Cadarso-Suárez C; Díaz-Louzao C; Galache C. Possible association of early - onset chondrodermatitis nodularis and risk of mortality. Results of a pilot retrospective case-control single-hospital study in Asturias, Northern Spain. Research Square 2022. DOI:10.21203/rs.3.rs-1496471/v1.