Severe Aplastic Anemia Associated With Eosinophilic Fasciitis

Report of 4 Cases and Review of the Literature

Adèle de Masson, MD,* Jean-David Bouaziz, MD, PhD,* Régis Peffault de Latour, MD, PhD, Ygal Benhamou, MD, Cécile Moluçon-Chabrot, MD, Jacques-Olivier Bay, MD, PhD, Annie Laquérière, MD, PhD, Jean-Michel Picqenot, MD, PhD, David Michonneau, MD, Vanessa Leguy-Séguin, MD, Michel Rybojad, MD, Bernard Bonnotte, MD, Fabrice Jardin, MD, PhD, Hervé Lévesque, MD, PhD, Martine Bagot, MD, PhD,† and Gérard Socié, MD, PhD†

Abstract: Diffuse eosinophilic fasciitis (Shulman disease) is a rare sclerodermaform syndrome that, in most cases, resolves spontaneously or after corticosteroid therapy. It has been associated with hematologic disorders, such as aplastic anemia. The clinical features and long-term outcomes of patients with eosinophilic fasciitis and associated aplastic anemia have been poorly described. We report the cases of 4 patients with eosinophilic fasciitis and associated severe aplastic anemia. For 3 of these patients, aplastic anemia was refractory to conventional immunosuppressive therapy with antithymocyte globulin and cyclosporine.

INTRODUCTION

As first described by Shulman in 1974,112 eosinophilic fasciitis (EF) is a rare connective tissue disease characterized by symmetrical swelling and progressive thickening and stiffness of the subcutaneous tissue, leading to a dimpled, “peau d’orange” presentation of the skin. Myalgia, inflammatory polyarthritis, pedal and lower extremity edema and morphea are also commonly reported.75 The hands may be affected by skin sclerosis, but facial involvement is rarely observed. Visceral involvement, Raynaud phenomenon, telangiectasia, calcinosis cutis, and nail-fold capillaroscopy abnormalities are very uncommon in EF;73 usually enabling its distinction from systemic sclerosis. In up to half of the cases, the onset of symptoms seems to follow a vigorous level of exercise to which the patient was unaccustomed. Peripheral eosinophilia and hypergammaglobulinemia are often present.75 A definitive diagnosis relies on histopathologic observation of modifications of the fascia and lower subcutis, including edema and infiltration by plasma cells, lymphocytes, histiocytes, and eosinophils; later, these changes manifest as thickening and collagenization of the fascia. These alterations can extend into the dermis and underlying muscle.8 The dermatologic prognosis after corticosteroid therapy is usually good, with complete remission in most patients, yet persistent disability resulting from residual fibrosis occurs in 29%–42% of cases.37,76 EF is sometimes associated with hematologic diseases, particularly with aplastic anemia (AA) (n = 19),2,22 but also with T-cell lymphoma (n = 5),27,36,65,72,83 cutaneous T-cell lymphoma (n = 1),25 Hodgkin disease (n = 3),52,90 myeloproliferative syndromes (n = 3),61,75,85 myelomonocytic leukemia (n = 2),75,85 chronic lymphocytic leukemia (n = 2),12,75 multiple myeloma (n = 1),68 and myeloblastic leukemia (n = 1),90 and, less commonly, with solid tumors such as breast cancer (n = 5),12,90,109,127 chordial melanoma (n = 1),125 colorectal cancer (n = 1),94 and prostate cancer (n = 1).90 Diffuse EF has also been reported in association with autoimmune disorders, such as Hashimoto thyroiditis (n = 6),2,5,13,59,112 systemic lupus erythematosus (n = 4),6,65,45,74 Crohn disease (n = 1),82 Graves disease (n = 1),116 glomerulonephritis (n = 1),85 rheumatoid arthritis (n = 1),81 type 1 diabetes (n = 1),86 and autoimmune cytopenias, including autoimmune hemolytic anemia (n = 2),545 immune thrombocytopenic purpura (n = 2),5111 amegakaryocytic thrombocytopenia (n = 2),26,48 and pure red-cell aplasia (n = 1).81

It is still uncertain whether AA associated with EF is an autoimmune disease and/or the initial manifestation of an evolving clonal myeloid disorder. Among the 19 reported patients with EF and associated AA,2,13,15,22,24,30,33,38,37,58,73,77,89,95,111,117,128 8 died of complications from AA. Although most of these deaths occurred in patients receiving corticosteroids and/ or antithymocyte globulin (ATG)-based regimens (without
cyclosporine A (CsA)) in the 1980s, the current conventional immunosuppressive therapy of ATG and CsA was ineffective in 3 of 6 (50%) cases. We report 4 patients with severe aplastic anemia (SAA) and EF and provide a comprehensive review of the literature, focusing on clinical presentation, therapeutic challenges, and the outcomes of AA associated with EF.

PATIENTS AND METHODS

Between 1996 and 2012, 4 patients with EF and associated SAA were analyzed retrospectively at 4 French university hospitals. All of the patients had clinical and histopathologic features of EF, together with pancytopenia and, upon bone marrow examination, marked hypocellularity, and they fulfilled the established criteria for SAA diagnosis.19 Two of these patients have been previously reported, and we provide additional information on their clinical features and long-term follow-up.

We searched the National Library of Medicine’s MEDLINE database (Bethesda, MD) for relevant literature using the keywords “fascitis” and “Shulman syndrome” together with “aplastic anemia” and “pancytopenia.” The bibliographies of all the selected articles were reviewed for additional case reports. We selected 19 patients from 15 different articles published between 1978 and 2009 in the English, French, German, and Portuguese literature.2,13,16,23,24,26,27,28,32,36,37,57,58,60,61,62,64,65,69,91,111,117,128 Patients were selected if they displayed clinical features of EF and pancytopenia and if AA was confirmed by bone marrow examination. The diagnosis of EF was confirmed by a deep skin biopsy, including the fascia, in all but 2 cases. In 1 case, a deep skin biopsy was not performed because of the risk of bleeding due to profound refractory thrombocytopenia;24 in another case,10 the deep skin biopsy was not conclusive, but it was performed after corticosteroid and ATG administration.

The clinical characteristics of the patients in the present and in previous reports were recorded and compared to those of 86 patients with EF and without AA from the benchmark Lakhampal clinical series (n = 52)26 and from a more recent retrospective clinical study (n = 34).24 Three major caveats should be noted regarding the interpretation: there was a lack of in-depth clinical descriptions in some cases, there was possible over-reporting of unusual clinical features in the case reports compared to the clinical series, and there was a lack of long-term follow-up data in many of the case reports. Therefore, a statistical analysis was not performed.

When available, skin and hematologic outcomes were assessed using the following criteria: remission (defined as the absence of residual clinical signs of EF or as transfusion independence), long-term remission (longer than 2 yr after the start of the treatment), improvement (without complete remission), no improvement, and AA-related death.

CASE REPORTS

Patient 1

A 65-year-old retired beautician experienced petechiae, nosebleeds, and hemorrhagic bullae of the oral mucosa. She reported a 6-month history of asthenia, weight loss, myalgia, and progressive stiffness of the skin, which the patient reported had started after a swim in a river. She had been exposed to pentachlorophenol and lindane for 20 years, which are 2 pesticides used to treat lumber beams in her house. A physical examination revealed firm induration of the subcutaneous tissue, including the digits but sparing the face. There was a peau d’orange appearance of the back and venous furrowing (groove sign) of the anterior part of the forearms. There was no evidence of Raynaud phenomenon, dyschromia, telangiectasia, calcinosis cutis, or gastroesophageal reflux. A complete blood count disclosed pancytopenia (Hb: 8.8 g/dL; reticulocytes: 27 g/L; leukocytes: 2 g/L; neutrophils: 0.55 g/L; and platelets: 11 g/L).

A bone marrow biopsy showed global hypoplasia with T lymphocyte and eosinophil infiltration. No paroxysmal nocturnal hemoglobinuria (PNH) clone was detected by flow cytometry. The antinuclear antibody titer was 1:80, and no antibodies to extractable nuclear antigens were detected, including anti-Scl70 or anticientromere antibodies. The direct Coombs test was positive with an anti-IgG antibody reagent. When the patient was admitted to the hospital, she required daily platelet transfusions, partly due to anti-HLA class I allo-sensitization. She received 3 mg/kg ATG and 2 mg/kg prednisone for 5 days and was discharged on 340 mg of oral CsA daily, weekly subcutaneous romiplostim injections, monthly intravenous immunoglobulin infusions, and platelet transfusional support 3 times per week. Six months later, her skin abnormalities had completely resolved. After transient hematologic improvement, a relapse occurred, and she required weekly platelet transfusions for 9 months after ATG treatment. Blood marrow aspiration showed persistent severe hypoplasia with 20% cellularity.

Patient 2

After a week of snowshoeing, a 57-year-old farm worker developed asthenia, myalgia, and rapidly progressive thickening of the skin on the trunk and on all 4 limbs. A physical examination revealed diffuse scleroderma, except on his face, with peau d’orange presentation of the abdomen (Figure 1) and thighs and venous furrowing of the forearms. The eosinophil count was 2.6 g/L. Three months after the onset of these symptoms, a full-thickness skin and muscle biopsy from the arm revealed perivascular lymphoplasmacytic infiltration of the hypodermis, fascia, and perimysium, indicative of EF (Figure 2). The patient was discharged on prednisone (1 mg/kg daily). Two months later, he was readmitted with diffuse petechiae and ecchymoses of the lower limbs. His platelet count was 7 g/L, hemoglobin 9.9 g/dL, reticulocytes 55 g/L, leukocytes 1.2 g/L, and neutrophils 0.4 g/L. Bone marrow aspiration disclosed severe hypocellularity (<20%) with a complete absence of megakaryocytes (Figure 3). He received ATG for 5 days, and a daily oral dose of 360 mg CsA was started. The CsA dose was tapered to 200 mg daily 6 months later after the onset of an axonal sensory polyneuropathy of the lower limbs.
Severe Aplastic Anemia and Eosinophilic Fasciitis

Patient 2

A 60-year-old man developed asthenia, weight loss, myalgia, pruritus, and progressive skin stiffness of his abdomen, limbs, and the superior part of the back. He was an insurer and reported no long-term exposure to toxins and no previous physical stress. His past history included a deep vein thrombosis of the left leg 3 months earlier and ulcerative colitis in remission. He was diagnosed with ulcerative colitis 6 years ago and was treated with corticosteroids; the dose had been decreased from 20 to 1 mg daily during the previous year. A physical examination showed thickening of the subcutaneous thigh tissue and deep morphea of the legs and forearms. Hypo- and hyperpigmentation of the thighs were also observed. His face and digits were not affected, and transfusions every 2 weeks. A clinical examination showed diffuse sclerosis of the skin and subcutaneous tissue, including sclerodactyly, affecting 90% of the total body surface area (Figure 4A). Venous furrowing (groove sign) was visible on the forearms, and the skin seemed dimpled with a peau d’orange appearance. The nipples, palms, and plantar surfaces were not affected. The edema and arthralgia resolved. A careful examination of the neck revealed patchy, ivory, atrophic lesions with a pigmented peripheral halo, indicative of guttate morphea. Raynaud phenomenon was present. Microhemorrhages, edema, giant capillaries, a decreased number of capillary loops and avascular areas were found on nail-fold capillaroscopy consistent with an organic microangiopathy. Neither gastroesophageal reflux nor renal failure was observed. Echocardiography revealed increased systolic pulmonary arterial pressure (41 mm Hg) with normal left ventricular function. The lung diffusion capacity for carbon monoxide was reduced (47% of the predictive value). High-resolution computed tomography of the chest was normal. The skin abnormalities gradually subsided (Figure 4B), but immunosuppressive therapy (2 courses of ATG plus CsA 5 mg/kg) failed to improve the aplasia after 24 months of follow-up. Unfortunately, no compatible donor was found for allogeneic hematopoietic stem cell transplantation (HSCT). The patient had severe Pseudomonas aeruginosa mastoiditis that required surgery and antibiotic treatment with partial sterilization; he then developed invasive pulmonary aspergillosis. He was still alive at the last follow-up.

Patient 3

A 35-year-old bricklayer experienced a rapid onset (a few days) of painful swelling of the limbs, arthralgia, and myalgia. He reported no previous physical stress. A clinical examination revealed thickening of the skin and subcutaneous tissue involving the trunk and all 4 limbs, including the digits. Laboratory studies revealed eosinophilia (1.15 g/L), an elevated erythrocyte sedimentation rate (23 mm/h), and polyclonal hypergammaglobulinemia (20 g/L). The antinuclear antibody titer was <1:80, with no antibodies to extractable nuclear antigens, including anti-Scl70 and anticientromere antibodies. A leg fascial biopsy showed a mononuclear infiltration of lymphoplasmocytes and eosinophils involving the perimysial tissue and the fascia, confirming the diagnosis of diffuse EF. The epidermis was normal, whereas thickened collagen bundles were observed in the dermis as were straightening with parallel orientation of the elastic fibers. Daily treatment with 1 mg/kg prednisone was started. Eight months later, he experienced massive hematemesis and was admitted to the intensive care unit. An esophago-gastroduodenoscopy revealed a normal esophagus, hematin-covered gastric lesions and a gastric ulcer with an adherent clot. His full blood count showed aplastic anemia (hemoglobin 8.3 g/dL, reticulocytes 36 g/L, platelets 3 g/L, and leukocytes 1.8 g/L. A bone marrow biopsy confirmed the diagnosis of SAA. There was no PNH clone detected. After 9 months of prednisone therapy, his skin condition did not improve, and the patient required blood and platelet transfusions every 2 weeks. A clinical examination showed diffuse sclerosis of the skin and subcutaneous tissue, including sclerodactyly, affecting 90% of the total body surface area (Figure 4A). Venous furrowing (groove sign) was visible on the forearms, and the skin seemed dimpled with a peau d’orange appearance. The nipples, palms, and plantar surfaces were not affected. The edema and arthralgia resolved. A careful examination of the neck revealed patchy, ivory, atrophic lesions with a pigmented peripheral halo, indicative of guttate morphea. Raynaud phenomenon was present. Microhemorrhages, edema, giant capillaries, a decreased number of capillary loops and avascular areas were found on nail-fold capillaroscopy consistent with an organic microangiopathy. Neither gastroesophageal reflux nor renal failure was observed. Echocardiography revealed increased systolic pulmonary arterial pressure (41 mm Hg) with normal left ventricular function. The lung diffusion capacity for carbon monoxide was reduced (47% of the predictive value). High-resolution computed tomography of the chest was normal. The skin abnormalities gradually subsided (Figure 4B), but immunosuppressive therapy (2 courses of ATG plus CsA 5 mg/kg) failed to improve the aplasia after 24 months of follow-up. Unfortunately, no compatible donor was found for allogeneic hematopoietic stem cell transplantation (HSCT). The patient had severe Pseudomonas aeruginosa mastoiditis that required surgery and antibiotic treatment with partial sterilization; he then developed invasive pulmonary aspergillosis. He was still alive at the last follow-up.

Patient 4

A 60-year-old man developed asthenia, weight loss, myalgia, pruritus, and progressive skin stiffness of his abdomen, limbs, and the superior part of the back. He was an insurer and reported no long-term exposure to toxins and no previous physical stress. His past history included a deep vein thrombosis of the left leg 3 months earlier and ulcerative colitis in remission. He was diagnosed with ulcerative colitis 6 years ago and was treated with corticosteroids; the dose had been decreased from 20 to 1 mg daily during the previous year. A physical examination showed thickening of the subcutaneous thigh tissue and deep morphea of the legs and forearms. Hypo- and hyperpigmentation of the thighs were also observed. His face and digits were not affected, and
there was no Raynaud phenomenon. The nail-fold capillaroscopy was normal. Fluctuating eosinophilia (maximum: 2.5 g/L) and an elevated erythrocyte sedimentation rate (50 mm/h) had been found during the onset of symptoms. Antinuclear antibodies, antibodies to extractable nuclear antigens, including anti-ScI70 and anticentromere antibodies, were absent. A deep skin biopsy showed edema and thickened collagen bundles in the hypodermis as well as a dense lymphohistocytic infiltrate, mainly around the capillaries in the hypodermis, fascia, and muscle walls. The same alterations were also noticed in the deep dermis, whereas the epidermis appeared normal. The corticosteroid dose was increased to 80 mg daily with no efficacy after 3 months. He was readmitted for fever 8 months after the onset of these symptoms, and a complete blood count disclosed aplastic anemia (Hb: 7.6 g/dL), leukopenia (leukocytes: 2.9 g/L), neutropenia (neutrophils: 0.7 g/L), and severe thrombocytopenia (platelets: 30 g/L). Antiplatelet glycoprotein IgG antibodies, detected using the monoclonal antibody-specific immobilization of platelet antigens assay, were present. Bone marrow aspiration revealed severe hypocellularity (<20%) and an absence of megakaryocytes. Fever resolution occurred after the patient was placed on empirical antibiotic therapy. He received ATG (300 mg/d) and CsA (4 mg/kg per d) for 5 days. One year later, his skin and hematologic conditions had normalized. The CsA dosage was gradually decreased and was stopped 8 years later. Four years after CsA withdrawal, he developed autoimmune hemolytic anemia (Hb: 7.6 g/dL; reticulocytes: 101 g/L; LDH: 552 IU/L, Direct Coombs test: positive using anti-IgG antibody reagent), which responded well to oral corticosteroids.

**DISCUSSION AND LITERATURE REVIEW**

**Age, Sex, and Environmental Factors**

Among the 23 patients with EF and concomitant AA from previous and present reports, most were aged more than 60 years (Table 1). The mean age was 56 years (range, 18–71 yr). Only 3 patients were under 40 years of age when they were diagnosed with EF. Of the 23 patients, 16 (70%) were men. These results contrast with the clinical characteristics of EF patients without associated AA,75,76 who tended to be younger (mean age, 47 yr75 or 53 yr76) and were more often women (66%75 or 59%76). As in the Lakhanpal case series, patients with EF and AA were most often white.

The professions of 11 patients were specified. Eight were manual workers: 3 were farm workers (Patient 2 and patients reported previously58,77), 1 a foundry worker,58 1 a dry cleaner,58 1 a mechanic,58 1 a brick mason (Patient 3), and 1 a beautician (Patient 1). Patient 1 reported exposure to lindane and pentachlorophenol for 20 years, which are 2 organochlorine pesticides used for wood preservation; these agents have been implicated in other reported cases of isolated AA.16,99 We are unaware of other reported cases of EF and AA following exposure to pesticides, but 1 case of AA and diffuse scleroderma following exposure to paradichlorobenzene and naphthalene in an employee of a clothing resale shop has been reported.100 These observations led us to speculate on the potential role of toxic exposure in the onset of the disease, although it must be remembered that no definitive conclusion can be drawn based on relatively few cases.

Benzene exposure80 and exposure to agricultural pesticides60 have been clearly shown to be linked to AA in case-control studies. The role of environmental factors has also been suspected in the context of EF, although no case-control study is available. In case reports, EF has been linked to infection with *Borrelia species*,2,9,47,51,87,107,116 brucellosis,90 chronic hepatitis C,90 tertiary syphilis,90 chemical exposure,11 trichlorehylene,12 insect bites,99,100 irradiation,99 and various pharmaceuticals, including sivamstatin,6,106 phenytoin,18 azothavastatin,13 fosinopir,19 alpha-methylidopa,19 subcutaneous heparin use,20 and antituberculosis therapy.104 Geographically clustering of scleroderma-like syndromes, including EF, was reported in a rural area in Italy.124 More importantly, eosinophilia-myalgia syndrome, which includes myalgia, scleroderma, constant peripheral eosinophilia, fasciitis in 25%–55% of cases, and sometimes severe peripheral neuropathies, is linked to L-tryptophan ingestion.51 Similarly, adulterated cooking oils have induced toxic-oil syndrome, which presents with myalgia, diffuse scleroderma, and peripheral eosinophilia, yet to our knowledge no associated fasciitis has ever been reported.70

**Clinical Features at EF Diagnosis**

Progressive skin stiffness was present in all 23 patients (see Table 1), with peau d’orange presentation in 9 cases. The digits were involved in 7 cases. Seven patients also reported weight loss, although this symptom was not reported in patients with EF from the Lakhanpal case series.72 It is likely, however, that it was simply not recorded in that particular case series; it was reported in 9 of 34 patients with EF (26%) in the retrospective clinical study from Lebeaux et al.76

Other clinical features of EF, such as pitting edema of the lower legs, inflammatory arthritis, a groove sign, carpal tunnel syndrome, and morphea plaques, were rarely reported in patients.

---

**FIGURE 4.** Patient 3. Redness, warmth, and woody induration of the skin of the left forearm (top). After 12 months of immunosuppressive therapy (bottom). Marked softening of the skin; veins have become visible. [This figure can be viewed in color online at http://www.md-journal.com]
Uncommon clinical features of EF were found in 10 patients. One patient had lymphadenopathy. A lymph-node biopsy showed lymphoid and reticular hyperplasia. Lymphadenopathy is rarely associated with EF; in a case series of 10 patients with EF and peripheral lymphadenopathy, 91 lymph-node biopsies revealed lymphoma in 6 cases.

With EF and AA, but this finding could be related to the scarcity of in-depth clinical descriptions.

Two patients exhibited seritis, including ascites and pleural effusion or pericarditis. Rare cases of EF with pleural or pericardial involvement, or both, 97 have been described previously. Two patients had peripheral neuropathy (our Patient 2 and a patient from the literature 30). However, in our patient, the role of cyclosporine toxicity could not be excluded. Three cases of EF with associated peripheral neuropathy have been reported. 86,101,106

One patient had acute, unilateral nongranulomatous iritis, 89 and 1 patient had bilateral chemosis. 89

One patient had dyschromia, microstomia, and dysphagia. 38

Similarly, Patient 3 had dyschromia, Raynaud phenomenon, and nail-fold capillaroscopy abnormalities. Finally, 1 patient exhibited calcinosis cutis. 24 These features are unusual in EF and can complicate the differentiation of this disease from systemic sclerosis. Moreover, apart from EF, 9 cases of diffuse scleroderma have been reported in association with AA7,14,21,29,39,41,66,118,122 or agemakaryocytic thrombocytopenia. 67 None of these patients had been diagnosed with EF. One patient had Raynaud phenomenon. 59 One had lung carcinoma and esophageal hypomotility. 41 Another patient 29 had Crohn disease, Raynaud phenomenon, esophageal dysmotility, and interstitial lung disease. These findings further blur the boundaries between EF, diffuse morphia, and systemic sclerosis, as these 3 diseases seem to be associated with AA; however, AA is more frequently associated with EF than the 2 other conditions.

### Associated Immune Diseases

Four patients (17%) had prior immune disease diagnoses. Two patients had Hashimoto thyroiditis, 2,13 and 2 others (Patient 4 and a patient reported previously 30) had ulcerative colitis. Hashimoto thyroiditis 2,13,59,114 and Crohn disease 82 have been previously reported as associated with EF but not AA in some case reports. AA is rarely associated with other immune diseases; in a

| TABLE 1. Clinical Features of Patients With EF and Associated AA and Patients With EF Without Associated AA |
|---------------------------------------------------------------|
| **Feature** | **EF and Associated AA**<sup>a</sup> | **EF Without AA**<sup>b</sup> | **EF Without AA**<sup>c</sup> |
| Mean age in yr (range) | 56 (18–71) | 47 (11–72) | 53 (NA) |
| Sex ratio: M/F | 16/7 (70/30) | 23/29 (44/66) | 14/20 (41/59) |
| White race | 11/13 (85)% | 52/52 (100) | NA |
| EF resistance to corticosteroids ± other immunosuppressive drug | 7/12 (58) | 9/34 (26) | 10/32 (31) |
| Clinical features of EF | | | |
| Skin stiffness | 23 (100) | 50 (96) | 30 (88) |
| Peau d’orange aspect | 9 (39) | 11 (21) | NA |
| Edema | 3 (13) | 17 (33) | 19 (56) |
| Inflammatory arthritis/arthralgia | 1 (4) | 21 (40) | 13 (38) |
| Carpal tunnel syndrome | 1 (4) | NA | NA |
| Hands skin involvement | 7 (30) | 28 (54) | NA |
| Groove sign | 2 (9) | NA | 18 (53) |
| Morphea plaques | 2 (9) | 15 (29) | 14 (41) |
| Weight loss | 7 (30) | NA | 9 (26) |
| Unusual clinical features | | | |
| Pigmentation abnormalities | 2 (9) | 1 (2) | NA |
| Facial involvement | 2 (9) | 3 (6) | NA |
| Raynaud phenomenon | 1 (4) | 1 (2) | NA |
| Other unusual signs | 10 (43)%<sup>†</sup> | 1 (2)%<sup>‡</sup> | NA |
| Associated immune disease | 4 (17)%<sup>§</sup> | NA | NA |
| Associated hematologic malignancy | 1 (4)%<sup>‖</sup> | 3 (6)%<sup>¶</sup> | NA |

Abbreviations: NA = not available.

<sup>a</sup>From present report and references 2,13,22,24,30,38,57,58,73,77,89,95,111,117,128.

<sup>b</sup>From reference 75.

<sup>c</sup>From reference 76.

<sup>*</sup>Race/ethnic origin of 10 patients not available.

<sup>†</sup>Including the following: lymphadenopathy (n = 1), 58 ascites and pleural effusion (n = 1), 89 pericarditis (n = 1), 22 dysphagia (n = 1), 38 polyradiculoneuritis (n = 2) (Patient 4 in present report and patient from literature 30), abnormal nailfold capillaroscopy (n = 1) (Patient 3 in present report), calcinosis cutis (n = 1), 24 acute iritis (n = 1), 58 bilateral cheimos (n = 1). 89

<sup>‡</sup>Esophageal hypomotility.

<sup>§</sup>Including the following: Hashimoto thyroiditis (n = 2) 2,13 and ulcerative colitis (n = 2) (Patient 4 in present report and patient from literature 30).

<sup>‖</sup>Small-cell lymphoproliferative disorder. 57

<sup>¶</sup>Chronic lymphocytic leukemia (n = 1), myelomonocytic leukemia (n = 1), myeloproliferative disorder (n = 1).

© 2013 Lippincott Williams & Wilkins www.md-journal.com | 73

Copyright © 2013 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.
| Patient (Publication Year) [ref.] | Age/Sex | Time Between EF Diagnosis and AA Onset | Successive Treatments (Duration) |
|----------------------------------|---------|--------------------------------------|--------------------------------|
| 1 (2013) (PR)                    | 65/F    | 6 mo                                 | ATG 3 mg/kg per d (5 d), CsA 340 mg/d |
| 2 (2013) (PR)                    | 57/M    | 2 mo                                 | ATG (5 d), CsA 360 mg/d |
| 3 (2013) (PR)                    | 35/M    | 8 mo                                 | Prednisone 80 mg/d (6 mo) |
| 4 (2013) (PR)                    | 60/M    | 8 mo                                 | Corticosteroids, MTX |
| 5 (2009)^2                       | 62/M    | 0                                    | CsA (24 d) |
| 6 (2006)^2                       | 62/F    | 0                                    | Prednisone (4 mo), CsA, danatrol |
| 7 (1998)^3                       | 43/M    | 9 mo                                 | High-dose methylprednisolone |
| 8 (1997)^1                       | 46/M    | 3 mo                                 | Prednisone 80 mg/d |
| 9 (1997)^1                       | 26/M    | 13 mo                                | Prednisone (4 mo) |
| 10 (1997)^1                      | 62/M    | 6 mo                                 | Prednisone |
| 11 (1997)^1                      | 18/F    | 5 yr                                 | Prednisone |
| 12 (1991)^1                      | 62/F    | 0                                    | CsA 250 mg/d, prednisone 50 mg/d, danaizol 800 mg/d |
| 13 (1991)^1                      | 71/F    | 7 mo                                 | ATG, methylprednisolone, norethandrolone |

**Skin Outcome**
- Remission
- No improvement
- Improvement
- Death after 2 mo (sepsis)

**Hematologic Outcome**
- Improvement, relapse after 6 mo
- Persistent central thrombocytopenia
- Improvement
- *No improvement
- *Remission
- No improvement
- No improvement
- Remission
- Remission

**Follow-Up After Onset of AA**
- 12 mo
- 30 mo
- 24 mo
- 43 mo
- >12 mo
- 2 mo
- 12 yr
- 30 mo
- 6 mo
| Year | Age | Sex | Duration | Treatment | Initial Response | Duration | Final Outcome | Cause of Death |
|------|-----|-----|----------|-----------|------------------|---------|---------------|----------------|
| 14 (1988) | 51/M | 6 mo | High-dose corticosteroids, PE | No improvement after 6 mo | No improvement | Remission, relapse after 6 mo | NA |
| 15 (1988) | 51/F | 0 | ATG 15 mg/kg per d, high-dose prednisolone, CsA 500 mg/d (1 y) | Remission | NA | No improvement | No improvement |
| 16 (1985) | 66/M | 0 | Prednisolone 60 mg/d, 12 × PE | Remission | NA | No improvement | 3 yr |
| 17 (1985) | 71/F | 27 mo | Prednisone 30 mg/d, colchicine | Partial improvement | NA | No improvement | 5 d |
| 18 (1982) | 63/M | 0 | Prednisone 100 mg/d, oxymetholone 150 mg/d | No improvement after 1 mo | No improvement | No improvement | 2 mo |
| 19 (1982) | 59/M | 4 mo | Prednisone 60 mg/d, nandrolone, vincristine, PE, lymphocyte depletion, cyclophosphamide | No improvement | NA | No improvement | 9 mo |
| 20 (1982) | 46/M | 5 mo | Prednisone 10 mg/d, oxymetholone | No improvement after 4 mo | * | 7 mo |
| 21 (1982) | 71/M | 2 mo | Prednisone 80 mg/d, oxymetholone | Death after 2 mo | NA | Death after 2 mo | 5 mo |
| 22 (1980) | 66/M | 0 | Nonsteroidal antiinflammatory drugs, salicylic acid, oxymetholone, prednisone | Partial improvement | * | No improvement | 5 m |
| 23 (1978) | 67/M | 0 | PE, Vinblastine-loaded platelets | No improvement | NA | No improvement | NA |

**Abbreviations:** See previous table. GVHD = graft-versus-host disease, MTX = methotrexate, PE = plasma exchanges, PR = present report, TBI = total body irradiation.

*Treatment of EF, started before AA onset.

†Skin outcome is not specified when the previous treatment resulted in a remission.
retrospective study of 1251 patients with AA, only 50 (4%) had prior autoimmune disease diagnoses.\textsuperscript{53} AA has been reported, however, in association with autoimmune enteropathy.\textsuperscript{100}

**Hematologic Involvement**

In most cases, the interval between the diagnosis of EF and the onset of AA was less than 6 months (mean delay, 7.2 mo; median, 4 mo; range, 0–60 mo) (Table 2). In 8 cases, EF and AA were diagnosed simultaneously. AA was revealed by cutaneous mucosal hemorrhagic syndrome in 14 cases. Among these cases, 2 patients experienced massive gastrointestinal bleeding (hematemesis in Patient 3, hematemesis and melena in a patient from the literature\textsuperscript{24}). In 3 cases, the patients presented with sepsis caused by undocumented pneumonia (Patient 4 and from the literature\textsuperscript{5}) and *Streptococcus fecalis* infection.\textsuperscript{73} In 5 patients, AA was discovered fortuitously by a complete blood count. Marrow hypocellularity was described as “profound,”\textsuperscript{20} “marked,”\textsuperscript{58} or “severe”\textsuperscript{58,73,60} in 7 cases. Marrow cellularity was <20% in 6 additional cases (4 patients in the current study and 2 previously described\textsuperscript{22,24}) and was 30% in another case;\textsuperscript{128} marrow cellularity was not specified in the remaining cases. Two cases also had positive direct Coombs test results (Patient 1 and a patient previously described\textsuperscript{24}). Patient 4 tested positive for anti-platelet glycoprotein IgG antibodies, detected using the monoclonal antibody-specific immobilization of platelet antigens assay, and this patient developed autoimmune hemolytic anemia several years later. Yet another patient\textsuperscript{128} had platelet IgG antibodies as determined by complement lysis inhibition.

Normal marrow cultures from healthy donors in the presence of diseased patient’s serum were performed in 4 cases.\textsuperscript{73,77,128} There was 90% inhibition of CFU-GM growth in the first case,\textsuperscript{73} no inhibition of myeloid progenitor cell growth in the second,\textsuperscript{77} inhibition of BFU-E and CFU-E growth in the third,\textsuperscript{73} and 92%, 100%, and 83% inhibition of CFU-M, CFU-E, and BFU-E growth, respectively, in the fourth case.\textsuperscript{57} Inhibition of myeloid progenitor cell growth was found to be restricted to the IgG fraction of the patient’s serum in the latter experimental condition.\textsuperscript{57} Co-cultures of the patient’s and healthy donors marrow cells were performed in 5 patients,\textsuperscript{73,128} and stem cell colony growth suppression was absent in all but 1 case, in which growth of CFU-E was 40%–75% of the predicted value.\textsuperscript{122} Finally, AA can coexist or evolve into clonal disorders such as PNH, myelodysplasia, or acute myeloblastic leukemia.\textsuperscript{30} Detection of a PNH clone was sought but not found in 3 of our patients (Patients 1, 3, and 4). No clonal myeloid disorders were described in 23 patients with EF and AA. However, apart from this literature review, there have been 3 reports of EF patients who experienced pancytopenia in whom an excess of blast cells,\textsuperscript{48} an evolving myeloproliferative process,\textsuperscript{34} or myelomonocytic leukemia\textsuperscript{2} were found upon bone marrow examination.

**Pathophysiology**

In general, AA is considered an autoimmune disease involving interferon-γ-secreting Th1\textsuperscript{113} and IL-17-producing Th17\textsuperscript{192} CD4 T cells as well as oligoclonal cytotoxic CD8 T cells,\textsuperscript{96} leading to the destruction of autologous hematopoietic stem and progenitor cells.\textsuperscript{130} Moreover, regulatory T cells (Tregs), which control and suppress autoreactive T cells, are decreased at disease presentation in almost all AA patients, suggesting their involvement in AA pathophysiology.\textsuperscript{115} Specific autoantibodies to kinectin,\textsuperscript{56} dizepam-binding inhibitor-related protein 1,\textsuperscript{110} postmitotic segregation-increased protein 1,\textsuperscript{55} and moesin\textsuperscript{120} have been found in the serum of patients with AA. Moesin is a cytoskeleton-membrane linker protein that is expressed on the surface of T cells, NK cells, and monocytes. Antimoesin antibodies have been shown to stimulate interferon-γ secretion from peripheral mononuclear cells retrieved from AA patients in vitro;\textsuperscript{119} therefore, these antibodies may contribute to AA pathophysiology. Abnormalities in telomere repair have also been identified in acquired AA patients.\textsuperscript{17} Telomeres are nucleotide repeats at the ends of the chromosomes that function as protective caps to prevent erosion of genomic DNA during cell division. Each time a cell divides, the telomeres shorten. When they become too short, the cell can no longer divide and becomes inactive. Critically short telomeres produce apoptosis, cell senescence, and chromosomal instability. Mutations in telomerase complex genes resulting in extremely short telomeres have been described in some patients with AA.\textsuperscript{129} In acquired AA, independent of known genetic alterations, the presence of short telomeres in leukocytes at the time of presentation affects the clinical course: patients with short telomeres respond to immunosuppressive interventions, but their relapse rate is almost double that of cases with normal telomere length. Additionally, virtually all clonal evolution occurs in patients in the lowest quartile of telomere length.\textsuperscript{103}

EF is also believed to be an immune-mediated disease. This conclusion is supported by the following evidence: 1) histologic features (cytotoxic CD8 T lymphocytes, monocytes, and eosinophilic infiltrates\textsuperscript{123} and IgG and C3 deposits\textsuperscript{4}); 2) the disease’s association with other autoimmune diseases (autoimmune cytopneasias, thyroiditis, or systemic lupus erythematosus); 3) the disease’s association with biologic abnormalities (polyclonal hypergammaglobulinemia\textsuperscript{9} and circulating immune complexes\textsuperscript{124}); and 4) reported cases of fasciitis in the context of allomimunity during chronic graft-versus-host disease after allogeneic stem cell transplantation.\textsuperscript{62} To date, few specific studies have been performed on the immune regulation of EF. However, this disease belongs to the group of localized scleroderma, also referred to as morphea or skin scleroderma,\textsuperscript{2} as illustrated by the association of plaque morphea with EF.\textsuperscript{75,76} Localized scleroderma is characterized by increased collagen deposition (fibrosis), which differs from systemic sclerosis in which collagen deposition and vasculopathy are predominant features. Nonetheless, systemic sclerosis shares clinical and pathophysio logical features with EF, such as increased serum levels of TGF-β, a potent profibrotic cytokine,\textsuperscript{5,42} and elevated levels of inhibitors of metalloproteinases in the affected tissues.\textsuperscript{64,69} Increased production of Th1 (that is, IL-2 and interferon-γ) and Th2 (that is, IL-5 and IL-10) cytokines have been found in EF patients after stimulation.\textsuperscript{126} Fewer circulating Tregs have been described in patients with systemic sclerosis and localized scleroderma in comparison with healthy individuals.\textsuperscript{3} Defects in telomerase biology have been described in systemic sclerosis with contradictory results.\textsuperscript{4,78} Dysregulation of B-cell homeostasis has been described in chronic graft-versus-host disease,\textsuperscript{110} and fasciitis similar in symptomology to EF is frequently seen in patients with systemic sclerosis.\textsuperscript{2,19} Zygomyces pneumonia,\textsuperscript{89} unspecified pneumonia,\textsuperscript{77} disseminated sepsis with cellulitis,\textsuperscript{58} and *Escherichia coli* and
TABLE 3. Treatment Regimens and Outcome in 19 Patients With EF-Associated AA, Present and Previous Reports

| Treatment Regimen | No. of Patients | Skin Outcome | Hematologic Outcome | Median Follow-Up After Treatment Onset, in mo (range) |
|-------------------|-----------------|--------------|---------------------|-----------------------------------------------------|
| Regimens containing ATG and CsA [PR Patients 1, 2, 3, 4; 30, * 73*] | 6 | Remission (n = 3) Improvement (n = 1) Improvement (n = 1) No improvement (n = 1) NA (n = 1) | Long-term remission (n = 1) Remission (n = 1) Persistent thrombocytopenia (n = 1) Relapse after 6 mo (n = 1) | 22 (12–204) |
| Allogeneic H SCT [24, 73*] | 3 | Remission (n = 1) NA (n = 2) | Long-term remission (n = 2) No improvement, AA-related death (n = 1) | 43 (3–144) |
| Regimens containing ATG (without CsA) [22, 30, * 73, * 89, 117] | 8 | Improvement (n = 2) NA (n = 6) | Remission after 6 mo (n = 1) Remission then relapse after 6 mo (n = 1) | 2.5 (0–6) |
| Corticosteroid-based regimens (no ATG or CsA) [58, 77, 95] | 6 | No improvement (6) NA (n = 6) | Long-term remission (n = 1) No improvement, AA-related death (n = 5) | 5 (0–36) |

*Some patients received diverse consecutive treatment regimens and are reported in different rows in this table.

Streptococcus pneumoniae.58 One patient died of an unspecified infection and bleeding.71 1 died of an aortic aneurysm rupture,58 and 1 died of an intracranial hemorrhage.58 Five of these patients were treated with corticosteroids and various other drugs, including androgens but not ATG or CsA for AA.58, 77 Additionally, 4 patients were treated with corticosteroids, ATG, and other drugs, excluding CsA.22, 73, 89 Among these 4 patients, 1 underwent allogeneic H SCT from an unrelated donor77 but eventually died 86 days after the transplantation.

Long-term remission (>2 yr) was reported in only 5 patients. One was treated with high-dose corticosteroids and plasma exchanges (3 yr of follow-up),95 whereas corticosteroids alone or together with androgens failed to improve the aplasia in all other cases. Two patients were treated with H SCT from a sibling donor24, 73 and had remission over 43 months of follow-up in the first case and 12 years in the second case. Patient 4 received a combination of CsA and ATG (17 yr of follow-up). The last patient with long-term remission was treated with CsA, corticosteroids and splenectomy (30 mo of follow-up after starting treatment).117

The combination of ATG and CsA is the current standard first-line therapy for patients with SAA and no available HLA-matched sibling donor.130 It has proven effective in randomized controlled trials, and an overall response is achieved in two-thirds of the patients, with a cumulative incidence of relapse of 20%–30% among responders. Allogeneic H SCT is considered a first-line therapy in patients with available HLA-matched related donors.130 Of the 6 patients with EF and AA who received ATG and CsA, 5 (83%) were partial (n = 3) or complete (n = 2) responders. Therefore, in this small number of patients with EF and SAA, the prognosis after standard immunosuppressive therapy seemed to be similar to that of isolated SAA in clinical trials.

Finally, Patient 2 underwent 2 courses of rituximab therapy (375 mg/m² per infusion, 4 monthly infusions during each course) with remission of both the skin and hematologic disorders 15 months after treatment, whereas ATG and CsA alone did not show efficacy after 15 months. To our knowledge, rituximab has shown efficacy in EF treatment in only 1 other single reported case102 and in AA in 3 cases with 5 months,49 4 years,121 and 6 months1 of follow-up. The last case had AA-related to systemic lupus erythematosus.

The evolutions of EF and AA were not always correlated. Unlike systemic sclerosis, EF is usually corticosteroid-sensitive. Thus, prednisone monotherapy proved effective in 42 of 55 patients (76%) in 4 recent studies22, 73, 89 and in 25 of 34 patients (74%) in the Lakhanpal case series.73 Among the 12 patients demonstrating AA associated with EF who were treated with corticosteroids as either monotherapy,73 or in addition to ATG,117 CsA,2 or colchicine,22 and for whom skin outcome data were available, only 5 (42%) showed EF improvement2, 22, 73 or remission.117 In the 7 remaining cases (Patients 3 and 4 and patients from the literature24, 30, 58, 77), no skin improvement was observed after corticosteroid therapy. It could be assumed that patients with EF and associated AA had more corticosteroid-resistant EF than patients with isolated EF; however, the mean delay between treatment initiation and the assessment of efficacy was short (mean, 3.5 mo; range, 1–6 mo), and the small number of patients does not allow us to draw firm conclusions.

Among the 4 patients who died of AA and for whom skin outcomes were available, 3 achieved partial improvement of EF22, 73, 77 and 1 did not show improvement.28 In the same way, 2 of our patients achieved complete (Patient 1) or almost complete (Patient 3) skin remission; however, they were still reliant on transfusions after ATG and CsA therapy. The 8 remaining patients for whom AA and EF outcomes were available (Patients 2 and 4 and patients reported previously13, 24, 30, 73, 117) achieved both hematologic and skin improvement or remission. In the patients who had relapses of AA, no concomitant relapse of EF was described. A small-cell lymphoproliferative disorder was revealed after the autopsy of 1 patient,57 but no other cases of evolving malignancy were described in the 18 remaining cases, nor were any found in our patients even after long-term follow-up.

Summary and Conclusions

We studied 4 patients with EF and associated SAA and reviewed 19 cases retrospectively. According to the data in the literature, AA seems to be the most frequently recorded hematologic disease associated with EF. It was the direct cause of death in...
at least 8 of 23 cases (35%). Compared to patients with isolated 
EF, patients with EF and associated AA were more likely to be 
men (70%) and older (mean age, 56 yr; range, 18−71 yr). It should 
be noted that unusual clinical features in the context of EF, such 
as systemic involvement (n = 7), Raynaud phenomenon (n = 1), 
calcinosis cutis (n = 1), and facial skin sclerosis (n = 2), were not 
rare in patients with EF and associated AA, even though they are 
usually considered to be the hallmark of systemic sclerosis. Four 
patients had other associated immune diseases: ulcerative colitis 
(n = 2), autoimmune thyroiditis (n = 2), and autoimmune 
cytopenias (n = 4). No clonal myeloid disorders were detected in 
these 23 patients.

The evolutions of EF and AA were not always correlated: 
remission of EF was not predictive of AA improvement, and no 
relapse of EF was observed in patients with AA relapses. 
Corticosteroid-containing regimens improved the skin condition 
in 5 of 12 cases (42%) but were ineffective in treating aplasia in 5 
of 6 cases (83%). Among our 3 patients who were refractory to 
ATG and CsA, 1 had 2 courses of rituximab therapy with both 
skin and hematologic improvement. Finally, long-term remission 
(>2 yr) was reported in 5 cases with the following treatments: 
corticosteroid-containing regimen (n = 1), allogeneic HSCT from 
sibling donor (n = 2), and CsA-containing regimen (n = 2). In 
conclusion, patients with EF should be carefully monitored for 
associated AA, which occurs mostly in the first year after EF di-
dagnosis. AA in this setting is usually severe and rapidly life-
threatening in the absence of early immunosuppressive therapy. 
The response of AA to immunosuppressive therapy can be slow, 
even after EF remission, and AA relapse does occur. Therefore, 
long-term suppressive treatment with CsA is recommended. 
Allogeneic HSCT should be considered in patients with an available 
HLA-matched related donor.

REFERENCES
1. Alishiri GH, Saburi A, Bayat N, Saadat AR, Saburi E. The initial 
presentation of systemic lupus erythematosus with aplastic anemia 
successfully treated with rituximab. Clin Rheumatol. 
2012;31:381−384.
2. Antic M, Lautenschlager S, Itin PH. Eosinophilic fasciitis 30 years 
after—what do we really know? Report of 11 patients and review of 
the literature. Dermatology. 2006;213:93−101.
3. Antiga E, Quaglino P, Bellandi S, Volpi W, Del Bianco E, Comessatti A, 
Osu-La-Abate S, De Simone A, Marrano A, Bernengo MG, Fabbi P, 
Caproni M. Regulatory T cells in the skin lesions and blood of patients 
with systemic sclerosis and morphoea. Br J Dermatol. 
2010;162:1056−1063.
4. Artlett CM, Black CM, Briggs DC, Stevens CO, Welch KI. Telomere 
reduction in scleroderma patients: a possible cause for chromosomal 
instability. Br J Rheumatol. 1996;35:732−737.
5. Bachmeyer C, Monge M, Dhote R, Sanguina M, Aractingi S, 
Mougeot-Martin M. Eosinophilic fasciitis following idiopathic 
thrombocytopenic purpura, autoimmune hemolytic anemia and 
Hashimoto’s disease. Dermatology. 1999;199:282.
6. Baffoni L, Frisoni M, Maccaferri M, Ferri S. Systemic lupus 
erythematosus and eosinophilic fasciitis: an unusual association. 
Clin Rheumatol. 1995;14:591−592.
7. Balaban EP, Sheehan RG, Lipsky PE, Frenkel EP. Treatment of 
cutaneous sclerosis and aplastic anemia with antithyroglobulin. 
Ann Intern Med. 1987;106:56−58.
8. Barnes L, Rodnan GP, Medsger TA, Short D. Eosinophilic fasciitis. A pathologic study of twenty cases. Am J Pathol. 1979;96:493−518.
9. Belot V, Mulleman D, Perrin auld DA, Abdallah-Lotf M, Macht MC, 
Macht L. [Eosinophilic fasciitis associated with Borrelia burgdorferi 
infection.] Ann Dermatol Venerol. 2007;134:673−677.
10. Biasi D, Caramaschi P, Carletto A, Bambara LM. Scleroderma and 
eosinophilic fasciitis in patients taking fosinopril. J Rheumatol. 
1997;24:1242.
11. Biasi D, Carletto A, Caramaschi P, Pacor ML, Spinaci E, Bambara LM. 
[Scleroderma induced by chemical agents. Description of a case and 
review of the literature.] Recent Prog Med. 1995;86:155−158.
12. Bischoff L, Derk CT. Eosinophilic fasciitis: demographics, disease 
pattern and response to treatment: report of 12 cases and review of the 
literature. Int J Dermatol. 2008;47:29−35.
13. Blaser KL, Steiger U, Wursch A, Speck B. [Eosinophilic fasciitis with 
aplastic anemia and Hashimoto’s thyroiditis. Review of the literature 
and report of a typical example.] Schweiz Med Wochenschr. 
1989;119:1899−1906.
14. Bonati A, Aielli F, Carnevali C. [A case of scleroderma associated 
with total medullary aplasia.] Ateneo Parmense Acta Biomed. 
1977;48:499−504.
15. Bonnaffe B, Aufricht B, Caillot D, Martin F, Lorcerie B. Successful 
treatment with antihytmocyte globulin and cyclosporin A of a severe 
aplastic anemia associated with an eosinophilic fascitis. Br J 
Rheumatol. 1998;37:1358−1359.
16. Brahamas D. L indane exposure and aplastic anemia. Lancet. 
1994;343:1092.
17. Brummendorf TH, Maciejewski JP, Mak J, Young NS, Lansdorp PM. 
Telomere length in leukocyte subpopulations of patients with aplastic 
anemia. Blood. 2001;97:895−900.
18. Buchanan RN, Gordon DA, Muckle TJ, McKenna F, Knaag G. The 
eosinophilic fasciitis syndrome after phenytin (dilantin) therapy. 
J Rheumatol. 1980;7:733−736.
19. Camitta BM, Rappeport JM, Parkman R, Nathan DG. Selection of 
patients for bone marrow transplantation in severe aplastic anemia. 
Blood. 1975;45:355−363.
20. Cantini F, Salvareni C, Oliveri I, Padula A, Senesi C, Bellandi F, 
Truglia MC, Nicholli L, Palchetti R. Possible association between 
eosinophilic fasciitis and subcutaneous heparin use. J Rheumatol. 
1998;25:383−385.
21. Carcassonne Y, Gautay JA. Pancytopenia and scleroderma. Br Med J. 
1976;1:1446.
22. Cayla J, Rondier J, Toubert A, Leblond Missenard V, Chomette G. 
[A new case of eosinophilic fasciitis complicated by bone marrow 
aplasia.] Rev Rhum Mal Osteoartic. 1985;52:263−265.
23. Cesaro S, Marsh J, Tridello G, Rove A, Maury S, Montante B, Massi T, 
Van Lint MT, Afanaseyv B, Iriondo Atienza A, Bierings M, Carbone 
C, Doubek M, Lanino E, Sarhan M, Ristano A, Steinervoa K, Wahlin 
P, Pergaro A, Passweg J. Retrospective survey on the prevalence 
and outcome of prior autoimmune diseases in patients with aplastic 
anemia reported to the registry of the European group for blood and 
marrow transplantation. Acta Haematol. 2010;124:19−22.
24. Cetkovsky P, Koza V, Cetkovska P, Svojgrova M. Successful treatment 
of severe Shulman’s syndrome by allogeneic bone marrow 
transplantation. Bone Marrow Transplant. 1998;21:637−639.
25. Chan LS, Hanson CA, Cooper KD. Concurrent eosinophilic fasciitis 
and cutaneous T-cell lymphoma. Eosinophilic fasciitis as a 
paraneoplastic syndrome of T-cell malignant neoplasms? Arch 
Dermatol. 1991;127:862−865.
26. Chaudhary UB, Eberwine SF, Hege KM. Acquired amegakaryocytic 
thrombocytopenia purpura and eosinophilic fasciitis: a long relapsing 
and remitting course. Am J Hematol. 2004;75:146−150.
27. Chevalier X, Hermine O, Authier FJ, Gaulard P, Gherardi RK. Carpal tunnel syndrome due to T cell lymphoma. *Arthritis Rheum.* 1995;38:1707–1709.

28. Choquet-Kastelyevsky G, Kanitakis J, Dumas V, Descotes J, Faure M, Claudy A. Eosinophilic fasciitis and simvastatin. *Arch Intern Med.* 2001;161:1456–1457.

29. Davies JM, Dunn HG. Interstitial lung disease developing during treatment with cyclosporine in a patient with diffuse scleroderma, aplastic anemia and Crohn's disease: implications for pathogenesis and treatment. *J Clin Rheumatol.* 1995;1:287–291.

30. Debusscher L, Bitar N, De Maubeuge J, De Conninck G, Stryckmans P. Eosinophilic fasciitis and severe aplastic anemia: favorable response to either antithymocyte globulin or cyclosporine A in blood and skin disorders. *Transplant Proc.* 1988;20:310–313.

31. DeGiovanni C, Churd M, Woollons A. Eosinophilic fasciitis secondary to treatment with atorvastatin. *Clin Exp Dermatol.* 2006;31:131–132.

32. de Latour RP, Visconte V, Takaku T, Wu C, Erie AJ, Sarcon AK, Desierto MJ, Scheinberg P, Kevyvanf K, Nunez O, Chen J, Young NS. Th17 immune responses contribute to the pathophysiology of aplastic anemia. *Blood.* 2010;116:4175–4184.

33. De Masson A, Bouaziz JD, Rybojad M, Peuffiat de Latour R, Robin M, Rodriguez-Otero P, Durant C, Socie G, Bagot M. EF/SSc overlap syndrome and aplastic anaemia resistant to immunosuppressive therapy. *Rheumatology (Oxford).* 2012;51:762–764.

34. Doyle JA, Connolly SM, Hoagland HC. Hematologic disease in scleroderma syndromes. *Acta Derm Venereol.* 1985;65:521–525.

35. Dziadzio L, Kelly EA, Panzer SE, Jarjour N, Huttonlocher A. Cytokine abnormalities in a patient with eosinophilic fasciitis. *Ann Allergy Asthma Immunol.* 2003;90:452–455.

36. Eklund KK, Anttila P, Leirisalo-Repo M. Eosinophilic fasciitis, myositis and arthritis as early manifestations of peripheral T-cell lymphoma. *Scand J Rheumatol.* 2003;32:376–377.

37. Endo Y, Tamura A, Matsushima Y, Iwasaki T, Hasegawa M, Nagai Y, Ishikawa O. Eosinophilic fasciitis: report of two cases and a systematic review of the literature dealing with clinical variables that predict outcome. *Clin Rheumatol.* 2007;26:1445–1451.

38. Falcao S, Mouro AF, Ribeiro C, Pinto TL, Mateus M, Araujo P, Nervo P, Pimentao JB, Branco JC. Eosinophilic fasciitis and aplastic anemia. *Acta Reumatol Port.* 2009;34:120–126.

39. Fenaux P, Merignargues S, Pagniez D, Janin A, Lucidarme D, Bauters F. Autoimmune thyroiditis in eosinophilic fasciitis. *Clin Rheumatol.* 2003;22:1967–1970.

40. Feng X, Chuhjo T, Sugimori C, Kotani T, Lu X, Takami A, Takamatsu H, Izumoto S, Harada S, Yamanouchi K, Ishikawa O. Polymerase chain reaction of Borrelia burgdorferi flagellin gene in Shulman syndrome. *Dermatologica.* 1996;192:136–139.

41. Focan C, Swale JL, Borlee-Hermans G, Claessens JJ. Systemic sclerosis, aplastic anemia and amyloidosis associated with lung amyloidosis-type cells. *Blood.* 2004;104:2425–2431.

42. Focan C, Swale JL, Borlee-Hermans G, Claessens JJ. Systemic sclerosis, aplastic anemia and amyloidosis associated with lung carcinoma. *Acta Clin Belg.* 1983;40:204–205.

43. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. *N Engl J Med.* 2009;360:1899–2003.

44. Gallardo F, Vadillo M, Mitjavila F, Martínez E, Sala E. Systemic lupus erythematosus associated with eosinophilic fascitis: a case report. *J Am Acad Dermatol.* 1998;39:283–285.

45. Garcia-Morteo O, Nitsche A, Maldonado-Cocco JA, Barcelo HA. Eosinophilic fasciitis and retroperitoneal fibrosis in a patient with systemic lupus erythematosus. *Arthritis Rheum.* 1987;30:1314–1315.
66. Kamada K, Kobayashi Y, Katada K, Takahashi Y, Chikayama S, Ikeda M, Kondo M. Scleroderma associated with anemia and thrombocytopenia that responded well to cyclosporin. *Acta Haematol.* 2000;104:106–109.

67. Katsurada Y, Suzuki T, Kuswana M, Hattori Y, Akizuki S, Sugihara H, Matsuoka Y. Anti-c-mp3 thrombopoietin receptor autoantibody-induced amegakaryocytic thrombocytopenia in a patient with systemic sclerosis. *Arthritis Rheum.* 2003;48:1647–1651.

68. Khanna D, Verity A, Grossman JM. Eosinophilic fasciitis with multiple myeloma: a new haematological association. *Ann Rheum Dis.* 2002;61:1111–1112.

69. Kikuchi K, Kadono T, Furue M, Tamaki K. Tissue inhibitor of metalloproteinase 1 (TIMP-1) may be an autocrine growth factor in scleroderma fibroblasts. *J Invest Dermatol.* 1997;108:281–284.

70. Kilbourne EM, Rigau-Perez JG, Heath CW Jr, Zack MM, Falk H, Martin-Marcos M, de Carlos A. Clinical epidemiology of toxic-oil syndrome. Manifestations of a New Illness. *N Engl J Med.* 1983;309:1408–1414.

71. Killen JW, Swift GL, White RJ. Eosinophilic fasciitis with pulmonary and pleural involvement. *Postgrad Med J.* 2000;76:36–37.

72. Kim H, Kim MO, Ahn MJ, Lee YY, Jung TJ, Choi YJ, Kim IS, Park CK. Eosinophilic fasciitis preceding relapse of peripheral T-cell lymphoma. *J Korean Med Sci.* 2000;1:346–350.

73. Kim SW, Rice L, Champlin R, Uddden MM. Aplastic anemia in eosinophilic fasciitis: responses to immunosuppression and marrow transplantation. *Haematologica (Budap).* 1997;28:131–137.

74. Kitamura Y, Hatamochi A, Hamasaki Y, Ikeda H, Yamazaki S. Eosinophilic fasciitis complicated with peripheral polyneuropathy. *Intern Med.* 1998;37:417–420.

75. Mosconi S, Streit M, Bronnimann M, Braathen LR. Eosinophilic fasciitis (Shulman syndrome). *Dermatology.* 2002;205:204–206.

76. Naouri A, Bousslama K, Abdallah M, Hamzaoui S, Arbi T, Bahri F, M’zabi S, Harmel A, Ennaffaa M, Ben Dridi M, M’rad S. Eosinophilic fasciitis (Shulman’s disease): a case series of 11 patients. *Rev Med Interne.* 2010;31:535–539.

77. Littlejohn GO, Keystone EC. Eosinophilic fasciitis and aplastic anemia. *Clin Lab Haematol.* 1988;10:471–474.

78. MacIntyre A, Brouilette SW, Lamb K, Radhakrishnan K, McGlynn L, Kondo M. Eosinophilic fasciitis associated with low-grade T-cell lymphoma. *Br J Dermatol.* 1998;139:928–930.

79. Michaels RM. Eosinophilic fasciitis complicated by Hodgkin’s disease. *J Rheumatol.* 1982;9:473–476.

80. Michet CJ Jr, Doyle JA, Ginsburg WW. Eosinophilic fasciitis: report of 15 cases. *Mayo Clin Proc.* 1981;56:27–34.

81. Moriguchi M, Terai C, Kuroki S, Tanaka E, Someya N, Tsunoda Y, Kashiwazaki S. Eosinophilic fasciitis complicated with peripheral polyneuropathy. *Intern Med.* 1998;37:417–420.

82. Martin JR, Williams JP, Barrowman JA. Diffuse (? eosinophilic) fasciitis, atypical rash, and chronic inflammatory disease of the colon (? Crohn’s disease).*J Rheumatol.* 1995;70:1068–1076.

83. Naschitz JE, Misselевич I, Yeshurun D, Rosner I. The fasciitis-panniculitis syndromes. *Clinical and pathologic features.* *Medicine (Baltimore).* 1996;75:6–16.

84. Naschitz JE, Misselевич I, Rosner I, Yeshurun D, Weiner P, Amor M, Amato L, Ciompi ML, Boss JH. Lymph-node-based malignant lymphoma and reactive lymphadenopathy in eosinophilic fasciitis. *Am J Med Sci.* 1999;318:343–349.

85. Naschitz JE, Yeshurun D, Misselевич I, Boss JH. Colitis and pericarditis in a patient with eosinophilic fasciitis. A contribution to the multisystem nature of eosinophilic fasciitis. *J Rheumatol.* 1989;16:688–692.

86. Peterson LS, Nelson AM, Su WP. Classification of morphea (localized scleroderma). *Mayo Clin Proc.* 1995;70:1068–1076.

87. Philpott H, Hissaria P, Warren L, Singhal N, Brown M, Proudntram S, Cleland L, Gillis D. Eosinophilic fasciitis as a paraneoplastic phenomenon associated with metastatic colorectal carcinoma. *Australas J Dermatol.* 2008;49:27–29.

88. Quilichini R, Chaffinjon P, Aubert L, Mugnier C, Pelissier JF, Gastaud JA, Carcassonne Y. A new case of eosinophilic fasciitis with bone marrow aplasia. Cure by high doses of corticoids. *Presse Med.* 1985;14:427.

89. Risitano AM, Maciejewski JP, Green S, Plaslova M, Zeng W, Youn G, Salmeron G, Patey N, de Latour RP, Raffoux E, Gluckman E, Brousse M, Loggetto S, Ribeiro AA, Borbolla JR, Pasquini R. Incidence and risk factors of aplastic anemia in Latin American countries: the LATIN case-control study. *J Rheumatol.* 2009;36:701–706.

90. Rugman FP, Constick R. Aplastic anemia associated with organochlorine pesticide: case reports and review of evidence. *J Clin Pathol.* 1990;44:98–101.

91. Rizzo S. Eosinophilic pleuropericarditis and fasciitis. A new case. *Monaldi Arch Chest Dis.* 2002;57:311–313.

92. Rodat O, Harousseau JL, Reynaud C, Milpied N, Stalder JF, Chupin M, Amato L, Ciompi ML, Boss JH. Colitis and pericarditis in a patient with eosinophilic fasciitis. *A contribution to the multisystem nature of eosinophilic fasciitis.* *J Rheumatol.* 1989;16:688–692.

93. Petersen LS, Nelson AM, Su WP. Classification of morphea (localized scleroderma). *Mayo Clin Proc.* 1995;70:1068–1076.

94. Philpott H, Hissaria P, Warren L, Singhal N, Brown M, Proudntram S, Cleland L, Gillis D. Eosinophilic fasciitis as a paraneoplastic phenomenon associated with metastatic colorectal carcinoma. *Australas J Dermatol.* 2008;49:27–29.

95. Quilichini R, Chaffinjon P, Aubert L, Mugnier C, Pelissier JF, Gastaud JA, Carcassonne Y. A new case of eosinophilic fasciitis with bone marrow aplasia. Cure by high doses of corticoids. *Presse Med.* 1985;14:427.

96. Risitano AM, Maciejewski JP, Green S, Plaslova M, Zeng W, Young NS. In vivo dominant immune responses in aplastic anaemia: molecular tracking of putatively pathogenic T-cell clones by TCR beta-CDR3 sequencing. *Lancet.* 2004;364:355–364.

97. Rizzo S. Eosinophilic pleuropericarditis and fasciitis. A new case. *Monaldi Arch Chest Dis.* 2002;57:311–313.

98. Rodat O, Harousseau JL, Reynaud C, Milpied N, Stalder JF, Chupin M. Eosinophilic fasciitis and Hodgkin’s disease. *J Clin Pathol.* 1982;55:2207–2209.

99. Rugman FP, Constick R. Aplastic anemia associated with organochlorine pesticide: case reports and review of evidence. *J Clin Pathol.* 1990;44:98–101.

100. Salmeron G, Patey N, de Latour RP, Raffoux E, Gluckman E, Brousse M, Loggetto S, Ribeiro AA, Borbolla JR, Pasquini R. Incidence and risk factors of aplastic anemia in Latin American countries: the LATIN case-control study. *Haematologica.* 2009;94:1220–1226.

101. Markusse HM, Breedveld FC. Rheumatoid arthritis with eosinophilic fasciitis and pure red cell aplasia. *J Rheumatol.* 1989;16:1383–1384.

102. Martin JR, Williams JP, Barrowman JA. Diffuse (? eosinophilic) fasciitis, atypical rash, and chronic inflammatory disease of the colon (? Crohn’s disease). *J Rheumatol.* 1980;7:928–929.

103. Masuoka H, Kikuchi K, Takahashi S, Kakinuma T, Hayashi N, Furue M. Eosinophilic fasciitis associated with low-grade T-cell lymphoma. *Br J Dermatol.* 1998;139:928–930.
Severe Aplastic Anemia and Eosinophilic Fasciitis

104. Sebold JR, Rodnan GP, Medsger TA Jr, Winkelstein A. Circulating immune complexes in eosinophilic fasciitis. *Arthritis Rheum.* 1982;25:1180–1185.

105. Seko Y, Tomya T, Kuro-o M, Takano K, Nojima Y, Terai C, Yamada A, Shimizu T, Inoue K, Takaku F. [A case of eosinophilic fasciitis with peripheral nerve disorder.] *Nihon Naika Gakkai Zasshi.* 1988;77:370–376.

106. Sepp N, Schmutzhard E, Fritsch P. Shulman syndrome associated with Borrelia burgdorferi and complicated by carpal tunnel syndrome. *J Am Acad Dermatol.* 1988;18:1361–1362.

107. Serrano-Grau P, Mascaro-Galy JM, Iranzo P. [Eosinophilic fasciitis after taking simvastatin.] *Actas Dermosifiliogr.* 2006;99:420–421.

108. Sherber NS, Wigley FM, Paget SA. Diffuse fasciitis with eosinophilia developing after local irradiation for breast cancer. *Clin Rheumatol.* 2009;28:729–732.

109. Shimabukuro-Vornhagen A, Hallek MJ, Storb RF, von Bergwelt-Baildon MS. The role of B cells in the pathogenesis of graft-versus-host disease. *Blood.* 2009;114:4919–4927.

110. Shimizu T, Inoue K, Takaku F. A case of eosinophilic fasciitis with hypergammaglobulinemia and thrombocytopenic purpura in diffuse eosinophilic fasciitis. *Arthritis Rheum.* 1979;22:659.

111. Shulman LE. Diffuse fasciitis with hypergammaglobulinemia and eosinophilia: a new syndrome? *J Rheumatol.* 1984;11:569–570.

112. Sloop E, Kim S, Maciejewski JP, Tisdale J, Fellmann D, Young NS. Intracellular interferon-gamma in circulating and marrow T cells detected by flow cytometry and the response to immunosuppressive therapy in patients with aplastic anemia. *Blood.* 2002;100:1185–1191.

113. Smiley AM, Husain M, Indenbaum S. Eosinophilic fasciitis in association with thyroid disease: a report of three cases. *J Rheumatol.* 1980;7:871–876.

114. Solomon EE, Rezvani K, Mielke S, Malide D, Keyvanfar K, Visconte V, Kajigaya S, Barnett AJ, Young NS. Deficient CD4+ CD25+ FOXP3+ T regulatory cells in acquired aplastic anemia. *Blood.* 2007;110:1603–1606.

115. Solomon EE, Rezvani K, Mielke S, Malide D, Keyvanfar K, Visconte V, Kajigaya S, Barnett AJ, Young NS. Deficient CD4+ CD25+ FOXP3+ T regulatory cells in acquired aplastic anemia. *Blood.* 2007;110:1603–1606.

116. Stanek G, Konrad K, Jung M, Ehringer H. Shulman syndrome, a scleroderma subtype caused by Borrelia burgdorferi? *Lancet.* 1987;1:1400.

117. Stehle C, Tichelli A, Gratwohl A, Dazzi H, Nissen C, Steiger U, Speck B. [Aplastic anemia combined with an autoimmune disease (eosinophilic fasciitis or glomerulonephritis).] *Schweiz Med Wochenschr.* 1991;121:873–876.

118. Suematsu E, Miyamura T, Itadzu K, Minami R, Yamamoto M. [Efficacy of anti-thymocyte globulin and cyclosporin A combined therapy in aplastic anemia complicated with limited cutaneous systemic sclerosis.] *Nihon Rinsho Meneki Gakkai Kaishi.* 2005;28:99–103.

119. Takamatsu H, Espinoza JL, Lu X, Qi Z, Okawa K, Nakao S. Anti-moesin antibodies in the serum of patients with aplastic anemia stimulate peripheral blood mononuclear cells to secrete TNF-alpha and IFN-gamma. *J Immunol.* 2009;182:703–710.

120. Takamatsu H, Feng X, Chuhjo T, Lu X, Sugimori C, Okawa K, Yamamoto M, Iseki S, Nakao S. Specific antibodies to moesin, a membrane-cytoskeleton linker protein, are frequently detected in patients with acquired aplastic anemia. *Blood.* 2007;109:2514–2520.

121. Takamatsu H, Yagasaki H, Takahashi Y, Hama A, Saikawa Y, Yachie A, Koizumi S, Kojima S, Nakao S. Aplastic anemia successfully treated with rituximab: the possible role of aplastic anemia-associated autoantibodies as a marker for response. *Eur J Haematol.* 2011;86:541–545.

122. Tooze JA, Marsh JC, Wickham N, Duke OL, Behrens J, Gordon-Smith EC. Response of aplastic anaemia and scleroderma to cyclosporin. *Br J Haematol.* 1993;85:829–831.

123. Toquet C, Hamidou MA, Renaudin K, Jarry A, Foule P, Barbatot S, Laboisse C, Mussini JM. In situ immunophenotype of the inflammatory infiltrate in eosinophilic fasciitis. *J Rheumatol.* 2003;30:1811–1815.

124. Valesini G, Litta G, Bonavita MS, Luan FL, Purpura M, Mariani M, Balsano F. Geographical clustering of scleroderma in a rural area in the province of Rome. *Clin Exp Rheumatol.* 1993;11:41–47.

125. Veyssier-Belot C, Zuech P, Lombroso-Le Rouic L, Recanati G, Dendale H. Humoral suppression of T cells by the immune complex in eosinophilic fasciitis. *Rev Med Interne.* 2008;29:1013–1016.

126. Viallard JF, Taupin JL, Ranchin V, Leng B, Pellegrin JL, Moreau JF. Analysis of leukemia inhibitory factor, type 1 and type 2 cytokine production in patients with eosinophilic fasciitis. *J Rheumatol.* 2009;36:570–574.

127. Watts RA, Merry P. Familial eosinophilic fasciitis and breast cancer. *Br J Rheumatol.* 1994;33:93–94.

128. Weltz M, Salvado A, Rosse W, Berenberg J. Humoral suppression of hematopoesis in eosinophilic fasciitis. *Blood.* 1978;52:218.

129. Yamaguchi H, Calado RT, Ly H, Kajigaya S, Baerlocher GM, Chanock SJ, Lansdorf PM, Young NS. Mutations in TERT, the gene for telomerase reverse transcriptase, in aplastic anemia. *Blood.* 2005;109:2520.

130. Young NS, Scheinberg P, Calado RT. Aplastic anemia. *Curr Opin Hematol.* 2008;15:162–168.