Erythema elevatum diutinum in a patient with well-controlled Crohn disease

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Abstract

Erythema elevatum diutinum is a rare, chronic cutaneous leukocytoclastic vasculitis, with prominent fibrosis at its later stage. In this article, we report a case of erythema elevatum diutinum in a 23-year-old woman with well-controlled Crohn disease. To our knowledge, erythema elevatum diutinum has been reported in only three other cases of Crohn disease, in which eruptions of erythema elevatum diutinum were associated with features of active Crohn. Our patient was in clinical remission at the time of erythema elevatum diutinum onset, making this report significant not only for its uncommon presentation, but more importantly, to aid readers. diagnosis and clinical management of similar cases.

Keywords: Crohn disease, erythema elevatum diutinum, inflammatory bowel, leukocytoclastic vasculitis

Introduction

Erythema elevatum diutinum is a rare, chronic form of cutaneous leukocytoclastic vasculitis. Clinically, erythema elevatum diutinum initially manifests as a symmetric eruption of soft, erythematous papules or plaques that favor extensor surfaces. Over time, gradual fibrotic replacement of the dermis eventuates in persistent firm, violaceous, red-brown, or yellow papules, plaques, or nodules. Although pathogenesis of erythema elevatum diutinum is poorly understood, it is believed to be an immune complex-mediated vasculitis. erythema elevatum diutinum has been associated with a number of systemic diseases including infections, hematologic disorders, and autoimmune disease, with eruptions often correlating with underlying disease activity.

Case Synopsis

A 23-year-old woman presented to clinic with a rash on her legs first noticed eight months prior and raised papules and nodules on her feet, knees, and elbows that began two months later. The leg rash was associated with a burning and itching sensation and had a waxing and waning course. These lesions typically resolved several days after appearing, leaving behind darkened skin. The papules and nodules on the feet, knees, and elbows were persistent and chronically painful. Prior treatment of the leg eruption with topical mupirocin and fluocinonide, and the raised lesions with cryotherapy, provided no relief of symptoms.

The patient's medical history was notable for Crohn disease, status-post ileocecectomy eight years prior and well controlled with intravenous infliximab since that time. Her course was complicated by iron deficiency anemia, for which she received periodic intravenous iron supplementation. She denied fevers, chills, unintentional weight loss, shortness of breath, cardiopulmonary symptoms, abdominal pain, diarrhea, constipation, hematochezia, recent infections, and new medications. She had no history of sexually transmitted diseases.

Physical examination revealed erythematous, urticarial linear plaques, irregularly shaped macules, and post-inflammatory hyperpigmentation on the

lower legs. Multiple red-brown papules and nodules varying in size from 3mm to 2.5cm were observed on the knees, elbows, and dorsal feet (**Figure 1**).

Histopathologic examination of a punch biopsy from a nodule on the right dorsal foot demonstrated a superficial and deep perivascular and interstitial inflammatory infiltrate composed of numerous neutrophils and lesser numbers of lymphocytes, histiocytes, and eosinophils (**Figure 2**). There was evidence of a small vessel vasculitis with fibrinoid necrosis and endothelial cell swelling. The inflammation extended around adnexal structures into the deep dermis and subcutaneous adipose tissue. Concentric fibrosis was observed surrounding multiple vessels within the deep dermis and karyorrhectic debris was also seen. The overlying epidermis was uninvolved. Grocott methenamine silver, acid fast bacilli, Fite, and *Mycobacterium tuberculosis* species-specific monoclonal antibody stains showed no evidence of infectious organisms.

By comparison, punch biopsy of a macule from the right thigh showed less prominent changes, with perivascular and periadnexal inflammation composed of numerous neutrophils and scattered eosinophils, lymphocytes, and histiocytes. Small vessels within the superficial dermis showed a neutrophilic infiltrate with karyorrhectic debris and red blood cell extravasation. Grocott methenamine silver and Gram stains were negative.

Laboratory evaluation, including blood tests for human immunodeficiency virus, hepatitis C virus, tuberculosis, and syphilis were negative, as were anti-nuclear antibody and rheumatoid. Serum protein electrophoresis showed polyclonal IgA and IgG gammopathy.

Based on the clinical findings, histopathologic features of perivascular fibrosis and leukocytoclastic

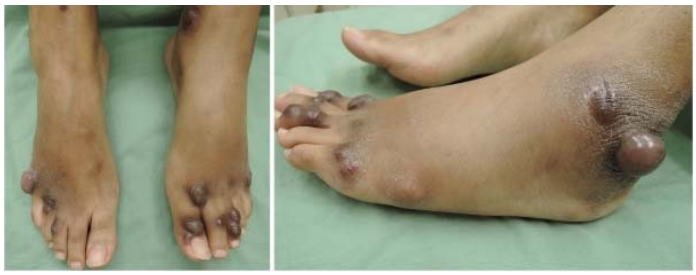

Figure 1. *Multiple red-brown papules and nodules varying in size from 3mm to 2.5cm on the dorsal toes, feet, and ankles.*

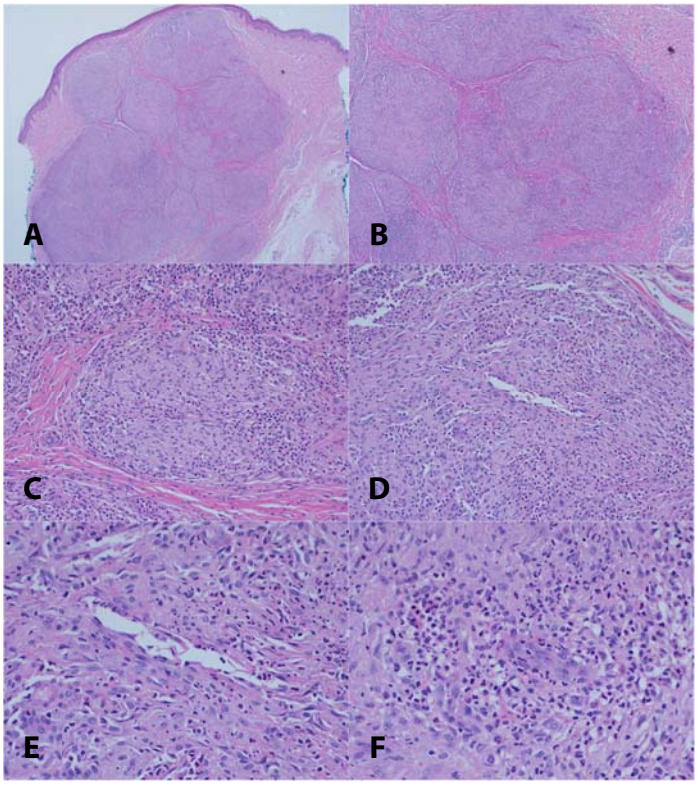

Figure 2. *H&E staining of a punch biopsy of a nodule on the right dorsal foot.* ***A, B)*** *A nodular infiltrate in the dermis with prominent fibrosis, 20×.* ***C)*** *The nodules are composed of areas of fibrosis with a concentric appearance, 200×. The nodular areas of fibrosis are centered around distinctive small vessels with vasculitis and leukocytoclastic foci;* ***D)*** *200×;* ***E, F)*** *400×.*

vasculitis, and history of Crohn disease, a diagnosis of erythema elevatum diutinum was made and oral dapsone therapy was initiated. Shortly after initiating dapsone, our patient experienced acute worsening of her chronic anemia and therapy was discontinued. Alternative treatment options including intralesional corticosteroids or methotrexate injections, oral chloroquine, colchicine, nonsteroidal anti-inflammatory drugs, and surgical removal were discussed at length. The patient agreed to a trial of intralesional triamcinolone injections of several of the more prominent nodules on her feet. After two rounds of injections, however, this proved to be ineffective, with the exception of reducing pain in the treated nodules. Surgical removal of two lesions was subsequently performed, one from the right knee and left elbow with shave removal and punch excision, respectively. At next appointment these lesions had healed well, especially the elbow. The patient was lost to follow-up after this point.

Case Discussion

Erythema elevatum diutinum is a rare, chronic cutaneous leukocytoclastic vasculitis, with prominent fibrosis at its later stage [1]. Clinically, erythema elevatum diutinum manifests as a symmetric eruption of violaceous, red-brown, or yellow papules, plaques, or nodules [1]. Lesions predilect acral and periarticular skin, especially the extensor surfaces of the fingers, hands, elbows, feet, ankles, and knees [1,2]. The clinical and histopathologic features of individual erythema elevatum diutinum lesions evolve over time [2-4]. In the acute phase, lesions tend to be soft, erythematous papules and plaques and exhibit histologic features of classic leukocytoclastic vasculitis, with a predominantly neutrophilic mixed perivascular infiltrate in the upper and mid reticular dermis [2-4]. This infiltrate is accompanied by karyorrhectic debris and fibrin deposition within and around small vessels. As was seen in our patient, some of these lesions may resolve, leaving behind hyperpigmentation, whereas others can persist and progress to late-stage lesions. These late-stage lesions often present as firm papules, plaques, or nodules secondary to gradual fibrotic replacement of the dermis with spindle cells, capillary sclerosis, and fibrinoid necrosis [2-4]. This variable presentation can make clinical diagnosis of erythema elevatum diutinum challenging, as both the early and late-stage lesions share features with multiple other disorders. The soft, erythematous papules and plaques observed in early-stage erythema elevatum diutinum may resemble Sweet syndrome, rheumatoid neutrophilic dermatosis, palisaded neutrophilic and granulomatous dermatosis, and granuloma faciale. However, disorders in the differential diagnosis for the firm violaceous-to-red papules, plaques, and nodules characteristic of later-stage erythema elevatum diutinum can include tuberous xanthomas, rheumatoid nodules, multicentric reticulohistiocytosis, or keloids. Thus, correlation of clinical findings with skin biopsy demonstrating histologic evidence of dermal leukocytoclastic vasculitis consistent with erythema elevatum diutinum is key to confirming the diagnosis.

The pathogenesis of erythema elevatum diutinum remains unclear. The leading hypothesis is that circulating immune complexes in the setting of systemic disease deposit in the perivascular dermis, inducing subsequent complement activation, neutrophil infiltration, tissue damage, and fibrosis [3,5,6]. This theory is supported by direct immunofluorescence revealing perivascular deposition of complement, IgG, IgM, IgA, and fibrin, although these studies are typically not required for diagnosis [5].

Erythema elevatum diutinum has been associated with a number of systemic diseases including infections (group A Streptococcus, hepatitis B virus, human immunodeficiency virus, tuberculosis), autoimmune diseases (granulomatosis with polyangiitis, inflammatory bowel disease, celiac, relapsing polychondritis, systemic lupus erythematosus, rheumatoid arthritis), and both benign and malignant hematologic disorders, especially monoclonal IgA paraproteinemia [6]. Eruptions of erythema elevatum diutinum typically correlate with underlying disease activity. Therefore, once a diagnosis of erythema elevatum diutinum is made, evaluation for underlying disease with a thorough history, complete review of systems and physical exam, and specific laboratory tests should be performed. Our patient was found to have elevated IgA and IgG. However, serum protein electrophoresis revealed this to be a polyclonal gammopathy, with no evidence of anomalous monoclonal immunoglobulins. Although in clinical remission, these findings were most likely related to the patient's Crohn disease, as opposed to an underlying lymphoproliferative disorder.

Crohn-associated erythema elevatum diutinum is exceptionally rare, with only three cases reported to the best of our knowledge (summarized in **Table 1**), [7-9]. The first case was observed in a 30-year-old woman diagnosed with Crohn disease at the age of 19, after undergoing partial resection of the small intestine owing to small bowel obstruction [7]. Although asymptomatic for many years, she reported a five-year history of a chronic anal fistula and occasional hematochezia. The onset of these symptoms was noted to coincide with the

development of red papules on her elbows, that progressed to involve the extensor surfaces of her fingers and knees. By the time of presentation, these lesions had evolved into firm, painful, smooth-surfaced, hyperpigmented nodules, measuring from one to three cm in diameter. Histopathologic examination showed leukocytoclastic and angioplastic vasculitis and direct immuno-fluorescence revealed focally positive perivascular IgM deposition. Laboratory analysis indicated mildly-elevated serum IgG and IgM and the presence of circulating immune complexes. After clinical correlation, these findings were believed to be most consistent with a diagnosis of erythema elevatum diutinum and dapsone therapy was initiated. Within 48 hours the patient reported a decrease in pain, followed by a gradual resolution of lesions over several months.

The second report was of a 25-year-old woman with a seven-year history of Crohn involving the rectum, terminal ileum, and stomach [8]. She presented with large, asymptomatic, firm, hyperpigmented, nodules that had gradually appeared on her feet, wrists, elbows, and ears over an 18-month period. A diagnosis of erythema elevatum diutinum was made after histopathologic analysis of these lesions revealed a dense dermal inflammatory cell infiltrate primarily composed of neutrophils, with significant leukocytoclasis and fibrinoid necrosis of superficial dermal vessels. Several loosely formed granulomas were also observed within the lower dermis that were similar in appearance to foci of granulomatous inflammation seen in rectal biopsy specimens. Intriguingly, nuclei of macrophage-like cells within granulomas of both skin and rectal biopsy specimens were found to harbor measles virus nucleocapsid protein. The patient also exhibited elevations of serum IgG and IgM and circulating IgG and IgA immune complexes. These findings led the authors to propose that immune complex-mediated reactions precipitated by persistent measles virus infection may have played a common role in the pathogenesis of both Crohn disease and erythema elevatum diutinum in this patient. However, little evidence has since been put forward to support this hypothesis. Unfortunately, neither treatment strategy nor outcome were reported for this case.

The third case was reported in a 51-year-old man with a medical history of treated tuberculosis and chronic hepatitis B virus infection, but no known history of Crohn disease [9]. However, this patient presented with a four-month history of symmetric, additive, polyarthralgia, occasional mucinous, bloody diarrhea, and unintentional weight loss. One month after these symptoms began, the patient noted the appearance of non-pruritic lesions on his arms and feet. On admission, physical examination revealed hyperpigmented papules on the extensor surfaces of the finger joints and hands, and purpuric nodules and plaques with ulceration on the elbows, digital pulps, legs, buttocks, and soles of the feet. Histopathologic assessment of these lesions showed perivascular neutrophilic infiltrate, karyorrhectic debris, and minor dermal fibrotic changes compatible with a diagnosis of erythema elevatum diutinum. As part of an extensive, multidisciplinary workup, the patient was found to have polyclonal hypergammaglobulinemia, elevated anti-citrullinated protein antibody titer, very high hepatitis B viral load, and endoscopic and histopathologic evidence of Crohn disease. Owing to the near simultaneous occurrence of intestinal, cutaneous, and articular symptoms, the authors propose that erythema elevatum diutinum and polyarthritis were likely initial manifestations of Crohn disease in this patient and not associated with the viral or rheumatologic findings. Treatment with oral prednisolone, sulphasalazine, and metronidazole resulted in regression of lesions to cicatricial changes by 16 weeks. Upon tapering the prednisolone dose, the patient experienced a relapse of intestinal and articular symptoms, but no recurrence of skin involvement. The addition of azathioprine mitigated these symptoms and allowed for further corticosteroid tapering until discontinuation at one year, with no disease relapse.

The relationship between Crohn disease and erythema elevatum diutinum remains poorly understood. Elevated serum immunoglobulin is a common feature of Crohn disease, and their levels have been reported to positively correlate with disease activity [10]. It has been suggested that increased mucosal permeability secondary to inflammation in the setting of active disease may

increase antigenic exposure of these immunoglobulins to induce or enhance the formation of circulating immune complexes that give rise to erythema elevatum diutinum. The previous cases described above support this notion, as each had elevated serum immunoglobulins and eruptions of erythema elevatum diutinum that coincided with active gastrointestinal inflammatory features of Crohn disease [7-9]. Two of these patients were also found to have increased levels of circulating immune complexes, one of which also exhibited focally positive perivascular IgM deposition [7,8]. In contrast, despite having elevated serum immunoglobulins, our patient was in clinical remission prior to the onset of erythema elevatum diutinum. This suggests a variation of the mucosal barrier dysregulation mechanism of immune complex formation proposed by prior authors. In doing so, our case also raises an important consideration when evaluating a patient with erythema elevatum diutinum, such that a history of Crohn disease should not be discounted as a potential underlying etiology even if workup fails to identify clinical manifestations of disease.

Unlike many of the systemic diseases it has been associated with, erythema elevatum diutinum is a benign disorder that often resolves spontaneously 5-10 years after onset but has been reported to last up to 40 years [5]. Many patients are asymptomatic and pursue treatment owing to the chronically disfiguring nature of the lesions [2]. However, similar to our patient, reports of pruritis and pain associated with lesions are not uncommon [2]. Owing to the rarity of this disorder, a paucity of evidence exists to guide therapy. Oral dapsone is generally considered the first-line therapy for erythema elevatum diutinum, with the majority of patients showing complete or partial resolution with treatment [2]. Among other well documented adverse effects, dapsone causes some degree of hemolysis in all patients [11]. Alternative treatment options including intralesional corticosteroids or methotrexate injections, oral chloroquine, colchicine, non-steroidal anti-inflammatory drugs, and surgical removal have shown variable degrees of effectiveness [2].

Conclusion

In summary, erythema elevatum diutinum is a rare, chronic cutaneous leukocytoclastic vasculitis believed to result from circulating immune complexes in the setting of infections, autoimmune diseases, and hematologic disorders. Herein, we report a patient with erythema elevatum diutinum associated with Crohn disease. To our knowledge, erythema elevatum diutinum has been reported in only three other cases of Crohn's disease, in which, eruptions were associated with features of active Crohn disease. Notably, despite being in clinical remission, our patient exhibited characteristic clinical and histological findings of both early- and late-stage erythema elevatum diutinum lesions. Early-stage lesions revealed leukocytoclastic vasculitis, whereas late-stage lesions showed increased prevalence of histiocytes, spindle cells, and concentric perivascular dermal fibrosis. Oral dapsone provides an effective clinical response in most patients and is considered first-line therapy for erythema elevatum diutinum. For those unable to tolerate dapsone, a variety of other local, systemic, and surgical therapies have been reported with varying degrees of success in small numbers of patients. Surgical excision showed promise as a treatment option for our patient, however, the long-term effectiveness of this, and trials of alternative treatment strategies were precluded by lack of follow-up.

Potential conflicts of interest

R Hal Flowers has served as principal investigator at Sun Pharmaceuticals, Abbvie, Regeneron/Sanofi, and on the advisory board at Argenx. The other authors report no related financial interests.

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Table 1. *Summary of features observed in previously reported cases of erythema elevatum diutinum associated with Crohn disease and the patient in this report.*

Age	Sex	Race	Associated disease	Lesion location(s)	Lesion morphology	Lesion pathology	Other laboratory tests:	Treatment	Response to therapy	Ref
30 years old	Female	Black	11-year history of Crohn disease	Elbows Dorsal finger joints Anterior knees	Firm, tender, hyperpigmented (dark brown) nodules, approximately 1-3 cm in diameter	Leukocytoclastic vasculitis with superficial and deep polymorphous infiltrate, nuclear dust, and fibrinoid necrosis. Direct immunofluorescence was focally positive for perivascular IgM. Negative for IgA, IgG, fibrin, or C3 deposition.	Laboratory tests within normal limits: ANA Anti-streptolysin O BMP C1q binding assay C3 level ESR Serum IgA level Abnormal laboratory tests: C4 level, 16mg/dl (normal 20-50mg/dL) Raji cell assay, 10µg/dL (normal <5µg/dlL) Rheumatoid factor, 1:10 Serum IgG, 1916mg/dL (normal 800-1800mg/dL) Serum IgM, 369mg/dL (normal 70-280mg/dL) SPEP gamma peak, 1.9gm/dL (normal 0.6-1.8gm/dL)	PO dapsone, 100mg/day	After initiation of dapsone therapy the patient noted a decrease in pain within 48 hours and a slow resolution of the lesions during the first several months of therapy.	[7]
25 years old	Female	West Indian	7-year history of Crohn's disease	Ears Elbows Dorsal wrists Dorsal feet	Asymptomatic, firm hyperpigmented nodules, approximately 0.5-4cm in diameter	Dense dermal, predominantly neutrophilic, inflammatory infiltrate with marked leukocytoclasis and fibrinoid necrosis of the	Laboratory tests within normal limits: Circulating immune complexes detected by polyethylene glycol precipitation: IgM, C3/C3c, C1q	Not reported	Not Reported	[8]

						superficial dermal vessels. Several loosely formed granulomas within the lower dermis. Positive measles virus antigen immunostaining in nuclei of macrophage-like cells within granulomas.	platelets, white blood cell count Serum IgA level <u>Abnormal laboratory tests</u> Anti-streptolysin O titer, 200U/L (normal <200U/L) Circulating immune complexes detected by polyethylene glycol precipitation: IgG, 0.2g/L (normal 0.015-0.15g/L); IgA, 0.027g/L (normal 0.003-0.025g/L) ESR, 21mm/hr (normal <20mm/hr) Serum IgG, 1970mg/dL (normal 800-1800mg/dL) Serum IgM, 3600mg/dL (normal 70-280mg/dL)			
51 years old	Male	Black	Diagnosed with Crohn's disease and spondyloarthritis at time of case report. 4-year history of chronic hepatitis B virus infection.	Elbows Dorsal finger joints Digital pulps Buttocks Legs Soles of feet	Hyperpigmented papules (extensor surfaces of the finger joints). Purpuric lesions with ulcerations (soles, elbows, digital pulps, legs, and buttocks).	Perivascular neutrophilic granulocytes, some eosinophils, and massive karyorrhexis, but without blood extravasation or fibrinoid deposits in the medium and reticular dermis. Advanced lesions showed slight dermal fibrosis. ERG and CD31 immunostaining demonstrated the presence of many capillary vessels.	<u>Laboratory tests within normal limits</u>: Alanine transferase Angiotensin converting enzyme Anti-double stranded DNA antibody cANCA and pANCA ANA Bacterial and mycobacterial examinations of blood, urine, stool and bronchiolavage	1) PO prednisolone, 1mg/kg/day, sulphasalazine 2g/day and metronidazole 1000mg/day for 16 weeks. 2) PO prednisolone tapered until reaching 0.5mg/kg/day. 3) Azathioprine added, continued	1) Regression of lesions to cicatricial changes. 2) Relapse of intestinal and articular symptoms. No relapse of skin lesions. 3) No relapse of disease.	[9]

						Gram, PAS, Grocott staining, bacteriological and mycobacteriological exams, including *Mycobacterium leprae*, all negative. Immunohistochemistry with anti-*Leishmania*, anti-*Mycobacterium tuberculosis* both negative.	HLA B27 and serum cryoglobulins Parasitological examination of stool Rheumatoid factor <u>Abnormal laboratory tests</u>: Anti-CCP, 40.2U/L, (normal <20 U/L) Aspartate transferase, 45U/L (normal <32) CRP, two mg/dL (normal <0.5mg/dL) ESR, 120mm/h (normal <20) HBV viral load (DNA HBV 314,100,000 UI/mL). Eosinophils 12% of total cell population (normal < 6%) Shift of the myeloid/erythroid ratio in favor of the granulocytic series. Hb 11.7g/dL (normal >13.0g/dL); normocytic Polyclonal hypergammaglobulinemia gamma fraction 3.21g/dL (normal 0.4-1.5g/dL) Prothrombin time (INR 1.3)	prednisolone taper out to one year, then discontinued.		
23 years old	Female	Black	8-year history of Crohn's disease	Elbows Upper/lower legs Knees	a) Painful, pruritic, red-brown papules and nodules varying in size from 3mm to 2.5cm	a) Superficial and deep perivascular and interstitial inflammatory infiltrate composed of numerous neutrophils and lesser numbers of	<u>Laboratory tests within normal limits</u>: ANA BMP	1) PO dapsone, 50mg/day 2) Intralesional triamcinolone injections 1.2ml	1) Acute worsening of chronic anemia,	This case

				Dorsal feet	(knees, elbows, and dorsal feet). b) Erythematous, urticarial linear plaques, irregularly shaped macules, and post inflammatory hyperpigmentation (upper and lower legs)	lymphocytes, histiocytes, and eosinophils. Small vessel vasculitis with fibrinoid necrosis and endothelial cell swelling. Inflammation around adnexal structures into deep dermis/subcutaneous adipose. Concentric fibrosis, karyorrhectic debris surrounding vessels in deep dermis. Overlying epidermis uninvolved. b) Less prominent changes, with perivascular and periadnexal inflammation (numerous neutrophils, scattered eosinophils, lymphocytes and histiocytes. Small vessels within superficial dermis showed neutrophilic infiltrate, karyorrhectic debris, red blood cell extravasation. a,b) Grocott, AFB, Fite staining, and *Mycobacterium tuberculosis* antibody stains all negative.	Bacterial, fungal, AFB cultures Hepatic panel HIV-1 and HIV-2 Antibodies, Quantiferon Gold, syphilis (treponemal IgG), hepatitis C antibody Lipid panel Reticulocyte count Rheumatoid factor Serum IgM level <u>Abnormal laboratory tests</u>: ESR, 130mm/h (normal <20) Serum IgA level, 915mg/dL (normal 68-378mg/dL) Serum IgE level, 819 IU/ml (normal 10-180 iu/ml) Serum IgG level, 2103mg/dl (normal 800-1800mg/dl) Serum free kappa light chain 4.82mg/dl (normal 0.33-1.94mg/dl); serum free lambda light chain 2.36mg/dl (normal 0.57-2.63mg/dl); kappa/lambda free light chain ratio 2.04 (normal ratio 0.26-1.65) SPEP: beta globulin, 136g/dl (normal 0.65-1.15g/dl); gamma globulin 172g/dL (normal 0.65-1.25g/dL)	of triamcinolone 40mg/ml (total 48mg) was injected into the larger lesions on the right and left feet. 3) Surgical excision	dapsone discontinued. 2) No change in physical appearance of lesions, though pain in treated nodules was reduced. 3) Excision sites healed well by next visit. Patient was lost to follow-up after this point.	

AFB, acid-fast bacillus; ANA, anti-nuclear antibody; CRP, C-reactive protein; anti-CCP, anti-cyclic citrullinated peptide; BMP, basic metabolic panel; cANCA, cytoplasmic antineutrophil cytoplasmic antibodies; ERG, erythroblast transformation specific related gene; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; HBV, hepatitis B virus; HIV, human

immunodeficiency virus; HLA, human leukocyte antigen; pANCA, perinuclear antineutrophil cytoplasmic antibodies; PAS, periodic acid-Schiff; PO, per os; Ref, reference; SPEP, serum protein electrophoresis.