Unique urticarial presentation of minocycline-induced lupus erythematosus

Ashley K Clark[1], Vivian Y Shi[2] MD, Raja K Sivamani[3],[4] MD MS CAT

Affiliations: [1]School of Medicine, University of California, Davis, Sacramento, CA USA, [2]Department of Medicine, Division of Dermatology, University of Arizona, Tucson, USA, [3]Department of Dermatology, University of California, Davis, Sacramento, CA USA, [4]Department of Biological Sciences, California State Univeristy, Sacramento, CA USA

Corresponding Author: Raja Sivamani, MD MS CAT, Department of Dermatology, University of California, Davis, 3301 C Street, Suite 1400, Sacramento, CA 95816, Tel: 916-703-5145, Fax: 916-734-7183, Email: raja.sivamani.md@gmail.com

Abstract

We present a 17-year-old boy who developed a generalized urticarial eruption, malar rash, fever, and arthralgia within one week of initiating minocycline therapy for acne. His workup showed positive anti-nuclear and anti-histone antibodies. His symptoms quickly resolved after discontinuing minocycline and starting oral prednisone. We believe the constellation of his symptoms, laboratory findings, and temporal association of minocycline initiation was suggestive of minocycline-induced lupus. Unique to this case is that his urticarial presentation was so striking that it could have been initially regarded as drug induced urticaria without considering drug-induced lupus. Since minocycline is so widely prescribed for acne among the dermatology community, we believe that it is important for dermatologists to be aware of this alternative clinical presentation of minocycline-induced lupus.

Keywords: minocycline, drug induced lupus, urticaria, drug reaction, anti-histone, lupus

Introduction

Minocycline is an antibiotic widely prescribed for acne vulgaris [1, 2] associated with adverse reactions including drug-induced lupus erythematosus (DIL). There is no consensus on the diagnostic criteria; it should be suspected in patients without a history of lupus who develop antinuclear antibodies (ANAs) and who have at least one clinical feature of lupus erythematosus after drug treatment [3]. Patients with minocycline-induced lupus (MIL) typically present with fever and polyarthralgia, ANA positivity, and elevated erythrocyte sedimentation rate, but negative levels of antihistone antibodies (AHAs) and anti-native DNA antibodies [4, 5]. Our report highlights an unusual urticarial presentation of MIL with rapid resolution after oral prednisone. To the best of our knowledge there is only one case of DIL with an urticarial presentation. The purpose of this report is to increase recognition of a unique presentation of DIL following minocycline treatment.

Case Synopsis

The University of California, Davis Dermatology inpatient services consulted on a 17 year-old boy with a history of acne vulgaris hospitalized for an extensive pruritic rash accompanied by fever to 38.4°C, and symmetric arthralgia on the hands and knees for 2 days. Eight days prior, minocycline was prescribed for poorly controlled acne.

On examination, he had severe erythematous acne scars on the face with multiple pink papules and comedones. Ill-defined bilateral erythema was noted over the malar prominences sparing the nasal bridge. Multiple blanchable, pink, nonscaly, urticarial papules and plaques with polycyclic borders were present on the neck, chest, arms, and legs, most confluent on the trunk and proximal extremities (**Figure 1**). Individual lesions faded within 24 hours of appearance. However, the malar erythema persisted throughout his hospitalization. He received intramuscular triamcinolone 60mg one day prior to hospitalization.

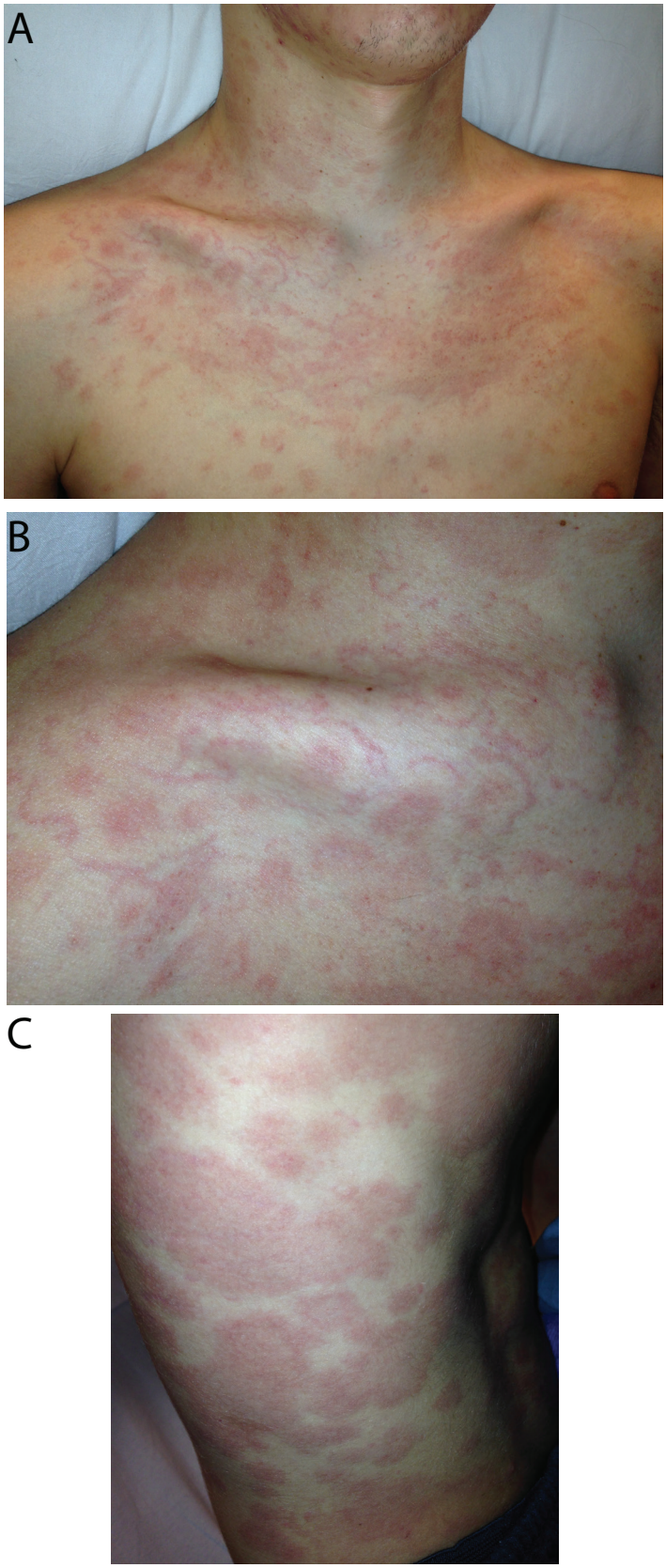

Figure 1. *Urticarial presentation of minocycline-induced lupus The patient presented with multiple blanchable, pink, nonscaly, urticarial papules and plaques with polycyclic borders that were present on the neck, chest, arms and legs. They were most confluent on the trunk and proximal extremities. A) Neck and upper chest, B) close up of clavicular area, C) flank.*

Complete blood count was significant for leukocytosis (20.2 K/mm3) with neutrophil predominance (18.40 K/mm3). In addition, slight CRP elevation (8 mg/L), positive anti-nuclear antibody (1:40, speckled pattern), and anti-histone antibody was present. Anti-dsDNA, -Smith, erythrocyte sedimentation rate (ESR), rheumatoid factor, and urinalysis were unremarkable.

A punch biopsy from the upper thigh revealed sparse perivascular and interstitial lymphocytic inflammatory infiltrate with dermal edema, eosinophils, and neutrophils. Hair follicles were spared and there was no evidence of vasculitis. Direct immunofluorescence showed no significant epidermal, junctional, or perivascular reactivity to albumin, IgA, IgM, IgG, C3, or fibrinogen. The patient was diagnosed with MIL with an atypical urticarial presentation. Minocycline was discontinued and the patient was treated with prednisone 60mg daily for 7 days and tapered over 4 weeks, along with oral antihistamines and topical corticosteroids. At one month, the patient was free of systemic and cutaneous symptoms.

Case Discussion

MIL is well established in the literature since the first case in 1992 [6]. The reaction occurs mostly in patients with a median age of 21 years and ≥80% are women [2]. The risk of developing lupus erythematosus during minocycline treatment was 8.5-fold higher than in the absence of treatment [7]. Other tetracycline-class drugs have not been strongly associated with DIL [8].

The most frequent clinical signs of DIL are arthralgia, myalgia, fever, malaise, anorexia, and weight loss. Cutaneous manifestations are uncommon in DIL related to minocycline (7-12%), [2, 7]. Compared to SLE, photosensitivity, purpura, and erythema nodosum are more frequent in DIL, whereas malar rash, alopecia, discoid lesions, and oral ulcers are rare [9]. Therefore, the urticarial manifestation and malar rash in our male patient further exemplifies the uniqueness of this case (**Table 1**).

Laboratory assessment of DIL includes an elevated ESR, which occurs in up to 80% of patients. C-reactive protein (CRP) is often normal, but is markedly increased in 89% of MIL patients [2]. Hematological

Table 1. *Urticarial Presentation of MIL Cases: Patient Characteristics, Laboratory Features and Clinical Findings at Initial Visit and Follow-up.*

Age/ sex	Time to onset	Symptoms	ANA	ESR	CRP	Anti-Sm anti-body	Anti-DNA anti-body	Anti-histone anti-body	Clinical outcome after discontinuation	Laboratory outcome after discontinuation	Author
17/M	6 days	Fever, arthralgia, urticaria	Pos. 1/40	3	5.29	Neg.	Neg.	Pos.	1 month	N/A	Present Case
15/F	1 year	Arthralgia, Myalgia, rash*	Pos. 1/80	8	NA	NA	Neg.	Pos.	2 months	Neg. ANA	Akin et al. [23]
17/F	6 weeks	Fever, fatigue, arthritis, hepatitis, myalgias, rash*	Neg.	38	NA	NA	Neg.	Pos.	4 months	Pos. 1/40	Akin et al. [23]
15/F	2 years	Fatigue, arhtirtis, alopecia, rash*	Pos. 1:640	38	NA	NA	Neg.	Pos.	2 months	Pos. 1:160	Akin et al. [23]

**Akin et al., one patient has a malar rash; one had an urticarial rash and one had a vasculitic rash, specifics details were not included in the paper. Table adapted from: Schlienger et al. [2].* N/A, not available. ESR in (mm/hr)

Table 2. *Characteristics of idiopathic, classical DIL, and MIL.*

Characteristics	Idiopathic SLE	Classic DIL	Minocycline DIL
Age of onset	Child-bearing age	Older	Younger population treated. No statistical interaction between age and minocycline use[8]
Female:Male	9:1	1:1	5:1*
Clinical course	Chronic, relapsing	Remits with drug cessation	Remits with drug cessation
Symptom severity	Mild to severe	Generally mild	Generally Mild
Fever	80%	40%	Common
Myalgia	80%	44-57%	Common
Arthalgia/arthritis	80%	18-63%	Most common
Major organ involvement	Common (renal and neurologic)	Rare (renal and neurologic)	Hepatic manifestations
Cutaneous involvement	54-70% (Malar, discoid rash, oral ulcers, photosensitivity)	<5-25% (photosensitivity, purpura)	Uncommon (Raynoud's, polyarteritis nodasa, erythema nodosum more frequently)
ANA	>99%	>99%	82.2% [23]
Anti-Histone Ab	Up to 50%	Up to 95%	Rare, (pANCA titers common 67%[24])
Anti-dsDNA ab	50-70%	<5%	Rare
Hypocomplementemia	51%	<1%	Uncommon

**Some studies report similar gender profile to classic DIL [8]*
Table adapted from Vedove et al., [9]

Table 3. *American College of Rheumatology Criteria for Classification of SLE (4 of 11 criteria) [24].*

Diagnostics Criteria	Definition	Patient
1. Malar rash	Fixed erythema, flat or raise, over the malar eminences, tending to spare the nasolabial folds	Present
2. Photosensitivity	Skin rash as a result of unusual reaction to sunlight	Absent
3. Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular scaling and follicular plugging; atrophic scarring may occur in older lesions	Absent
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a clinician	Absent
5. Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling or effusion	Present
6. Serositis	Pleuritis or pericarditis	Absent
7. Renal disorder	Persistent proteinuria or cellular casts	Absent
8. Neurologic disorder	Seizures or psychosis	Absent
9. Hematologic disorder	Hemolytic anemia with reticulocytosis or leukopenia, or lymphopenia, or thrombocytopenia	Absent
10. ANA	Abnormal titer	Present
11. Immunologic disorders	Anti-DNA, or Anti-Sm or antiphospholipid antibody	Absent

involvement, in particular leukopenia and cytopenia, is present in 5-25% of DIL cases [7]. In this case, the patient had an elevated CRP, consistent with most studies, and an unremarkable ESR. The paradoxical finding of leukocytosis may be a side effect of intramuscular triamcinolone given prior to hospitalization [10].

Similar to idiopathic SLE, DIL is characterized by the presence of antinuclear antibodies (ANA), suggested as a prerequisite for diagnosis. Anti-histone antibodies (AHAs) are classically associated with DIL [11] and have a specificity of 95% [12]. Anti-histone antibodies are detected in >90% of DIL patients, but only 32% of MIL [2]. Therefore, a positive AHA is strongly correlated with DIL. However, AHAs are present in several other autoimmune diseases, including SLE-unrelated to medications and juvenile rheumatoid arthritis [12]. In addition, urticaria was not reported in these cases outside of DIL (**Table 2**).

Chronic autoimmune urticaria (CAU) has been reported at the onset of SLE, especially in adults [13-15]. Spadoni et al. evaluated the prevalence of CAU in a large population of juvenile SLE patients and showed a rare frequency [16]. Additionally, a retrospective study of 39 children with SLE reported 3 patients with atypical presentations of SLE and urticaria [17]. The diagnosis of CAU requires the presence of daily symptoms lasting ≥ 6 weeks [16] and our patient's transient skin lesions excludes this diagnosis. Additionally, the constellation of his symptoms does not fit the diagnostic criteria for SLE (**Table 3**) since our patient only had 3 of the criteria with a malar rash, joint disease, and positive ANA [18].

Serum-sickness-like reactions present within 6 to 21 days after antigen administration. The four cardinal manifestations are fever, urticaria, lymphadenopathy, and joint symptoms. Diagnosis is based on clinical presentation, duration of illness, response to treatment, discontinuation of offending drug, normal to low complement concentrations, and absence of nephritis [19]. Serum-sickness-like reactions to minocycline are extremely rare and only a handful of cases have been reported [20]. ANAs are negative in serum-sickness-like reactions, which is inconsistent with our patient's presentation.

Urticaria must be differentiated from hypocomplementemic urticarial vasculitis in SLE patients. This manifestation generally has a fixed location, persists for longer than 24 hours, may be associated with burning sensation, and is rarely reported in children [16, 21]. Complement levels were not measured in this patient, but the classic histopathologic features of vasculitis were not present.

Conclusion

MIL can present with a unique urticarial manifestation. Recognizing the cutaneous manifestation in conjunction with systemic inflammatory symptoms may aid in early diagnosis and treatment.

References

1. Eady EA, Jones CE, Tipper JL, Cove JH, Cunliffe WJ, Layton AM. Antibiotic resistant propionibacteria in acne: need for policies to modify antibiotic usage. BMJ (Clinical research ed). 1993;306(6877):555-6. Epub 1993/02/27. [PMID: 8461769].
2. Schlienger RG, Bircher AJ, Meier CR. Minocycline-induced lupus. A systematic review. Dermatology (Basel, Switzerland). 2000;200(3):223-31. Epub 2000/06/01. [PMID: 10828631].
3. Yung RL, Richardson BC. Drug-induced lupus. Rheumatic diseases clinics of North America. 1994;20(1):61-86. Epub 1994/02/01. [PMID: 7512273].
4. Sturkenboom MC, Meier CR, Jick H, Stricker BH. Minocycline and lupuslike syndrome in acne patients. Archives of internal medicine. 1999;159(5):493-7. Epub 1999/03/13. [PMID: 10074958].
5. Elkayam O, Levartovsky D, Brautbar C, Yaron M, Burke M, Vardinon N, Caspi D. Clinical and immunological study of 7 patients with minocycline-induced autoimmune phenomena. The American journal of medicine. 1998;105(6):484-7. Epub 1998/12/31. [PMID: 9870833].
6. Byrne PA, Williams BD, Pritchard MH. Minocycline-related lupus. British journal of rheumatology. 1994;33(7):674-6. Epub 1994/07/01. [PMID: 8019798].
7. Borchers AT, Keen CL, Gershwin ME. Drug-induced lupus. Annals of the New York Academy of Sciences. 2007;1108:166-82. Epub 2007/09/26. [PMID: 17893983].
8. Margolis DJ, Hoffstad O, Bilker W. Association or lack of association between tetracycline class antibiotics used for acne vulgaris and lupus erythematosus. The British journal of dermatology. 2007;157(3):540-6. Epub 2007/06/29. [PMID: 17596147].
9. Vedove CD, Del Giglio M, Schena D, Girolomoni G. Drug-induced lupus erythematosus. Archives of dermatological research. 2009;301(1):99-105. Epub 2008/09/18. [PMID: 18797892].
10. Jackson S, Gilchrist H, Nesbitt LT, Jr. Update on the dermatologic use of systemic glucocorticosteroids. Dermatologic therapy. 2007;20(4):187-205. Epub 2007/11/01. [PMID: 17970885].
11. Fritzler MJ, Tan EM. Antibodies to histones in drug-induced and idiopathic lupus erythematosus. The Journal of clinical investigation. 1978;62(3):560-7. Epub 1978/09/01. [PMID: 357449].
12. Zirwas MJ, Kress DW, Deng JS. The utility of antihistone antibody screening in the diagnosis of drug-induced lupus erythematosus. Archives of dermatology. 2004;140(4):494-5. Epub 2004/04/21. [PMID: 15096389].
13. Yell JA, Mbuagbaw J, Burge SM. Cutaneous manifestations of systemic lupus erythematosus. The British journal of dermatology. 1996;135(3):355-62. Epub 1996/09/01. [PMID: 8949425].
14. Kutlu A, Ozturk S, Onem Y, Nalbant S, Kiralp MZ, Taskapan O, Ozcakar L. Simple urticaria and systemic lupus erythematosus: why the(y) wait? Lupus. 2010;19(3):334. Epub 2009/11/11. [PMID: 19900980].
15. Aydogan K, Karadogan SK, Adim SB, Tunali S. Hypocomplementemic urticarial vasculitis: a rare presentation of systemic lupus erythematosus. International journal of dermatology. 2006;45(9):1057-61. Epub 2006/09/12. [PMID: 16961508].
16. Spadoni M, Jacob C, Aikawa N, Jesus A, Fomin A, Silva C. Chronic autoimmune urticaria as the first manifestation of juvenile systemic lupus erythematosus. Lupus. 2011;20(7):763-6. Epub 2010/12/25. [PMID: 21183563].
17. Iqbal S, Sher MR, Good RA, Cawkwell GD. Diversity in presenting manifestations of systemic lupus erythematosus in children. The Journal of pediatrics. 1999;135(4):500-5. Epub 1999/10/13. [PMID: 10518085].
18. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, Bruce IN, Isenberg D, Wallace DJ, Nived O, Sturfelt G, Ramsey-Goldman R, Bae SC, Hanly JG, Sanchez-Guerrero J, Clarke A, Aranow C, Manzi S, Urowitz M, Gladman D, Kalunian K, Costner M, Werth VP, Zoma A, Bernatsky S, Ruiz-Irastorza G, Khamashta MA, Jacobsen S, Buyon JP, Maddison P, Dooley MA, van Vollenhoven RF, Ginzler E, Stoll T, Peschken C, Jorizzo JL, Callen JP, Lim SS, Fessler BJ, Inanc M, Kamen DL, Rahman A, Steinsson K, Franks AG, Jr., Sigler L, Hameed S, Fang H, Pham N, Brey R, Weisman MH, McGwin G, Jr., Magder LS. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis and rheumatism. 2012;64(8):2677-86. Epub 2012/05/04. [PMID: 22553077].
19. Harel L, Amir J, Livni E, Straussberg R, Varsano I. Serum-sickness-like reaction associated with minocycline therapy in adolescents. The Annals of pharmacotherapy. 1996;30(5):481-3. Epub 1996/05/01. [PMID: 8740328].
20. Bettge AM, Gross GN. A serum sickness-like reaction to a commonly used acne drug. JAAPA : official journal of the American Academy of Physician Assistants. 2008;21(3):33-4. Epub 2008/04/25. [PMID: 18432045].
21. Davis MD, Brewer JD. Urticarial vasculitis and hypocomplementemic urticarial vasculitis syndrome. Immunology and allergy clinics of North America. 2004;24(2):183-213, vi. Epub 2004/05/04. [PMID: 15120147].
22. Akin E, Miller LC, Tucker LB. Minocycline-induced lupus in adolescents. Pediatrics. 1998;101(5):926. Epub 1998/05/23. [PMID: 9565427].
23. Antonov D, Kazandjieva J, Etugov D, Gospodinov D, Tsankov N. Drug-induced lupus erythematosus. Clinics in dermatology. 2004;22(2):157-66. Epub 2004/07/06. [PMID: 15234017].
24. Ines L, Silva C, Galindo M, Lopez-Longo FJ, Terroso G, Romao VC, Rua-Figueroa I, Santos MJ, Pego-Reigosa JM, Nero P, Cerqueira M, Duarte C, Miranda LC, Bernardes M, Goncalves MJ, Mourino-Rodriguez C, Araujo F, Raposo A, Barcelos A, Couto M, Abreu P, Oton-Sanchez T, Macieira C, Ramos F, Branco JC, Silva JA, Canhao H, Calvo-Alen J. Classification of Systemic lupus erythematosus: Systemic Lupus International Collaborating Clinics versus American College of Rheumatology criteria. Arthritis care & research. 2015. Epub 2015/01/13. [PMID: 25581417].