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

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**ABSTRACT**

Granuloma annulare (GA) can be seen in both genders and all age groups, but is most commonly seen in women between the ages of 30-60 years. GA has a striking geometric presentation, with near perfect circles and ovals, a central clear zone and a pinwheel configured peripheral rim. We designed a retrospective case series comparing biometric and pharmaceutical data in middle aged women with and without GA to ascertain correlates of the disease. Women with GA were heavier and took more drugs. 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. Hormone Replacement Therapy (HRT) was seen more commonly in the control group. We propose that the key features of granuloma annulare (female predominance, annular morphology with central clearing, and abrupt onset in the later reproductive years) may relate to events in the fertility cycle that change with age and could be altered by medications.

**Keywords**
Granuloma annulare; Microtubules; Aneuploidy; Polypharmacy.

**Keypoints**
- Granuloma annulare has a striking architectural presentation and occurs more commonly in women in their later reproductive years.
- Diseases that occur more commonly in women have been associated with physiologic changes across the fertility cycle.
- Granuloma annulare may be a cutaneous manifestation of a stressed response to adaptive changes in cell physiology.

## 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. Microtubules 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 aneuploidy, 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 aneuploidy 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

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.[27] 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).

**Figure 1.** *Mitotic Spindle in a Human Cell; Microtubules in Green, Chromosomes in Blue and Kinetochores in Pink (Wikipedia). Microtubule Orienting Centers, Pictured at Opposite Poles, can Rapidly Re-orient to Establish Immune Platforms Near the Edge of the Cell*

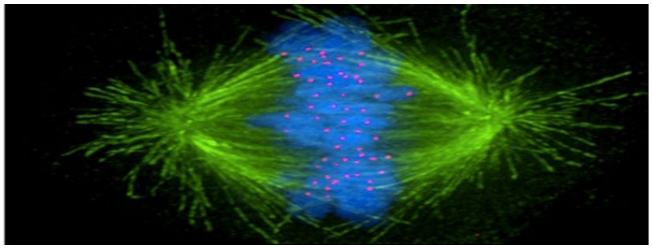
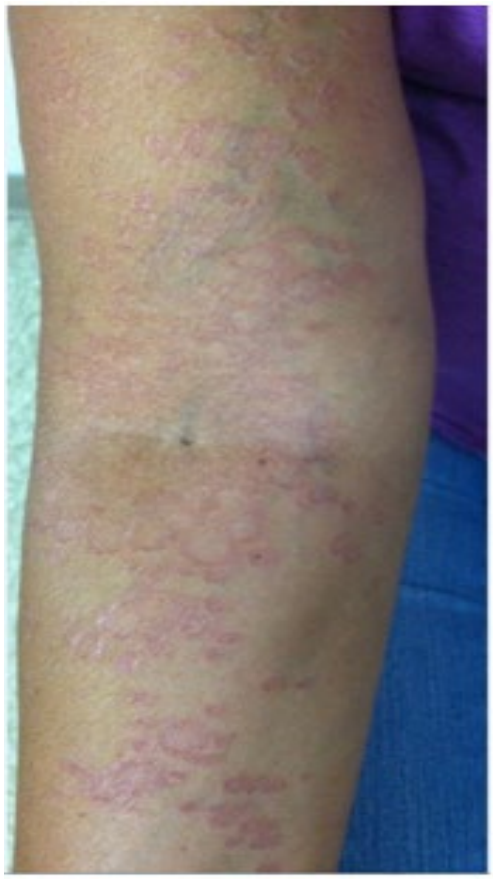


**Figure 2.** *Granuloma Annulare on the Ventral Forearms of a 56-Year-Old Female*



## 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).

**Table 1.** *Incidence of Granuloma Annulare Along the Growth and Development Continuum*

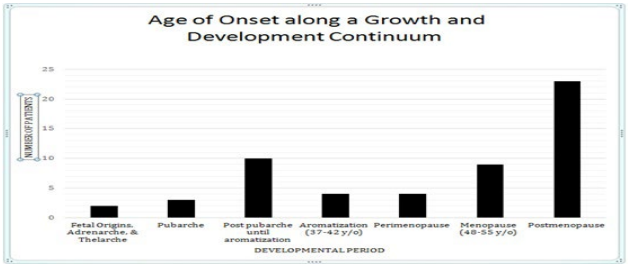


**Table 2.** *Comparison of Drug and Biometric Data*

| | Study population | | Control Group | |
|---|---|---|---|---|
| | Females, Age 40-70 years | | Females, Age 40-70 years | |
| | # of pts | % | # of pts | % |
| BMI>25 | 15/23 | 65% | 35/93 | 38% |
| Lateralidty>50% difference | 15/24 | 62% | N/A | N/A |
| Statins | 6/24 | 25% | 24/93 | 26% |
| PPIs | 4/24 | 17% | 10/93 | 11% |
| HRT or OCP | 4/24 | 17% | 28/93 | 30% |
| Beta blockers | 3/24 | 13% | 12/93 | 13% |
| Ca channer blockers | 2/24 | 8% | 7/93 | 8% |
| Diuretics | 3/24 | 13% | 6/93 | 7% |
| Angiotensin II receptor blockers | 2/24 | 8% | 4/93 | 4% |
| ACE inhibitors | 2/24 | 8% | 8/93 | 9% |
| Anti-anxiety/antidepressants | 7/24 | 29% | 19/93 | 20% |

BMI=body mass index. PPIs=proton pump inhibitors. HRT=hormone replacement therapy. OCPs=oral contraceptive pills. BBs=beta blockers. CCBs=calcium channel blockers. ARBS=angiotensin II receptor blockers. ACEIs=angiotensin-converting-enzyme inhibitors.

## 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 in the control group. Drugs may affect the presentation of GA by different mechanisms. Drug metabolism competes with the nuclear receptors utilzed in cholesterol catabolism.[28] The competition between drug and cholesterol catabolism may be further complicated due to common drug classes that are specifically targeting this important pathway for glucose and metabolic reasons.[29-31] Fitzpatrick phototyping, a clinical rating of pigment level in the skin, was included as a potential marker of vitamin D metabolism and genetic variance in aromatase. In this study, GA was primarily seen in women with Fitzpatrick 1-3 phototypes, suggesting a genotypic vulnerability in women of northern European ancestry.

## 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.

## INSTITUTIONAL REVIEW BOARD

The above referenced study was reviewed and determined to be exempt from IRB review and approval in accordance with the Federal Regulations 45 CFR Part 46.101(b).

This study was classified as exempt in accordance with exemption criteria #4 in the Federal Guidelines 45 CFR Part 46 as follows: "Research involving the collection or study of existing data, documents, records, pathological specimens or diagnostic specimens, if these sources are publicly available or if the information is recorded by the Investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to subjects."

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

## CONSENT

The authors have received written informed consent from the patient.

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