Concise report

Eosinophilic fasciitis (Shulman disease): new insights into the therapeutic management from a series of 34 patients

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Abstract

Objective. To analyse therapeutic management of eosinophilic fasciitis (EF).

Methods. We reviewed 34 adult patients with biopsy-proven EF. Analyses focused on the therapeutic management, including treatment modalities, responses and associated or predictive factors.

Results. Thirty-four patients were included with a diagnosis age of 53 (15) years. They were featured by cutaneous manifestations (88%) including morphoea (41%), myalgia (86%) and hypereosinophilia (85%). Thirty-two patients (94%) were eligible for treatment evaluation and all received CSs as a first-line therapy. Fifteen patients (47%) received methylprednisolone pulses (MPPs) at treatment initiation and 14 patients (44%) received an immunosuppressive drug (ISD), usually MTX (86%), as a second-line therapy. Complete remission was achieved for 69% of patients, remission with disability 19% and failure 12%. A poor outcome was associated with a diagnosis time delay of >6 months [odds ratio (OR) = 14.7] and the lack of MPPs (OR = 12.9).

Conclusion. Our study reports new insights into the therapeutic management of EF: (i) CS treatment remains the standard therapy for EF, taken alone or in association with an ISD; (ii) MPPs at initiation of treatment are associated with a better outcome and a lower need of ISD use; (iii) an ISD, usually MTX, might be useful as a second-line therapy, mainly in patients with morphoea-like lesions. Naturally, these practical conclusions should be confirmed by a prospective and multicentre study.

Key words: fasciitis, eosinophilia, treatment, methotrexate, morphoea.

Introduction

In 1975, Shulman described eosinophilic fasciitis (EF) as a rare connective tissue disease characterized by a symmetrical and painful swelling with a progressive induration of the skin and soft tissues [1, 2]. In the absence of international diagnostic criteria, diagnosis of EF is now based on the association of characteristic skin or subcutaneous abnormalities and a thickened fascia with an inflammatory infiltration, mostly composed of lymphocytes and eosinophils [3, 4]. Peripheral eosinophilia is present in 63–93% of patients, although not mandatory for EF diagnosis [3, 4].

Therapeutic management of EF is one of the most significant challenges, as the clinical, biological and pathological features are well defined. Mainstay therapy is based on steroids with a partial or complete response in just over 60% of patients [4]. Use of immunosuppressive drugs (AZA, CYC, MTX, ciclosporin and, more recently,
anti-TNF-α and rituximab) is not codified, and is mostly justified by failure of, or dependence on, high doses of CsA [4–11].

The aim of our study was to highlight new insights into EF therapeutic management. We set up a retrospective study of 34 adult patients with biopsy-proven EF and analysed their therapeutic management, including treatment modalities, response and associated prognostic factors.

Methods

Study design

We retrospectively reviewed medical charts of adult patients treated or referred to our University Hospital for EF between January 1992 and May 2010. EF diagnosis was based on suggestive clinical and laboratory findings and a biopsy-proven fascia involvement [1, 4, 5]. No patient had an L-tryptophane-associated eosinophilia–myalgia syndrome. Informed consent was obtained for each patient.

Data collection and variables of interest

Collected data included demographic parameters, presence, type and distribution of cutaneous, articular and muscular involvement. Morphea was diagnosed clinically when skin sclerosis was noticed and histologically when a dermal fibrosis was noticed [4, 12]. Subcutis sclerosis was diagnosed clinically when a deep subcutis induration was present without involvement of the superficial skin. Baseline biological data included eosinophil count, creatinine phosphokinase (CPK), CRP, serum gammaglobulin level and, when available, immunological markers: ANCA, ANA, anti-ENA antibodies. Peripheral hypereosinophilia was defined by an absolute number of peripheral eosinophils >500/mm³ [3].

Skin-fascio–muscular biopsy

All patients underwent a full thickness skin to muscle biopsy following a standard protocol and the pathological analyses were performed in the same laboratory by M.T. or D.O. Diagnosis of EF was assessed by the evidence of a fasciitis with a thickened fascia and inflammatory infiltrates composed of lymphocytes and/or eosinophils [4].

Treatment

Data regarding treatment regimen, clinical and biological responses were collected. Recorded treatments included oral steroids, i.v. methylprednisolone pulses (MPPs), immunosuppressive drugs (ISDs) (MTX, AZA) and immunomodulatory drugs (HCQ, colchicine). Prescribed treatment was the responsibility of the patient’s physician.

Treatment response definitions

Response to treatment was defined as: (i) failure (patients with persistent active physical signs and symptoms); (ii) remission (patients with disability, i.e. persistent joint contractures, tendon retraction or subcutis sclerosis); and (iii) complete remission (free of symptoms at end of follow-up and resolution of physical findings). A poor outcome was defined as failure or presence of a disability.

A complete laboratory response was defined as the normalization of peripheral eosinophil count.

Statistical analysis

Continuous variables were compared using the t-test or the Kruskal-Wallis test, and categorical variables using Fisher’s exact or χ² tests as appropriate. A stepwise multiple logistic regression analysis was used to assess independent associations based on the results of univariate analyses (P < 0.1). Rates of event-free survival (ISD, poor outcome) over time were plotted by Kaplan-Meier’s method and compared using the log-rank test. A Cox proportional hazards multiple regression model was used to evaluate the relative risk (RR) associated with the introduction of an ISD. All tests were two-tailed and a P ≤ 0.05 was considered statistically significant. All statistical analyses were performed using the MedCalc software version 11.1.1.0 (Mariakerke, Belgium).

Results

Patients characteristics and clinical manifestations

Thirty-four patients were included (Table 1). At diagnosis, a cutaneous involvement was present in 30 (88%) patients and upper extremities were affected in all cases. Eighteen (53%) patients had a groove sign on forearm (Fig. 1A) and 14 (41%) patients exhibited morphea-like lesions (Fig. 1B). Thirteen (38%) patients had arthralgia and 29 (86%) complained of muscle pain involving upper (86%) and lower extremities (59%). Nine (26%) patients experienced weight loss and 13 (38%) patients asthenia, but none had fever.

Biological findings and skin-fascio–muscular biopsy

Mean eosinophil count and mean CRP level were 1451.1 (1045.8)/mm⁳ (median = 1135/mm³; range: 20–4100/mm³) and 19.2 (17.5) mg/l, respectively. Gammaglobulin level was 14.2 (6.7) g/l and hypergamma-globulinaemia (>13 g/l) was present in 12 (46.2%) of the 26 patients. Two (6%) patients had raised CPK levels and five (5/33, 15%) patients had positive ANA. All patients underwent a full skin to muscle biopsy, which demonstrated a fasciitis. Inflammatory infiltrates in all patients, including lymphocytes and eosinophils, were found in 26 (77%) patients.

Treatment regimen

Treatment regimens were evaluated in 32 (94%) patients as 2 patients were lost to follow-up. All 32 patients received oral steroids as a first-line therapy with a mean duration of 45.7 (31.2) months (median = 37 months; range: 6–115 months). Mean daily dose of prednisone at initiation was 0.77 (0.29) mg/kg (median = 0.93 mg/kg; range: 0.16–1.13 mg/kg), corresponding to 52.7 (22.6) mg daily (median = 60 mg; range: 10–90 mg). Fifteen (47%) patients received i.v. MPP (500–1000 mg daily for 3 consecutive days) before prednisone treatment. After treatment initiation, due to a considered unsatisfactory clinical response, 14 (44%) patients received an ISD as a
second-line therapy in association with steroid treatment in a 16.9 (20.3) month mean time interval (median = 6.5 months; range: 1-67 months). Mean duration of the ISD treatment was 28.1 (23.7) months (median = 21.5 months; range: 5-93 months). The ISD was MTX for 12 (86%) patients with a 24.7 (23.3) month mean duration (median = 19.5 months; range: 5-93 months) and AZA for 2 patients (14%). Fourteen (44%) patients received colchicine and two (6%) patients received HCQ.

Response to treatment
All patients experienced laboratory remission with a normalization of eosinophil count. Twenty-two (69%) patients had complete remission, six (19%) patients had remission with disability and four (12%) patients had failure with persistent active disease. Complete remission was achieved in 17 (94%) of the 18 patients who received steroids alone and in 5 (36%) of the 14 patients who received an ISD. At the end of follow-up, 17 (53%) patients were free of treatment, 12 (38%) patients were receiving a 2–10 mg prednisone daily dose and three (9%) patients a 15–35 mg prednisone daily dose. Four (12%) patients were still receiving a 15, 15, 20 and 30 mg MTX weekly dose, respectively, and one (3%) patient a 50 mg AZA daily dose. No patient died during the follow-up.

Patients who received MPPs
Fifteen (47%) patients received MPPs at treatment initiation. Compared with patients who did not, patients who received MPPs less frequently received an ISD (20 vs 65%, \( P = 0.02 \)) and were more likely to have complete remission (87 vs 53%, \( P = 0.06 \)). After multivariate analysis, MPP therapy remained negatively associated with the use of an ISD [odds ratio (OR) = 0.14; 95% CI 0.027, 0.68; \( P = 0.015 \)].

Patients who received an ISD
Compared with those who did not (\( n = 18 \)), patients who received an ISD (\( n = 14 \)) more frequently had subcutis sclerosis (93 vs 61%; \( P = 0.05 \)), dermal fibrosis (64 vs 17%; \( P = 0.01 \)) and clinical and/or histological morphea-like lesions (71 vs 28%; \( P = 0.03 \)) (Table 1). They less frequently received MPPs at treatment initiation (21 vs 67%; \( P = 0.016 \)). After multivariate analysis, two variables remained significantly associated with the requirement of an ISD: presence of clinical and/or histological morphea-like lesions (OR = 15.3; 95% CI 1.6, 149.2; \( P = 0.019 \)) and the lack of MPPs at treatment initiation (OR = 17.2; 95% CI 1.8, 169.0; \( P = 0.016 \)). The RR of requiring an ISD was 4.7 times higher in patients with clinical and/or histological morphea (95% CI 1.6, 22.8;
and 4.4 times higher in patients who did not receive MPPs (95% CI 1.2, 15.6;  

\[ P = 0.0245 \]) (Figs 1C and D).

Patients with a poor outcome

Ten patients experienced a poor outcome (four patients with failure and six patients with remission with disability). They tended to have a longer diagnosis time delay [8.1 (5.3) months vs 5 (3) months;  

\[ P = 0.07 \] (Table 1). They more frequently received an ISD (90 vs 23%;  

\[ P < 0.01 \]) and inversely they tended to less frequently receive MPPs (20 vs 59%;  

\[ P = 0.06 \]). After multivariate analysis, two baseline parameters remained independently associated with patients having a poor outcome: a diagnosis delay >6 months (OR = 14.7; 95% CI 1.5, 147.7;  

\[ P = 0.023 \]) and the absence of MPPs at treatment initiation (OR = 12.9;  

95% CI 1.7, 142.7;  

\[ P = 0.037 \]).

Features of patients with morphea-like lesions

Fifteen (44%) patients had a clinical and/or histological morphea at diagnosis. Seven (47%) patients received MPPs before oral steroids and 10 (67%) patients received an ISD, which was MTX in all cases, as a second-line therapy. Complete remission was achieved in nine (60%) patients, remission with disability in three (20%) patients and failure in three (20%) patients. Compared with patients without morphea-like lesions (n = 19), patients with morphea-like lesions were more likely to have a subcutis sclerosis (100 vs 53%;  

\[ P = 0.002 \]), a groove sign (73 vs 37%;  

\[ P = 0.045 \]), a histological fascia fibrosis (67 vs 21%,  

\[ P = 0.013 \]) and higher CRP level [29.6 (19.6) mg/l vs 12.6 (12.5) mg/l;  

\[ P = 0.02 \]). They more frequently received an ISD (67 vs 23%;  

\[ P = 0.03 \]), mostly MTX.

Discussion

Since the first description by Shulman in 1975, up to 300 cases of EF have been reported [1, 3–5]. However, although clinical, biological and histological features of EF patients are well defined, therapeutic management remains unclear. We therefore designed this study and focused on therapeutic management and its associated factors.

Our patients received CSs at initiation as a first-line therapy and MPPs were given to 47% of patients at treatment initiation. A second-line therapy, based on the use of
an ISD, usually MTX, was necessary for 44% of patients, due to an unsatisfactory response to steroid treatment. Taking into account all treatments, complete remission was achieved in 69% of patients. A poor outcome was present in one-third of patients and was associated with two independent factors: a diagnosis time delay >6 months (OR = 14.7; P = 0.023) and the lack of MPPs at treatment initiation (OR = 12.9; P = 0.037). Interest in early treatment after symptom onset has already been reported by Endo et al. [3]. The use of MPPs was associated with a better outcome and allowed a significant decrease of the risk of requiring of an ISD treatment as a second-line therapy.

Another main point of our study was the focus on patients presenting morpoea-like lesions. It is well established that morpoea can reveal or complicate EF [3, 4, 13, 14]. Clinical morpoea were present in 41% of patients, higher than the 19 and 28% reported in previous studies [3, 4]. This difference is probably explained by the presence of senior dermatologists in our department (C.F., S.B.). A systematic review of previous reports suggested that presence of morpoea-like skin lesions could be a risk factor for residual fibrosis [3]. We identified frequent use of ISDs in patients with morpoea-like lesions, probably because those lesions are more difficult to cure. In our study, MTX was used in most patients, based on previous reports of disabling morpoea [15, 16]. Good results of MTX treatment combined with MPPs have also been reported in paediatric studies [15, 16]. This regimen warrants further study to assess whether early treatment with an ISD improves the outcome in these often recalcitrant patients.

Some biases including a retrospective design and the lack of standardized criteria for the evaluation of treatment response might have impacted the results of the present study. We also agree that our results are not generalizable and might simply reflect the treatment preferences of a single centre. This being said, our study leads to practical conclusions regarding EF management and might help to set up a mandatory prospective and multicentre study.

Rheumatology key messages

- CS treatment remains the standard therapy for EF.
- MPPs might allow a better outcome and a lower need of ISDs for EF.
- An ISD, usually MTX, might be useful in patients with morpoea-like lesions.

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References