Granuloma Annulare in Women: Evaluating the Annular Configuration in the Context of Germline Repair

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Article information
Received: November 11th, 2018; Revised: December 9th, 2018; Accepted: December 17th, 2018; Published: December 18th, 2018

Cite this article
doi: 10.17140/WHOJ-4-127

INTRODUCTION

Granuloma annulare (GA) is characterized by the abrupt onset of annular plaques with central clearing in the skin.1 GA commonly occurs in the skin around joints in women in their later reproductive years.2,3 Diseases that occur more commonly in women have been associated with sex-related immune differences, non-hormonal factors on X and Y chromosomes, and pregnancy related changes in immune and metabolic function.4-8 Cell biologists have outlined the mechanisms of organelle movement during cell stress. Micrtubules and actin, which form the internal structure and lattice like transport system within the cell, are continually reorienting in response to cellular need. These needs may present internally, as a response to aneploidy, or externally, in response to an allergen or infectious agent.

The process of germ line duplication is dynamic, staged, and has distinct architecture and polarity during meiosis.9,14 The process is error prone and aneploidy is common. Aneuploidy increases with age, and is much less tolerated in women due to the additional maternal responsibilities for growth in the early embryo.15-17 Aneuploidy activates a pause mechanism that stops cell division to allow time for the microtubules to capture and correct the attachments between chromosomes and the central spindle.18,19 Correctly attached chromosomes confer stability and allow the development of a pulling force between the poles. The generation of force pulls the spindle apart and cell division is completed.20,21

The cytoskeletal elements required in germline duplication and division are also utilized in other cellular stress responses, such as formation of an immune synapse in response to infection or allergen or in epithelial migration for wound repair.22,23 Microtubules and actin filaments rapidly depolymerize and reorient near the cell wall closest to changing physiologic demands.24,26 It

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is possible that the stress provoked responses of the intracellular cytoskeleton may underlie what clinicians see in patients with granuloma annulare.

Medication intake was included for several reasons. Several drug classes, taxanes, colchicine, chloroquine, and others, specifically target structure/function relationships in the intracellular cytoskeleton for therapeutic use in cancer, gout and other conditions. Drug lists can also provide additional information on underlying health issues and access to care. Drug metabolism competes with cholesterol catabolism and the bile salt pathways that contain the nuclear receptors involved in steroidogenesis and protection of the endocrine system. Twenty three percent of patients in this study believed that a change in medication, whether an addition or removal, was related to the skin eruption (Figures 1 and 2).

**METHODS**

This retrospective case series was conducted out of a general dermatology clinic in the Midwest. The study was reviewed by the Institutional Review Board of the University of Missouri-Kansas City and documented assent was obtained. Forty eight female patients with GA were compared to an age matched control group of women without granuloma annulare. The data collection included age, gender, body mass index (BMI), Fitzpatrick photo typing, laterality and drug lists. The drug categories measured were oral contraceptives, hormone replacement therapy (HRT), statins, proton pump inhibitors (PPI), anti-hypertensives and antidepressants. Fitzpatrick photo typing was included as a potential biomarker of genetic variation in aromatase.

**STATISTICAL ANALYSIS**

The results were analyzed with SPSS software, Chicago, USA. Means and standard deviations were calculated for continuous parameters. Unpaired t-tests and analysis of variance were used to compare quantitative variables. Fisher’s Exact Test was utilized to assess statistical significance and a p<0.05 was considered to be statistically significant.

**RESULTS**

Forty eight female patients were identified. 22/48 (46%) noted the onset of disease between ages 40-70 years. Within this older group of women aged 40-70 years, 15/22 (65%) had a BMI>25 versus 35% of the control group (p-value=0.020).

Eleven (23%) of the female GA patients believed that a drug change precipitated the skin eruption. Comparison of drug utilization between cases and controls revealed that statins, proton pump inhibitors and serotonin reuptake inhibitors were seen more commonly among the patients over controls but the differences were not statistically significant. HRT was seen more commonly in the control group. In the group with recorded Fitzpatrick photo typing, 44/46 (96%) had a Fitzpatrick score of 1-3 suggesting that women of Northern European ancestry may be more vulnerable (Tables 1 and 2).
DISCUSSION

Our results are consistent with other studies that show that granuloma annulare (GA) occurs more commonly in females in their mid to later reproductive years. In this study, patients with GA were heavier and on more medications than those without the disease. Eleven of the patients thought a drug change caused GA. This number may be low, as some patients were seen long after the onset of GA and could not remember the sequence of events. The use of statins, proton pump inhibitors and serotonin reuptake inhibitors were seen more commonly among the cases but the differences were not statistically significant. HRT was seen more commonly among the cases but the differences were not statistically significant. HRT was seen more commonly among the cases but the differences were not statistically significant. The authors have received written informed consent from the patient.

CONCLUSION

We conclude that the key features of granuloma annulare (female predominance, annular morphology with central clearing, and abrupt onset in the later reproductive years) may be related to events in the cell cycle that change with age and can be altered by medications. Granuloma annulare could be an in vivo model for disruption of microtubule movement required for a variety of cellular needs, such as aneuploidy, immune surveillance and wound repair. The initial evaluation of patients presenting with granuloma annulare should include a complete drug and supplement history. In addition, the evaluation of female patients presenting with GA should include specifics about their reproductive history and metabolic response to pregnancy. The information from this study could expand our understanding of a common skin disease that occurs more frequently in women.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES


