Clin Rheumatol (2012) 31:183–187
DOI 10.1007/s10067-011-1866-3

CASE BASED REVIEW

D-penicillamine in the treatment of eosinophilic fasciitis: case reports and review of the literature

CU Manzini · M Sebastiani · D Giuggioli · A Manfredi · M Colaci · AM Cesinaro · C Ferri

Received: 28 July 2011 / Revised: 15 August 2011 / Accepted: 24 September 2011 / Published online: 12 October 2011

Abstract Eosinophilic fasciitis (EF) is a rare disease characterized by symmetrical thickness and hardening of the skin, especially localized to forearms and thorax, with eosinophilia. Corticosteroids represent the first-line therapy, even if some patients are scarcely responsive and/or may develop important side effects due to long-term treatment. Here, we describe three cases of EF, two of them refractory to previous steroid therapy, successfully treated with D-penicillamine. The present clinical observations together with the updated review of the literature suggest usefulness of D-penicillamine in EF patients, as well as its potential steroid-sparing value.

Keywords Eosinophilic fasciitis · D-penicillamine

Introduction

Eosinophilic fasciitis (EF), or Shulman syndrome [1], is a rare disease characterized by symmetrical thickness and hardening of the skin, especially localized to the forearms and thorax, with eosinophilia, increased erythro-sedimentation rate (ESR), and hypergammaglobulinemia. In the acute phase, the histological studies show an inflammatory infiltration, containing B-lymphocytes, plasmacells, macrophages, and eosinophils, primarily localized to the subcutaneous tissues, particularly to the fascia [1]. Subsequently, the infiltration decreases, while collagen deposition increases leading to frank fibrosis.

In some cases, patients with EF may develop various organ alterations involving kidney [2–4], pleura, pericardium, lung [5–7], joints [8, 9], and peripheral nervous system [10]; sometimes, it can be also associated to distinct diseases, especially hemopathies [11–16] or other autoimmune disorders [16–18]. The etiology of EF is still unknown; it has been hypothesized that excessive physical efforts [19–22], trauma [23], exposure to toxic substances [24], and/or drug intake [25–29] may represent the triggering factors of the disease.

Corticosteroids represent the gold standard therapy, although favorable results were obtained with cimetidine [28], cyclosporine [29, 30], D-penicillamine [31–39], methotrexate [40], hydroxyzine [41], polyvalent immunoglobulins [42], extracorporeal photochemotherapy [43, 44], allogenic bone transplantation [45], and fasciectomy [46].

Here, we describe three cases of EF, two of them refractory to previous steroid therapy, successfully treated with D-penicillamine (D-pen).

Case reports

Case 1

CM, 59 year-old male, with history of alcoholism, arterial hypertension, and ischemic heart disease. In March 2003,

C. Manzini · M. Sebastiani (✉) · D. Giuggioli · A. Manfredi · M. Colaci · C. Ferri
Rheumatology Unit, Department of Internal Medicine, University of Modena e Reggio Emilia, Medical School, Via del Pozzo, 71, 41121 Modena, Italy
e-mail: marco.sebastiani@unimore.it

A. Cesinaro
Anatomia e Istologia Patologica, University of Modena e Reggio Emilia, Medical School, Modena, Italy

he referred the appearance of pain, weakness, and stiffness to the limbs, especially to the arms, during a period of intense physical activity. The skin appeared thickened, hardened, and "peau-d'orange-like"; flexion contractures of elbows and fingers were also associated.

Laboratory investigations revealed marked blood hypereosinophilia (35%; WBC 8.200/ml) and ESR of 35 mm (range 0–15); nailfold capillaroscopy examination excluded the presence of a scleroderma pattern.

The biopsy of skin and muscle at deltoid level showed the thickening of hypodermal fascia, perivascular inflammatory infiltrate containing T-lymphocytes, plasmacells, eosinophils, and some mastcells, while no histological alterations of cutis or muscle were found.

Immunohistochemical analysis revealed the predominance of CD8 T-suppressor lymphocytes, low positivity of CD4 T-helper lymphocytes, CD68 cells (macrophages), and mastcells.

The bone marrow biopsy revealed a 50–60% cellularity with marked hyperplasia of eosinophilic granulocytopoiesis, lymphocytosis, and plasmocytosis. Moreover, the elastometry and ecotomography showed an increased thickness with reduced elasticity of the skin in the examined areas.

In July 2003, the patient stopped alcohol abuse and was treated with high dosage of steroids (50 mg/day of prednisone, slowly tapered to 6.25 mg/day into 3 months). In February 2004, because of the persistence of skin manifestations, D-pen was associated to steroids.

The D-pen treatment determined a clear-cut improvement of cutaneous manifestations with satisfying recovery of mobility; the therapy was stopped 6 months later because of the appearance of bullous dermatitis of the lower limbs, even if in the absence of EF clinical relapse.

The clinical improvement was confirmed by elastometry and ecotomography showing the reduction of the skin thickness of the forearms with increased elasticity of the hands and legs. Moreover, laboratory tests revealed the normalization of altered parameters; in particular, eosinophils markedly decreased from 35% to 5.8%.

During the next 12 month follow-up, the skin changes were almost disappeared together with the main clinical symptoms; therefore, the patient returned to his normal activities.

Case 2

RA, 60 year-old female, was evaluated for the first time in July 2005, for the appearance, 3 months before, of skin thickening of trunk, thigh, and leg bilaterally and flexory surface of upper limbs, after a physical stress. Burning pain and skin erythema were also present in the absence of Raynaud's phenomenon.

Laboratory investigations showed hypereosinophilia (20%; WBC 7.300/ml), ESR 42 mm (range 1–15), reactive C protein (RCP) 2.6 mg/dl (range 0.5–1), and hemoglobin 11.7 g/dl.

The presence of lymphohisthiocytic and eosinophilic infiltrates in reticular dermis extended to fat layer, with a slight thickening of fibrotic septa observed at skin and muscle biopsy; chronic inflammatory infiltrate and occasional eosinophils in the fascia were also detected.

Immunohistochemical analysis of bioptical tissues revealed the presence of CD3 and CD68-positivity (in some groups of histiocytes, mainly in deep reticular dermis and subcutaneous adipose tissue); isolated B-cell CD20 positivity. No positivity for CD56 (NK) was found.

In September, the patient began D-pen treatment (600 mg/day) and steroids (prednisone 20 mg). About 6 weeks later, we observed the disappearance of hypereosinophilia with clear symptoms improvement, namely, the skin became softer, particularly in the forearms, while erythema and itch disappeared.

During the following 12 months, the patient showed a progressive clinical improvement; consequently, the dosage of both steroids and D-pen was gradually tapered, until the discontinuation within 1 year.

Case 3

A 45 year-old woman was admitted to our Rheumatology Unit in the July 2003 because of the appearance in May 2003 of transient swelling of lower limbs, which recently evolved to symmetrical hardness of the skin at the trunk and the extremities, subsequent to an intense physical effort.

During the following 10 weeks, the areas of "tight skin" expanded to forearms and shanks; groove sign at the forearms, muscle weakness, and arthralgias localized to feet and hand were also present.

Laboratory examinations revealed hypereosinophilia (24%; eosinophils count 1,800/ml), high ESR (65 mm; range 0–15), and mild hypergammaglobulinemia (23.4%).

The skin and muscle biopsy showed abundant perivascular infiltrates of eosinophils and lymphoid cells in the skin and fascia.

The patient was treated with three pulses of methylprednisolone (500 mg/day, for 3 days) and then with oral methylprednisolone (initially 32 mg/day); steroid dosage was gradually tapered to 4 mg every 2 weeks. Due to the scant therapeutical effect of steroids, 1 month later, D-pen (600 mg/day) was associated. The laboratory alterations, i.e. hypereosinophilia, high ESR, and hypergammaglobulinemia were normalized within 4 months of therapy. Concomitantly, skin lesions gradually improved, and muscle weakness and arthromyalgias markedly improved within 3 months

of D-pen therapy. During the first 6 months of treatment, steroid dosage was progressively tapered upto 4 mg/day, and D-pen was reduced to 300 mg/day. The treatment was discontinued after 1-year follow-up period, when clinical manifestations were completely recovered; only dyschromic alterations of the skin persisted.

Interestingly, all three patients remained stable after long-term clinical follow-up, ranging from 5 to 7 years. Table 1 summarizes the results of all cases present in the literature. Besides the three patients here described, a clear-cut improvement of EF was observed in other four cases [32, 35–37]; among the remaining 12 patients treated with D-pen, a variable clinical improvement was observed in ten [34, 38, 39], while in two, no significant clinical variations were recorded [33].

Discussion

The results observed in the three patients herein described suggest the therapeutical usefulness of D-pen therapy in patients with EF. During the treatment, the typical clinico-serological and histopathological features of EF showed a complete clinical remission that remained stable during long-lasting follow-up.

As previously observed in some clinical reports [17–21], our patients developed the disease after a period of intense physical activity. Therefore, physical stress might be regarded as triggering factor of EF immunological abnormalities; at the least it could contribute to the clinical emergence of the disease in predisposed subjects.

With regard to hypereosinophilia, the laboratory hallmark of EF, it is not well ascertained whether eosinophils are directly involved in the inflammatory process responsible for the disease or their increase could represent the expression of a previous contact with triggering allergens or other elements. In addition, we cannot exclude that the two different pathogenetic mechanisms could be involved in EF: one is allergic as testified by the presence of eosinophilia, the other one is as testified by cellular polymorphic infiltrate, in the fascia.

It is also known that eosinophils, like macrophages and T-lymphocytes, can produce TGF-α, the predominant cytokine in the pathogenesis of fibrosis [47, 48]. The eosinophils seem to be actively involved in the pathogenesis of fascial alterations, although the discrepancy between the haematic hypereosinophilia and the limited presence or absence of these cells at the fascia level raises some important doubts [19, 49, 50].

Other questions remained not completely resolved: the role of lymphocytes, macrophages and mastcells in the inflammatory infiltrate of fascia, as well as the possible relationship between these cells and peripheral eosinophilia. Histologic and ultrastructural investigations [49] on subcutaneous tissue from a patient with EF, the presence of lymphocytes (most of them with cerebral-like nucleus, similar to that of "Sezary cells"), plasmacells, histiocytes but especially mastcells, shows clear signs of degranulation. It is known that mastcells play a key role in allergic responses, which may recall, into the flogistic sites, leukocytes (including lymphocytes T-CD8+ and eosinophils); these latter are able to present T-cell antigens and are also involved in the fibrotic process and tissue-remodeling [51]. Other Authors reported in 10 of 11 patients with EF the presence of flogistic subcutaneous infiltrate including numerous macrophages, lymphocytes and a few eosinophils [50]. Besides, the fascial lesions showed macrophages and T lymphocytes CD8+; some of them, containing granzyme B (a strong apoptotic), which suggests the existence of a cytotoxic response, probably after the exposure of these cells to an antigen or other stimuli [50].

Moreover, T lymphocyte themselves are involved in the immune response of the recognition and elimination of antigens (both endogenous and exogenous) and the same cells, once activated, can produce pro-fibrotic growth factors like the TGFα1 cytokine that are able to stimulate the fibroblast proliferation and production of large amount of extracellular matrix [29].

Table 1 D-penicillamine treatment in patients with eosinophilic fasciitis

Authors	Patient no.	Duration of therapy	Results	Side effects
Epler et al. [41]	1	6 months	Remission	Dyspnea; leucopenia
Coyle et al. [39]	1	6 weeks	Partial remission	No
Caspi et al. [32]	1	Not indicated	Remission	No
Kovalev et al. [37]	1	28 days	Remission	No
Martinez-Osuna et al. [33]	2	Not indicated	Mild improvement	No
Farrington et al. [38]	7	2–4 years	Marked improvement	No
Stork et al. [34]	1	2 years	Marked improvement	Vitiligo
Kato et al. [31]	1	42 weeks	Remission; therapy discontinued	Myasthenia gravis
Present series 2011	3	6–12 months	Remission	1/3 Bullous dermatitis

Our histological and immune-histochemical investigations on fascial and perifascial inflammatory infiltrate showed that it is mainly composed of lymphocytes CD8+, with activated phenotype, and that the macrophages and mastcells, fairly represented, are numerically superior to lymphocytes T-CD4+.

So we can suppose that these discordant findings may represent different evolutionary steps of the inflammatory process present at the time of biopsy and/or different individual immune reactivity.

The hypothesis that an immune mechanism could sustain the pathogenesis of EF is strongly supported by numerous epidemiological and clinico-pathological aspects: complementary injury, immunoistochemical findings, detection of Ig deposits in subcutaneous tissue [22], increased ESR, gamma-globulin, and circulating immune complexes [1]; the consideration that EF can join or occur in the course of other immune diseases; and lastly, the therapeutical usefulness of steroids and other immunosuppressive drugs.

In this regard, the D-pen can play an important role in the treatment of EF as steroid-sparing drug that is able to reduce the immune-mediated alterations and the disease progression. The beneficial effect of D-pen observed in our patients confirmed some anecdotical observations [31–35]. Contrarily to that reported in previous therapeutical attempts, D-pen treatment was well tolerated by all three patients, in the absence of relevant drug-related side effects.

The rarity of EF was a major problem in performing a controlled clinical trial with D-pen in EF patients; perhaps a multicenter study leads to statistically definite results. However, the observed clinical variations in our patients clearly suggest the usefulness of D-pen in EF patients, as well as its potential steroid-sparing value. Although this is limited to a few case reports, the literature provides valuable data keeping with this hypothesis.

Disclosures None.

References

1. Shulman LE (1974) Diffuse fasciitis with hypergammaglobulinemia and eosinophilia: a new syndrome? J Rheumatol 1:S46
2. Miret C, Nonell F, Cervera R, Rodrigues FE, Torres M (2003) IgA nephropathy associated with eosinophilic fasciitis: report a case. Clin Exp Rheum 21:268
3. Kirschstein M, Helmchen U, Jensen R, Kuster RM, Lehmann H (1999) Kidney involvement in a 17-year old boy with eosiniphilic fasciitis. Clin Nephrol 52:183–187
4. Takeda SI, Takarakura E, Fukui Y (1995) Tubulointerstitial nephritis in a patient with eosinophilic fasciitis and IgA nephropathy. Nephron 69:314–317
5. Rizzo S (2002) Eosinophilic pleuropericarditis and fasciitis. A new case Monaldi Arch Chest Dis 57:311–313
6. Killen JW, Swift GL, White RG (2000) Eosinophilic fasciitis with pulmonary and pleural involvement. Postgrad Med 76:36–37
7. Cayla J, Rondier J, Thibierge M, Emerit I, Malherbe M, Guiraudon C (1981) Un cas de fasciite à eosinophiles avec péricardite. Rev Rhum Mal Osteoartic 48:809–812
8. Giordano M, Ara M, Cicala C, Valentini G, Chianese U, Vatti M (1980) Eosinophilic fasciitis. Am J Med 93:645–646
9. Rosenthal J, Benson MD (1980) Diffuse fasciitis and eosinophilia with symmetric polyathritis. Ann Int Med 92:507–509
10. Moriguchi M, Terai C, Kuroki S, Tanaka E, Someya N, Tsunoda Y, Kashivazaki S (1998) Eosinophilic fasciitis complicated with peripheral polyneuropathy. Intern Med 37:417–420
11. Farrell AM, Ross JS, Bunker CB (1999) Eosinophilic fasciitis associated with autoimmune thyroid disease and myelodisplasia treated with pulsed methylprednisolone and antihistamines. Br J Dermatol 140:1185–1188
12. Khanna D, Verity A, Grossman JM (2002) Eosinophilic fasciitis with multiple myeloma. Ann Rheum Dis 61:1111–1112
13. Masuoka H, Kikuchi K, Takahasi S, Hayashi N, Farue M (1998) Eosinophilic fasciitis associated with low-grade T cell Lymphoma. Br J Dermatol 139:928–930
14. Junca J, Cuxart A, Tural C, Ojanguren I, Flores A (1994) Eosinophilic fasciitis and non-Hodgkin lymphoma. Eur J Haematol 52:34–36
15. Garcia VP, de Quiros JF, Caminal L (1998) Autoimmune hemolitic anemia with eosinophilic fasciitis. J Rheumatol 25:1864–1865
16. Backmayer C, Monge M, Dhote R, Sanguina M, Aractingi S, Mougeot-Martin M (1999) Eosinophilic fasciitis following idiopathyc trombocytopenic purpura, autoimmune hemolytic anemia and Hashimoto's disease. Dermatology 199:282
17. Gallardo F, Vadello M, Mitjavila F, Servitje O (1998) Systemic lupus erithematosus after eosinophilic fasciitis:a case report. J Am Acad Dermatol 39:283–285
18. Cervini C, Scuppa L, Grassi W, Piergiacomi G (1982) La fasciite à eosinophiles: description d'un cas clinique avec syndrome de Sjogren et syndrome du tunnel carpien. Rev Rhum 25:1180–1185
19. Manzini CU, Dotoli R, Villani M, Mascia MT, Manzini E (1986) La fascite eosinofila. Contributo casistico (Considerazioni patogenetiche e nosografiche). Boll Soc Med Chir Modena 1–2:53–62
20. Liou CH, Huang GS, Taylor JA, Juan CJ, Gao HW, Chen CY (2003) Eosinophilic fasciitis in a military recruit: MRI evaluation with clinical correlation. Skeletal Radiol 32:152–157
21. Velasquez X, Gutierrez MA, Rosenberg H, Figueroa F, Bronstein E, Jacobelli S (2002) Eosinophilic fasciitis; report of 3 cases. Rev Med Chil 130:206–14
22. Barnes L, Rodnan GP, Medsger TA Jr, Short D (1979) Eosinophilic fasciitis. A pathologic study of twenty cases. Am J Pathol 96:493–517
23. Romero AG, Fernandez JG, Calataynd JC (2001) Eosinophilic fasciitis associated with simple traumatism. Acta Dermatovenereol Croat 9:287–290
24. Hamilton M (1991) Eosinophilic fasciitis associated with L-tryptofan ingestion. J Rheum Dis 50:55–56
25. Choquet-Kastylevvski G, Kanikatis J, Dumas V, Descotes J, Faure M, Claudy AR (2001) Eosinophilic fasciitis and simvastatin. Arch Int Med 161:1456–1457
26. Cantini F, Salvarani C, Olivieri I, Padula A, Senesi C, Bellandi F, Truglia et al (1998) Possible association between fasciitis and subcutaneous heparin use. J Rheumatol 25:383–385
27. Smith JD, Chang KL, Gums JG (1988) Possible lansoprazole-induced eosinoplic sindrome. Ann Pharmacother 32:196–200
28. Solomon G, Barland P, Rifkin H (1982) Eosinophilic fasciitis responsive to cimetidine. Ann Intern Med 97:547–549
29. Hayashi N, Igarashi A, Matsuyama T, Harada T (2000) Eosinophilic fasciitis following exposure to trichloroethylene: successful treatment with cyclosporin. Brit J Dermatol 142:830–832
30. Valencia IC, Chang A, Kirsner RS, Kerdel FA (1999) Eosinophilic fasciitis responsive to treatment with pulsed steroids and cyclosporine. Int J Dermatol 38:369–372

31. Kato Y, Naito Y, Narita Y, Kuzuhara S (1997) D-penicillamine-induced myasthenia gravis in a case of eosinophilic fasciitis. J Neurol Sci 146:85–86
32. Caspi D, Fishel R, Varon M, Yona E, Baratz M, Yaron M (1982) Multisystem presentation of eosinophilic fasciitis. Rheumatol Rehabil 21:218–221
33. Martínez-Osuna P, Wallach PM, Seleznick MJ, Levin RW, Silveira LH, Jara LJ, Espinoza LR (1991) Treatment of the eosinophilia-myalgia syndrome. Semin Arthritis Rheum 21:110–121
34. Stork J, Němcová D, Hoza J, Kodetová D (1996) Eosinophilic fasciitis in an adolescent girl with lymphadenopathy and vitiligo-like and linear scleroderma-like changes. A case report Clin Exp Rheumatol 14:337–344
35. Bischoff L, Derk CT (2008) Eosinophilic fasciitis: demographics, disease pattern and response to treatment: report of 12 cases and review of the literature. Int J Dermatol 47:29–35
36. Epler GR, Snider GL, Gaensler EA, Cathcart ES, FitzGerald MX, Carrington CB (1979) Bronchiolitis and bronchitis in connective tissue disease. A possible relationship to the use of penicillamine. JAMA 242:528–532
37. Kovalev VM, Krivenko ZF (1989) New aspects of the pathogenesis and treatment of Schulmann's eosinophilic fasciitis. Vestn Dermatol Venerol 12:13–15
38. Farrington ML, Haas JE, Nazar-Stewart V, Mellins ED (1993) Eosinophilic fasciitis in children frequently progresses to scleroderma-like cutaneous fibrosis. J Rheumatol 20:128–132
39. Coyle HE, Chapman RS (1980) Eosinophilic fasciitis (Shulman syndrome) in association with morphoea and systemic sclerosis. Acta Derm Venereol 60:181–182
40. Pouplin S, Daragon A, Le Loet X (1998) Treatment of eosinophilic fasciitis with methotrexate. J Rheumatol 25: 606–607
41. Uckum A, Sipahi T, Akgun D, Oksai A (2002) Eosinophilis fasciitis successfully treated with oral hydroxyzine: a new therapeutic use of an old drug? Eur J Pediatr 161:118–119
42. Boni-Sadr F, Leautez S, El Kouri D, Hamidou M, Barrier JH, Raffi F (2000) Intéret des immunoglobulines au cours de la fasciite de Shulman. La Presse Méd 6:307
43. Romano C, Rubegni P, De Aloe G, Stanghellini E, D'Ascenzo G, Andreassi L, Fimiani M (2003) Extracorporeal photochemotherapy in the treatment of eosinophlic fasciitis. Eur Acad Dermatol Venereol 17:10–13
44. Schiener R, Behrens-Williams SC, Gottlober P, Pillekamp H, Peter RU, Kerscher M (2000) Eosinophilic fasciitis treated with psoralen-ultraviolet. A bath photochemotherapy. Br J Dermatol 142:804
45. Cetkovsky P, Koza V, Cetkovska P, Svojgrova M (1998) Successful treatment of severe Shulman' syndrome by allogenic bone marrow transplantion. Bone Marrow Transpl 21:637
46. Neumeister MW, Robertson GA (1998) Therapeutic fasciectomy for eosinophilic fasciitis. Ann Plasturgery 41:208–210
47. Naschitz JE, Boss JH, Misselevich I, Yeshurun D, Rosner I (1996) The fasciitis-panniculitis syndromes. Clinical and pathologic features. Medicine 75:6–16
48. Gardner H, Strehlow D, Bradley L, Widom R, Farina A, de Fougerolles A et al (2004) Global expression analysis of the fibroblast transcriptional response to TGFγά. Clin Exp Rheumatol 22:S47
49. Gabrielli A, De Nictolis M, Campanati G, Cinti S (1983) Eosinophilic fasciitis: a mast cell disorder? Clin Exp Rheumatol 1:75–80
50. Toquet C, Hamidou MA, Renaudin K, Jarry A, Foule P, Barbarot S, Laboisse C, Mussini J (2003) In situ immunophenotype of the inflammatory infiltrate in eosinophilic fascitis. J Rheumatol 30:1811–1815
51. Mekori YA (2004) The mastocyte: the«other»inflammatory cell in immunopathogenesis. J Allergy Clin Immunol 114:15–21