

# Treatment with Doxycycline of Generalized Annular Elastolytic Giant Cell Granuloma Associated with *Borrelia burgdorferi* Infection

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## ABSTRACT

*This is a case of generalized annular elastolytic giant cell granuloma (AEGCG) associated with borrelia infection and genes of p-30, p-31, p-39. A possible cross-mediated reaction from the T-cell type which might have induced the AEGCG is discussed from the concept of "heat-shock proteins (HSPs) and molecular mimicry".*

**Keywords:** Annular elastolytic giant cell granuloma, *Borellia burgdorferi*, heat-shock proteins, Lyme disease, molecular mimicry

# Tratamiento con Doxiciclina del Granuloma Anular Elastolítico de Células Gigantes Generalizado Asociado con Infección por *Borrelia burgdorferi*

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## RESUMEN

*Se trata de un caso de granuloma elastolítico anular de células gigantes (GEACG) generalizado, asociado con infección por Borrelia y con los genes de p-30, p-31, p-39. Una posible reacción transmediada del tipo de célula T que podría haber inducido la GEACG, se discute a partir del concepto de "proteínas de shock térmico (PST) y mímica molecular".*

**Palabras claves:** Granuloma anular elastolítico de células gigantes, *Borrelia burgdorferi*, proteínas de shock térmico, enfermedad de Lyme, mímica molecular

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## INTRODUCTION

Lyme disease is a multisystemic infectious disease caused by spirochetes called *Borrelia burgdorferi*, as a result of an infected tick bite. The three characteristic cutaneous manifestations are erythema chronicum migrans (EM), lymphadenitis benigna cutis and acrodermatitis chronica atrophicans (1). Besides the classical manifestations of cutaneous borreliosis, evidence is growing that at least, in part, other skin manifestations, especially morphea, lichen sclerosus and cases of cutaneous B-cell lymphoma are causally related to infections with borrelia (2, 3). There are also single reports of other skin manifestations associated with borrelia infections such as cutaneous sarcoidosis, necrobiosis lipoidica, necrobiotic xanthogranuloma, systemic sclerosis, eosinophilic fasciitis, lichen sclerosus et atrophicus, atrophoderma of Pasini and

Pierini, pseudolymphoma, septal panniculitis resembling erythema nodosum, progressive facial hemiatrophy of Parry-Romberg, sclerodermatous porphyria cutanea tarda, granuloma annulare (GA) and interstitial granulomatous dermatitis (2–4). Additionally, in recent years, because of the presence of activated T-cells in the lesions of some granulomatous diseases such as GA (5) and sarcoidosis (6, 7), it has been suggested that a T-cell mediated immune response might have been responsible for the pathogenesis of these diseases.

## CASE REPORT

A 52-year old Caucasian woman was admitted to hospital because of unhealed and spreading lesions for one year. According to the history, the patient was bitten by three ticks two years previously. Four weeks after the tick bites, three itchy, annular and erythematous plaques emerged at the bite sites and they cleared two months later. The patient had no therapy for the lesions and she had been in good health until one year ago. Thereafter, the patient noticed some papular lesions on the right shoulder, right wrist and back. The lesions spread

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throughout the body in a one-year period. She had treatment with oral and topical antihistaminics and topical steroids for the lesions, however, they did not recover. In the dermatologic examination, multiple, flesh-coloured or pink, annular lesions (5–65 mm in size) which were composed of small papules were seen on the whole body (especially on the back, shoulders and arms). The middle of the annular lesions was pale and slightly atrophic (Fig. 1A–C). The lesions were symptomless.

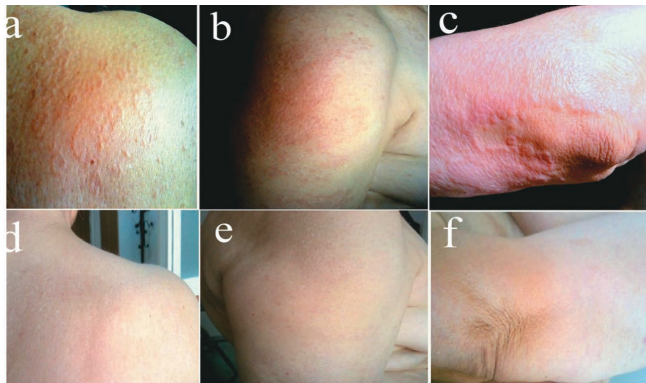


Fig. 1: The clinical appearances of the lesions before the treatment (A–C) and four weeks after the treatment with doxycycline (D–F).

Other dermatological and systemic examinations and laboratory tests (including blood glucose values, glycated haemoglobin (HbA<sub>1c</sub>), tumour markers, rheumatoid factor, antinuclear antibody, anti-ds DNA, peripheral blood smear, VDRL, TPHA and anti-HIV antibodies) were negative or within the normal limits. In the serologic screening, borrelia IgM was negative and IgG was positive (17.11 RU/mL) in the enzyme-linked immunosorbent assay (ELISA) tests, which examined the peripheral blood. In the Western immunoblotting tests for the purpose of verifying the results, borrelia IgG was strongly positive against p-30, p-31 (OspA) genes and weakly positive to the p-39 gene. Immune responses to other antigens of *B burgdorferi* [VLsE, p17, p19, p21, OspC (p25)] were negative (Fig. 2).

In the histopathological and immunohistochemical examination of an excisional biopsy specimen, there were interstitial multinuclear histiocytes which settled between and around the collagen bundles and a few interstitial and perivascular lymphocytes in the superficial dermis. The epidermis was normal (Fig. 3A–B). Elastic fibres were diminished and fragmented [with Elastan Verhoeff-Van-Gieson] (Fig. 3C). The histiocytes were stained with CD68 positively (Fig. 3D). No mucin was observed with PAS-AB staining.

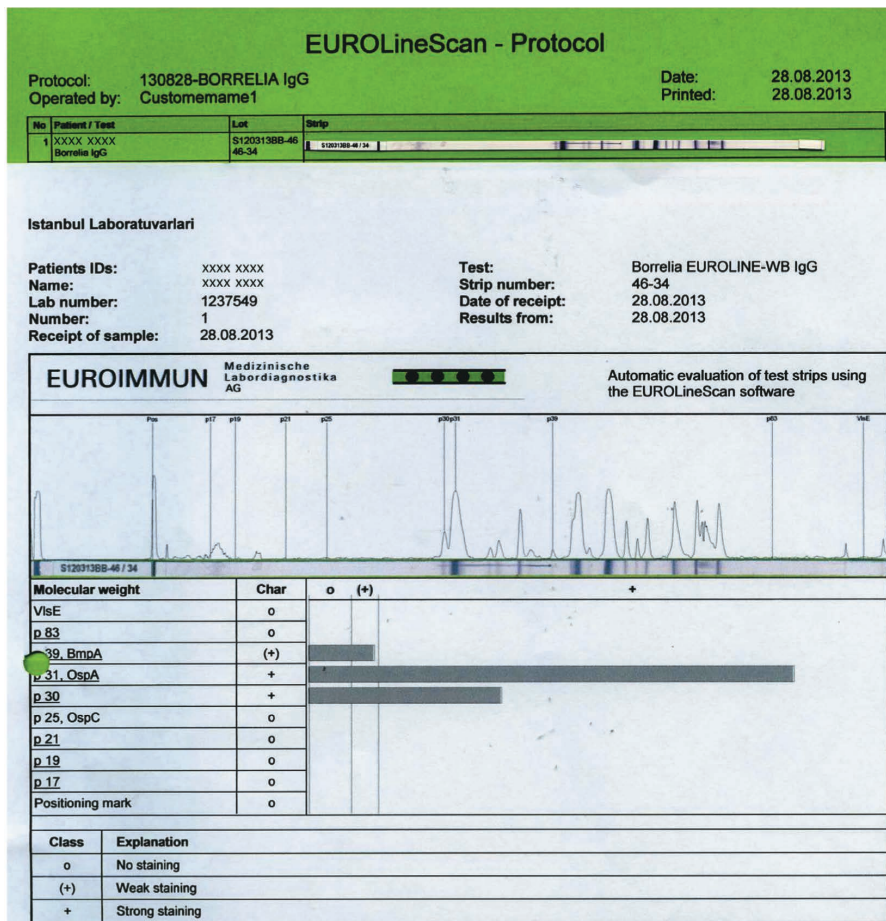


Fig. 2: The strong IgG positivity against p-30, p-31 (OspA) genes and weak positivity to the p-39 gene in the Western immunoblotting test.

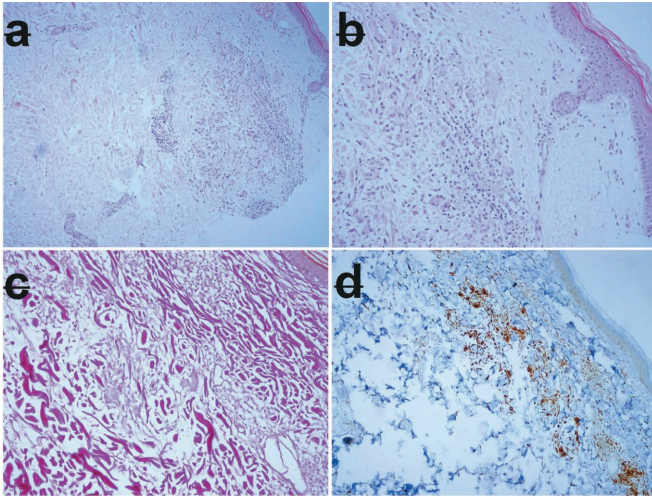


Fig. 3: Histopathology of the lesions: (A) HE  $\times$  100, (B) HE  $\times$  200, (C) EVG  $\times$  200, (D) CD 68  $\times$  100.

Based upon the clinical, histopathological and immunological findings, the lesions were diagnosed as generalized annular elastolytic giant cell granuloma (AEGCG) associated with the late borrelia infection. The patient was treated with oral doxycycline for four weeks (200 mg/day). No additional systemic treatment or topical treatment was applied to the patient. The patient was checked weekly. No adverse effects were observed during the treatment. The lesions gradually decreased throughout the two weeks. All lesions of the patient disappeared completely three weeks after the initiation of the treatment (Fig. 1D–F).

## DISCUSSION

Annular elastolytic giant cell granuloma is an uncommon dermatological condition firstly described by Hanke *et al* as annular lesions associated with a granulomatous elastolytic pattern (8, 9). It usually appears in sun-exposed areas, such as the face and neck, and is rarely seen on the trunk, back and extremities (9). The majority of cases occur in middle-aged Caucasian women. The common presentations of the lesions are annular plaques and patches often with elevated borders and central atrophy. It can sometimes be only papular (8). Some authors believe that AEGCG is a subtype of GA which settles in the sun-exposed areas. Actually, there are some reports showing an overlap between AEGCG and GA (9). Our patient had generalized erythematous papules arranged in annular configuration with slight atrophic and pale centres, especially on the back, trunk and upper extremities. This appearance of the lesions was consistent with an AEGCG.

The aetiopathogenesis of AEGCG is controversial. It has been suggested that cellular immunological reactions induced by modified function of antigenicity of elastic fibres play a role in the mechanism of AEGCG formation, and ultraviolet radiation may be responsible for the antigenicity of elastic fibres (9). The disease can accompany some endocrine and tumoral diseases such as diabetes mellitus (8, 9), solid organ

tumours and haematologic malignancy (8) as in GA. On the other hand, it has been suggested that some granulomatous diseases such as GA and interstitial granulomatous dermatitis might be partly caused by *B burgdorferi* or similar strains (2, 10). The presence of activated T-cells in the lymphocytic infiltrate of GA has been demonstrated, suggesting there is a cell-mediated immune response to various precipitating factors (3). On the other hand, Strle *et al* stated that the emergence of the lesions of GA can begin two months after the tick bite, and persist for up to one year (10). Late Lyme borreliosis (LB) may develop among some untreated patients many months to a few years after tick-transmitted infection appears (11). Whereas borrelia IgM antibodies rise 2–4 weeks after the tick bite and may persist at high levels for many years, borrelia IgG might not rise until many years after the tick bite (12, 13). Moreover, both IgM and IgG may persist for many years after successful treatment of Lyme borreliosis. Patients with late manifestations of Lyme borreliosis usually have a high concentration of antibodies by first-step tests and have numerous immunoreactive bands in IgG immunoblots (11). In our case, we did not find another reason that might have been responsible for the aetiology of the disease except the high-titre antibody positivity against borrelia antigens, and we determined IgG antibodies in both ELISA and Western blot tests, two years after the tick bite, as well. As our patient had a history of tick bites and multiple erythema chronicum migrans two years previously, we thought that the patient might be in the late stage of Lyme disease. However, we could not find any case of AEGCG associated with borrelia infection in the literature.

In a different aspect, molecular mimicry is one mechanism by which infectious agents trigger an immune response against the host antigens. When a susceptible host acquires an infection with an organism that has antigens immunologically similar to the host antigens but different enough to induce an immune response when presented to T cells, it results in a loss of tolerance to host antigens. Furthermore, there is development of a pathogen-specific immune response that cross-reacts with host structures to cause tissue damage and disease (14–16). Autoreactivity is based on antigenic cross-reactivity between epitopes common to borrelia and a human host, especially situated on the so-called heat-shock proteins (HSPs), and many HSPs of *B burgdorferi* have been identified such as p60, p66, p43, p72, p24, p35 and p28 (17–19). Some diseases have been reported to be possibly associated with the mechanism of molecular mimicry, such as insulin-dependent diabetes, Lyme disease and syphilis (15, 20). For example Tchernev *et al* have stated that an autoimmune aetiology of sarcoidosis could possibly occur through a process of molecular mimicry of infectious or other environmental antigens to host antigens. This could lead to a cross-mediated immune response and induction of autoimmune disease (6, 7). Similar to this situation, this concept has been argued by identification of “leukocyte function associated antigen 1 alpha” as a candidate auto-antigen, which might cross-react with an outer surface protein A peptide epitope in the patient with treatment-refrac-

tory Lyme arthritis. Moreover, it has been stated that Lyme arthritis might be derived from a persistent infection of the pathogen that was suggested by the presence of borrelia DNA retained spirochetal antigens with no living bacteria present, and these DNA products might induce an autoimmunity resulting from a T-cell-receptor epitope mimicry (21). Additionally, it has been postulated that the antibodies against some immunodominant borrelia proteins such as p41, OspC (p25), p35, p37 (11) and p45 (22) might be detected more in the early stage of Lyme disease, whereas some others such as p31 [OspA], p34 [OspB] (11, 22), p28 and p30 (22) might be detected more in the late stage of the disease. Aguero-Rosenfeld *et al* have stated that the antibodies against p39 were more detected in the convalescence phase (11). Due to the negativity of the OspC (p25), weak positivity of the p39 and the strong positivity of both p30 and p31 in our patient, it was thought that the stage of the disease might be more chronic.

When the biting time, the time of appearance of the EM, the subtypes and strengths of positive antibody bands of IgG were taken into account, the disease stage of our patient was more compatible with the late stage of Lyme borreliosis. Based on this information, we thought that an antigen mimicry might be responsible for the clinical picture of AEGCG. In this picture, a cross-mediated reaction from the T-cell type might have developed between the host proteins and borrelia antigens, and the proteins (p-30, p-31 and p-39) of *B burgdorferi* might have been aetiologically guilty of acting as three of the eventual HSPs of the *B burgdorferi*. Additionally, we thought that AEGCG might be one of the presentations of the late stage of Lyme disease that developed after many years. These probable aetiopathogenetic associations have not been reported between AEGCG and Lyme disease previously.

The diagnosis of AEGCG is made with clinical and distinct histopathological findings. These histopathological findings are the presence of granulomatous reaction with elastolysis and phagocytosis of elastic fibres by multinucleated giant cells, and the absence of palisading histiocytes, necrobiosis, lipid or mucin (23). Our findings were compatible with those of the literature. Because of the absence of a palisading granuloma and mucin, and the absence of necrobiosis and lipid, the diagnoses of GA and necrobiosis lipidica were excluded, respectively. Additionally, the presence of CD68 positive histiocytes around the collagen bundles (24) supported our diagnosis. Other differential diagnoses include sarcoidosis, annular lichen planus, lichenoid photosensitivity reactions, subacute cutaneous lupus erythematosus and inflammatory mid dermal elastolysis-type 2 (23).

There is no specific treatment for AEGCG. Sometimes a spontaneous remission can occur (23). Many treatment modalities have been tried such as clofazimine, chloroquine, corticosteroids, hydroxychloroquine (9), quinacrine, retinoid-PUVA, narrow-band UVB, fumaric acid esters, cyclosporine, topical pimecrolimus and tacrolimus (23). On the other hand, Lyme borreliosis should be treated in all stages of the disease (21). Doxycycline is the mainstay of therapy of cutaneous

manifestations of borrelia infections (1). In the late skin manifestations of Lyme disease such as acrodermatitis chronica atrophicans, it is recommended that the duration of treatment should be at least four weeks (21). We treated our patient with doxycycline for four weeks due to the strong positivity of the late stage antibodies. We obtained an excellent response in three weeks. The index case was reported because of the interesting association with the borrelia antigens. We believe that reporting of more cases such as our patient will shed light on the relation between Lyme disease and its unusual late cutaneous presentations and perhaps with AEGCG.

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