Lack of an association between generalized granuloma annulare and malignancy: A case-control study

To the Editor: Granuloma annulare is a benign inflammatory skin disorder presenting as annular grouped papules. The localized form (the most common) usually occurs on the back of the hands or feet. Generalized granuloma annulare (GGA; defined by the presence of ≥10 skin lesions or widespread annular plaques affecting the trunk or extremities)[1,2] is infrequent, occurs at a later age at onset, and has a more chronic and relapsing course. GGA has been linked to autoimmune thyroiditis, HIV infection, and lipid abnormalities.[1-3] Other conflicting associations reported are diabetes mellitus (recently rejected)[4] and malignancy, of which many cases have been published,[1,5] but this association has not been studied using a case-controlled method.

If GGA is associated with cancer, a high prevalence of neoplasms would be expected in these patients. Therefore, we designed a case-control analysis to review the medical records of 60 GGA patients (confirmed by histopathology) seen at our Department of Dermatology during the period 2000-2018. For every GGA patient, 5 age-matched and sex-matched control patients who attended the department for other reasons during the same period (totaling 300 controls), were randomly chosen for study inclusion. Immunosuppressed patients or patients with paraneoplastic disease were excluded from both groups. Diagnosis of the neoplasm (excluding nonmelanoma skin cancer) was annotated before or after the appearance of the GGA in the case group and before or after the moment of consultation in the control group. In total, 14 men and 46 women comprised the GGA group (average age 63.58 [range 25-95] years, standard deviation [SD] 13.91 years). The average follow-up time was 89.78 (range 10-216) months (SD 58.80 months) for GGA cases and 76.40 (range 6-186) months (SD 45.76 months) for controls.

A total of 6 of 60 (10%) GGA patients and 28 of 300 (9.33%) controls presented malignancy, a nonsignificant difference ($P = .87$, χ^2 test). The age and sex of cancer cases in the GGA group and control group were similar (Table I). The time interval from the diagnosis of GGA in cases or the consultation period in controls relative to the moment of diagnosis of the malignancy was similar ($P = .98$, t test; Table II).

To our knowledge, this is the first case-control study on the prevalence of malignancy in GGA. The results showed that the prevalence was virtually identical in patients with and without GGA, which excludes a correlation between GGA and cancer. Therefore, we consider that if any linkage exists it must be rare and would not justify the exhaustive performance of tests to detect an internal neoplasm. Of note, the average age of patients with GGA and cancer in this study was 74 years, supporting the opinion of some authors that the reported cases of malignancy-associated GGA could be explained simply by the fact that both GGA and cancer are more likely to occur at this advanced age.[4]

Limitations of this study include single-institution design, but the long follow-up period and high number of patients are strengths. In conclusion, our results do not support an association between GGA and malignancy.

Table I. Demographic data of patients with cancer in GGA and controls

Demographic	GGA patients	Control patients
Sex		
Male	3	14
Female	3	14
Total	6	28
Age, y	n = 6	n = 28
Mean (range)	74 (63-95)	73.82 (50-95)
Median (SD)	70 (12.63)	75.50 (13.78)

GGA, Generalized granuloma annulare; *SD*, standard deviation.

Table II. Organs affected by the neoplasm and time to malignancy in GGA and control groups

Cohort	Cancer type	Patients, n	Time interval, months*
GGA			
	Cervical	1	−144
	Colonic	1	72
	Gingival	1	12
	Breast	1	−72
	Prostate	2	3, 72
Control			
	Cervical	3	−132, 12, 60
	Colonic	4	−5, −1, 48, 48
	Gastric	1	12
	Lymphoma	2	−96, −24
	Breast	8	−120, −16, 12, 24, 24, 72, 96, 108
	Myeloma	1	−96
	Pancreatic	1	60
	Prostate	5	−96, −84, −72, 36, 48
	Urinary bladder	1	−132
	Uveal melanoma	1	−72
	Lung	1	−1

GGA, Generalized granuloma annulare.
*Time interval from diagnosis of GGA in cases or moment of consultation in controls to apparition of malignancy. Numbers are negative if before GGA diagnosis or consultation.

Vicente Haro Gabaldón, MD,[a] *and Victor Haro-González-Vico, MS*[b]

From the Department of Dermatology, Infanta Margarita Hospital, Cabra-Córdoba, Spain[a]*; and School of Medicine, Granada University, Granada, Spain*[b]

Funding sources: None.

Conflicts of interest: None disclosed.

Reprint requests: Vicente Haro Gabaldon, C/San Pedro, 21-4-bajo H 14900 Lucena, Cordoba, Spain

E-mail: vicentehar@yahoo.es

REFERENCES

1. Keimig EL. Granuloma annulare. *Dermatol Clin*. 2015 Jul;33(3):315-329.
2. Thornsberry LA, English JC III. Etiology, diagnosis, and therapeutic management of granuloma annulare: an update. *Am J Clin Dermatol*. 2013;14:279-290. PMID: 23696233.
3. Wu W, Robinson-Bostom L, Kokkotou E, Jung HY, Kroumpouzos G. Dyslipidemia in granuloma annulare: a case-control study. *Arch Dermatol*. 2012 Oct;148(10):1131-1136.
4. Nebesio CL, Lewis C, Chuang TY. Lack of an association between granuloma annulare and type 2 diabetes mellitus. *Br J Dermatol*. 2002;146:122-124.
5. Mestre T, Rodrigues AM, Cardoso J. Disseminated granuloma annulare and hepatocellular carcinoma association or coincidence? *BMJ Case Rep*. 2014;2014. PMID: 25352383.

https://doi.org/10.1016/j.jaad.2019.02.056