

Follicular mucinosis and mycosis-fungoides-like drug eruption due to leuprolide acetate: a case report and review

Leuprolide acetate represents a gonadotropin-releasing hormone agonist, used as part of the treatment of prostate cancer. We report an unusual case of disseminated urticarial rash following leuprolide injection in a 67-year-old man that histopathologically and immunohistochemically resembled mycosis-fungoides, including the presence of follicular mucinosis and eosinophils in the follicles. This histopathologic pattern has not been previously described as a drug reaction pattern due to leuprolide, and it underscores the importance of correlation with the clinical impression to arrive at a correct diagnosis.

Keywords: atypical lymphocytic proliferation, drug reaction, follicular mucinosis, leuprolide

Shalin SC, Brantley J, Diwan AH. Follicular mucinosis and mycosis-fungoides-like drug eruption due to leuprolide acetate: a case report and review.

J Cutan Pathol 2012. © 2012 John Wiley & Sons A/S.

Sara C. Shalin¹, Julie Brantley² and A. Hafeez Diwan¹

¹Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX, USA and

²Dermatology Associates of Sugarland, Sugarland, TX, USA

Hafeez Diwan, MD, PhD
Department of Pathology and Immunology
Baylor College of Medicine
One Baylor Plaza
Houston, TX 77030, USA
Tel: +1 713 798 3497
Fax: +1 713 798 5838
e-mail: ahdiwan@bcm.edu

Accepted for publication June 16, 2012

Cutaneous eruptions due to therapeutic drug administration may have widespread histopathologic manifestations, and may potentially lead to pitfalls in diagnosis if clinical correlation is not applied. Leuprolide acetate, a gonadotropin-releasing hormone agonist, is used in the treatment of hormone responsive cancers such as prostate cancer, as well as gynecologic disorders such as endometriosis or in vitro fertilization. Cutaneous drug reactions following leuprolide acetate have not been widely reported and includes case reports of drug injection site granulomas, systemic allergic dermatitis, papuloerythroderma and dermatitis herpetiformis. Here, we report a case of follicular mucinosis with intra-follicular eosinophils, mimicking mycosis fungoides, following leuprolide administration.

Case report

A 67-year-old man was referred to a dermatology clinic for a widespread disseminated rash. He had

been diagnosed with prostate cancer approximately 3 months prior to the presentation and had been treated with radiation and two injections of leuprolide acetate (Lupron®). After the first injection, the patient developed a disseminated rash which he attributed to poison oak. The rash resolved but recurred more severely upon receiving the second leuprolide injection, approximately 9 weeks after the first. At this point, he was referred to the dermatology clinic where physical examination revealed erythematous and coalescing urticarial plaques involving the trunk, back, face, scalp and extremities (Fig. 1). There were no targetoid or pustular lesions seen, and mucosal involvement was not identified. The clinical impression was that of urticaria and drug reaction to leuprolide.

Histopathologically, two biopsies showed interface damage with intra-follicular eosinophils (Fig. 2A and B), as well as follicular mucinosis (Fig. 3), with atypical intraepidermal lymphocytes (Fig. 2C and D).

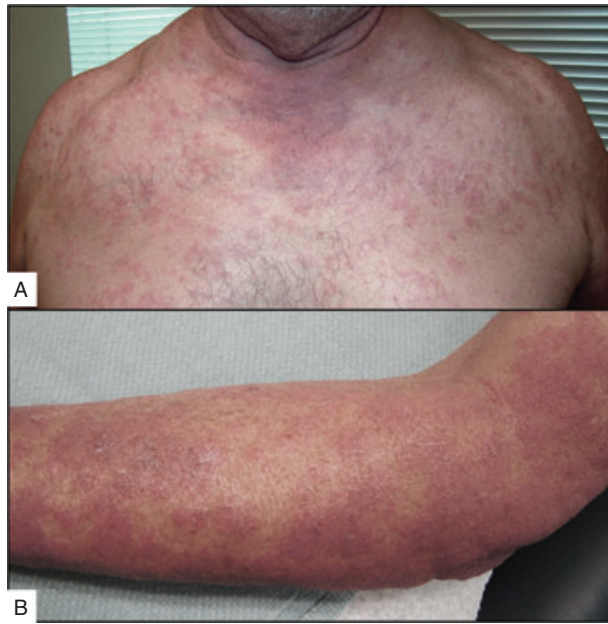


Fig. 1. Following each of two injections of leuprolide acetate for the treatment of prostate cancer, the patient developed erythematous, urticarial plaques all over his body (A and B). The rash involved the trunk, back, face, scalp and extremities. There were no targetoid or pustular lesions seen.

Follicular mucin was highlighted with an alcian blue stain (not depicted). By immunohistochemistry, the atypical lymphocytes showed cluster of differentiation 4 (CD4) predominance over CD8 and focal loss of CD7, mimicking mycosis fungoides (not depicted). Despite the unusual histopathology, the findings were felt to be consistent with the clinical impression of drug reaction.

The patient was treated with cessation of the drug and treatment with corticosteroids (oral and topical). Following the treatment, eruption subsided and showed marked improvement, which further supported the notion that the findings represented a drug reaction.

Discussion

Leuprolide acetate is rarely a reported cause of cutaneous drug eruption. The most common adverse dermatologic manifestation due to leuprolide consists of subcutaneous granulomas at the site of drug injection.¹⁻⁴ Histopathologically, sarcoidal-type granulomas have been noted with multinucleated giant cells containing lipid-like droplets.^{2,4} While initial speculation was that the granulomas were formed because of a reaction to the polymer used as a vehicle for the drug, other reports have suggested a reaction to the drug itself or to the method of injection (intramuscular vs. subcutaneous) as the cause.^{2,4} Clinical familiarity

with this potential side effect is important for two reasons: the granuloma reaction may interfere with subsequent drug absorption and distribution,¹ and the subcutaneous nodules may clinically mimic metastatic disease.⁴

Disseminated cutaneous adverse reactions to leuprolide have been rarely reported. Dermatitis herpetiformis occurring following administration of leuprolide has been reported twice;^{5,6} however, these cases may represent induction of a secondary autoimmune disorder with dermatologic manifestations because of the hormonal manipulation rather than a peculiar drug reaction pattern. Leukocytoclastic vasculitis induced by leuprolide acetate has also been reported.⁷ Systemic allergic dermatitis was reported in one patient and subsequently determined to be because of the hypersensitivity to the solvent in which the leuprolide was dissolved.⁸

A single case of a disseminated eruption because of the leuprolide has been reported, but it differs from our present case in several aspects. In the case reported by Sugita and colleagues, the rash developed gradually over a period of 2 months and first appeared after 5 years of continued treatment with the drug.⁹ The clinical appearance was that of coalescing papules resembling papuloerythroderma, and microscopic examination showed superficial dermal perivascular lymphocytic inflammation with eosinophils.⁹ In our case, the rash was urticarial, and it appeared rapidly upon exposure to the drug. The histopathologic pattern was also different, showing atypical lymphocytes and follicular mucin, raising the question of mycosis fungoides.

Follicular mucinosis has been reported after treatment with imatinib,¹⁰ and dermal mucin and follicular lymphocytic inflammation has been reported occurring at the site of interferon injection.¹¹ In one case, folliculotropic mycosis fungoides was observed in a patient receiving methotrexate therapy for psoriasis.¹² In this particular case, Di Lernia et al. hypothesized that the immunosuppressive effects of methotrexate predisposed the patient to a lymphoproliferative malignancy.¹²

The association of eosinophilic folliculitis with follicular mucinosis has been described.^{13,14} Distinguishing mycosis fungoides-associated follicular mucinosis from non-lymphoma follicular mucinosis may be difficult, and some authors argue that it may not be possible to do so on histopathologic grounds.¹⁵ Mycosis fungoides-associated follicular mucinosis may have a deceptively bland population of intra-follicular lymphocytes.¹⁶ However, it has been suggested that mycosis fungoides-associated follicular mucinosis may have fewer eosinophils.¹⁷

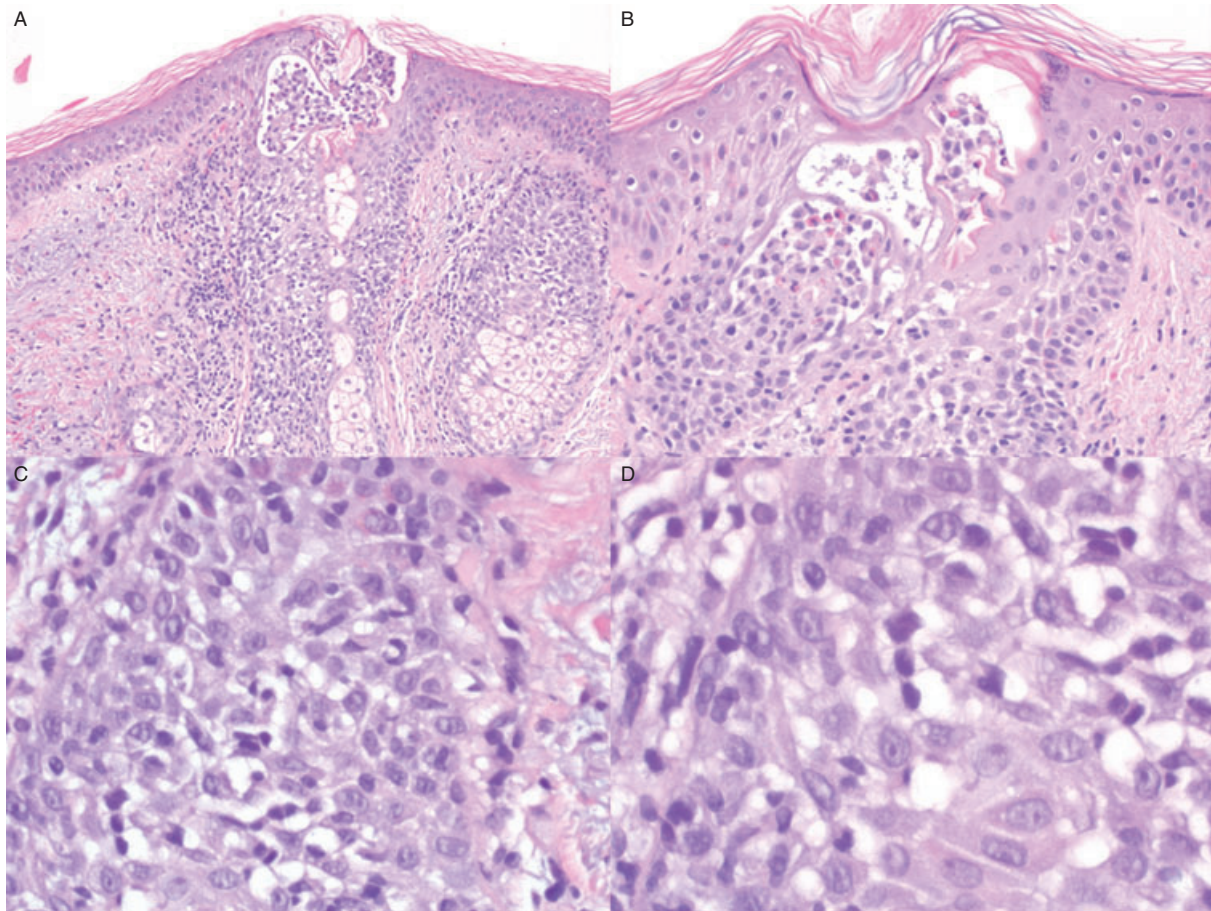


Fig. 2. Panels (A) shows intrafollicular lymphocytes (100 $\times$) and (B) highlights a pocket of eosinophils in the upper portion of the follicle (200 $\times$). Panels (C) 400 $\times$ and (D) 600 $\times$ show atypical intrafollicular lymphocytes.

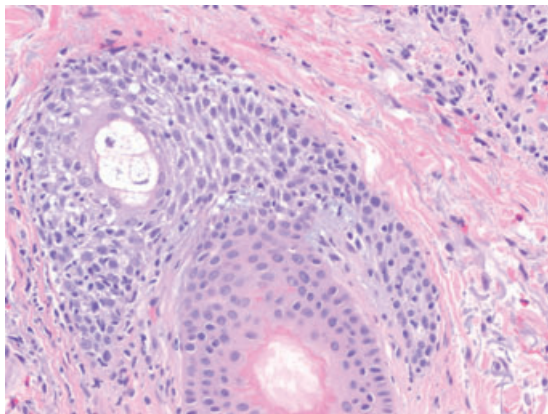


Fig. 3. Follicle with increased bluish mucin. The surrounding dermis shows scattered eosinophils and grayish elastosis.

In summary, the present case represents, to our knowledge, the first described disseminated eruption with follicular mucinosis and mycosis-fungoides-like reaction pattern following leuprolide acetate administration. Folliculotropic mycosis fungoides is an aggressive variant of cutaneous T-cell lymphoma,¹⁸ and treatment for it would follow a vastly different course than for a drug reaction. Resolution of our patient's rash following corticosteroid treatment and cessation of the drug argues against folliculotropic mycosis fungoides as a diagnosis, and supports the initial clinical impression of a drug eruption. This case highlights the importance of consideration of the clinical context in arriving at an accurate diagnosis.

References

1. Dangle P, Palit V, Sundaram SK, Weston P. Noninfective cutaneous granuloma with leuprolerin acetate-reality or myth. *Urology* 2007; 69: 779.e5.
2. Sakamoto R, Higashi Y, Mera K, Kanekura T, Kanzaki T. Granulomas induced by subcutaneous injection of leuprolerin acetate. *J Dermatol* 2006; 33: 43.
3. Shiota M, Tokuda N, Kanou T, Yamasaki H. Injection-site granulomas resulting from the administration of both leuprolerin acetate and goserelin acetate for the treatment of prostatic cancer. *J Nippon Med Sch* 2007; 74: 306.
4. Yasukawa K, Sawamura D, Sugawara H, Kato N. Leuprolerin acetate granulomas: case reports and review of the literature. *Br J Dermatol* 2005; 152: 1045.
5. Grimwood RE, Guevara A. Leuprolide acetate-induced dermatitis herpetiformis. *Cutis* 2005; 75: 49.

6. Yu SS, Connolly MK, Berger TG, McCalmont TH. Dermatitis herpetiformis associated with administration of a gonadotropin-releasing hormone analog. *J Am Acad Dermatol* 2006; 54(Suppl. 2): S58.
7. Turk BG, Dereli T, Dereli D, Akalin T. Leuprolide acetate-induced leukocytoclastic vasculitis. *Acta Obstet Gynecol Scand* 2007; 86: 892.
8. Ruiz-Hornillos J, Henriquez-Santana A, Moreno-Fernandez A, Gonzalez IG, Sanchez SR. Systemic allergic dermatitis caused by the solvent of Eligard. *Contact Dermatitis* 2009; 61: 355.
9. Sugita K, Kabashima K, Tokura Y. Disseminated maculopapular eruption caused by leuprorelin acetate. *Eur J Dermatol* 2008; 18: 603.
10. Scheinfeld N. Imatinib mesylate and dermatology part 2: a review of the cutaneous side effects of imatinib mesylate. *J Drugs Dermatol* 2006; 5: 228.
11. Arrue I, Saiz A, Ortiz-Romero PL, Rodriguez-Peralto JL. Lupus-like reaction to interferon at the injection site: report of five cases. *J Cutan Pathol* 2007; 34(Suppl. 1): 18.
12. Di Lernia V, Ricci C, Grenzi L, Froio E, Piana S. Folliculotropic mycosis fungoides in a psoriatic patient under methotrexate treatment. *J Dtsch Dermatol Ges* 2009; 7: 1068.
13. Buezo GF, Fraga J, Abajo P, Rios L, Daudén E, Garcia-Diez A. HIV-associated eosinophilic folliculitis and follicular mucinosis. *Dermatology* 1998; 197: 178.
14. Lee JY, Tsai YM, Sheu HM. Ofuji's disease with follicular mucinosis and its differential diagnosis from alopecia mucinosa. *J Cutan Pathol* 2003; 30: 307.
15. Cerroni L, Fink-Puches R, Bäck B, Kerl H. Follicular mucinosis. A critical reappraisal of clinicopathologic features and association with mycosis fungoides and Sézary syndrome. *Arch Dermatol* 2002; 138: 182.
16. Guitart J. Alopecia mucinosa is mycosis fungoides [book review]. *Am J Dermatopathol* 2006; 28: 72.
17. Nickoloff BJ, Wood C. Benign idiopathic versus mycosis-fungoides-associated follicular mucinosis. *Pediatr Dermatol* 1985; 2: 201.
18. Gerami P, Rosen S, Kuzel T, Boone SL, Guitart J. Folliculotropic mycosis fungoides: an aggressive variant of cutaneous T-cell lymphoma. *Arch Dermatol* 2008; 144: 738.