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APLASTIC ANEMIA COMPLICATING EOSINOPHILIC FASCIITIS: A LITERATURE REVIEW

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ABSTRACT – *Objective:* Eosinophilic fasciitis (EF) is an uncommon rheumatological disorder that may complicate with aplastic anemia (AA). We aimed at reviewing the literature on AA associated with EF.

Materials and Methods: Published articles were selected using the following entry terms: "eosinophilic fasciitis", "Shulman's disease" and "aplastic anemia". All-important data were collected.

Results: Case descriptions on 16 patients were reported. Age varied from 18 to 62 years, most males and AA appeared, in general, within the first year after EF diagnosis. In three patients, rituximab was used, and bone marrow transplantation was done in 4 of them. Paroxysmal nocturnal hemoglobinuria (PNH) clone was searched in 6 of the reviewed patients and was positive in 2.

Conclusions: AA in EF showed a predominance of older males; most of them developed AA within 12 months after EF diagnosis and treatment included glucocorticoid, ATG and immune suppressive drugs, bone marrow transplantation and rituximab.

KEYWORDS: Aplastic anemia, Eosinophilic fasciitis, Bone marrow transplantation, Anti-thymocyte globulin.

INTRODUCTION

Eosinophilic fasciitis (EF) is a disease from the scleroderma spectrum that is characterized by limb or trunk edema and erythema that evolves to collagenous thickening of the subcutaneous fascia[1,2]. In the early stage of this disease, eosinophilia is a relevant laboratory finding, although not always present in active early cases and less important in later phases[1,2]. Its etiology is unknown, but some possible triggers are strenuous exercises, *Borrelia burgdorferi* infection, and exposure to certain medications such as check point inhibitors, phenytoin, etc.[3-6].

Skin involvement characterized by non-pitting edema that progresses to induration with puckering, giving for the skin a texture of orange peel (peau d'orange) is one of the most typical clinical findings of EF, which leads to joint contractures and loss of physical function. Other findings include arthritis, myalgias, myositis and neuropathies. Visceral involvement, Raynaud phenomenon, telangiectasia, nail-

fold capillaroscopy abnormalities, and calcinosis are nearly always absent allowing the distinction from systemic sclerosis[1,2,7,8]. Nevertheless, associated hematological disorders occurs in up to 10% of patients and includes aplastic anemia, myeloproliferative disorders, chronic lymphocytic leukemia, myelodysplastic syndromes, lymphomas and multiple myeloma[9,10].

Aplastic anemia (AA) is a life-threatening form of bone marrow failure which has a high mortality rate. Usually, it is caused by an injury to multipotent hematopoietic stem cells that leads to a decrease in mature blood cells and, in later stages, to pancytopenia[11]. It may co-occur with or progress into another hematologic disorder (e.g., paroxysmal nocturnal hemoglobinuria or PNH, myelodysplastic syndromes, multiple myeloma and acute myeloid leukemia). PNH disorder in peripheral blood cells have been detected by flow cytometry in patients with AA[12] and has been identified as predictor of prognosis[13] and treatment response with immunosuppressant drugs[13]. A review of 120 patients from Russia with acquired AA showed that 67% of them had PNH clone[15]. During long-term observation, it was observed that the transformation of AA into classic PNH is possible[15]. AA in EF is a poorly studied clinical situation and it is believed to be either an autoimmune disease or the result of a clonal myeloid disorder[10].

EF usually has a good response to glucocorticoid therapy alone (76% of cases)[10]. However, patients with AA associated to EF seem to be more resistant to treatment. De Masson et al[10] observed that patients with AA associated to EF, when treated with glucocorticoid alone or in combination to cyclosporine, anti-thymocyte globulin and colchicine, showed improvement of skin disease in only 42% of the cases, suggesting that the combination of EF with AA leads to a more difficult-to-treat disease.

Herein we reviewed the literature of the last 30 years (1990-2020) on AA associated to EF aiming to recognize the epidemiological, treatment and outcome features of these group of patients.

MATERIALS AND METHODS

Articles published in English language in PubMED/MEDLINE, SCOPUS, LILACS and Scielo from 1990 to 2020 were screened and selected using the following entry terms: “eosinophilic fasciitis”, “Shulman’s disease” and “aplastic anemia”. The reference lists of the selected articles were analyzed to identify other publications. The Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) was used to produce the text. Two independent reviewers carried out the paired selection in the databases of electronic libraries. The articles found from the search strategy were submitted to the reading of the titles and abstracts, and the articles included in the review were read in full by the reviewers. Extracted information from relevant articles included authors and year of publication, demographic data, time elapsed between diagnosis of EF and AA, possible presence of PNH clone and treatment used for AA.

RESULTS

The above search resulted in 13 abstracts. The selection of reviewed articles was done according to the flow chart at Figure 1. In these 10 articles, 16 patients were described[10, 16-24]. The summary of the data found is reported in Table 1 which displays that the diagnosis of AA was done in patients from 18 to 62 years; most of them were males (12/16 or 75%) and AA appeared, in general, within the first year after EF diagnosis (with exception of 3 cases). In one case only the AA appeared prior to EF. Glucocorticoid, cyclosporine and anti-thymocyte globulin were the most used medications. In three patients, rituximab was used, and bone marrow transplantation was done in 4 of them.

DISCUSSION

AA is a rare complication of EF, that is also an uncommon disease. This case series allows a glimpse of its possible epidemiological profile. It shows that most of patients had AA appearing shortly after EF diagnosis (most within the first year); only one case of AA prior to EF was identified.

While eosinophilic fasciitis is a disease with a female-to-male ratio of 1:1[25], the present patients’ series of AA in EF showed a male prevalence. It is also possible to observe that most patients were on their fifties or sixties years of age; only 5/16 were younger than 46 years. These are findings in agreement with those of De Masson et

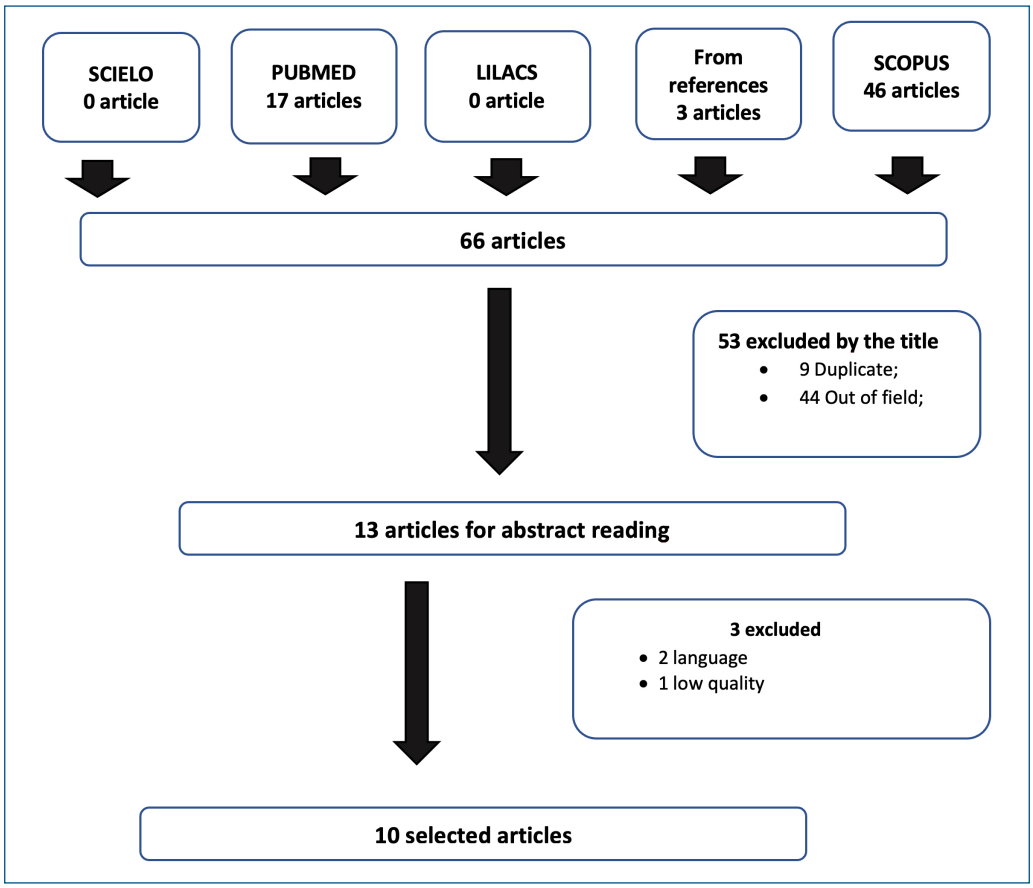

Figure 1. Flowchart of the included studies.

al[10], that – comparing patients with EF with and without AA – also observed that those with AA were older and with higher proportion of males. This report contrasts with what is known that AA in general occurs equally in males and females, in addition to appearing in the first three decades of life in half of them[26,27].

AA is a life-threatening form of bone marrow failure which, if untreated, is related with high mortality. Treatment failure and the development of late clonal disorders are the most common problems[28]. In these series, 4 patients have died during the observation period: three with possible complications from AA (infections and hemorrhage) and 1 with acute myeloid leukemia that appeared later on. So, all efforts treating these complications are worthwhile. Treatment programs for patients with acquired AA embrace two main options: combined immunosuppressive therapy or allogeneic bone marrow transplantation (BMT). Combined use of immunosuppressant drugs is the most common choice, generally using anti-thymocyte globulin (ATG) and cyclosporin[29]. Several problems remain unsolved related to the combination of ATG and cyclosporin: cost, toxicity and late clonal disorders in some of them[30]. In this series, 11 patients received ATG[10,16,17,22,24]; two courses of this form of treatment were done in two of them[10,24]. About 5 patients did not have clinical improvements with this drug (including those who received it twice).

BMT was done in 4 patients[17,23,24] and only one did not have any benefit with this treatment[24]. Indeed, Bacigalupo[28] demonstrated that, if an HLA-matched family donor is identified, BMT should be the first-line treatment in individuals younger than 40 years. Nevertheless, in older patients, as most of those seen so far, the benefits of this treatment declines[28]. Rituximab was also an option; three patients used it, good responses were observed in two of them, and one had a partial response.

Search for PNH clone was done in only 6 of the reviewed patients[10,17-19] and was positive in 2 of them[17,18], but only one of them developed mild clinical features of PNH and died 7 years later with acute leukemia[18]. Clonal PNH expansion is strongly linked to the histocompatibility antigen HLA-DR2 in all clinical varieties of the disease, and according to Maciejewski et al[31], it suggests an immune component to its pathophysiology and predicts response to immunosuppressive treatment.

Table 1. Case reports in aplastic anemia (AA) in eosinophilic fasciitis (EF).

Author; publication year	Age/ sex	Time between diagnosis of EF and AA	PNH clone	Treatment	Outcome
Kastsianok et al (16)	58/male	AA prior to EF (6 months)	NA	High dose glucocorticoid + ATG (40 mg/kg/day for 4 days), cyclosporine 400mg/day + eltrombopag	Skin- definitive improvement AA- initial good response; relapse after 3 months after therapy cessation. Oral cyclosporine was re-started with remission
Sasaki et al (17)	51/male	NA	Positive	Failure of high-dose steroids, methotrexate (4 months), oral cyclophosphamide (1 month); Partial response to ombination of ATG (3 days – 40 mg/kg/day) with cyclosporin (5 mg/kg/day for 90 days) Allogenic peripheral blood stem cell transplantation • Conditioning – busulfan and fludarabine • G.v H. prophylaxis – tacrolimus and methotrexate	Improvement of AA and skin with BMT
Boysson et al (18)	59/male	EF prior to AA (11 months)	At diagnosis- negative; 2 years later- positive	Cyclosporin and glucocorticoid followed by IVIG monthly (120 g for 2 days) during 8 months- with persistent pancytopenia Rituximab - four weekly 700 mg pulses	Skin – data NA AA-well-tolerated pancytopenia Death 7 years later -acute myeloid leukemia
Masson et al (10)	65/female	EF prior to AA (6 months)	Negative	ATG (3 mg/kg – 5 days), cyclosporin (340mg/day), weekly romiplostim injections and monthly intravenous immunoglobulin infusions	Skin- resolved in 6 months; AA- relapse after transient improvement, requiring repeated ATG
Masson et al (10)	57/male	EF prior to AA (5 months)	NA	Failure - ATG for 5 days, cyclosporin (360mg/day tapered to 200mg/day in 6 months) and glucocorticoid; Rituximab- 5 cycles of 375 mg/m^2 per week for 4 weeks	Skin improved after 2nd cycle of rituximab AA- relapsed 6 months after the first course of rituximab but of rituximab but improved after 4 more cycles. Cyclosporine tapered to 80 mg/ day. Followed 6 months with no relapse

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Table 1 *(continued)*. Case reports in aplastic anemia (AA) in eosinophilic fasciitis (EF).

Author; publication year	Age/ sex	Time between diagnosis of EF and AA	PNH clone	Treatment	Outcome
Masson et al (10)	35/male	EF prior to AA (8 months)	Negative	Glucocorticoid Failure - ATG (2 courses) + cyclosporin (5 mg/kg/day)	No improvement of AA neither skin
Masson et al (10)	60/male	EF prior to AA (8 months)	NA	Glucocorticoid ATG (300 mg/d) + cyclosporin (4mg/kg/day)	Good response of AA and skin; Cyclosporin stopped 8 years later; Glucocorticoid responsive hemolytic anemia 4 years after stopping cyclosporin
Patel et al (19)	42/male	NA	Negative	Failed glucocorticoid, cyclosporin and Rituximab (4 weeks) Glucocorticoid, ATG + G- CSF	Skin- data NA AA- partial response; waiting BMT
Falcão et al (20)	62/male	4 months	NA	Glucocorticoid, cyclosporin (150mg/dia), Erythropoietin; G-CSF	Death by infection in 24 days
Antic et al (21	62/female	NA	NA	Failed isolated glucocorticoid; Cyclosporin, danazol glucocorticoid.	Skin -data NA AA-Slow recovery
Bonnotte et al (22)	60/male	EF prior to AA (3 months)	NA	Isolated glucocorticoid- ineffective; ATG (300mg/day- 5 days) + 1 year of cyclosporin	Skin- data NA Cell count normalized 9 months after treatment
Cetkovsky´ et al (23)	18/female	EF prior to AA (5 years)	NA	Glucocorticoid BMT from HLA identical sister • Conditioning – cyclophosphamide • G.v H. prophylaxis – methotrexate and cyclosporin	Skin and AA improved in 5 months 5 months later- G. v H. treated with gluco-corticoid -(remission) AA- doing well 34 months after BMT
Kim et al (24)	46/male	EF prior to AA (3 months)	NA	Failed isolated glucocorticoid; ATG (4days)- no improvement 2X allogenic BMT related donor • Conditioning- Cyclophospha-mide and total body irradiation • Prophylaxis G.v H. – Cyclo-sporine, methotrexate, glucocorticoid	Death after 86 days (sepsis + hemorrhage)
Kim et al (24)	26/male	EF prior to AA (13 months)	NA	Failed isolated glucocorticoid; Failed -ATG 2X (160mg/kg/day) + glucocorticoid – Cyclosporin - improvement	Skin improved with isolated glucocorticoid AA - recovery; followed for >12 months

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Table 1 *(continued)*. Case reports in aplastic anemia (AA) in eosinophilic fasciitis (EF).

Author; publication year	Age/ sex	Time between diagnosis of EF and AA	PNH clone	Treatment	Outcome
Kim et al (24)	18 /female	EF prior to AA (5 years)	NA	Prednisone Failure of ATG (160mg/Kg/8days); Allogenic BMT related donor • Conditioning – cyclophosphamide + total body irradiation	Skin improved with isolated glucocorticoid; AA- remission after BMT
Kim et al (24)	62/male	EF prior to AA (6 months)	NA	Isolated prednisone – failure ATG 160 mg/kg/day – 8 days + glucocorticoid	Skin improved with glucocorticoid; AA- no improvement Death 2 months - sepsis

AA= aplastic anemia; BMT= bone marrow transplantation; ATG= anti-thymocyte globulin; G.v H.= Graph vs. Host; G-CSF = granulocyte-colony stimulating factor; NA= not available.

The relationship between EF and the pathogenesis of AA is poorly understood but there is some speculation about the possible presence of autoantibodies against hematopoietic progenitor cells in this context. Studies i*n vitro* have shown that IgG serum factors from EF patients with AA, but not from those with EF without hematological disorders, are able to impair the growth and differentiation of normal and autologous hematopoietic stem cells[32].

Limitations in this review include the lack of information about treatment details in some cases and the low number of recently described cases with patients receiving a more modern treatment support that would favor the patient's outcome.

CONCLUSIONS

The reviewed cases of AA in EF showed a predominance of older males; most of them developed AA within 12 years after EF diagnosis; 25% of patients evaluate to death and treatment is based on glucocorticoid, ATG, immune suppressive drugs, BMT and rituximab.

Conflict of interest:
The Authors declare no conflicts of interest.

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All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and give their approval for this version to be published.

Data availability:
All data of our study is available at request.

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