



Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2011 June ; 11(3): 298–302. doi:10.1016/j.cml.2011.03.020.

Complete Response to Thalidomide and Dexamethasone in a patient with Necrobiotic Xanthogranuloma Associated with Monoclonal Gammopathy A Case Report and Review of The Literature

Yvonne Efebera, M.D.^{1,2}, Elizabeth Blanchard, M.D.^{1,2}, Charles Allam, M.D.¹, Andrew Han, BS^{1,3}, Saem Lee, BA^{1,3}, and Nikhil Munshi, M.D.^{1,3}

¹Boston VA Healthcare System, Boston, MA

²Boston University Medical Center, Boston MA

³Dana Farber Cancer Institute, Harvard Medical School, Boston MA

Abstract

Necrobiotic Xanthogranuloma (NXG) was first described in 1980 by Kossad and Winkelmann in which they discussed 8 patients with xanthomatous plaques, noted to have monoclonal gammopathy, predominantly IgG kappa type¹. Since then, more than 50 patients with this disorder have been described, with approximately 80% of them associated with a monoclonal gammopathy.

We describe the first case of NXG with associated monoclonal gammopathy, treated with thalidomide plus dexamethasone, achieving complete resolution of the skin lesions and sustaining response more than three years after treatment.

Case

The patient is a 79 y/o male who presented in 2003 with multiple painful lesions of the skin (Figure 1). The lesions were raised and ulcerated. He had no facial or peri-orbital lesions. Biopsy of a lesion confirmed the diagnosis of NXG involving the deep dermis and subcutaneous fatty tissue. Granulomatous changes were seen in an ulcerative background. Plasma cells, which were faintly positive for kappa light chain, were found in small amounts through out. Work up included an IgG kappa monoclonal spike on serum protein electrophoresis, serum IgG of 1980mg/dl (normal: 751–1560), and Kappa of 2040mg/dl (normal: 629–1350). Hematocrit, urine protein electrophoresis, myeloma survey, liver and kidney function were normal. Bone marrow biopsy showed 10% plasma cells. He was diagnosed with NXG with smoldering myeloma. He was started on thalidomide and dexamethasone (TD, T 100mg daily, then 200mg after one month; D 20mg/day for 4 days/2 weeks, then 20mg/day for 4 days/month 6 months later). D was stopped 3 months later due to intolerance. Eight months after starting treatment, his lesions completely dried up (Figure 1). Thalidomide was stopped 2 years after starting it due to symptomatic bradycardia, otherwise, he tolerated it very well with no evidence of neuropathy. He has not required treatment since then and his lesions have remained closed almost 4 years later (Figure 1). Lowest IgG and kappa levels were 750mg/dl and 339mg/dl respectively, correlating with clinical response of the skin lesions.

Discussion and Review of The Literature

Mehregan and Winkelmann reported in 1992 on 48 known cases² and Ugurlu et al further reported in 2000 on 28 additional cases³. The clinical picture of NXG is a slowly progressive, destructive and infiltrating xanthomatous plaques and cutaneous lesions associated with paraproteinemia. The plaques and lesions may involve the trunk and extremities, but more than 80% of patients present with periorbital involvement. The lesions may ulcerate and most often there are areas of indurations consisting of yellow or xanthomatous discoloration. Histologically, NXG is characterized by granuloma formation within the subcutaneous and dermal layers, with focal areas of necrobiosis. The granulomas consist of multinucleated giant cells of several types. Cholesterol clefts within the areas of necrobiosis give the foamy appearance that is often seen. Physical findings outside of the skin lesions are often unrevealing, but in the case series by Mehregan, more than 20% had hepatomegaly, and almost 20% had splenomegaly². Most patients do not have pain or paresthesias, unlike our patient who did. Up to 80% of patients have monoclonal gammopathy of IgG type with either Kappa or Lambda light chain. Hematologic involvement may include neutropenia, cryoglobulinemia, hypocomplementemia, and hyperlipidemia. Systemic involvements have included multiple myeloma, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukemia, lung and heart involvement⁴⁻⁷. However, the most common association is monoclonal gammopathy of uncertain significance (MGUS).

The pathogenesis of NXG remains unclear. Proposed mechanisms include foreign body giant cell reaction precipitated by deposition in the skin of increased serum immunoglobulins complexed with lipid⁸; secondary proliferation of macrophages caused by elevation of paraprotein⁹ and granuloma formation by paraprotein acting as lipoproteins, binding to histiocyte receptors¹⁰. NXG remains a rare condition, thus precluding it from being studied on a large scale. Management of NXG has included surgery, radiation, plasmapheresis, intralesional corticosteroids, and systemic and cytotoxic agents such as chlorambucil, melphalan, interferon alpha-2b, cyclophosphamide, methotrexate, hydroxychloroquine, azathioprine, nitrogen mustard, and high dose steroids^{3,9,11-30}. Two cases have reported use of thalidomide^{30,31}. In the first, only half of the skin ulcers healed without modification of the xanthomatous skin lesions on thalidomide 200mg/day³⁰. Etrretinate 50mg/day was added but patient relapsed 6 months later with leg ulcers. The second was a patient with scleritis, who was treated for an unknown duration and dose of thalidomide and dexamethasone. Our patient was treated with thalidomide 200mg/day for 2 years and dexamethasone for 9 months. Hence a longer duration and higher dose of thalidomide is likely needed to achieve prolonged response. A recent case report showed a complete response in a patient with NXG associated with MGUS treated with lenalidomide and dexamethasone³². Lenalidomide is a more potent analog of thalidomide. Our case is the first in using a combination of thalidomide and pulse dexamethasone, and achieving and sustaining complete response and resolution of lesions more than 3 years after cessation of treatment. Table 1 lists cases reported from 1993 to current except cases from the Mayo Clinic, which have been reported by Ugurlu in 2000³. Prior cases have been reported by Mehregan².

Conclusion

We describe the first case of necrobiotic xanthogranuloma and associated IgG kappa monoclonal gammopathy that responded very well to a combination of pulse dexamethasone and thalidomide and sustaining remission more than 3 years after cessation of treatment. The remission of the patient's skin lesions has correlated with a decrease and stabilization of his IgG kappa levels, suggesting a correlation with his plasma cell dyscrasia and the activity of his skin disease. NXG has been treated with a wide range of therapies, including systemic

cytotoxic drugs that have a wide range of toxic effects. Thalidomide in combination with pulse dexamethasone, which in our case was both successful and well tolerated, should be considered for first line treatment in NXG cases that need systemic therapy.

References

1. Kossard S, Winkelmann RK. Necrobiotic xanthogranuloma with paraproteinemia. *J Am Acad Dermatol.* 1980; 3:257–270. [PubMed: 7451693]
2. Mehregan DA, Winkelmann RK. Necrobiotic xanthogranuloma. *Arch Dermatol.* 1992; 128:94–100. [PubMed: 1739294]
3. Ugurlu S, Bartley GB, Gibson LE. Necrobiotic xanthogranuloma: long-term outcome of ocular and systemic involvement. *Am J Ophthalmol.* 2000; 129:651–657. [PubMed: 10844059]
4. Winkelmann RK, Litzow MR, Umbert IJ, Lie JT. Giant cell granulomatous pulmonary and myocardial lesions in necrobiotic xanthogranuloma with paraproteinemia. *Mayo Clin Proc.* 1997; 72:1028–1033. [PubMed: 9374976]
5. Umbert I, Winkelmann RK. Necrobiotic xanthogranuloma with cardiac involvement. *Br J Dermatol.* 1995; 133:438–443. [PubMed: 8547001]
6. Hunter L, Burry AF. Necrobiotic xanthogranuloma: a systemic disease with paraproteinemia. *Pathology.* 1985; 17:533–536. [PubMed: 4069775]
7. Novak PM, Robbins TO, Winkelmann RK. Necrobiotic xanthogranuloma with myocardial lesions and nodular transformation of the liver. *Hum Pathol.* 1992; 23:195–196. [PubMed: 1740305]
8. Bullock JD, Bartley GB, Campbell RJ, Yanes B, Connelly PJ, Funkhouser JW. Necrobiotic xanthogranuloma with paraproteinemia. Case report and a pathogenetic theory. *Ophthalmology.* 1986; 93:1233–1236. [PubMed: 3101022]
9. Char DH, LeBoit PE, Ljung BM, Wara W. Radiation therapy for ocular necrobiotic xanthogranuloma. *Arch Ophthalmol.* 1987; 105:174–175. [PubMed: 3813945]
10. Rappersberger K, Wrba F, Heinz R, Zonzits E, Honigsmann H. Necrobiotic xanthogranuloma in paraproteinemia. *Hautarzt.* 1989; 40:358–363. [PubMed: 2666345]
11. Finelli LG, Ratz JL. Plasmapheresis, a treatment modality for necrobiotic xanthogranuloma. *J Am Acad Dermatol.* 1987; 17:351–354. [PubMed: 3114339]
12. Venencie PY, Le Bras P, Toan ND, Tchernia G, Delfraissy JF. Recombinant interferon alfa-2b treatment of necrobiotic xanthogranuloma with paraproteinemia. *J Am Acad Dermatol.* 1995; 32:666–667. [PubMed: 7896960]
13. Barzilai A, Trau H, Shpiro D, Yorav S. Necrobiotic xanthogranuloma with paraproteinemia. *Cutis.* 1996; 57:320–322. [PubMed: 8726711]
14. Johnston KA, Grimwood RE, Meffert JJ, Deering KC. Necrobiotic xanthogranuloma with paraproteinemia: an evolving presentation. *Cutis.* 1997; 59:333–336. [PubMed: 9218893]
15. Georgiou S, Monastirli A, Kapranos N, Pasmazi E, Sakkis T, Tsambaos D. Interferon alpha-2a monotherapy for necrobiotic xanthogranuloma. *Acta Derm Venereol.* 1999; 79:484–485. [PubMed: 10598773]
16. Nestle FO, Hofbauer G, Burg G. Necrobiotic xanthogranuloma with monoclonal gammopathy of the IgG lambda type. *Dermatology.* 1999; 198:434–435. [PubMed: 10490307]
17. Randell PL, Heenan PJ. Necrobiotic xanthogranuloma with paraproteinaemia. *Australas J Dermatol.* 1999; 40:114–115. [PubMed: 10333627]
18. Chave TA, Chowdhury MM, Holt PJ. Recalcitrant necrobiotic xanthogranuloma responding to pulsed high-dose oral dexamethasone plus maintenance therapy with oral prednisolone. *Br J Dermatol.* 2001; 144:158–161. [PubMed: 11167699]
19. Chave TA, Hutchinson PE. Necrobiotic xanthogranuloma with two monoclonal paraproteins and no periorbital involvement at presentation. *Clin Exp Dermatol.* 2001; 26:493–496. [PubMed: 11678872]
20. Machado S, Alves R, Lima M, Leal I, Massa A. Cutaneous necrobiotic xanthogranuloma (NXG)--successfully treated with low dose chlorambucil. *Eur J Dermatol.* 2001; 11:458–462. [PubMed: 11525957]

21. Criado PR, Vasconcellos C, Pegas JR, et al. Necrobiotic xanthogranuloma with lambda paraproteinemia: case report of successful treatment with melphalan and prednisone. *J Dermatolog Treat.* 2002; 13:87–89. [PubMed: 12060508]
22. Burdick AE, Sanchez J, Elgart GW. Necrobiotic xanthogranuloma associated with a benign monoclonal gammopathy. *Cutis.* 2003; 72:47–50. [PubMed: 12889715]
23. Martinez Fernandez M, Rodriguez Prieto MA, Ruiz Gonzalez I, Sanchez Sambucety P, Delgado Vicente S. Necrobiotic xanthogranuloma associated with myeloma. *J Eur Acad Dermatol Venereol.* 2004; 18:328–331. [PubMed: 15096146]
24. Meyer S, Szeimies RM, Landthaler M, Hohenleutner S. Cyclophosphamide-dexamethasone pulsed therapy for treatment of recalcitrant necrobiotic xanthogranuloma with paraproteinemia and ocular involvement. *Br J Dermatol.* 2005; 153:443–445. [PubMed: 16086766]
25. Vieira V, Del Pozo J, Martinez W, Veiga-Barreiro JA, Fonseca E. Necrobiotic xanthogranuloma associated with lymphoplasmacytic lymphoma. Palliative treatment with carbon dioxide laser. *Eur J Dermatol.* 2005; 15:182–185. [PubMed: 15908304]
26. Langlois S, Brochet P, Reguiat Z, et al. Necrobiotic xanthogranuloma with multiple myeloma. Case report and pathogenic hypotheses. *Joint Bone Spine.* 2006; 73:120–122. [PubMed: 16085444]
27. Oumeish OY, Oumeish I, Tarawneh M, Salman T, Sharaiha A. Necrobiotic xanthogranuloma associated with paraproteinemia and non-Hodgkin's lymphoma developing into chronic lymphocytic leukemia: the first case reported in the literature and review of the literature. *Int J Dermatol.* 2006; 45:306–310. [PubMed: 16533236]
28. Torabian SZ, Fazel N, Knuttel R. Necrobiotic xanthogranuloma treated with chlorambucil. *Dermatol Online J.* 2006; 12:11. [PubMed: 16962026]
29. Ito Y, Nishimura K, Yamanaka K, et al. Necrobiotic xanthogranuloma with paraproteinemia; an atypical case. *J Dtsch Dermatol Ges.* 2008; 6:40–43. [PubMed: 17941882]
30. Hauser C, Schifferli J, Saurat JH. Complement consumption in a patient with necrobiotic xanthogranuloma and paraproteinemia. *J Am Acad Dermatol.* 1991; 24:908–911. [PubMed: 1904889]
31. Wilhelmus KR, Yen MT, Rice L, Font RL. Necrobiotic xanthogranuloma with posterior scleritis. *Arch Ophthalmol.* 2006; 124:748. [PubMed: 16682604]
32. Silapunt S, Chon SY. Generalized necrobiotic xanthogranuloma successfully treated with lenalidomide. *J Drugs Dermatol.* 9:273–276. [PubMed: 20232591]

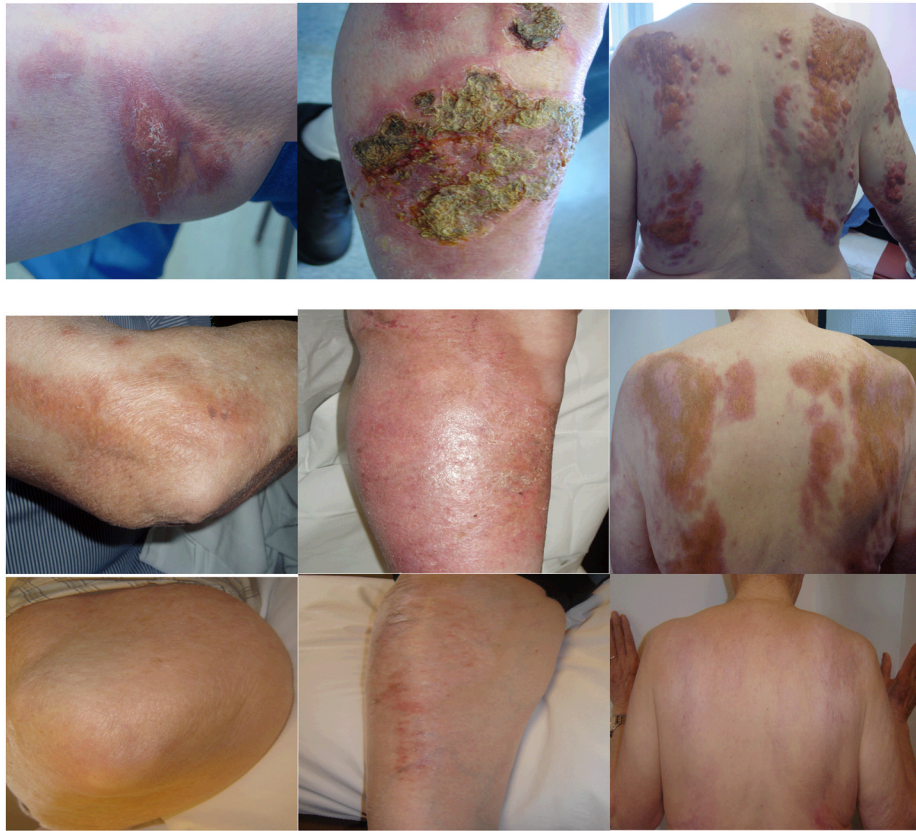


Fig 1. Initial presentation (top panel); 8 months into treatment (middle); 3yrs after end of treatment (bottom)

Table 1

Reported cases of necrobiotic xanthogranuloma.

Author/yr	Age, y/sex	Location	Paraprotein	BM	Other organ involvement	Treatments received / outcome
Venencie ¹² 1995	65/F	Periorbital, presternal, shoulders	IgG kappa	<10% plasma cells	none	Initial Melphalan+ prednisone, then Interferon alfa-2b+prednisone. Still on prednisone 1.5 yrs later. Lesions flattened with residual pigmentation
Barzilai ¹³ 1996	85/F	Face, trunk extremities	IgG kappa	Not done	Possibly cardiac	None. Patient refused
Johnston ¹⁴ 1997	69/F	Thighs, arms, back	IgG kappa	Normal	None	Intralesional corticosteroid injection of symptomatic lesions. Outcome not noted
Georgiou ¹⁵ 1999	82/M	Chest, back	Not indicated	Not done	None	Interferon alpha -2a. Resolution after 4 months therapy. No recurrence 22 months after therapy
Nestle ¹⁶ 1999	77/F	Neck, trunk, arms, legs	IgG lambda	Normal	None	Initial PUV A and radiotherapy. Then melphalan x 6 cycles with resolution. No long-term follow up noted.
Randell ¹⁷ 1999	51/F	Periorbital	IgG lambda	Normal	None	Treatment not discussed.
Chave ¹⁸ 2001	66/F	Periorbital, neck, chest, abdomen	IgG kappa	Normal	None	Chlorambucil, cytoxan, melphalan, etoposide plasmapheresis and IFN- α 2b all ineffective. high-dose dexamethasone x 2 cycles with continued prednisolone with encouraging response
Chave 19 2001	75/M	Periorbital, Upper back, shoulders, arms, thigh	IgG kappa IgG lambda	2% plasma cells	None	No systemic treatment at 1 year since presentation
Machado ²⁰ 2001	51/M	Neck, trunk	IgG lambda	5–10% plasma cells	Cryoglobulinemia, splenomegaly	Chlorambucil x 7 mos with eventual disappearance of all lesions. No recurrence at 9 mos follow up
Vasconcellos ²¹ 2002	40/F	Periorbital, legs, thighs, back	IgG lambda	Normal	None	Melphalan +prednisone. Stopped treatment after 2 mos- reason not given
Burdick ²² 2003	57/F	Periorbital, upper body	IgG lambda	Xanthogranuloma within medullar No malignancy	Hepatomegaly	No treatment initiated
Fernandez ²³ 2004	73/M	Periorbital	IgG kappa	14% plasma cells	Multiple myeloma	Surgical removal of eyelid skin. Melphalan ongoing at 9 mos
Meyer ²⁴ 2005	53/F	Periorbital	IgG kappa	5% plasma cells	None	Numerous nonresponsive therapies. Stable therapeutic response after 9 cycles of intravenous cytoxan+dexamethasone (mesna given for bladder protection. Treatment was ongoing.

Author/yr	Age, y/sex	Location	Paraprotein	BM	Other organ involvement	Treatments received / outcome
Viera ²⁵ 2005	68/F	Periorbital, buttocks	IgG lambda	Not done	Prior history of lymphoplasmacytic lymphoma	Carbon dioxide laser for 3 sessions with residual lesions of NXG present. No relapse at 12 months follow-up.
Langlois, ²⁶ 2006	75/F	Periorbital, neck, arms, torso, neck, umbilical	IgG lambda	Not reported	Multiple myeloma	Melphalan+prednisone. Skin lesions faded after 2 courses. Length of treatment not noted
Oumeish ²⁷ 2006	56/F	Periorbital, face, chest, back,	IgG kappa	NHL, CLL	NHL, CLL	Cytoxan, endoxan, leukeran, melphalan and prednisolone. Excellent response of the NHL and CLL. Unsatisfactory response of skin lesions despite cyclosporine and systemic steroids
Torabian ²⁸ 2006	55/M	Periorbital, extremities, trunk	IgG lambda	2% plasma cells	None	Chlorambucil. Flattening and disappearance of skin lesions but persistent Paraprotein spike at 6 mos of treatment
Ito ²⁹ 2007	86/F	Limbs	IgG lambda	Patient refused	None	Patient died of myocardial infarction shortly after diagnosis
Silapunt 2010	81/M	Extremities, trunk, face	IgG Kappa	10% plasma cells	None	Lenalidomide and dexamethosone x 3 months with resolution of skin lesions.. no recurrence at 12 months follow-up

CLL means chronic lymphocytic leukemia, NHL non hodgkins lymphoma