Grover Disease (Transient Acantholytic Dermatosis) Induced by Anastrozole

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We present the case of a 79-year-old woman with a history of breast cancer who developed Grover disease (transient acantholytic dermatosis) following initiation of an aromatase inhibitor, anastrozole, as adjunctive treatment of her breast cancer. A number of drugs have been associated with this condition; however, to our knowledge, this case is the first report of anastrozole-induced Grover disease.

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Grover disease (transient acantholytic dermatosis) is a pruritic papulovesicular eruption of the trunk and proximal limbs typically seen in white men during the fifth decade of life. The pathogenesis of the disease is unknown, but solar damage, heat, and sweating are commonly associated with this entity.[1] Other conditions associated with Grover disease include any febrile illness; immunodeficiency; and malignancy, especially leukemia and lymphoma.[2] A number of pharmaceutical agents have been implicated as possible triggers for the disease. We present here a case of anastrozole-induced Grover disease in an elderly woman being treated for breast cancer.

Case Report

A 79-year-old white woman with a medical history of breast cancer presented to the Saint Louis University Department of Dermatology with an extremely pruritic rash involving her trunk and proximal extremities of 9 months' duration. She had been treating her rash with a moisturizer and steroid ointment twice daily prior to evaluation with no improvement. Physical examination revealed pink, somewhat scaly papules on the trunk, arms, and thighs. The clinical differential diagnosis included drug hypersensitivity, Grover disease, and pemphigus foliaceus.

Punch biopsies were performed for routine histology and direct immunofluorescence. Pathology demonstrated acantholysis and dyskeratosis of keratinocytes as well as a superficial perivascular inflammatory infiltrate with scattered eosinophils (Figure); these findings were consistent with Grover disease.

On further questioning of the patient, it was discovered that her rash began following the initiation of anastrozole therapy for breast cancer. The patient had been taking triamterene prior to the initiation of anastrozole and had not experienced a rash or any other skin reaction on triamterene alone. After discussion with the patient's primary care physician and oncologist, anastrozole was discontinued. The patient's triamterene also was discontinued because it is a more common cause of drug reactions; however, to our knowledge, Grover disease has never been reported in association with triamterene. Within 3 weeks of discontinuing anastrozole, the patient's pruritus had substantially improved. She returned to the clinic 3 months after her initial presentation with only a few residual scaly papules on the trunk and proximal extremities. Based on the timeline between commencement of anastrozole and the eruption as well as resolution on discontinuation, it was presumed that anastrozole was the inciting agent; however, an interaction between anastrozole and triamterene cannot be entirely excluded. Unfortunately, the patient died shortly after this appointment making further follow-up impossible.

Comment

The pathogenesis of Grover disease is poorly understood; however, it has been postulated that occlusion of damaged eccrine intraepidermal ducts is the underlying cause.[3] Grover disease has been observed in association with various conditions including UV radiation,[4,5] heat and excessive sweating,[6,7]

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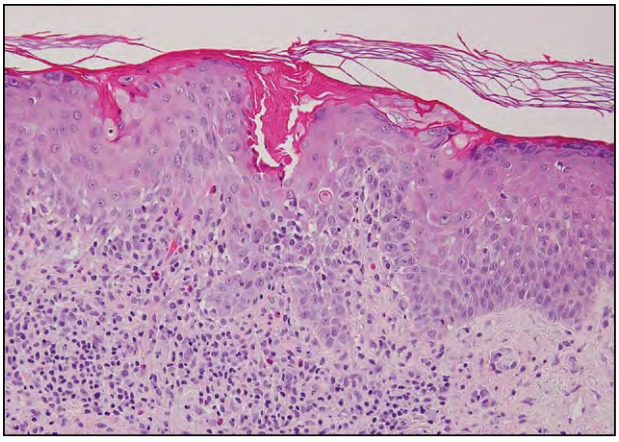

Focal keratinocyte acantholysis and dyskeratosis with an associated perivascular inflammatory infiltrate with scattered eosinophils in the superficial dermis (H&E, original magnification ×100).

drugs,[8-13] infection,[13] and malignancy.[14-17] In this case of Grover disease, anastrozole was identified as the most likely trigger.

Anastrozole is an aromatase inhibitor used to treat postmenopausal women with hormone receptor–positive early breast cancer. The inhibition of estrogen biosynthesis starves estrogen receptor–positive tumor cells and restricts their growth.[18,19] In this case, the patient's symptoms of Grover disease coincided with the initiation of anastrozole treatment and the resolution of her symptoms closely followed discontinuation of this drug. A review of the medical literature was performed to look for an established correlation between anastrozole and adverse skin reactions. Plourde et al[19] evaluated the efficacy and safety of anastrozole in the treatment of gynecomastia in 82 boys aged 11 to 18 years. Rash was reported in 9.3% of patients treated with anastrozole, while no patients in the placebo group reported rash.[19] Osborne et al[20] evaluated the safety and efficacy of anastrozole versus fulvestrant in 400 postmenopausal women with locally advanced or metastatic breast cancer. The incidence of rash was 15% (29/193) for patients treated with anastrozole and 11% (23/204) in the fulvestrant treatment group.[20] Boccardo et al[21] compared treatment with tamoxifen citrate, anastrozole, or placebo for the prevention of gynecomastia and breast pain in men with localized, locally advanced, or recurrent prostate cancer receiving bicalutamide daily. The incidence of rash was 5.5% (2/36) in the anastrozole treatment group, 2.5% (1/40) in the placebo group, and 0% (0/37) in the tamoxifen treatment group.[21] Further characterization of the rashes in each of these studies was not provided. One case report was found describing anastrozole-induced subacute cutaneous lupus erythematosus in an elderly woman[23]; however, no reports of anastrozole-induced Grover disease were found from a PubMed search of articles indexed for MEDLINE using the terms *anastrozole*, *arimidex*, *Grover's disease*, *Grover disease*, *transient acantholytic dermatosis*, *rash*, and *eruption*. Interestingly, a laboratory study in which newborn rats were treated with subcutaneous anastrozole found increased keratinization, stippling, hypertrophic epidermal cells, disorganization of epidermal cells, and most importantly acantholysis on histopathologic analysis of the rats' skin.[23] The results of these studies seem to further implicate anastrozole as the likely causal factor of Grover disease in our patient.

A number of drugs have been reported as possible triggers of Grover disease including penicillamine, ribavirin, 2-chlorodeoxyadenosine, cetuximab, and IL-4.[8-13] Our patient was not being treated with medications associated with induction of Grover disease. An increased incidence of Grover disease also has been observed in cancer patients. Although malignancy has been associated with Grover disease, it is most commonly seen with hematogenous malignancies and rarely is induced by solid tumors.[2,14-17] One case of breast cancer–induced Grover disease has been reported in the medical literature.[24]

Conclusion

We report a case of anastrozole-induced Grover disease. Although it is possible that triamterene played a role in this patient's disease, it is more likely that anastrozole was the inciting agent. The timeline of administration of anastrozole and the appearance of cutaneous lesions as well as the remission of symptoms on discontinuation of the drug supports the conclusion that this patient's disease was induced by anastrozole.

REFERENCES

1. Freedburg I. *Fitzpatrick's Dermatology in General Medicine*. 5th ed. The McGraw Hill Companies; 2005. http://www.accessmedicine.com. Accessed Novmber 18, 2008.
2. Quirk CJ, Heenan PJ. Grover's disease: 34 years on. *Australas J Dermatol*. 2004;45:83-86.
3. Antley CM, Carrington PR, Mrak RE, et al. Grover's disease (transient acantholytic dermatosis): relationship of acanthosis to acrosyringia. *J Cutan Pathol*. 1998;25:545-549.
4. Grover RW. Transient acantholytic dermatosis. *Arch Dermatol*. 1970;101:426-434.
5. Chalet M, Grover R, Ackerman AB. Transient acantholytic dermatosis: a reevaluation. *Arch Dermatol*. 1977;113:431-435.
6. Hu CH, Michel B, Farber EM. Transient acantholytic dermatosis (Grover's disease). a skin disorder related to heat and sweating. *Arch Dermatol*. 1985;121:1439-1441.

7. Hu CH. Sweat related dermatoses: old concept and new scenario. *Dermatologica*. 1991;182:73-76.
8. Mahler SJ, De Villez RL, Pulitzer DR. Transient acantholytic dermatosis induced by recombinanant human interleukin 4. *J Am Acad Dermatol*. 1993;29(2, pt 1):206-209.
9. Cohen PR, Kurzrock R. 2-chlorodeoxyadenosine–associated transient acantholytic dermatosis in hairy cell leukemia patients. *Am J Dermatopathol*. 1999;21:106-108.
10. Zvulunov A, Grunwald MH, Avinoach I, et al. Transient acantholytic dermatosis (Grover's disease) in a patient with progressive systemic sclerosis treated with D-penicillamine. *Int J Dermatol*. 1997;36:476-477.
11. Villalon G, Martin JM, Monteagudo C, et al. Clinicopathological spectrum of chemotherapy induced Grover's disease. *J Eur Acad Dermatol Venereol*. 2007;21:1145-1147.
12. Tscharner GG, Bühler S, Borner M, et al. Grover's disease induced by cetuximab. *Dermatology*. 2006;213:37-39.
13. Antunes I, Azevedo F, Mesquita-Guimarães J, et al. Grover's disease secondary to ribavirin. *Br J Dermatol*. 2000;142:1257-1258.
14. Guana AL, Cohen PR. Transient acantholytic dermatosis in oncology patients. *J Clin Oncol*. 1994;12:1703-1709.
15. Horn TD, Groleau GE. Transient acantholytic dermatosis in immunocompromised febrile patients with cancer. *Arch Dermatol*. 1987;123:238-240.
16. De Argila D, Ortiz-Frutos J, Vanaclocha F. Transient acantholytic dermatosis (Grover's disease) in a patient with gastric carcinoma. *Acta Derm Venereol*. 1997;77:245-246.
17. Miralles ES, Núñez M, Ledo A. Transient acantholytic dermatosis associated with superior vena cava syndrome in a patient with carcinoid tumor of the thymus. *Acta Derm Venereol*. 1995;75:410.
18. Chabner BA, Amrein PC, Druker BJ, et al. Antineoplastic agents. In: Brunton L, Lazo J, Parker K, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. The McGraw Hill Companies; 2005. http://www.accessmedicine.com/content.aspx?aID=957513. Accessed November 18, 2008.
19. Plourde PV, Reiter EO, Jou HC, et al. Safety and efficacy of anastrozole for the treatment of pubertal gynecomastia: a randomized, double-blinded, placebo-controlled trial. *J Clin Endocrinol Metab*. 2004;89:4428-4433.
20. Osborne CK, Pippen J, Jones SE, et al. Double-blinded, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of North American trial. *J Clin Oncol*. 2002;20:3386-3395.
21. Boccardo F, Rubagotti A, Battaglia M, et al. Evaluation of tamoxifen and anastrozole in the prevention of gynecomastia and breast pain induced by bicalutamide monotherapy of prostate cancer. *J Clin Oncol*. 2005;23:808-815.
22. Transcart M, Cavailhes A, Balme B, et al. Anastrozole-induced subacute cutaneous lupus erythematosus [published online ahead of print December 6, 2007]. *Br J Dermatol*. 2008;158:628-629.
23. Akcali C, Inaloz S, Karakok M, et al. The effects of anastrozole on neonatal rat skin. *Eur J Gynaecol Oncol*. 2007;28:534-536.
24. Manteaux AM, Rapini RP. Transient acantholytic dermatosis in patients with cancer. *Cutis*. 1990;46:488-490.