

A case of subacute cutaneous lupus erythematosus as a result of ranibizumab (Lucentis) treatment

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Cutaneous lupus erythematosus is a previously undiagnosed side-effect of ranibizumab. Here, we present a case of an 82-year-old female Caucasian patient with wet age-related macular degeneration. Following a single intraocular injection of Lucentis (ranibizumab), she developed a subacute cutaneous lupus erythematosus which, with treatment, took nearly 12 months to resolve. This shows that cutaneous lupus erythematosus is a potential side-effect of many medications, including ranibizumab, as in our case and, in an aging population where polypharmacy is a growing reality, clinicians should be aware of how to diagnose and best manage such cases.

Key words: Drug reaction, drug-induced, ranibizumab, subacute cutaneous lupus erythematosus

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Ranibizumab (Lucentis) is an intravitreal drug used for the treatment of neovascular age-related macular degeneration (AMD), the leading cause of irreversible blindness among older individuals throughout the developed world. Ranibizumab is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment that binds to and inhibits human vascular endothelial growth factor A, an angiogenic stimulator found in high levels in the vitreous and plasma of patients with neovascular AMD. Despite being well-tolerated, many adverse reactions, both ocular and non-ocular, have been documented; however, our case presents a complication not previously described in the literature.

Case Report

An 82-year-old female was referred to a dermatologist with a generalized, scaly, symmetric, non-palpable but very erythematous, almost hemorrhagic rash which was painful and associated with a mild itch. It was initially on the face, neck and forearms in light-exposed areas [Figs. 1 and 2]. The presence of the rash on her legs [Fig. 3] at that stage is uncertain as they were bandaged following surgery and subsequent ulceration. It had developed over two weeks following an injection of Lucentis as part of her treatment for neovascular AMD.

She had been diagnosed with “wet” AMD in 2002. Over the following two years, she was treated with seven doses of Verteporfin (Visudyne) and a single dose of Bevacizumab (Avastin). Her general health was good and, in addition to AMD, her medical history consisted of well-controlled hypothyroidism, hypertension and recently

stripped varicose veins. Her medications included aspirin, thyroxine, amlodipine, and calcium and cholecalciferol supplements, all of which she had been using for a prolonged period.

In August 2008, she received a single 2.3-mg intravitreal injection of ranibizumab. Five days later, she developed a few “flat, brown spots” which over the next 10 days, evolved into the rash described above. Her dermatologist prescribed topical methylprednisolone ointment for the face and betamethasone ointment for the rest. None of the other medications had been changed or added in the months preceding this episode. Arthralgia and myalgia were not present.

A biopsy [Fig. 4] showed a prominent lichenoid inflammatory process with some necrotic keratinocytes in keeping with a drug reaction and, considering the clinical history, consistent with the diagnosis of drug-induced, subacute cutaneous lupus erythematosus (SCLE).

Immunofluorescence was negative but she had already been using steroids. She was commenced on oral steroids which were initially ceased by her vascular surgeon due to slow healing of her leg wounds. They were restarted and she improved markedly at 25 mg/day.

The dose was being weaned until it was again ceased, this time by an immunologist. The rash flared quite markedly and steroids were recommenced. In February 2009, hydroxychloroquine (Plaquenil) was introduced as a steroid-sparing agent and surprisingly, her rash flared again. A second biopsy in April was also suggestive of SCLE.

Her standard bloods were unremarkable except for a mild anemia (111 g/L). Erythrocyte sedimentation rate (ESR) was initially elevated at 30 mm/h (normal < 20 mm/h) which decreased to 4 mm/h over several months. Antinuclear antibodies (ANA)/anti-SSA in particular SSA (Ro60) and SSB (La) were present. Anti-DNA, complement, ANCA,

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Figure 1: Erythematous rash on patient's hands



Figure 2: Rash on patient's forearms



Figure 3: Rash on patient's leg

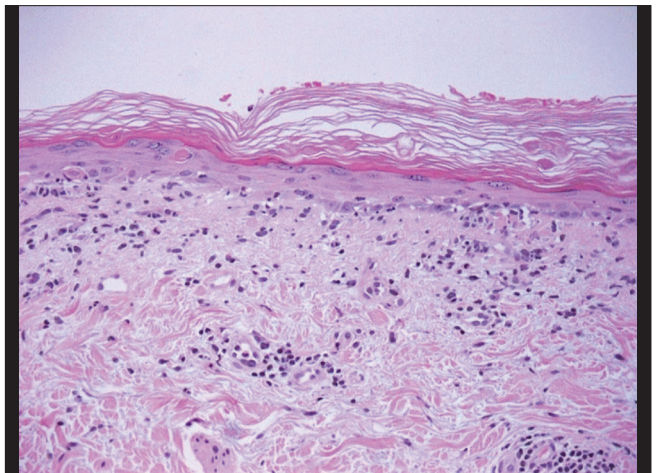


Figure 4: Histopathology of skin biopsies showing hyperkeratosis, epidermal atrophy, basal hydropic degeneration and Civatte and colloid body formation

cardiolipin, and mitochondrial and ribosomal antibodies were all within normal limits.

By July 2009, she was on 15 mg of prednisolone and, excluding her upper back, the rash was much improved. Her chest, face and arms were virtually clear.

Discussion

The first to recognize that SCLE can be induced by a drug were Reed *et al.*, in 1985 with an estimated incidence of 0.7/100,000 persons per year.^[1,2] Many medications have been implicated, including hydrochlorothiazides, calcium channel blockers, angiotensin-converting enzyme inhibitors, statins and a growing number of anti-tumor necrosis factor agents and monoclonal antibody medications such as efalizumab.^[3] A 2009 review by Sontheimer *et al.*, reviewed 71 published cases of drug-induced SCLE.^[3] This is the first recorded case of SCLE following ranibizumab treatment.

We compared our case to data in the 2009 review. The large majority was also Caucasian females and their mean age at presentation was 59.5 years. The older age of our patient could be explained by the fact that ranibizumab is used for macular degeneration, a disease affecting mostly older individuals. The

time to first appearance of SCLE lesions was found to range from 2 weeks to 3.2 years. In our case, the rash developed from Day 5 to Day 15 post administration.

Her investigations showed results which were consistent with those published previously. A mild anemia and occasionally pancytopenia have been reported.^[4] An elevation in ESR has been reported in 15-60% of patients with SCLE.^[5] The ANA pattern in our case was similar to a number of other cases, with antibodies to Ro and La Antigens being present in 50-71% of patients with SCLE.^[6,7] Anti-DNA was not elevated as with other studies which have found it to be elevated in systemic lupus erythematosus but not in SCLE.^[6-8] As with other studies, complement and ANCA were normal as was cardiolipin although it may be elevated in 16% of patients with SCLE.^[4,5,7,8] A transient depression of complement levels has also been reported.^[4]

As with other cases, the distribution of the rash suggested that photosensitivity plays an important role in SCLE.^[5,6,9]

The recent review found that the rash cleared in an average of 5.75 weeks (with a range of 1-24 weeks) after ceasing

the medication whilst in our case, the SCLE only resolved 12 months later. This could be explained by the fragmented course of steroid and a similar reaction to hydroxychloroquine. Another case of hydroxychloroquine-induced SCLE was noted in the review by Sontheimer *et al.*^[5]

A genetic link in SCLE has been discussed for over 27 years with various human leucocyte antigens implicated in idiopathic and drug-induced SCLE.^[3,4,7,8,10]

A variety of factors and many common medications contribute to patients developing drug-induced SCLE. Our case involved concurrent care between multiple specialties, including general practice, ophthalmology, dermatology, rheumatology/immunology and even vascular surgery. This highlights the fact that in order to best manage this often prolonged and unpredictable condition, all clinicians should be aware of SCLE, regardless of specialty.

References

1. Reed BR, Huff JC, Jones SK, Orton PW, Lee LA, Norris DA. Subacute cutaneous lupus erythematosus associated with hydrochlorothiazide therapy. *Ann Intern Med* 1985;103:49-51.
2. Popovic K, Nyberg F, Wahren-Herlenius M, Nyberg F. A serology-based approach combined with clinical examination of 125 Ro/SSA-positive patients to define incidence and prevalence of subacute cutaneous lupus erythematosus. *Arthritis Rheum* 2007;56:255-64.
3. Sontheimer RD, Henderson CL, Grau RH. Drug-induced subacute cutaneous lupus erythematosus: A paradigm for bedside-to-bench patient-oriented translational clinical investigation. *Arch Dermatol Res* 2009;301:65-70.
4. Lyon CC, Blewitt R, Harrison PV. Subacute cutaneous lupus erythematosus: Two cases of delayed diagnosis. *Acta Derm Venereol* 1998;78:57-9.
5. Sontheimer RD. Subacute cutaneous lupus erythematosus. A decade's perspective. *Med Clin North Am* 1989;73:1073-90.
6. MacCauliffe DP. Distinguishing subacute cutaneous from other types of lupus erythematosus. *Lancet* 1998;351:1527-8.
7. Fenniche S, Dhaoui A, Ammar FB, Benmously R, Marrak H, Mokhtar I. Acebutolol-induced subacute cutaneous lupus erythematosus. *Skin Pharmacol Physiol* 2005;18:230-3.
8. Romiti N, Dinato SL, Almeida JR, Lapoli A, Sementilli A. Subacute cutaneous lupus erythematosus (SCLE) manifested clinically as annular erythema centrifugum. *An Bras Dermatol* 2004;79:353-8.
9. Kuhn A, Bijl M. Pathogenesis of cutaneous lupus erythematosus. *Lupus* 2008;17:389-93.
10. Lehmann P, Holzle E, Kind P, Goerz G, Plewig G. Experimental reproduction of skin lesions in lupus erythematosus by UVA and UVB radiation. *J Am Acad Dermatol* 1990;22:181-7.

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