

The use of an elevated aldolase in diagnosing and managing eosinophilic fasciitis

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Abstract Eosinophilic fasciitis (EF) is a rare localized fibrosing disorder of the fascia whose diagnosis is often suspected based on clinical findings and laboratory values. These lab abnormalities can be transient in early disease and may not always be present. We have reviewed a case series of patients to assess the utility of the various laboratory abnormalities in diagnosing EF. We performed a retrospective review of EF patients seen at Georgetown University Hospital in the Division of Rheumatology during 2009 and 2013. This review included 15 adult patients with EF with a mean age at diagnosis of 45 years (range 18 to 77 years). The majority of patients 13/15 had classic skin thickening documented on all four extremities. Only eight patients had peripheral eosinophilia ranging between 8 and 38 %. In these patients, the peripheral eosinophilia was an early but transient finding. Inflammatory markers including the erythrocyte sedimentation rate (ESR) was elevated in 5/14 and C-reactive Protein (CRP) was elevated in 7/11. At disease presentation, only one of eleven patients checked had an elevated creatine phosphokinase (CPK). Aldolase levels were available for 12 of the 15 patients, and they were increased in 11 out of 12 patients. We have found that in this case series, aldolase was more likely to be abnormal than peripheral eosinophilia, hypergammaglobulinemia, and ESR particularly after starting treatment. Aldolase should be measured in all patients suspected of having EF, and may also play a useful role in following disease activity.

Keywords Aldolase · Eosinophilic fasciitis · Scleroderma-like illnesses

Introduction

Eosinophilic fasciitis (EF) is a rare localized fibrosing disorder of the fascia that was first described in 1974 [1]. The diagnosis of EF is often suspected based on skin findings and laboratory values such as peripheral eosinophilia and increased sedimentation rate and hypergammaglobulinemia [2]. Magnetic resonance imaging (MRI) may be useful in evaluating patients thought to have EF. Full-thickness skin and subcutaneous tissue biopsy can be of value in differentiating EF from systemic sclerosis. The traditionally associated lab abnormalities can be transient in early disease and may present in less than half of confirmed cases [3]. While CPK is usually normal in EF, elevation of aldolase in EF has been reported [4]. In this case series, we looked at the frequency of an abnormal aldolase in patients with eosinophilic fasciitis.

Materials and methods

The study protocol was approved by the Investigational Review Board of Georgetown University Hospital. We performed a retrospective review of the adult patients with a diagnosis of EF seen in the Georgetown University Rheumatology clinic between 2009 and 2013. The diagnosis of EF was made the author (VDS), an experienced rheumatologist in the field of scleroderma and scleroderma-like diseases. This diagnosis was primarily based on the typical clinical findings which included edema, thick, woody indurated skin of the extremities without involvement of the fingers in the absence of Raynaud's or autoantibodies. MRI's and/or a full thickness biopsy were usually performed. Laboratory findings including

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inflammatory markers, eosinophilia, serum protein electrophoresis, creatine kinase, and aldolase were performed. In patients who continued to be followed after diagnosis, the response of the laboratory abnormalities was determined.

Results

We identified 15 adult patients with the new diagnosis of eosinophilic. There were eight males and seven females. The mean age at diagnosis was 45 years (range 18 to 77 years). The majority of patients (13 of 15) had classic eosinophilic fasciitis skin thickening including woody texture to skin ($n=15$), "peau d'orange" ($n=8$) and/or groove signs ($n=12$) on all four extremities. Two patients also had trunk involvement, upper chest, and/or breasts in addition to the arms and legs. Two patients only had forearm involvement at initial presentation. None of the patients had a history of Raynaud's phenomenon, skin thickening of the fingers and none was positive for antinuclear antibodies. Only one patient had a history of vigorous exercise, but even in that patient, it was not new or a recent change in his usual 60 mile bicycling trips. MRI was performed in eight patients, and six of these studies revealed characteristic fascial thickening with inflammatory enhancement. A routine "punch" skin biopsy was not diagnostic in three patients in whom it was done. This is a common problem since punch skin biopsies do not get deep enough to get fascia. A full-thickness skin biopsy was performed in seven patients and showed inflammatory changes with eosinophilia in the fascia.

Some laboratory values were available in all patients prior to any steroid treatment. Only eight patients had documented peripheral eosinophilia ranging between 8 and 38 % (see Table 1). In these individuals, the eosinophilia was an early and transient finding with complete resolution in all patients by 2 months after starting treatment. In five of the seven patients without eosinophilia, the patients had symptoms for a longer period of time, 3 to 15 months before any laboratory tests were obtained. Inflammatory markers, either ESR or CRP were also not always abnormal. The ESR was elevated in only five and CRP was elevated in another two, but six had a normal ESR and CRP. Hypergammaglobulinemia without a monoclonal spike was present in four patients who also had increased inflammatory markers. One additional patient had an IgA monoclonal spike consistent with MGUS with a negative bone marrow for myeloma.

At disease presentation, only one of 13 patients had an elevated CPK. In contrast, the aldolase was increased in 11 of the 12 patients. In four of these patients, the aldolase was obtained only after starting steroids at a time when eosinophilia and inflammatory markers had normalized, and yet the aldolase remained increased. All patients improved, and within several months had no eosinophil, a normal ESR, and a

normal aldolase, but the aldolase was the last of the three parameters to return to normal, (2 to 9 months after starting steroids, mean 3.6 months.)

All patients were treated with prednisone with a range between 10 mg daily up to 60 mg daily for initial therapy. Four patients were also treated with hydroxychloroquine, while seven patients were also given methotrexate as a steroid-sparing agent. Significant clinical and laboratory improvement occurred in all patients by 6 months. Patients slowly tapered steroids and other medications over the next 2–5 years. Residual taut skin on the lower legs was present in four patients. One patient had recurrent lower extremity ulcers. Two patients had residual flexion contraction in elbows, and two others had difficulty extending fingers when the wrist was extended (tightening of the forearm tendons in the fascia). During that time, four patients had symptomatic flares with increased skin findings of inflammation. In three of the four patients, an increased aldolase was the only abnormal lab finding. The fourth patient had a recurrence of eosinophilia and an increased sedimentation rate.

Discussion

The first cases of eosinophilic fasciitis (EF), published by Schulman in 1975, described two men with skin changes in the extremities. The mean onset of disease is middle age, and sex distribution has been variable between case series. The etiology of EF remains unclear after many causes have been postulated. A correlation between strenuous exercise and onset of disease has been seen in multiple case series; however, a direct causal link has not been established [5]. We did not identify this association in our patients.

Presentation with EF is characterized by symmetrical edema and induration often in all four extremities with forearms and lower extremities between knee and ankle being the most common sites [2]. As the edema abates the characteristic puckering of peau de orange may be seen. The groove sign, an indentation coursing along the tract of superficial veins caused by retraction of the subcutaneous tissue, is seen with elevation of an involved limb. This sign is classically seen on the volar aspect of the forearm and may help to distinguish EF from systemic sclerosis. The most prevalent secondary complaint in EF is joint pain with decreased range of motion of joints adjacent to or underlying the affected fascia. Early and aggressive physical therapy is therefore an important component of therapy.

MRI is increasingly being used to establish the diagnosis of EF, and for monitoring response to therapy [6]. T1-weighted images show thickening of superficial fascia, while T2-weighted and STIR (short tau inversion recovery) imaging shows signal abnormality and thickening in both the superficial and deep fascia. Some patients also have minor

Table 1 Laboratory studies in patients with eosinophilic fasciitis prior to treatment except the aldolase (as indicated)

Patient	Eosinophils %	ESR	CRP	SPEP	CPK	Aldolase
1	2	15	NL	NL	NL	10.4
2	2	35	NA	↑GG	NL	7.1 (NL)
3	8	NA	INC	NL	NA	16.8
4	1	12	NL	IGA monoclonal	NL	NA
5	22	50	NA	NL	NA	7.8 ^a
6	3	8	NL	NL	NL	NA
7	18	42	NA	↑GG	NL	11.2
8	15	10	INC	NL	INC	10 ^a
9	38	13	INC	NL	NL	12.9
10	14	31	INC	↑GG	NL	10
11	0	12	NL	NL	NL	9.9 ^a
12	1	8	NA	NL	NL	8.9
13	10	18	NL	NL	NL	NA
14	3	30	INC	↑GG	NL	10.9
15	25	10	NL	NL	NL	10.2 ^a
Number Abnormal (%)	8/15 53 %	5/14 37 %	5/11 45 %	4/15 27 %	1/13 8 %	11/12 92 %

^a Obtained after starting steroids

enhancement of the muscle adjacent to the affected fascia. In follow-up imaging after prolonged treatment, there may be mild increased in intensity of superficial fascia on T2 non-contrast imaging; however, deep fascia and muscle are typically normal [7].

The classic surgical “en bloc” biopsy including skin, subcutaneous tissue, fascia, and muscle is still the gold standard for diagnosis, although in many institutions, obtaining this en bloc is not successful even with the best planning. The epidermis is generally normal; dermis may be normal or fibrotic. Moderate to marked sclerosis was seen in the subcutaneous tissue of most patients. Significant eosinophil infiltration, most often found in the lower subcutis and fascial layers can be only focal and transient [8].

Therefore, eosinophilia on en bloc biopsy is helpful but not necessary for the diagnosis of EF. A standard skin biopsy does not include deeper tissue such as the fascia and/or muscle tissue and thus, is not diagnostic or helpful. In this current case series, biopsy was helpful in making a diagnosis in a minority of patients. A rheumatologist or dermatologist with experience with scleroderma-like diseases can make a clinical diagnosis based on clinical appearance in conjunction with labs and MRI findings, without the absolute need for a surgical biopsy.

Laboratory testing is an integral part of diagnosis in order to exclude thyroid abnormalities and scleroderma autoantibodies. The classically described laboratory abnormalities are serum eosinophilia, elevated erythrocyte sedimentation rate, and hypergammaglobulinemia. There have been several case reports noting aldolase elevation in EF and particularly the

discrepancy in muscle enzyme testing with elevated aldolase levels and normal CPK levels [4]. This was also noted with epidemic eosinophilic myalgia syndrome from the contaminated tryptophan [9].

In this case series of 15 patients, an increased aldolase was present in more patients than the other lab abnormalities. In three patients with a normal ESR, CRP, SPEP and no eosinophilia, the aldolase was the lone abnormality and in 4 it was the last abnormality to normalize after treatment with steroids normalized the other tests. Additionally, in three of the four patients with a cutaneous flare during steroid taper, the aldolase was the only test to confirm this flare.

A discordance between CPK and aldolase has been reported in myopathies that have inflammation primarily involving the perimysium, the connective tissue that surrounds the fascicles that together make up a complete muscle [10]. One theory raised by Nakajima et al. in 1997 was that the discrepancy was created by the ability of superficial muscle fibers to release aldolase and not CPK [11]. MRI imaging could potentially support this theory that the limited distribution of muscle involvement in EF favors release of aldolase over CPK. There is no widespread involvement or uniform enhancement of muscles on MRI imaging as would be typical of inflammatory myositis. In EF, slight contrast enhancement is typically only noted in the muscle tissue directly adjacent to the fascia and significant increases in CPK are rarely seen. Gross pathologic specimens have demonstrated that the thickened fibrotic fascia is firmly adherent to the epimysial layer (outer-most tissue covering of muscle groups that is adjacent to the fascia) of adjacent skeletal muscles. The epimysium has

been described as “frequently sclerotic and inflamed as a result of what appeared to be spillover from the fasciitis” [5]. The muscle in EF can be completely normal or show some degree of perivascular infiltrate of inflammatory cells including eosinophils [12].

Treatment of EF is generally with steroid and sometimes with a steroid sparing agent. The small population of affected patients has limited the ability for controlled clinical trials to determine optimal therapy. Prednisone is the mainstay of initial therapy for eosinophilic fasciitis. The initial recommended dose is often 1 mg/kg; however, we have found low to moderate dose Prednisone (10–20 mg daily) to be effective for resolution of swelling and softening of the affected limbs and along with aggressive physical therapy to prevent contractures. Rapid resolution of inflammatory markers and eosinophilia is seen within 1 to 2 months of initiation of even low to moderate dose steroids. Plaquenil has been utilized as adjunctive with Prednisone therapy, but we have found that Methotrexate works well as a steroid-sparing agent in recalcitrant disease. More than half of the patients in this cohort have been treated with Methotrexate.

The aldolase tends to be the last marker to improve and may be the first to increase with a flare. If the patient was started on steroids before diagnosis, it may be the only marker that is helpful in diagnosis or in patients with a less acute process over a longer duration of symptoms, it may be the only lab abnormality present since eosinophilia and other inflammatory markers may only be transient. It may also be helpful as evidence of a reactivation of the disease as medication is tapered [4].

Conclusion

Almost four decades after Schulman’s initial description of eosinophilic fasciitis many questions remain unanswered about this scleroderma-like illness. Laboratory abnormalities typically recognized in EF, including peripheral eosinophilia and elevation of inflammatory markers were seen in a minority of patients in this cohort. An elevated aldolase (with a normal CPK) was the most frequent abnormal test being elevated in 11 of the 12 patients who had it evaluated. Thus, aldolase is a useful marker for EF and should be part of the

laboratory screen when EF is suspected. The discordance of aldolase elevation and normal CPK may be a reflection of the perimysial fascial and focal muscle enhancement found on MRI and en bloc biopsy. Further studies are needed to determine whether aldolase level may also be utilized for monitoring disease activity and response to therapy.

Conflict of interest Drs. Nashel and Steen have nothing to declare and have no disclosures and no conflict of interest related to this manuscript.

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