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Case Report OMICS International

A 67-Year-Old Patient with Severe Generalized Oedema

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Abstract

We report a case of a 67-year-old Caucasian man who was admitted to the emergency department with severe and generalized oedema accompanied by a rash of both lower legs. The patient was treated with loop diuretics throughout four months without success. Laboratory examinations displayed a leukocytosis with a high proportion of eosinophils. A comprehensive diagnostic work up was started.

Finally, a full-thickness skin biopsy including fascia showed eosinophilic infiltration suitable for an eosinophilic fasciitis. Briefly after starting a glucocorticoid therapy the patient lost 10 kg on body weight, the generalized oedema resolved.

Key words:

Hypereosinophilia; Oedema; Muscle biopsy; Steroidal therapy

Case Report

A 67-year-old Caucasian man presented to the emergency department with severe peripheral oedema, extending from both lower legs to the upper extremities, neck and face. Additionally, both lower legs were slightly erythematous and hyper thermic, appearing as pruritic dermatitis.

With the exception of a pasty pattern of lower leg movements, the remaining physical examination was normal. Notably, no obvious pathology was observed in cardiorespiratory auscultation.

Four months earlier, the patient recognized a small red spot on his right ankle that enlarged proximally with localized swelling.

The patient was first treated with three different antibiotics including amoxicillin/clavulanic acid, ciprofloxacin, and doxycycline, all of which were ineffective. Due to the persistence of the lower leg oedema, the general practitioner then prescribed a loop diuretic through four months without symptomatic improvement.

In fact, the oedema increased and involved both arms, neck and face excluding however trunk and abdomen. After four months with no identifiable cause and no improvement in symptoms the patient was transferred to the emergency department of our hospital. At this time the patient complaint weakness and reported a weight gain of 10 kilograms in the last four months, salty disguise, and occasional night sweating.

A more thorough history revealed that he was a non-smoker, rarely consumed alcohol, did not suffer on angina or respiratory distress and had no allergies. He had two hip prostheses related to bilateral coxarthrosis, appendix and tonsils were removed years before.

The patient had not travelled in the few months preceding his presentation, and reported no contact to obvious toxic materials. He remembered a tick bite a few months before which were located on the left thigh, however. The patient took no premedication except loop diuretics.

At physical examination, the patient was awake, alert and oriented. Vital signs were normal. His face appeared swollen including his eyelids and neck.

Pupillary reaction, oculomotor and general neurologic tests were normal. Physical examinations revealed no heart murmurs or extraordinary lung sounds. Abdominal examination was normal.

No scrotal oedema was detected. Both lower legs and upper extremities presented erythematous with pitting oedema (Figures 1 and 2). The recognized red spot on his right ankle four months ago was not visible anymore. Laboratory examinations revealed a significant leukocytosis with an absolute eosinophilia of 20% (3000 eosinophil granulocytes in total) and a moderately increased C-reactive protein of 66.6 mg/L (standard value 0 mg/L to 5 mg/L) (Table 1).

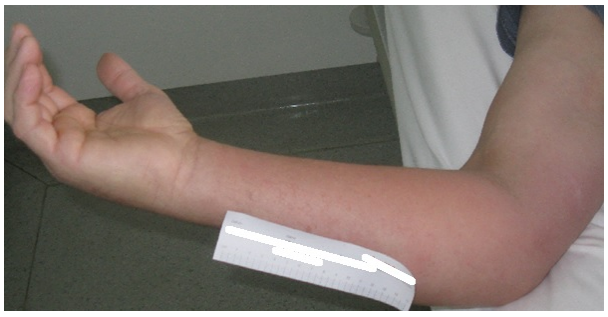

Figure 1: Severe oedema of the right arm with a discrete rash at the day of hospital admission.

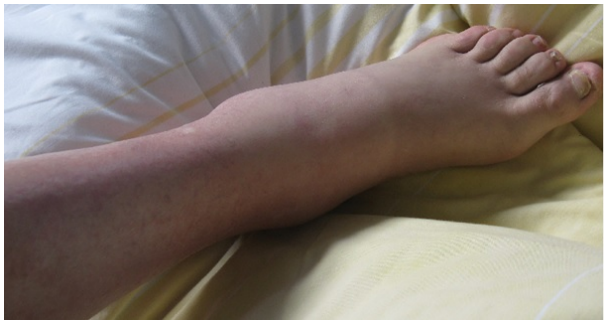

Figure 2: Oedema and skin rash of the left leg at the day of hospital admission.

Blood parameters	Value
WBC (×109/L)	15.7
RBC (×1012/L)	4.73
Haemoglobin (g/dl)	13.4
Haematocrit (%)	41
MCH (pg/cell)	28
MCV (fl)	86
MCHC (g/dl)	33
Platelet count (×109/L)	416
Neutrophils (%)	58.5
Eosinophils (%)	20.9
Basophils (%)	0.5
Lymphocytes (%)	13
Monocytes (%)	7.1
Prothrombin time (%)	80
Glucose (mg/dl)	115
Glycosylated haemoglobin - HbA1C (%)	6.3
Bilirubin total (mg/dl)	0.42
Alkaline phosphatase (U/L)	87
Aspartate aminotransferase - AST (U/L)	27
Alanine aminotransferase - ALT (U/L)	11
Gamma glutamyl transferase - GGT (U/L)	32
Creatine kinase (U/L)	38
Lactate dehydrogenase (U/L)	287
ProBNP (pg/ml)	79
Urea (mg/dl)	42
Creatinine (mg/dl)	0.96
Uric acid (mg/dl)	5.99
Glomerular filtration rate (1,73 m2/ml/min)	>60.0
Cholesterol, total (mg/dl)	140
Triglyceride (mg/dl)	162
Cholesterol, HDL (mg/dl)	36
Cholesterol, LDL (mg/dl)	72
Triiodothyronine - T3 free serum (pmol/L)	4.6
Thyroxine - T4 free serum (pmol/L)	16.1
Thyroid-Stimulating Hormone -TSH (µu/ml)	0.93
Erythrocyte Sedimentation Rate - First hour	8
Erythrocyte Sedimentation Rate - Second hour	21
C- reactive protein (mg/dl)	6.66
Potassium (mval/L)	3.37
Sodium (mval/L)	136
Chloride (mval/L)	95
Calcium (mmol/L)	2.1
Magnesium (mmol/L)	0.84
Phosphorus, inorganic (mmol/L)	1.02
Iron (µg/dl)	74
Transferrin (mg/dl)	195
Transferrin saturation (%)	27
Ferritin (ng/ml)	189
Prostate Specific Antigen - PSA (ng/ml)	0.277
Protein, total (g/dl)	5.22
Albumin (%)	50
Alpha1-Globulin (%)	7.7
Alpha2-Globulin (%)	14.8
Beta-Globulin (%)	11.4
Gamma-Globulin (%)	16.1
Osmolality (mOsmol/kg)	290
Procalcitonin (ng/ml)	0.05
Vitamin B 12 (pg/ml)	263
Cryoglobulins	negative
IgG (mg/dl)	916
IgA (mg/dl)	188
IgM (mg/dl)	54
IgE (kU/L)	87.5
Complement component 3 (mg/dl)	97

Complement component 4 (mg/dl)	29.4
Tryptophan (µmol/L)	5.38
ANA	negative
ANCA	negative
PR3-ANCA	negative
MPO-ANCA	negative
Echinococcus serology	negative
Urine sample	
Specific gravity	1.02
pH	5
Nitrites	negative
WBCs	negative
RBCs	25
Protein	25
Glucose	norm
Ketones	negative
Urobilinogen	norm
Bilirubin	negative
Osmolality (mOsmol/kg)	674
Stool cultures	
Worm eggs	negative
Parasites	negative

Table 1: Laboratory examinations.

A comprehensive workup towards eosinophilia followed: The echinococcus serology and antibodies to *Borrelia* as well as cryoglobulins were negative. Immunoglobulins, total IgE and complement factors C3/C4, were all in the normal range. A urine sample showed 25 erythrocytes per high power field and a protein value of 25 mg/L. A stool culture was negative; no parasites or worm eggs were detected.

Abdominal sonography and computer tomography (CT) of the thorax and abdomen did not reveal any pathological results. A deep vein thrombosis was excluded.

An electrocardiogram revealed a right bundle branch block, an absolutely normal transthoracic echocardiography with respect to functional and structural results and a NTproBNP below 80 pg/ml excluded congestive heart failure. Other typical causes of oedema, protein loss, liver cirrhosis and renal failure were also excluded.

Differential diagnosis

Antibiotic hypersensitivity reactions: Does the patient suffer from any reaction to antibiotic intake?

Four types of hypersensitivity reactions (Gell and Coombs) are well known. Our patient's symptoms did not fit to any of these hypersensitivity reactions however. Type I is IgE-mediated, appears less than one hour after drug intake and has a risk of life-threatening anaphylaxis.

Angioedema, urticarial rash and gastrointestinal symptoms are possible manifestations. It is rarely accompanied by an absolute eosinophilia. Type II-IV are delayed types, with symptoms starting more than one hour after intake. In particular, type IV presents with skin involvement such as morbilliform eruptions, Stevens Johnson syndrome and toxic epidermal necrolysis. Here skin lesions typically first appear in the face and upper trunk [1].

Our patient presented with dermatitis-like skin involvement, which erupted after antibiotic intake.

However, the lesions first appeared in the lower legs. The trunk was never involved and the skin manifestation was rather typical for congestive dermatitis. He also showed no characteristics of baboon syndrome that has been described following therapy with betalactamase antibiotics.

Hypereosinophilic syndrome: Hypereosinophilic syndrome is defined as an eosinophilia of more than 1500 eosinophil granulocytes per microliter and an organic dysfunction lasting longer than one month. It is classified as primary (neoplastic), secondary (reactive) or idiopathic.

Eosinophilia-associated diseases include allergic diseases, infectious diseases especially parasitic infections, hematologic disorders, neoplastic disorders and immunologic reactions. However, dermatologic involvement is normally described as plaques, erythroderma or urticaria. Specific laboratory findings include reduced cd3/cd4 and usually elevated IL-4, IL-5 and IL-13 [2].

Our patient presented with marked eosinophilia with skin involvement without visceral involvement, complement factors and immunoglobulins were in the normal range. We did not measure cytokines such as IL-4, IL-5 and IL-13.

Gleich's syndrome: This syndrome may be a variant of the hypereosinophilic syndrome appearing with an episodic angioedema associated with eosinophilia. Patients suffering from Gleich's syndrome present with urticaria, fever and rapid body weight gain. There are no other organic involvements described.

Symptoms usually decrease dramatically with glucocorticoid therapy, but there are also cases with spontaneous remission. An association with multilineage cell cycling disorders as well as elevated IgM and IgE levels have been discussed [3-5].

The clinical course of the Gleich`s syndrome seems similar to this case, but our patient did not have any urticaria or fever. Furthermore, there was no spontaneous resolution of his symptoms or of the eosinophilia, as there were no elevated immunoglobulins.

Eosinophilic granulomatosis with polyangiitis (EGPA): EGPA, formerly known as Churg-Strauss syndrome, is an ANCA-associated vasculitis of the small to medium-sized vessels. Main characteristics include a blood and tissue eosinophilia, asthma, and symptoms due to granulomatous vasculitis involving the ear, nose and throat [6,7]. Our case did not fit this definition.

Scleroderma: Scleroderma, also called systemic sclerosis, is a connective tissue disorder involving progressively the skin, starting

with acrosclerosis and inner organs and may be accompanied by eosinophilia. Patients suffer from such symptoms as leathery skin fibrosis, Raynaud's phenomenon, contractures, digital ulcerations, deformed nails and loss of facial wrinkles and expression. Extracutaneous manifestations include alveolitis, pulmonary fibrosis, and motility disturbances of the oesophagus, myocardial fibrosis and proteinuria [8].

Although there were some similarities in the described skin manifestation, we did not find visceral involvements in this case.

Eosinophilic fasciitis: The Shulman syndrome is a skin disorder involving subcutaneous tissue (fascia) accompanied by eosinophilia.

Eosinophilic fasciitis is described as a scleroderma-like disorder, but in contrast to scleroderma there is no other organ involvement [9,10]. Raynaud's phenomena are normally absent as well. Patients with eosinophilic fasciitis report limited joint mobility, muscle pain and weakness.

Laboratory examinations usually show eosinophilia and in some cases a hypergammaglobulinaemia and elevated erythrocyte sedimentation rate [11,12]. Eosinophilic fasciitis has an uncertain aetiology and there are only few cases listed in the literature covering patients with a long term medication intake.

Ingestion of L-Tryptophan, phenytoins, statins, lansoprazole and the use of subcutaneous heparin are thought to induce Shulman syndrome. There are also cases in association with Borrelia burgdorferi infections. Other possible triggers of the syndrome are robust exercise or trauma [12-20].

Deep biopsy of the muscle fascia confirms the diagnosis. However, magnetic resonance imaging of muscular system may suggest the syndrome when blood eosinophilia and no other organ involvement occur.

Our patient presented with symmetrical pitting oedema and an erythematous lesion predominantly on the lower extremities. The clinical signs and symptoms and laboratory examinations of our patient were suggestive for eosinophilic fasciitis. A possible trigger could be the long-term intake of loop diuretics in combination with different antibiotics. We undertook a full-thickness biopsy including fascia for histological examination.

Clinical diagnosis

Generalized oedema with hypereosinophilia (Shulman Syndrome).

Pathological diagnosis: The histological findings of the deep muscle biopsy disclosed dermatitis, with atrophy, panniculitis and eosinophilic infiltration. In accordance with the clinical presentation the results are compatible with an eosinophilic fasciitis. It shows the deep dermis and septa of a thickened and fibrosclerotic subcutis. There you can see inflammatory infiltration including lymphocytes, eosinophils, few neutrophils and as a sign of acute disease extravasation of erythrocytes.

Hospital course and management: Glucocorticoid therapy in a dosage of 1 mg/kg/day was started. Immediately, on the following day, the oedema decreased. Within one week, the patient lost almost ten kilograms of his weight and had almost returned to his former weight (Figure 3).

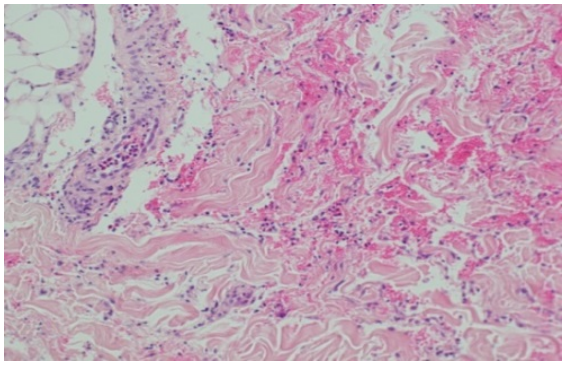

Figure 3: Skin biopsy specimen of the right leg.

Conclusion

The number of eosinophils, as well as the C-reactive protein, regressed. After one month of steroidal therapy, the dosage was incrementally reduced to 0.5 mg/kg/day. The follow-up examination revealed a normal skin texture without any oedema, as well as normalised eosinophilic counts.

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