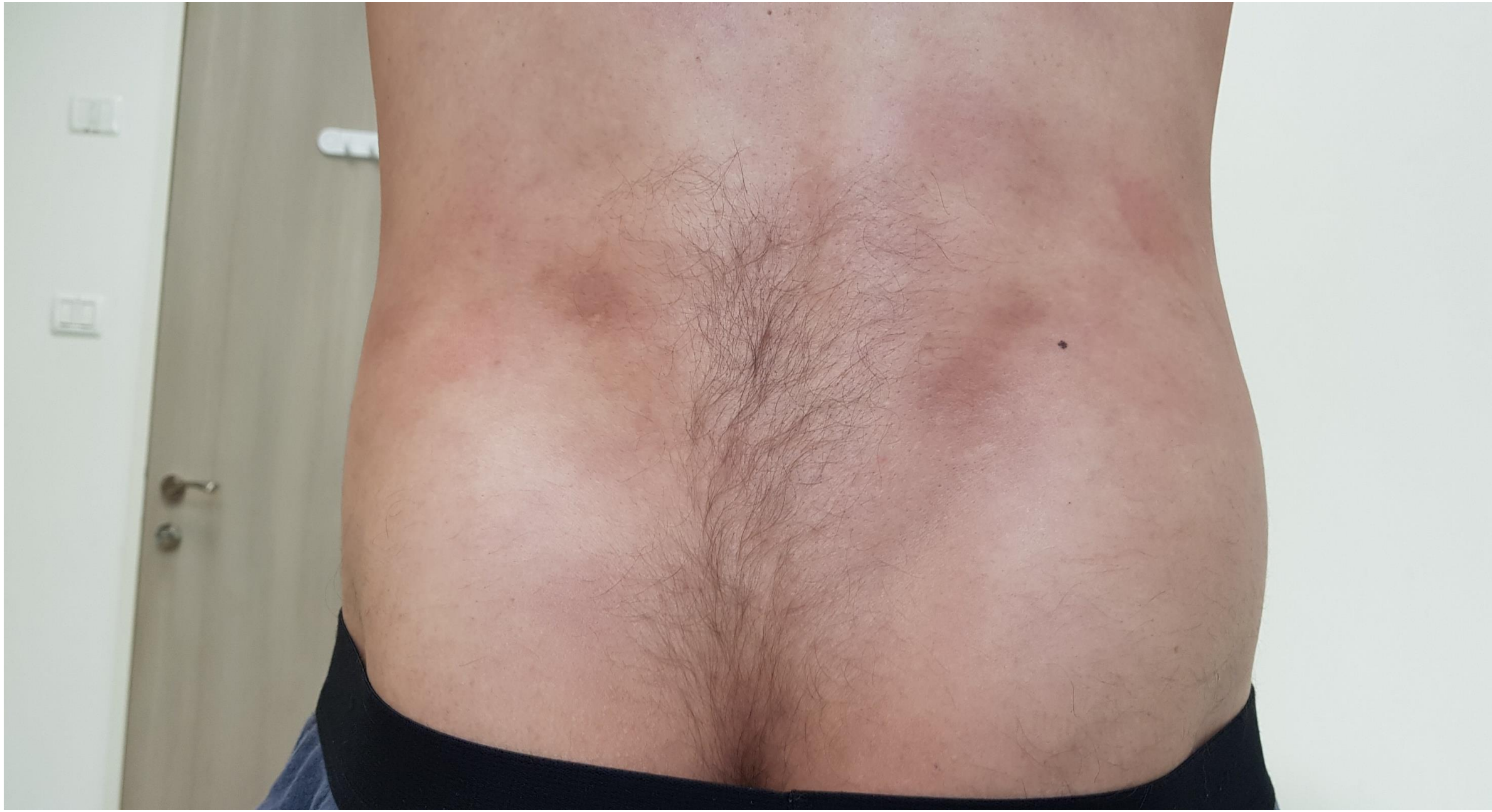
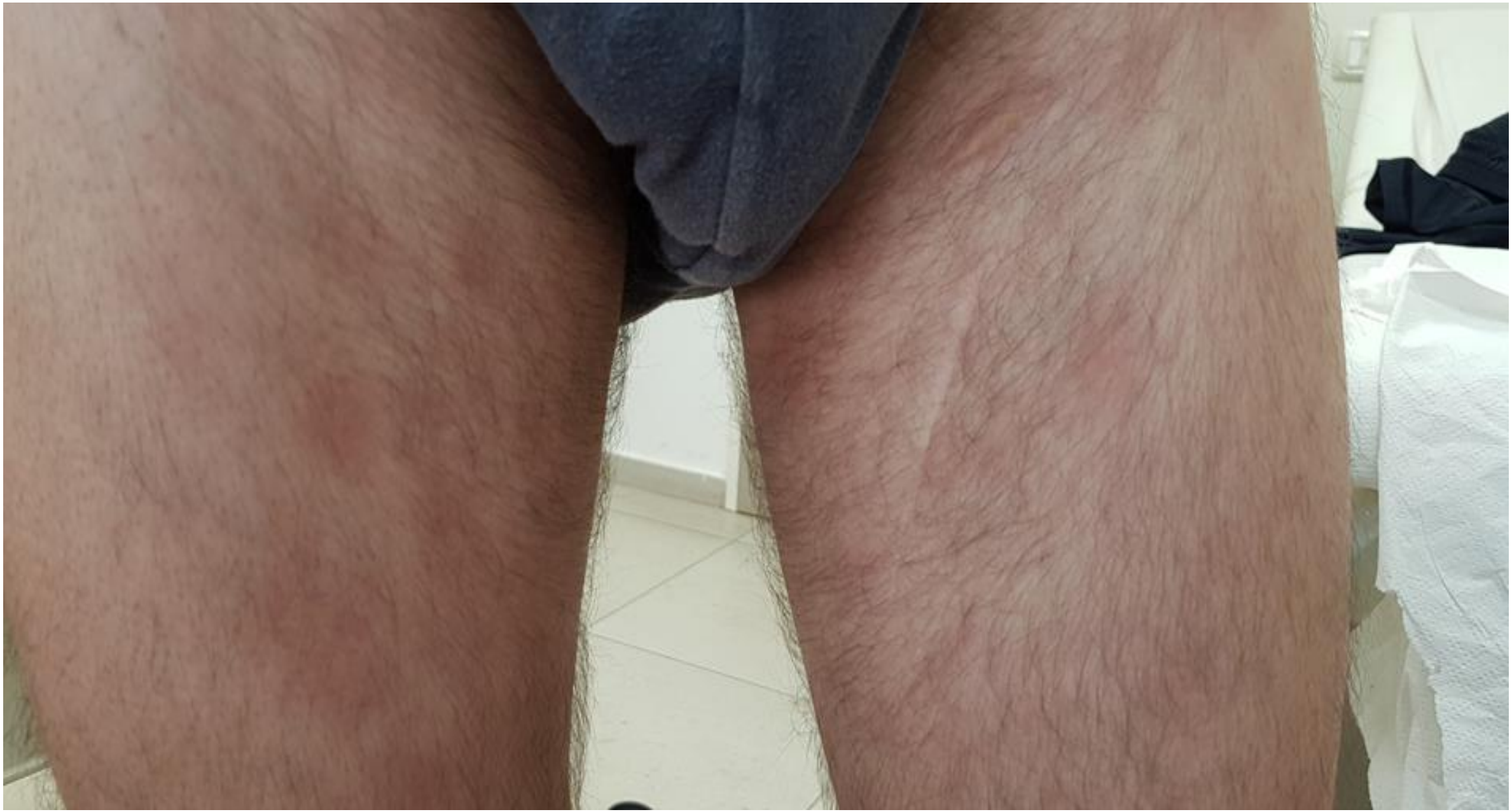
Case report : Medical history

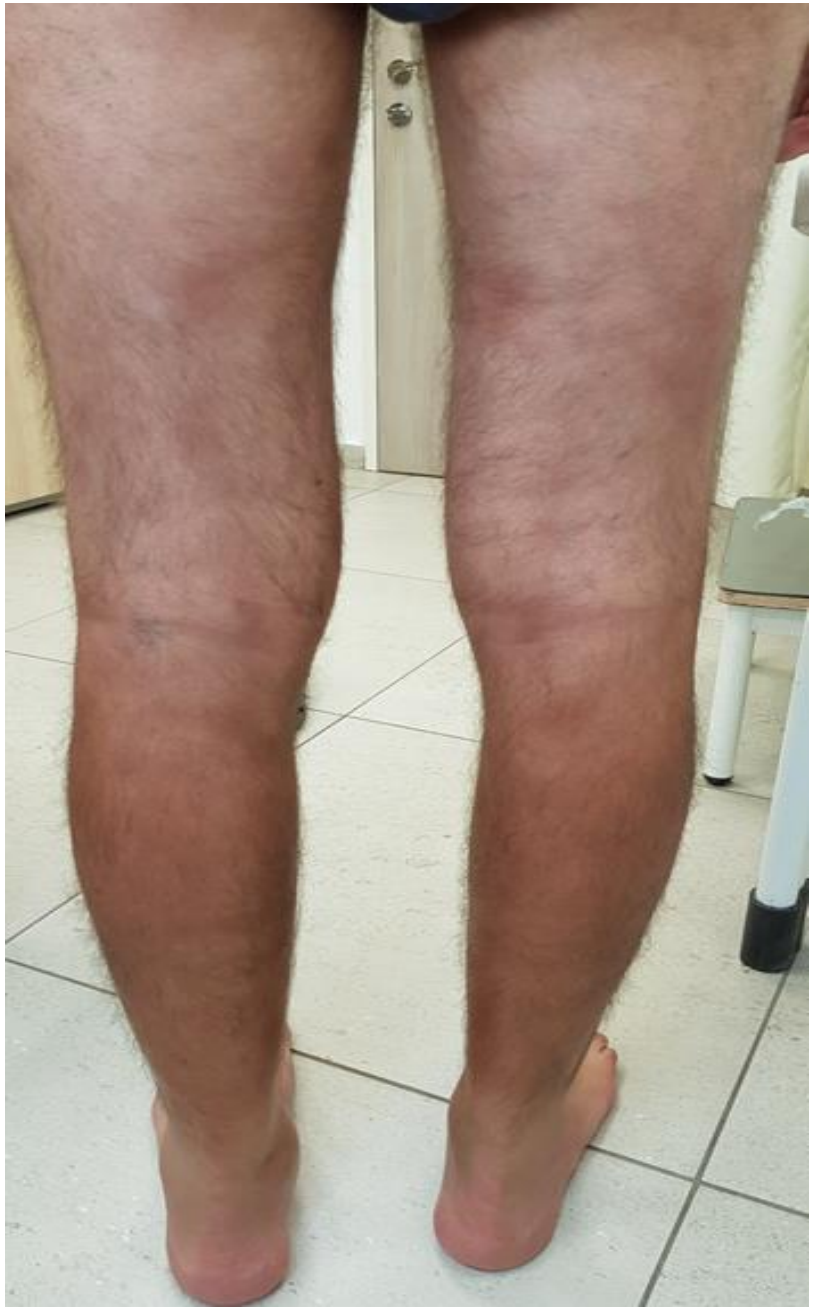
- 42 years old man , married with 3 children , a sport teacher by profession
- Two weeks : **swelling & pain** in ankles that had spread to calves, thighs and lower back.
- He negates other phenomena or chronic disease. He takes no medicine
- **In physical examination** : An **athlete** . An internal inspection is normal .
- In his **skin** was observed macular lesion with hypo/hyper **pigmentation**. **hard and tense skin**.

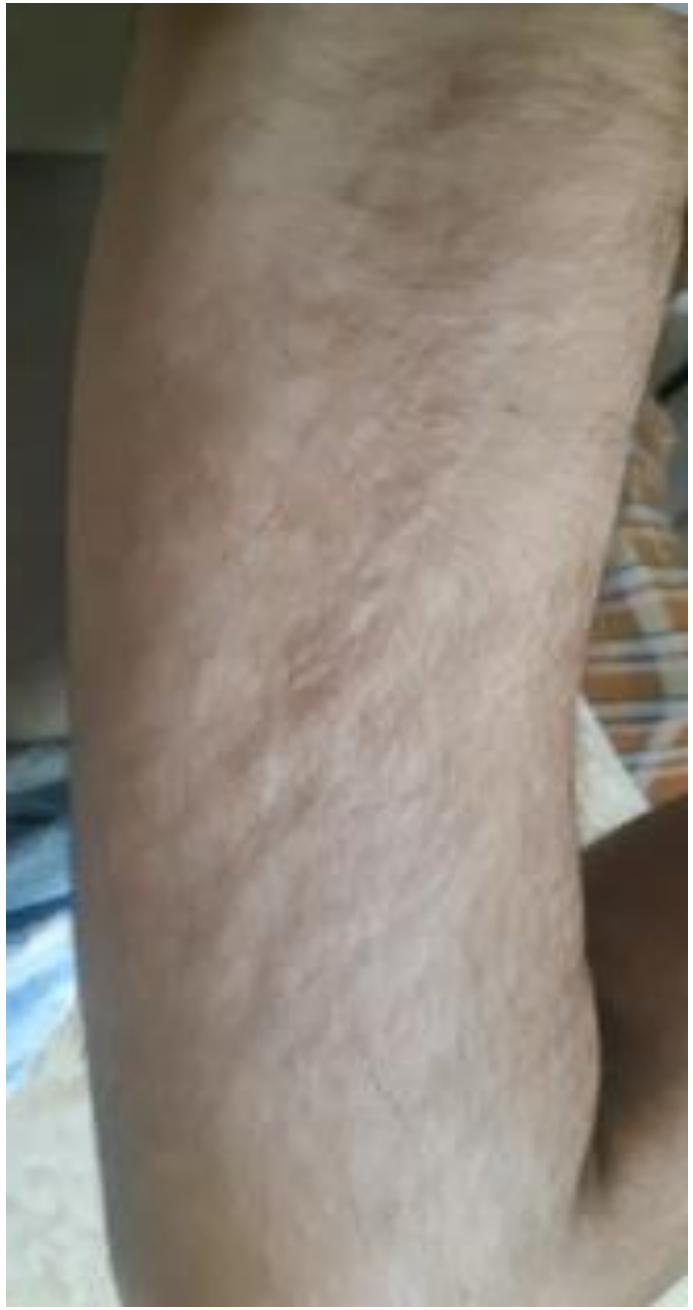
See pictures

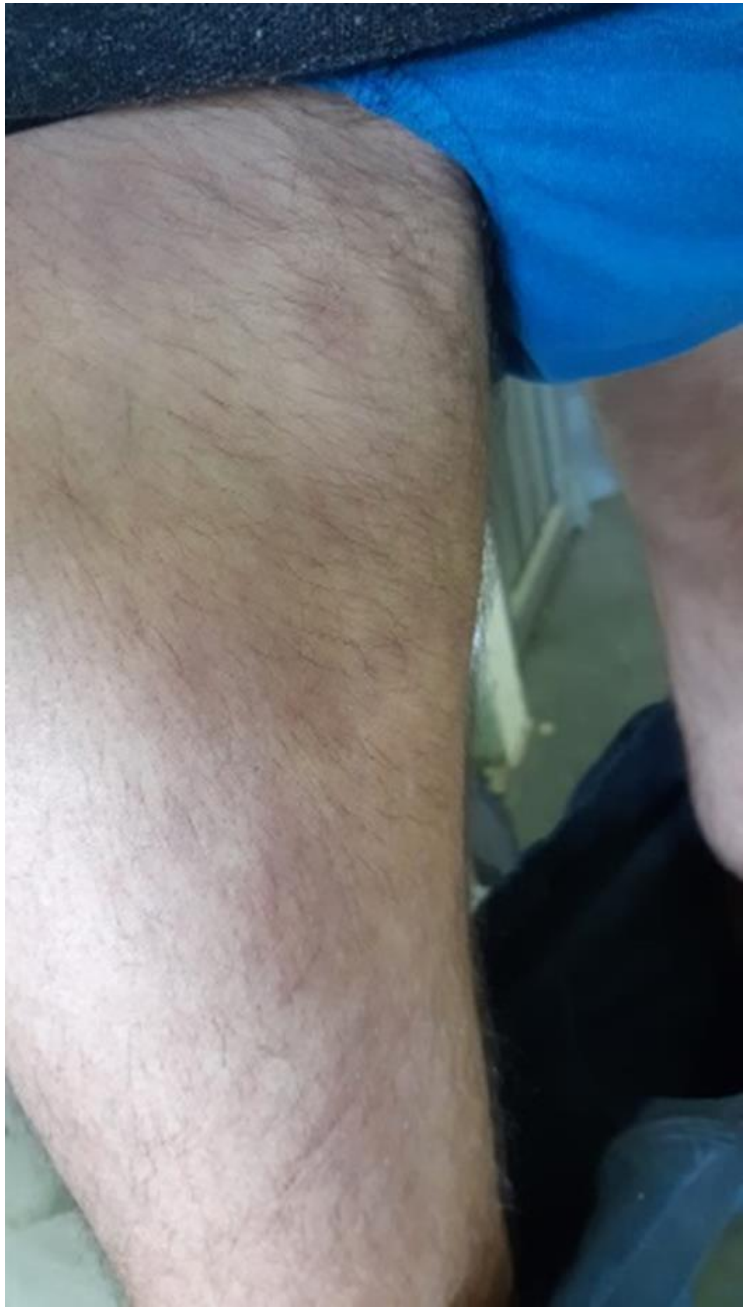

FOX











Laboratory tests-Eosinophilia

שם בדיקה **	מעבדה / תאריך / טווח על פי מעבדה אחרונה	העמק 26/03/2019 08:37	העמק 08/01/2019 08:17	העמק 06/11/2018 08:46	העמק 25/09/2018 08:14	העמק 05/09/2018 14:36	העמק 03/07/2018 08:44	העמק 29/05/2018 09:19
HYPO %	0.0 - 2.5 %	1.5	5.5*	1.9	5.7*	2.2	2.6*	
HDW	2.20 - 3.20 g/dL	2.62	2.95	2.52	2.88	2.94	2.33	
MPXI	-10.0 - 10.0	3.5	-2.8	2.8	2.6	-1.8	-2.1	
MACRO%	0.0 - 4.0 %	0.1	0.0	0.0	0.1	0.0	0.0	
MICRO %	0.0 - 4.0 %	3.3	3.1	5.7*	3.2	5.1*	4.3*	
HYPER%	0.0 - 2.5 %	0.5	0.5	0.3	0.3	1.0	0.2	
WBC	4.50 - 11.50 K/ul	4.81	7.28	6.10	7.89	6.97	7.91	7.75
NEUT%	%	63.4	72.5*	65.8*	71.5*	62.3	66.0*	53.5
NEUT.abs	1.50 - 8.00 K/ul	3.05	5.28	4.02	5.64	4.34	5.22	4.15
LYM%	%	24.4	18.7*	20.8*	17.5*	21.0*	17.0*	17.3*
LYMP.abs	1.50 - 5.00 K/ul	1.17*	1.36*	1.27*	1.38*	1.47*	1.35*	1.34*
MONO%	%	5.8	4.3	6.6	4.9	6.3	7.3	7.6
MONO.abs	0.10 - 0.80 K/ul	0.28	0.31	0.40	0.39	0.44	0.58	0.59
EOS.abs	0.00 - 0.80 K/ul	0.16	0.24	0.33	0.35	0.59	0.62	1.64*
EOS %	%	3.4	3.3	5.4	4.4	8.5*	7.8*	21.2*
BASO %	%	0.2	0.1	0.2	0.2	0.4	0.7	0.4
BASO abs	0.00 - 0.20 K/ul	0.01	0.01	0.01	0.02	0.03	0.05	0.03
LUC%	0.0 - 4.0 %	2.9	1.1	1.2	1.3	1.4	1.2	
LUC abs	0.00 - 0.40 K/ul	0.14	0.08	0.08	0.11	0.10	0.10	
RBC	4.50 - 5.50 M/ul	5.55*	5.45	5.62*	5.44	5.89*	5.83*	5.62*
HB	14.0 - 17.0 g/dL	14.7	13.6*	14.2	14.5	14.6	14.5	14.3
HCT	40.0 - 54.0 %	44.8	42.5	43.2	42.5	45.3	45.6	42.3
MCV	80.0 - 95.0 fL	80.8	78.0*	76.8*	78.0*	76.9*	78.2*	75.3*
MCH	27.0 - 31.0 pg	26.4*	25.0*	25.3*	26.6*	24.8*	24.9*	25.4*
MCHC	32.0 - 35.0 g/dL	32.7	32.1	32.9	34.1	32.3	31.9*	33.8
CH		27	25	25	25	26	25	
RDW	11.5 - 14.5 %	14.3	12.6	14.2	13.1	13.9	14.2	14.0
PLT	150 - 450 K/ul	197	256	234	232	295	183	231
MPV	7.1 - 11.1 fL	7.9	8.3	9.0	9.2	9.9	8.1	9.5
ESR	0.0 - 15.0 mm		17.0*				5.0	

Laboratory tests-Serology

תוצאות פרופיל: כללית - אימונו-סרו

** שם בדיקה	גורם שולח / מעבדה / תאריך טווח על פי מעבדה אחרונה	רמת הייב העמק 26/03/2019 08:37	רמת הייב העמק 26/03/2019 08:37	רמת הייב העמק 08/01/2019 08:17	רמת הייב העמק 03/07/2018 08:44	רמת הייב העמק 03/07/2018 08:44	רמת הייב העמק 03/07/2018 08:44	נצרת יעצת העמק 29/05/2018 09:14	חסן יוסף העמק 12/09/2003 08:25
ANTI-MYELOPEROXIDASE	0.0 - 1.0 AI				<0.2				
anti Proteinase 3	0.0 - 1.0 AI				<0.2				
ENA PROFILE			Negative		Negative				
ANTINUCLEAR Ab_(ANA)	0 - 0.155								0.045 NEGATIVE
ANA PATTERN			Negative		Negative				
ANA TITER			NEGATIVE 1:160		NEGATIVE 1:160				
C-REACTIVE PROTEIN	0.00 - 0.50 mg/dL	0.34		**0.90***		**2.25***		**15.90***	
RHEUMATOID FACTOR	0 - 15 IU/ml						<10		

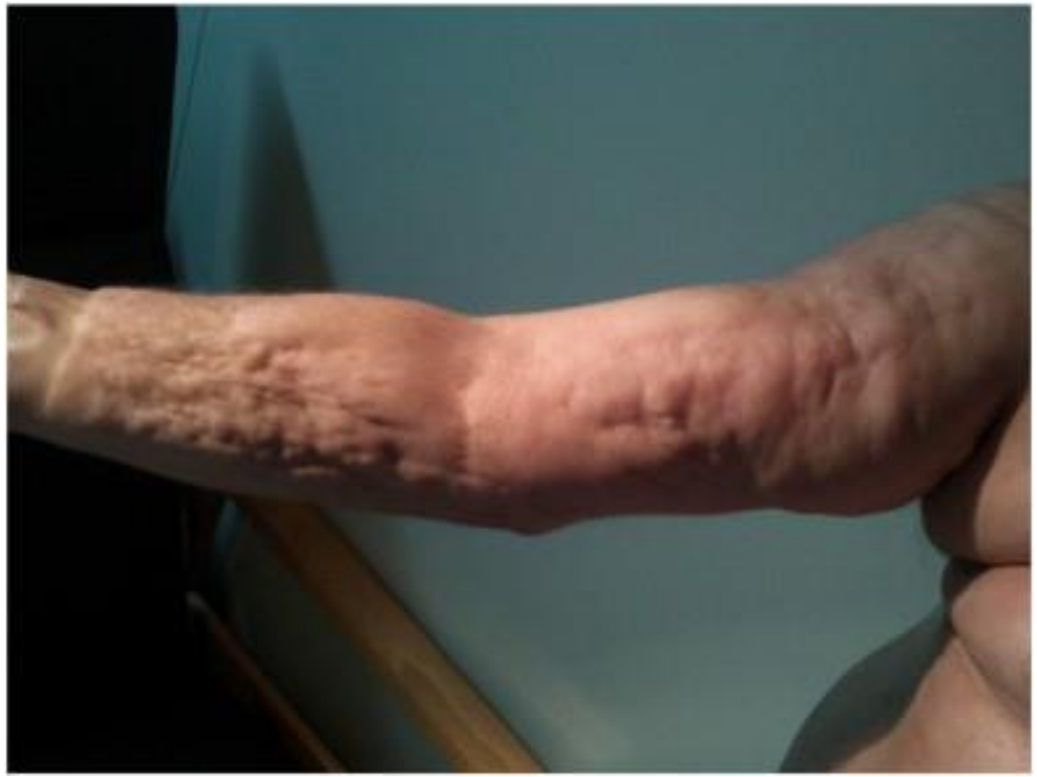
Biopsy [skin + fascia + muscle]

Compatible with Eosinophilic Fasciitis without muscle involvement

treatment

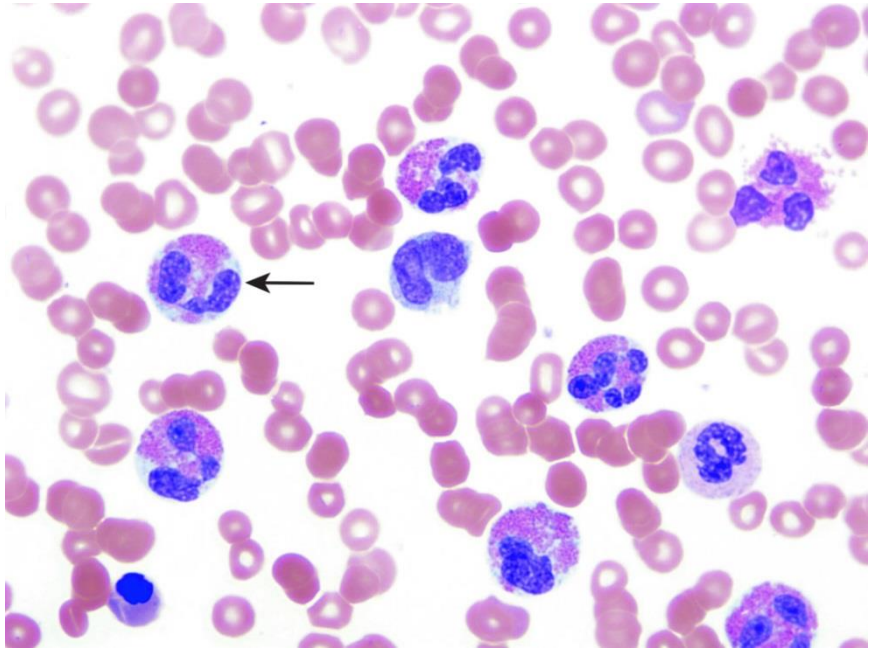
- ✓ Prednisone 80 mg with tapering
- ✓ MTX 15 mg
- ✓ Excellent response

Eosinophilic Fasciitis (EF)
Shulman syndrome



INTRODUCTION

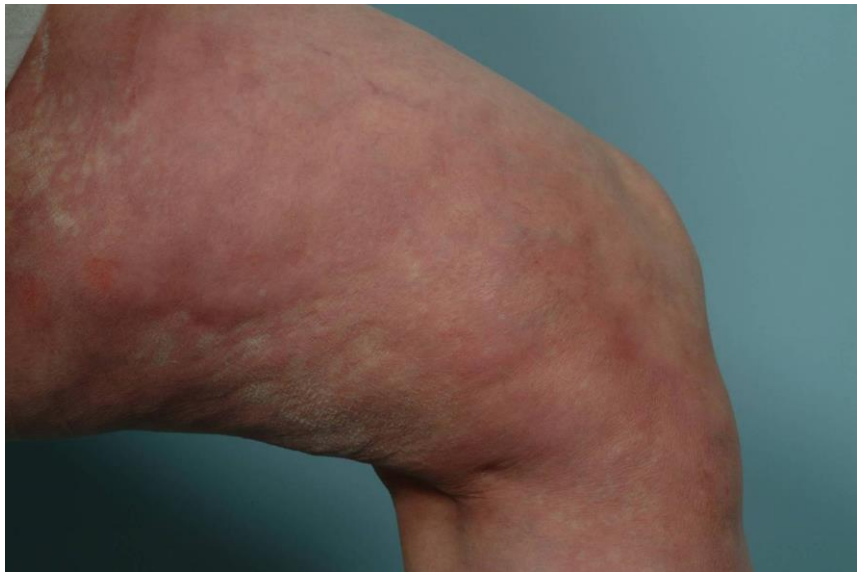
- EF is an **uncommon** disorder of **unknown** etiology and **poorly understood** pathogenesis [1].
- **Early phase : limb or trunk erythema and edema** . **Eosinophilia** is a prominent
- **Later phase** : **collagenous thickening of subcutaneous fascia**. less prominent eosinophilia [2].



- 1.Shulman LE. Diffuse fasciitis with eosinophilia: a new syndrome? Trans Assoc Am Physicians 1975; 88:70.
- 2.Falanga V, Medsger TA Jr. Frequency, levels, and significance of blood eosinophilia in systemic sclerosis, localized scleroderma, and eosinophilic fasciitis. J Am Acad Dermatol 1987; 17:648.

history

- **Shulman in 1975**, described **two cases** of men with a scleroderma-like affecting the extremities, associated with **eosinophilia, hypergammaglobulinemia and elevated ESR** (1)
- **Distinct from scleroderma** : sparing fingers, absence of Raynaud's, favorable response to steroid
- **Rodnan** later termed this condition **eosinophilic fasciitis**, due to **marked thickening** of the fascia and an **intense lympho-plasmocytic inflammatory infiltrate** noted on skin biopsy (3).



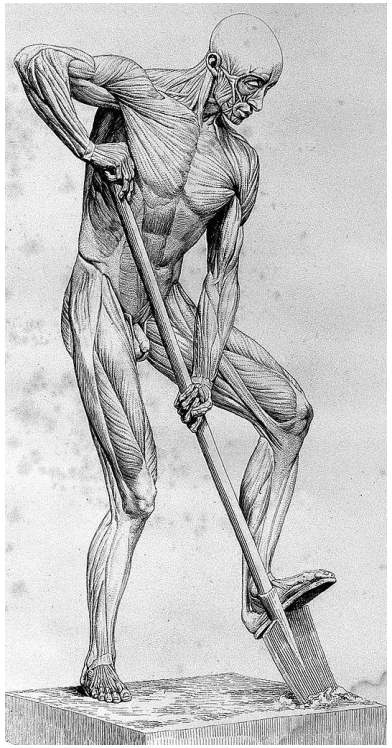
3. Rodnan GP, DiBartolomeo A, Medsger TA Jr. Proceedings: Eosinophilic fasciitis. Report of six cases of a newly recognized scleroderma-like syndrome. Arthritis and rheumatism. 1975; 18(5):525.

Epidemiology

- The incidence and prevalence is **unknown.**
- It has a **male predominance** (1.5:1) and is more common in **Caucasian** ethnicity.
- EF has been reported in the **3rd to 6th** decades of life
- Considered **rare disease**, many **unreported cases,** Only **100 case reports** from Japan (130 M)

Triggers

Possible triggers That have been suggested :



- ***Strenuous exercise [1]*** **(bicyclitis)**
- Initiation of **hemodialysis** [4]
- **Infection** with Borrelia burgdorferi (**Lyme dis**) [5]
- **Physical factors** such as **radiation** therapy and **burns**

- Graft-versus-host disease **(GVHD)**
- **Medications** : statins, phenytoin, ramipril, and heparin [8]
- **Autoimmune** dis : thyroid disease ,PBC , SLE, Sjögren's [9]
- **Hematologic** disorders [9]

most cases of EF are considered idiopathic

- 4.Florell SR, Egan CA, Gregory MC, et al. Eosinophilic fasciitis occurring four weeks after the onset of dialysis in a renal failure patient. J Cutan Med Surg 2001; 5:33.
- 5.Granter SR, Barnhill RL, Duray PH. Borrelial fasciitis: diffuse fasciitis and peripheral eosinophilia associated with Borrelia infection. Am J Dermatopathol 1996; 18:465.
- 8.Long H, Zhang G, Wang L, Lu Q. Eosinophilic Skin Diseases: A Comprehensive Review. Clin Rev Allergy Immunol 2016; 50:189.
- 9.Bachmeyer C, Monge M, Dhôte R, et al. Eosinophilic fasciitis following idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia and Hashimoto's disease. Dermatology 1999; 199:282.

Association with other disorders

Para-neoplasm ???

❑**Hematologic disorders can be associated with EF in up to 10% include [26,36]:**

- Lymphoma
- Lymphocytic & eosinophilic leukemia
- Multiple myeloma
- Paroxysmal nocturnal hemoglobinuria

- Aplastic anemia
- Amegakaryocytic thrombocytopenia
- Myeloproliferative disorders
- Myelodysplastic syndromes

- EF is complicated by **localized scleroderma** in 20-30% of cases.
- Other **autoimmune complications :** SLE, RA , Sjogren's, thyroiditis

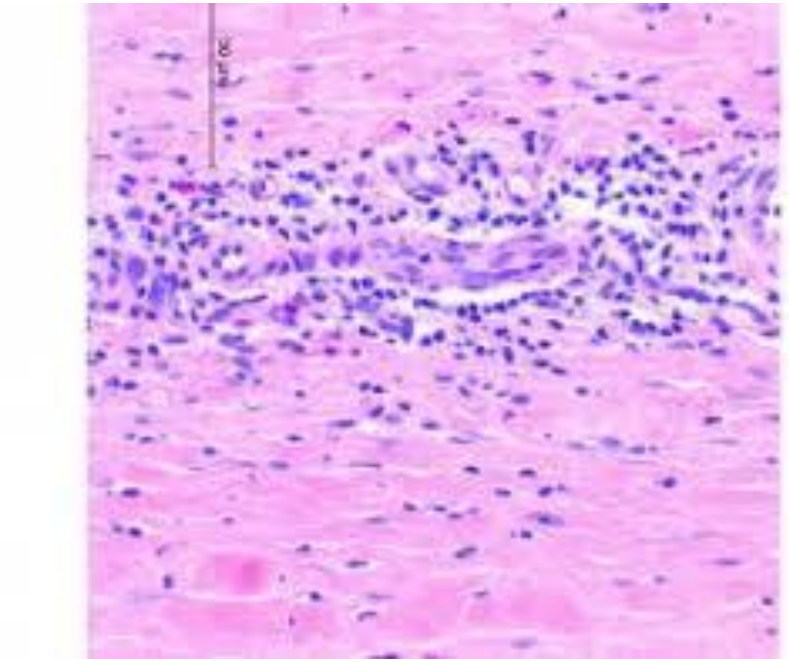
- 26.Doyle JA, Connolly SM, Hoagland HC. Hematologic disease in scleroderma syndromes. Acta Derm Venereol 1985; 65:521.
- 36.Eklund KK, Anttila P, Leirisalo-Repo M. Eosinophilic fasciitis, myositis and arthritis as early manifestations of peripheral T-cell lymphoma. Scand J Rheumatol 2003; 32:376.

Etiology

- ✓ It is induced **by strenuous exercise or labor**, which might provoke an autoimmune response targeting the damaged fascia (see planter fasciitis and exercise)
- ✓ An **autoimmune mechanism** is presumed due to the presence of hyper-gammaglobulinemia , response to steroids, presence of RF , ANA and IC
- ✓ Elevated levels of **eosinophilic proteins and serum IL-5, eosinophilic migration capacity, suggesting that eosinophils contribute to the mechanism** of onset.

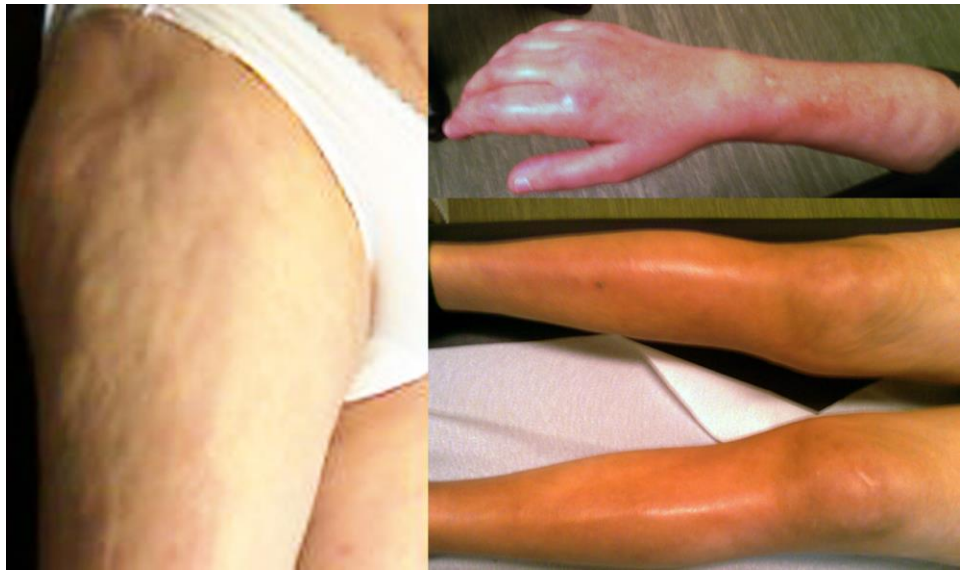
pathophysiology

- The dermal fibroblasts of EF exhibit **greater expression of type I collagen and fibronectin**.
- Fibrosis is generated by **the increased production of TIMP-1, MMP-1, collagenase**.
- The involvement of **mast cells** has also been indicated, with an increase in plasma **histamine** .
- There have also been reports of **increased levels IL- 2, IFN-g, leukemia inhibitory factor (LIF) , CD40 , and superoxide dismutase (SOD)**.



Clinical Features

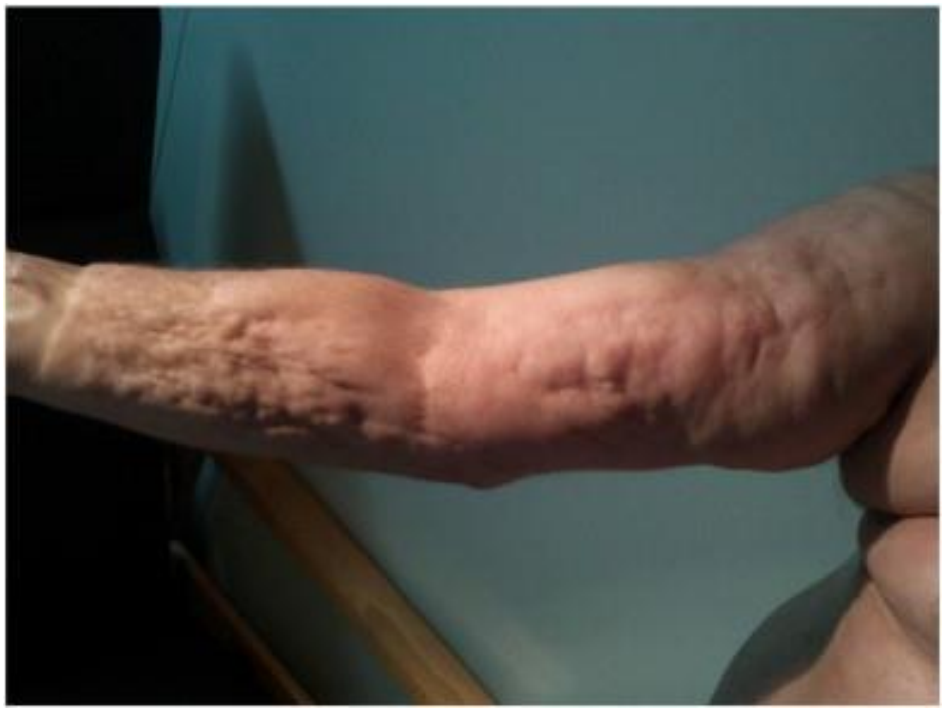
- EF is characterized by **symmetrical induration of skin and deeper muscular fascia** [14].
- Initially, there is a **marked, non-pitting edema of skin**, of extremities, neck, and trunk.
- The onset is typically **acute (early)** : erythema, swelling, and induration with eosinophilia [16].
- A **subacute** course (**late phase**) : thickening of skin similar to scleroderma disorders.

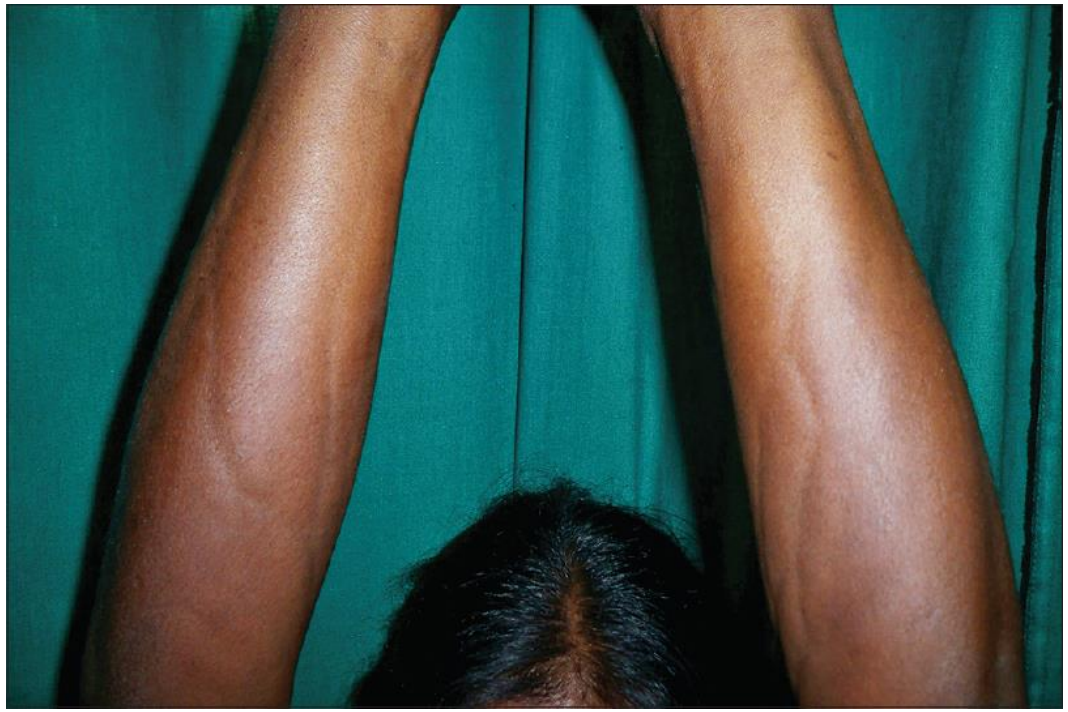


- 14.Rodnan GP, DiBartolomeo A, Medsger TA Jr. Proceedings: Eosinophilic fasciitis. Report of six cases of a newly recognized scleroderma-like syndrome. Arthritis Rheum 1975; 18:525.
- 16.Varga J, Griffin R, Newman JH, Jimenez SA. Eosinophilic fasciitis is clinically distinguishable from the eosinophilia-myalgia syndrome and is not associated with L-tryptophan use. J Rheumatol 1991; 18:259.

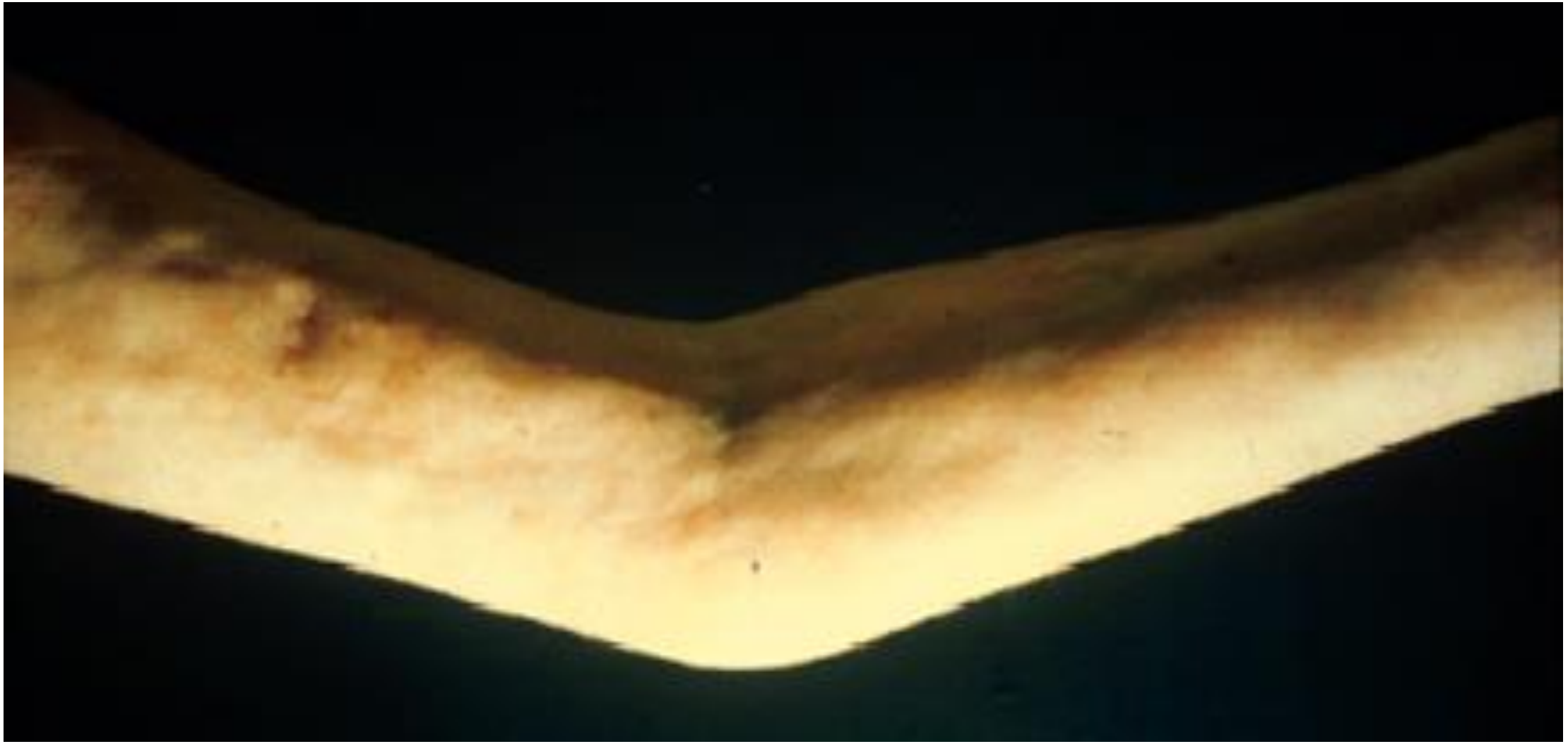
Skin involvement

- **The swelling is replaced by induration** that gives the skin irregular **woody texture of orange peel (peau d'orange=*pudorange*)** (distinct from smooth, shiny skin in scleroderma).
- **Elevation of an affected limb**, reduces venous pressure, and causes indentation along the superficial veins - the **"groove sign"**

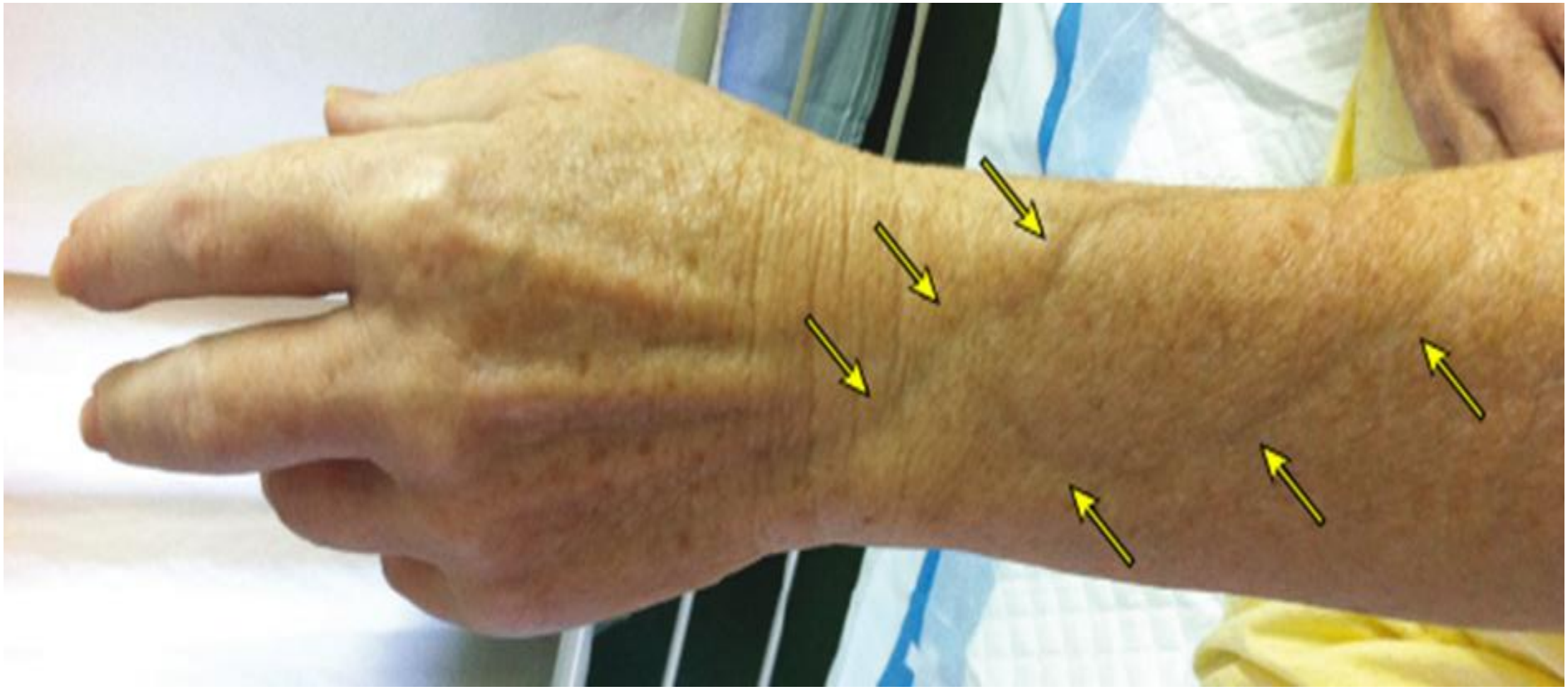




Peau d’orange



Groove sign



Arthritis & Myositis

- **Inflammatory arthritis** occurs in **40 %** in one study of 52 patients, [17]. Usually joints adjacent to fasciitis, result in loss of pliability of skin and fascia and **Joint contractures may develop in 56%** .
- **Muscle pain and muscle weakness are common** symptoms in EF [19]. Deep skin and fascial involvement merging into peri-myositis. **Inflammatory myositis is uncommon**.

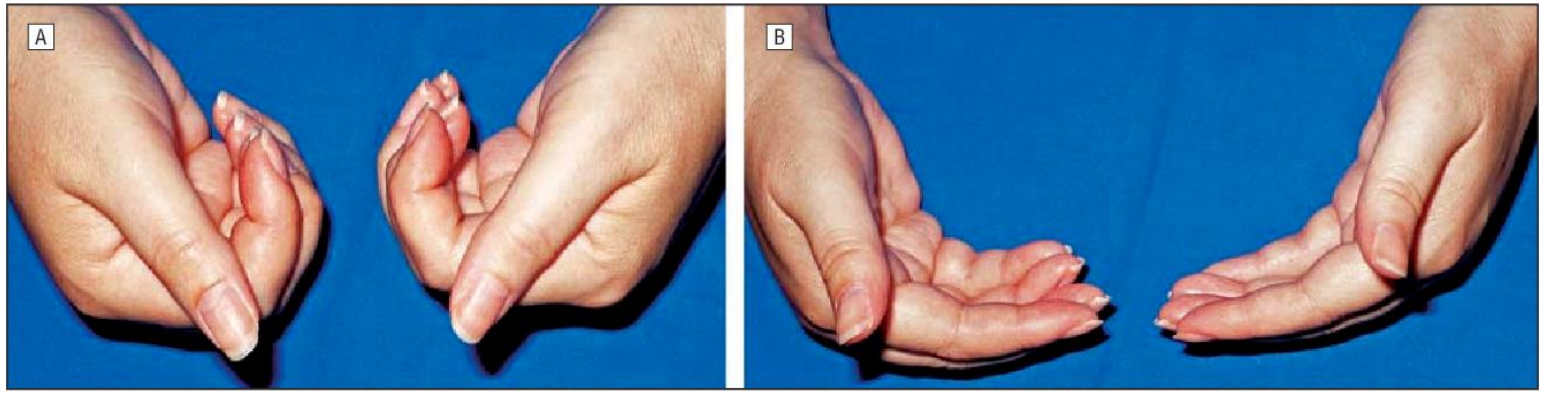
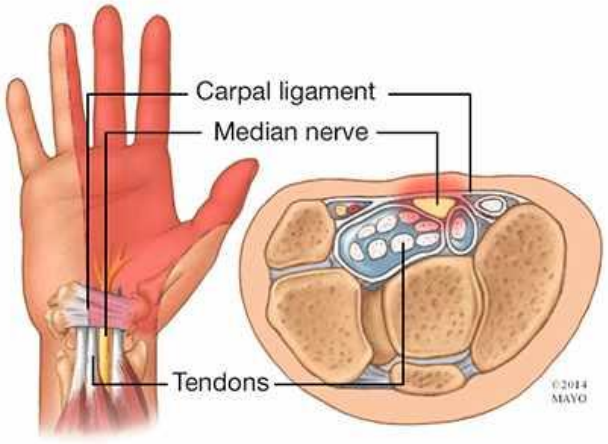


Figure 1 Marked limitation of finger movement at presentation, shown by the inability to make a fist (A) and limited extension of the fingers (B)

- 17.Lakhanpal S, Ginsburg WW, Michet CJ, et al. Eosinophilic fasciitis: clinical spectrum and therapeutic response in 52 cases. Semin Arthritis Rheum 1988; 17:221.
- 19.Nassonova VA, Ivanova MM, Akhnazarova VD, et al. Eosinophilic fasciitis. Review and report of six cases. Scand J Rheumatol 1979; 8:225.

Neuropathies & Visceral involvement

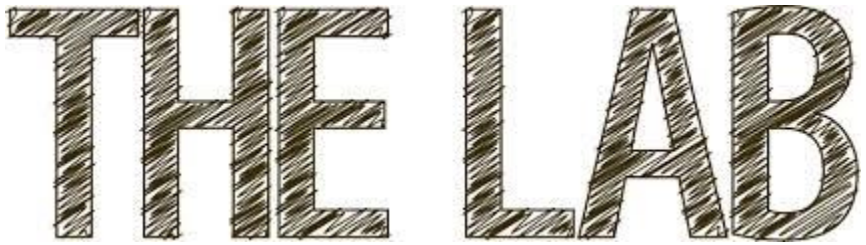
- **CTS** has been commonly described in EF, occurring in (23%) in one series [20].
- In one case, a **peripheral neuropathy** (mononeuritis multiplex) was diagnosed by EMG [21].
- A few cases of pleural effusions[22], pericarditis[23], renal involvement[24] have been described.
- The **absence of Raynaud's and sclerodactyly** helps to distinguish EF from systemic sclerosis.



- 21.Moriguchi M, Terai C, Kuroki S, et al. Eosinophilic fasciitis complicated with peripheral polyneuropathy. Intern Med 1998; 37:417.
- 22.Killen JW, Swift GL, White RJ. Eosinophilic fasciitis with pulmonary and pleural involvement. Postgrad Med J 2000; 76:36.
- 23.Rizzo S. Eosinophilic pleuropericarditis and fasciitis. A new case. Monaldi Arch Chest Dis 2002; 57:311.
- 24.Kirschstein M, Helmchen U, Jensen R, et al. Kidney involvement in a 17-year-old boy with eosinophilic fasciitis. Clin Nephrol 1999; 52:183.

Laboratory findings

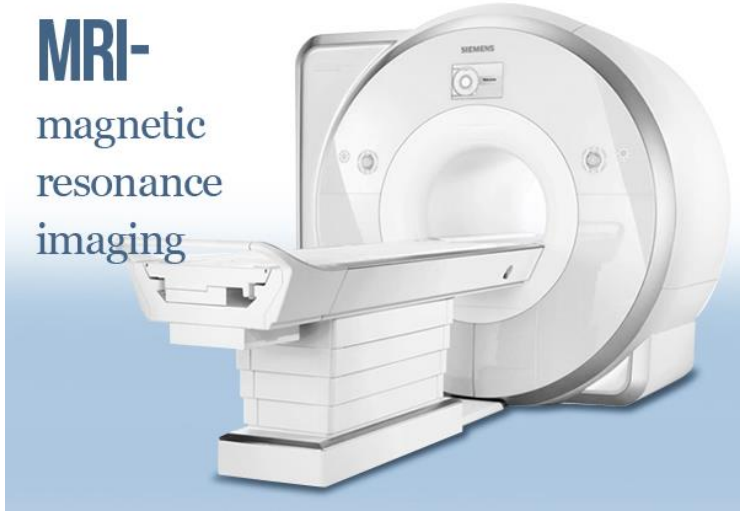
- The majority of EF have a **transient eosinophilia** [17]. no correlation with disease severity.
- Over 50% have an **elevated ESR and CRP as well as hyper-gammaglobulinemia** [25].
- Serum **ANA and RF** have been reported to be present in EF only 10% [15].
- Serum **CPK are typically normal**, even in patients with myalgia.
- **Serum type III procollagen peptide** (PIIIP) reflect the disease activity (highly useful marker)



25.Lebeaux D, Sène D. Eosinophilic fasciitis (Shulman disease). Best Pract Res Clin Rheumatol 2012; 26:449

Magnetic resonance imaging

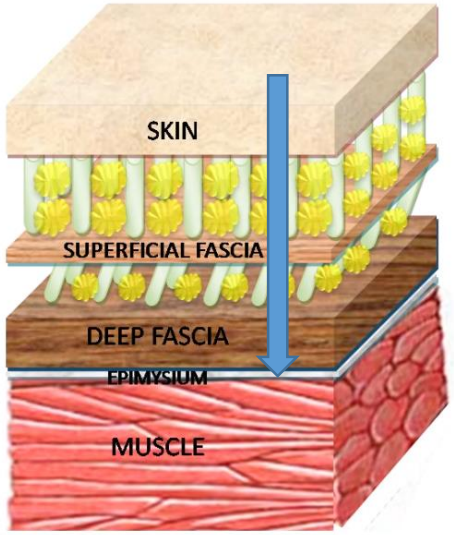
- Findings on MRI are helpful to **confirm fascial inflammation and helps to locate biopsy** erea [41] .
- **Increased T2 signal** in subcutaneous and deep fascia and **enhancement on fat-suppressed T1** images **after gadolinium** administration have been noted [46].
- If MRI is contraindicated, **other modalities can be used include US and FDG-PET/CT** [47].



- 46.Baumann F, Brühlmann P, Andreisek G, et al. MRI for diagnosis and monitoring of patients with eosinophilic fasciitis. AJR Am J Roentgenol 2005; 184:169.
- 47.Kim HJ, Lee SW, Kim GJ, Lee JH. Usefulness of FDG PET/CT in the diagnosis of eosinophilic fasciitis. Clin Nucl Med 2014; 39:801.

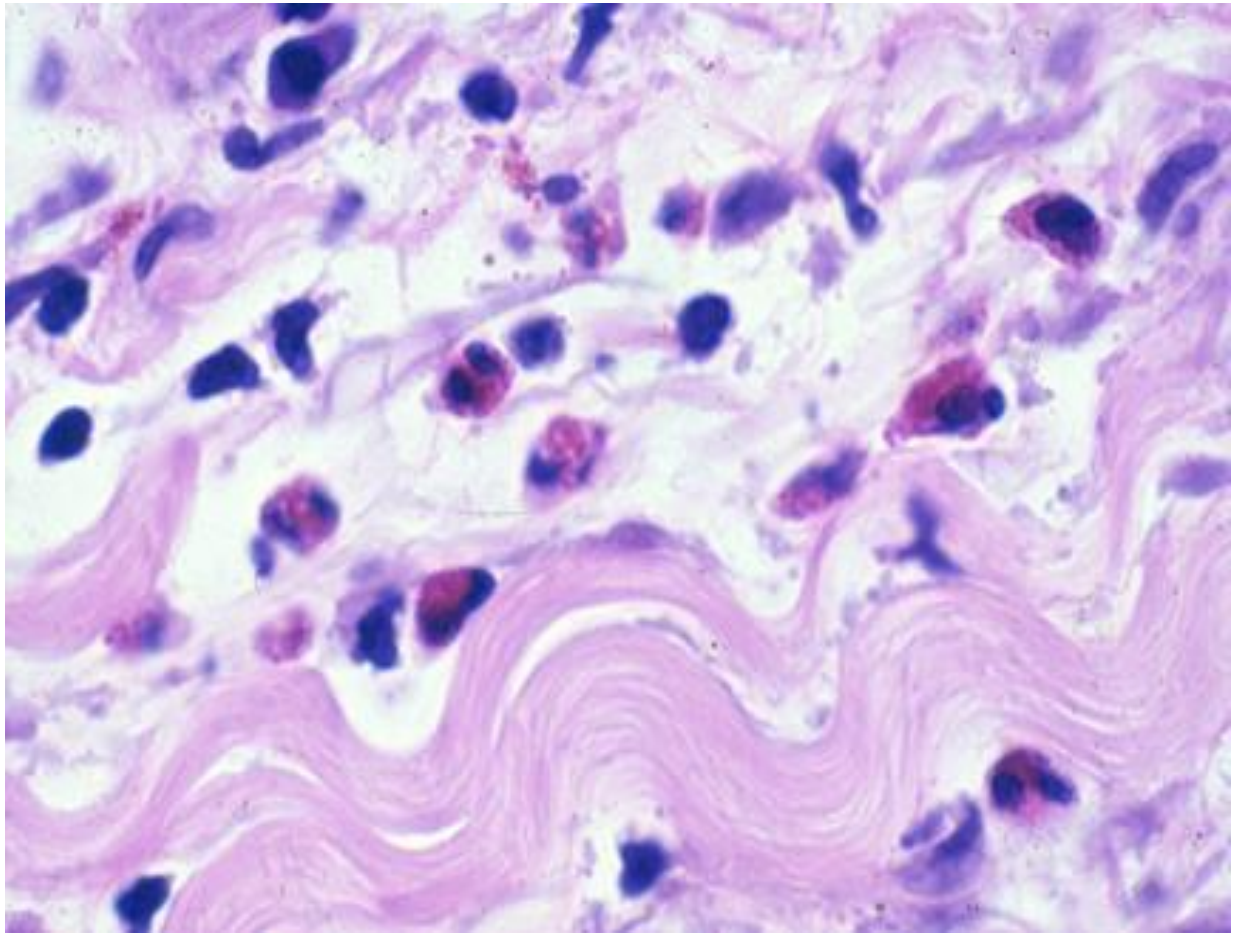
DIAGNOSIS-Biopsy

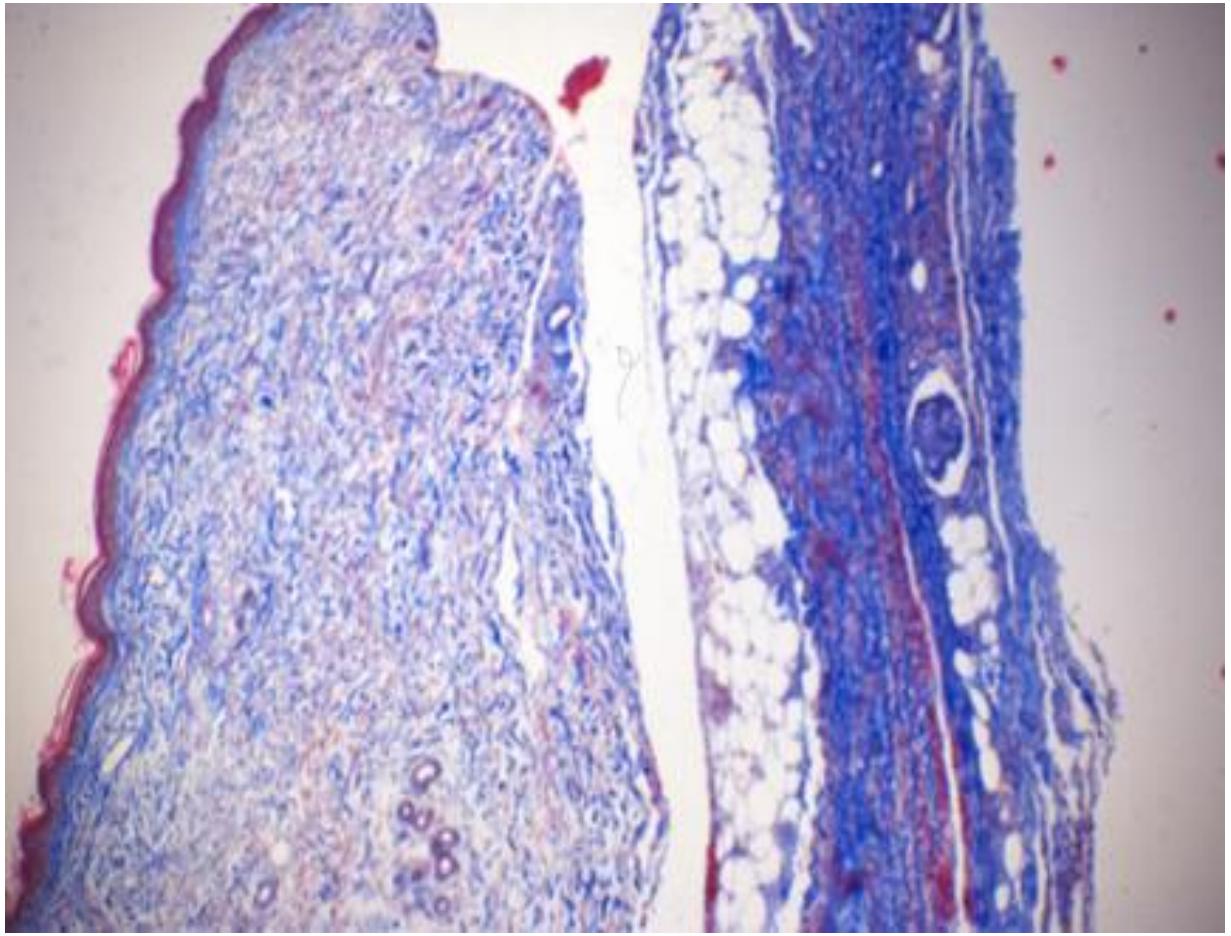
- Skin **biopsy of full thickness of skin and subcutaneous tissues down to the muscle surface**.
- There is no pathognomonic finding, the finding is **helpful in ruling out scleroderma-like** disorders.
- **In early disease** : infiltration of lymphocytes, plasma cells, histiocytes, and eosinophils [8].
- **In late disease** : These structures become thickened and sclerotic [37].
- **In 15%** inflammation occurs in epi/peri/endo mysium, within **muscle fibers**[40]



- 37.Barnes L, Rodnan GP, Medsger TA, Short D. Eosinophilic fasciitis. A pathologic study of twenty cases. Am J Pathol 1979; 96:493.
- 40.Huang KW, Chen XH. Pathology of eosinophilic fasciitis and its relation to polymyositis. Can J Neurol Sci 1987; 14:632.

Pathological findings





2016 Diagnostic criteria

Major criterion:

- Symmetrical plate-like sclerotic lesions on four limbs.
- lacks Raynaud's phenomenon (to exclude systemic sclerosis).

Minor criteria 1:

Biopsy of fascia (fibrosis and thickening and infiltration of eosinophils).

Minor criteria 2:

Thickening of fascia by MRI , US , PET-CT

A definitive diagnosis : major criterion and one or two of the minor criteria

DIFFERENTIAL DIAGNOSIS

- Systemic and localized scleroderma
- Scleroderma-like disorders
- Nephrogenic systemic fibrosis
- Sclero-myxedema

- Scler-edema
- Eosinophilia myalgia syndrome
- Toxic oil syndrome
- Graft-versus-host disease

TREATMENT

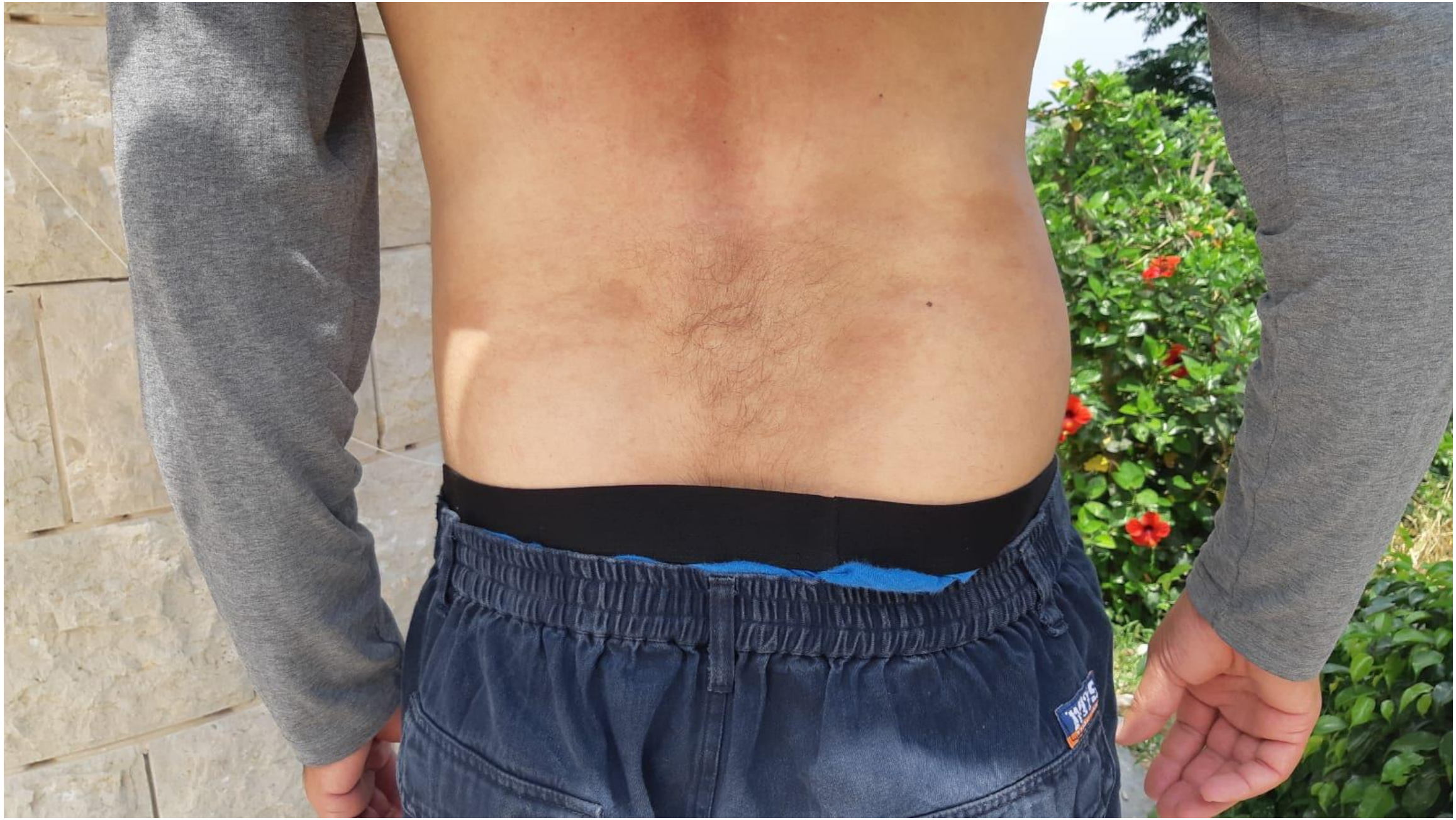
- The majority (75%) respond to **glucocorticoid**, starting prednisone from 1-1.5 mg/kg [57], often with a rapid resolution of eosinophilia and normalization of ESR. can last from weeks to months.
- Without steroid response, **use MTX** (15-25 mg weekly), mycophenolate or PLQ (limited data) [17].
- Based on **case series** : sulfasalazine, azathioprine, IVIG, cyclosporine A, penicillamine and biologics such as infliximab, rituximab, tocilizumab [17,25,57,65].
- Surgical release of contractures, Surgical fasciectomy in patients resistant to steroids [66].

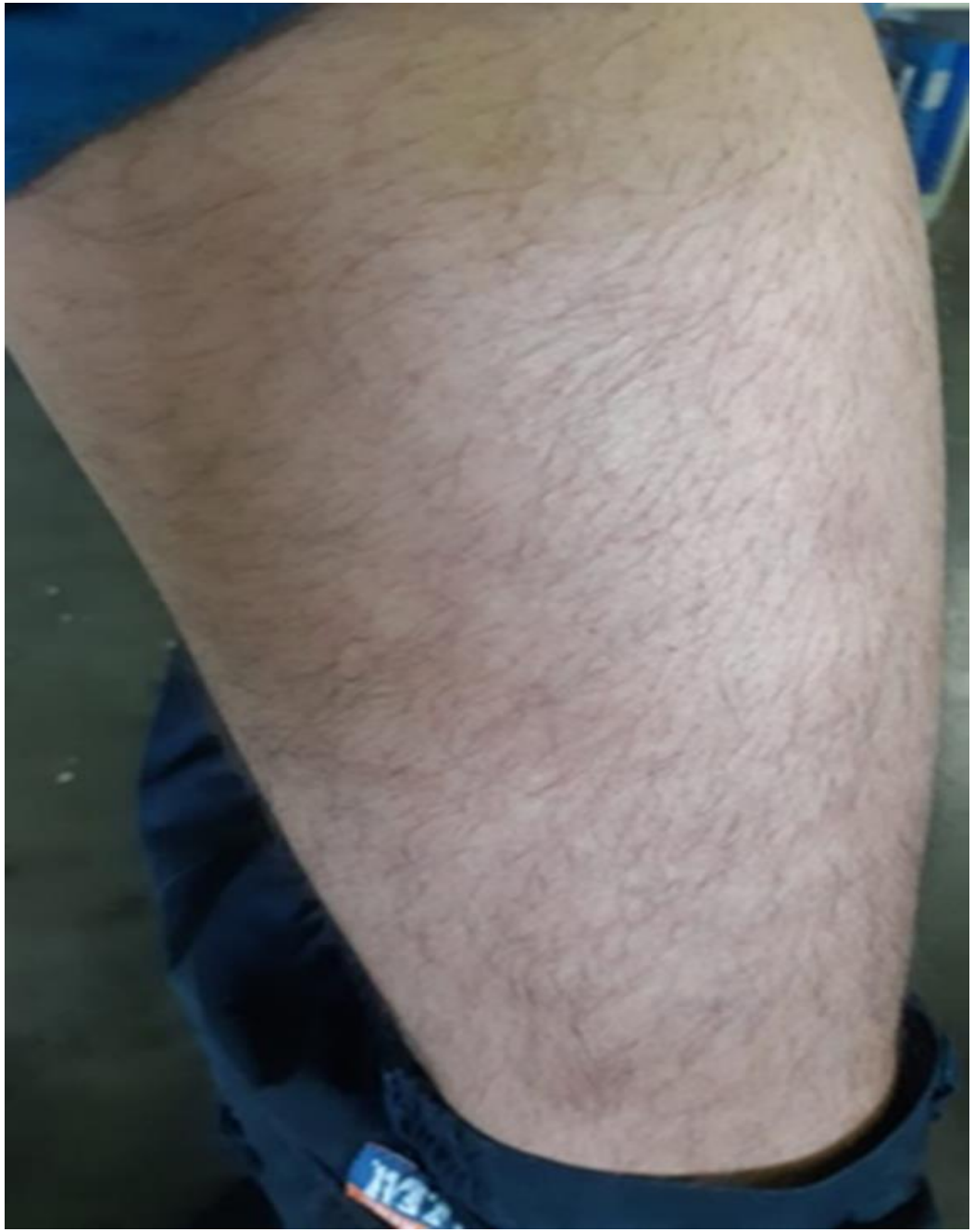
57. Bischoff L, Derk CT. Eosinophilic fasciitis: demographics, disease pattern and response to treatment: report of 12 cases and review of the literature. Int J Dermatol 2008; 47:29.

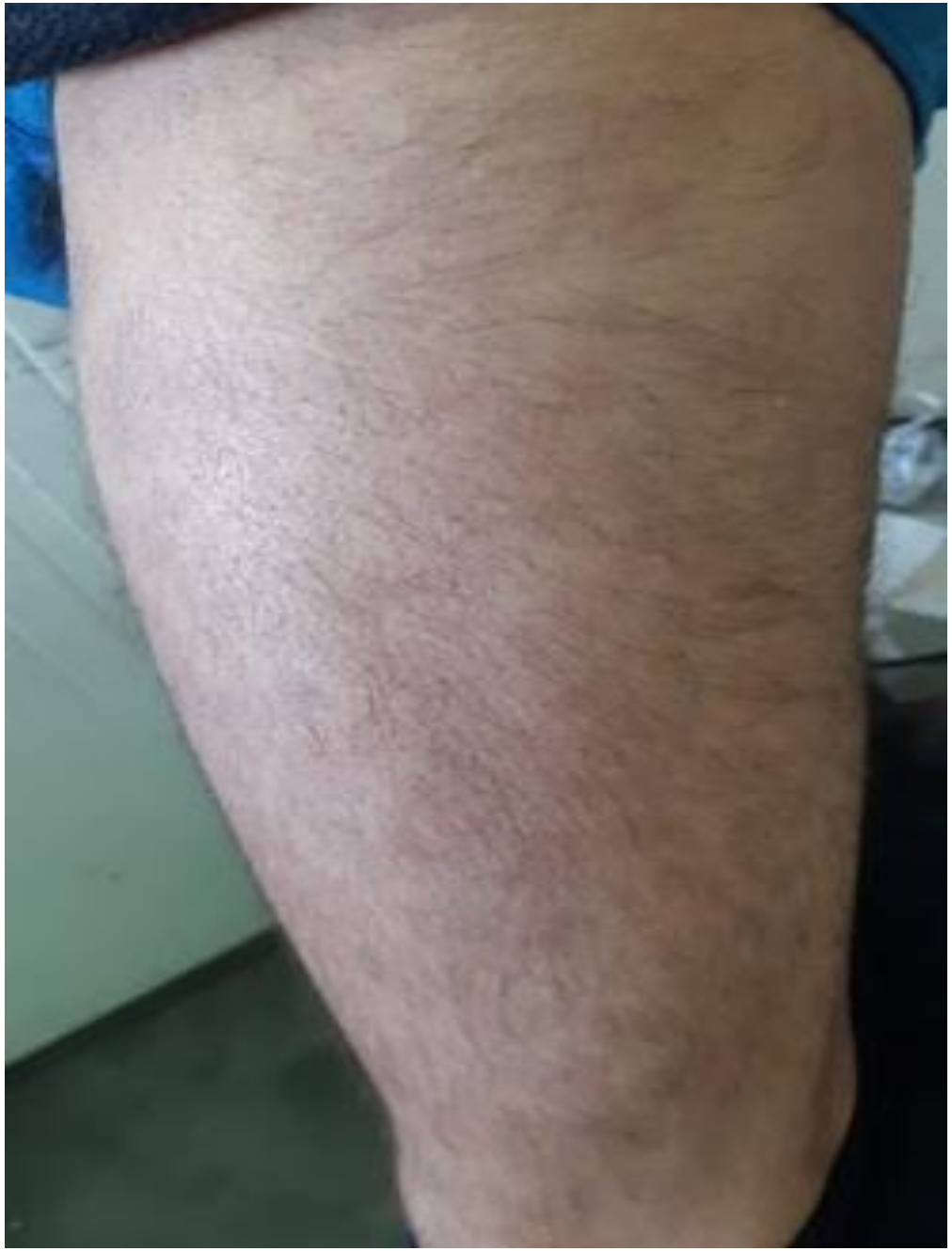
66. Suzuki G, Itoh Y, Horiuchi Y. Surgical management of eosinophilic fasciitis of the upper extremity. J Hand Surg Br 1997; 22:405.

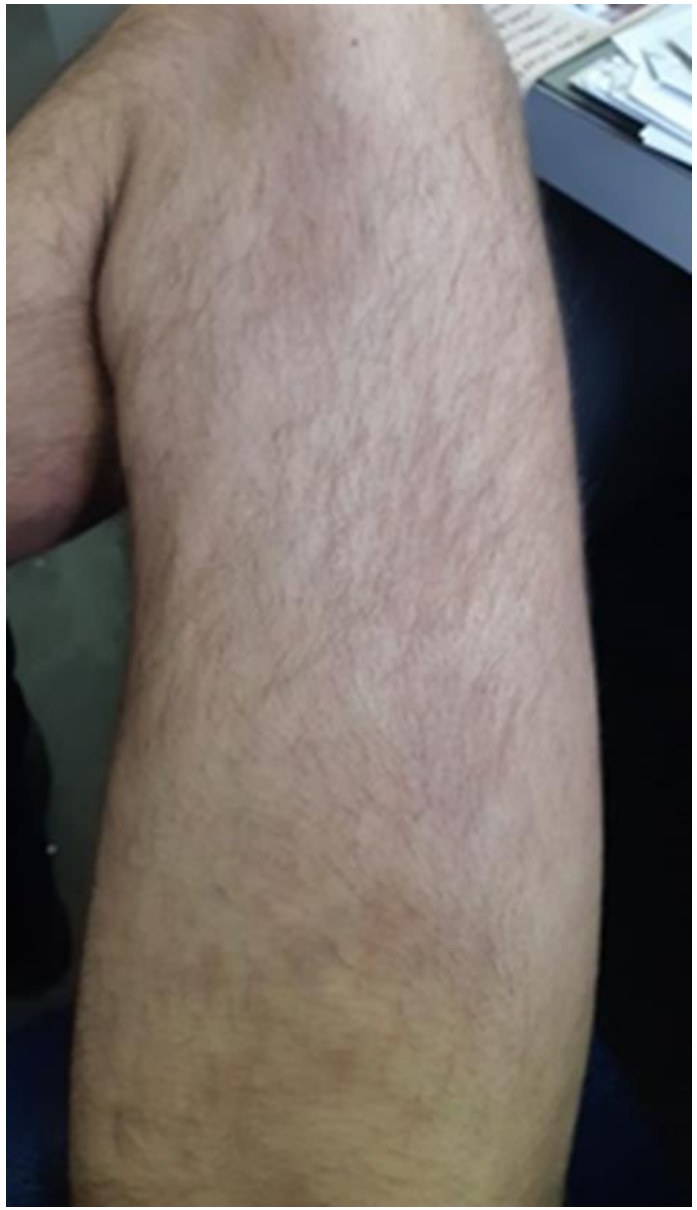
PROGNOSIS

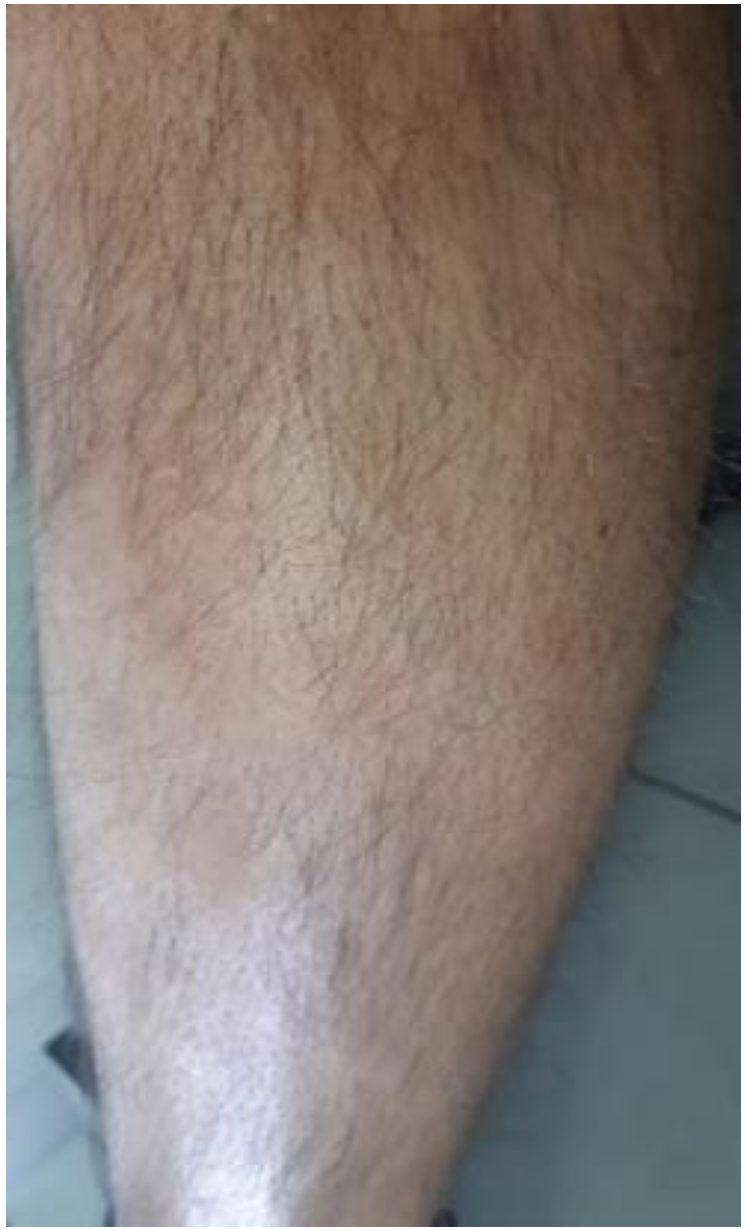
- Adjunctive **physiotherapy** is recommended to minimize the development of flexion contractures
- The goal of treatment is to achieve **complete remission**
- Overall the **prognosis of EF is good**, with the majority of cases achieving **full remission**.
- **Spontaneous resolution** has been reported in some cases.

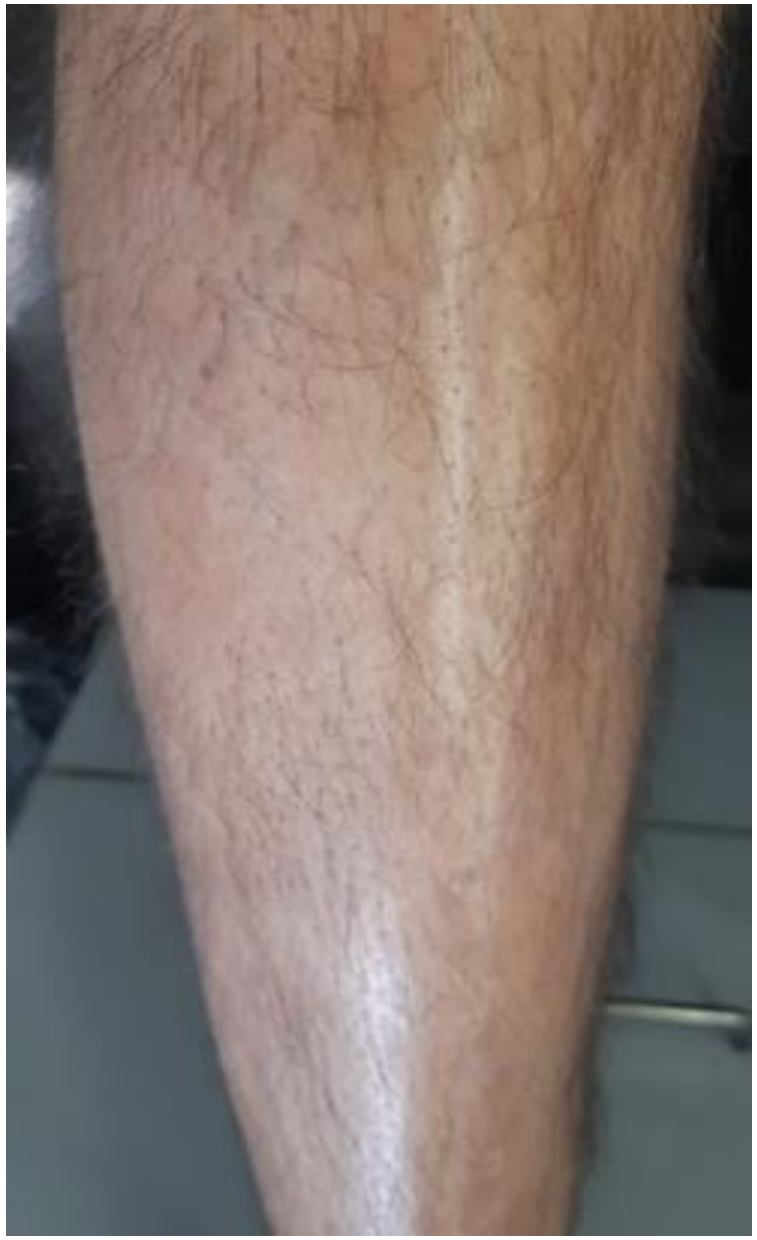












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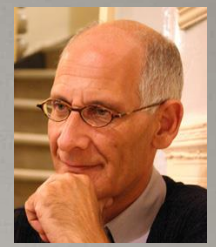

MULTISYSTEM PRESENTATION OF EOSINOPHILIC FASCIITIS

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SUMMARY

A 20-year-old man experienced the onset of progressive scleroderma-like skin changes with eosinophilia and hypergammaglobulinaemia after strenuous military activity. A biopsy showed fasciitis. Concomitant splenomegaly, polysynovitis, restrictive lung function, myositis, decreased hepatic clotting factors and proteinuria were documented. He responded well to corticosteroids, relapsed upon their discontinuation and had a complete remission of both skin and systemic features while on penicillamine and azathioprine. He is now in good health and has received no medication for the past two years.


Thank
you !