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Multi-system mitochondrial disorder with recurrent steroid-responsive eosinophilia

Josef Finsterer, MD, PhD (1), Stefan Höger, MD (2)

(1) Neurological Department, Krankenanstalt Rudolfstiftung, Vienna, Vienna

(2) Neurological Department, Krankenhaus Oberwart, Oberwart, Austria

Running head: Eosinophilia in mitochondriopathy

Corresponding author:

J. Finsterer, MD, PhD

Schindlergasse 9/10

1180 Vienna

Austria, Europe

Tel. +43-1-71165-92085

Fax. +43-1-4781711

E-mail: fipaps@yahoo.de

Abstract

Objectives: Though mitochondrial disorders due to a respiratory chain defect may manifest with haematological abnormalities such as anaemia, neutropenia, or thrombocytopenia, recurrent steroid-responsive eosinophilia has not been reported as a manifestation of a mitochondrial disorder.

Clinical presentation and intervention: In a polymorbid 65yo female recurrent erythema, asthma, chronic bronchitis, gastritis with eosinophilic granuloma, recurrent episodes hypereosinophilia, and polyarthralgia suggested Churg-Strauss syndrome, which was excluded upon absence of eosinophilic vasculitis on any of the biopsies. However, corticosteroids were effective for hypereosinophilia. In addition to the hypereosinophilic syndrome a mitochondrial disorder with multi-system affection was diagnosed upon short stature, basal ganglia calcification, pituitary adenoma, hypoacusis, tinnitus, atrial fibrillation, diffuse weakness of all four limbs, diffuse wasting, tetraspasticity, muscle aching, restless-leg syndrome, axonal neuropathy, polyarthralgia, osteoporosis, arterial hypertension, occasional thrombocytopenia, hypercholesterolaemia, hyponatraemia, elevated liver function parameters, and a muscle biopsy indicative of a mitochondrial disorder. Hypereosinophilia was interpreted as a manifestation of the mitochondrial disorder after exclusion of various differentials.

Conclusion: Mitochondrial disease may go along with marked eosinophilia mimicking Churg-Strauss syndrome. Steroids may be useful to resolve episodic eosinophilia but may be ineffective and contraindicated for mitochondrial myopathy.

Key words: respiratory chain, central nervous system, brain, neuromuscular, myopathy, multi-system disease

Introduction

Mitochondrial disorders due to a respiratory chain defect frequently manifest as multi-system disorders, affecting the central nervous system, peripheral nervous system, endocrinological system, heart, eyes, ears, gastrointestinal tract, kidneys, dermis, or the bone marrow [1]. Haematological manifestations of mitochondrial disorders include anaemia, neutropenia, or thrombocytopenia [2]. Recurrent steroid-responsive eosinophilia has not been reported as a manifestation of a mitochondrial disorder.

Case report

The patient is a 65-yo, HIV-negative, Caucasian female (height: 161cm, weight: 59kg), with the following history: recurrent herpetic keratitis since age 14y; recurrent erythema at changing skin locations since about age 40y; coughing and chronic bronchitis due to suspected asthma bronchiale after discontinuation of smoking since age 50y; bronchoscopy at age 53y and 54y to treat recurrent atelectases; resection of the left lower lobe of the lung because of bronchiectasias and atelectasis at age 54y; recurrent eosinophilia since at least age 54y, for which she received steroids during two months with success.

At age 60y she was hospitalised for chest pain. Acute myocardial infarction was excluded but echocardiography showed mitral insufficiency with dilation of the left atrium and tricuspid insufficiency. There was slight leucocytosis, extensive eosinophilia, and slight thrombocytopenia (table 1). IgE were elevated to 834U/l (n, <120U/l). Upon gastroscopy a chronic gastritis and an eosinophilic granuloma were detected. Colonoscopy revealed a non-specific colitis. Skin biopsy for the extensive exanthema of the skin revealed alterations initially being interpreted as eosinophilic vasculitis. Churg-Strauss syndrome (CSS) was suspected and corticosteroids were restarted. After dismissal hypercholesterolaemia with a maximum value of 318mg/dl (n <200mg/dl) and hyperhomocysteinaemia with a maximum value of 18.6 μ mol/l were found. A statin therapy was initiated. Since about age 60y she complained about arthralgias in the distal

interphalangeal joints being attributed to rhizarthrosis at age 64y. Tinnitus was noted since age 62y. After discontinuation of corticosteroids at age 62y nasal congestion and running nose occurred, being attributed to chronic sinusitis. Also at age 62y discontinuation of steroids during three months resulted in a relative eosinophilia count of 30% (table 1), why corticosteroids were restarted with immediate benefit. At age 64y bilateral coxarthrosis with left-sided coxitis and moderate osteoporosis were diagnosed. Since age 64y she complained about muscle aching in the thighs after exercise. At the same age a pituitary adenoma was detected on cerebral MRI and successfully removed by surgery at age 65y. Postoperatively, temporary diabetes insipidus and hyponatraemia required adequate substitution. Since surgery arterial hypertension occurred and was sufficiently treated with bisoprolol. At age 64y cyclophosphamide was tried but had to be discontinued after 2 weeks because of gastrointestinal side-effects. At age 64y interferone- α 2a was given three times without discontinuation of corticosteroids. At age 66y atrial fibrillation was documented for the first time and oral anticoagulation started. Occasionally, glutamate-oxalate transaminase (GOT), glutamate-pyruvate transaminase (GPT), and α -amylase were elevated, but creatine-kinase was normal throughout the observational period (table 1). Echocardiography at age 64y. carried out to assess the degree of cardiac involvement, revealed normal thickness of the left ventricular myocardium, slight mitral insufficiency, dilation of the left atrium, and a minimal tricuspid insufficiency. At age 65y corticosteroids were discontinued and methotrexate was tried but had to be discontinued because of elevated liver function parameters. Corticosteroids were restarted. At age 65y she developed permanent muscle aching and cramps and transient muscle tenderness in all muscles of the left upper limb, carpopedal spasms, and hypaesthesia of the fingers upon voluntary contractions. Recurrent erythema, was lastly interpreted as atopic dermatitis after exclusion of a vasculitis by several skin biopsies. Concerning the family history her mother experienced a myocardial infarction twice and her father suffered from diabetes and a stroke. A neuromuscular disorder had not been reported.

Clinical neurologic examination revealed hypoacusis with left-sided predominance, a positive Brudzinski sign, postural tremor, discrete diffuse weakness of the upper limbs with left-sided predominance, weakness for hip flexion (M5-) bilaterally, diffuse wasting on the upper and lower limbs, an exaggerated biceps tendon reflex on the right side, and exaggerated patella tendon reflexes bilaterally. Nerve conduction studies at age 64y revealed reduced amplitude of the compound muscle action potentials in the left median, left ulnar, and right median nerves, and reduced nerve conduction velocity of the left median nerve. Needle electromyography of the biceps, triceps, and brachioradialis muscles on the left side at age 64y revealed abnormal spontaneous activity in form of positive sharp waves and extensive pseudomyotonic discharges, normal motor unit architecture, and a dense interference pattern with an amplitude of 0.5mV. Biopsy of the left deltoid muscle at age 64y showed mild myopathic changes with single ragged-red fibres (figure 1a and 1b), COX negative fibres (figure 1c) and slight glycogen increase, suggestive of metabolic/mitochondrial myopathy. Ultrastructurally, no intramitochondrial paracrystalline inclusions were demonstrable. In addition, a myoadenylate-deaminase-deficiency was observed (figure 1c). The MRI of the cerebrum at age 64y revealed cortical atrophy and the pituitary adenoma. Antibodies against *Filaria*, *Trichinella spiralis*, *Toxocara*, *Taenia solium*, *Fasciola hepatica*, *Toxoplasma gondii*, *Entamoeba histolytica* were negative. After discontinuation of statins, because of the mitochondrial disorder, a statin and ezetimibe had to be restarted for recurring hyperlipidemia. The patient refused to consent for investigations of the CHIC2 deletion, FIP1L1 FDGFR fusion, or for lymphocyte-variant eosinophilia by PCR for T-cell receptor gene rearrangement, by IL-5 level determination, or by flow on the PB or marrow to look for clonal populations. The aspergillus IgE level was not determined.

Discussion

The described patient was presented for the unusual occurrence of eosinophilia together with a mitochondrial disorder. The mitochondrial disorder was diagnosed upon the clinical findings, electromyography, and the muscle biopsy findings. The patient

presented with short stature, had a history of pituitary adenoma, basal ganglia calcification, tetraspasticity, restless legs, hypoacusis and tinnitus, paroxysmal atrial fibrillation, myopathy, polyneuropathy, polyarthralgia, osteoporosis, recurrent thrombocytopenia, occasionally hyponatraemia, slightly increased GOT and GPT, and hyperlipidemia [3]. Haematologic abnormalities are a frequent finding in patients with a mitochondrial disorder and include anaemia, neutropenia, thrombocytopenia, pancytopenia, or thrombocytosis [2], but eosinophilia has not been reported [4]. Generally, episodic eosinophilia is attributable to nonparasitic or parasitic (helminthic or protozoan) infection, allergic or atopic disease, to skin disorders, immunologic or rheumatologic diseases, hypoadrenalism, neoplastic or lymphoreticular disorder, hypereosinophilic syndromes, irradiation, or drugs [5]. Arguments for an allergic reaction are that eosinophilia was first detected during an episode of asthma attacks, that the dermal abnormalities were interpreted as atopic dermatitis, that IgEs were elevated once, and that asthma, dermatitis and eosinophilia responded well to steroids. Arguments against allergy, however, are that no causative allergen could be identified and that eosinophilic infiltrates were also found in the stomach. Infection as the cause of eosinophilia was excluded upon absent signs of inflammation and negative tests for antibodies against the most common parasites. Hypocorticism was excluded upon normal aldosterone and cortisol levels and normal morphology of the suprarenal gland on imaging studies. A haematological malignancy or lymphoreticular disease was excluded upon a normal bone marrow aspirate.

CSS was initially considered responsible for the cutaneous, pulmonary, and hematological abnormalities but was lastly excluded since the findings did not fulfill the criteria of the American College of Rheumatology for CSS [6,7]. According to these criteria CSS is diagnosed in the presence of asthma, eosinophilia >10%, mononeuritis multiplex or polyneuropathy, transient, non-fixed, pulmonary infiltrates on chest X-ray, paranasal sinus abnormalities, such as allergic rhinitis, nasal polyposis, recurrent sinusitis, or a biopsy, showing a blood vessel with extravascular, eosinophilic tissue infiltration [6,7]. Rare manifestations of CSS comprise eosinophilic gastroenteritis,

cutaneous vasculitis, nephropathy, or arthromyalgia [8]. According to these criteria CSS takes a progressive course and follows three stages [9]. The first stage, lasting for years, starts with allergic rhinitis followed by nasal polyposis, allergic sinusitis, or asthma [8]. The second stage is characterised by blood and tissue eosinophilia with eosinophilic infiltrations of the respiratory system and the gastrointestinal tract. In the third stage, symptoms of systemic vasculitis occur with a mean delay of 3y after onset [6]. Corticosteroids are the treatment of choice for all stages. In patients with severe life-threatening manifestations, however, cyclophosphamide may be helpful [10]. In cases with better prognosis, methotrexate can be given to reduce the cumulative dose of corticosteroids. If corticosteroids or cyclophosphamide are ineffective, immunoglobulins or anti-TNF blocking agents, like infliximab or etanercept, may be tried. A therapeutic effect of cyclosporin, mofetil, azathioprin, or interferon, is unproven.

Arguments for CSS in the presented patient are the occurrence of asthma, eosinophilic gastric granuloma, occasionally eosinophilia >10%, and the prompt response to steroids. Arguments against CSS are the absent progression of the disease, the absence of allergic rhinitis, nasal polyposis, and recurrent sinusitis, the normal blood sedimentation rate, and the absence of a biopsy showing eosinophilic vasculitis [7]. The initial diagnosis of an eosinophilic vasculitis was lastly turned down by the dermatologists. Furthermore, chest X-ray did not show patchy, non-segmental, peripheral infiltrates, often fleeting or non-specific in nature [6,8], p-ANCA were not elevated, which is the case in 66% of the cases, and the rheumatoid factor was not elevated, which is the case in >80% of the cases. Furthermore, muscular manifestations did not resolve under corticosteroids, which is usually the case in CSS, but progressed despite long-term administration of steroids. Additionally, muscle biopsy did not show any eosinophilic infiltrations.

Differentials of eosinophilia with neuromuscular disease excluded in addition to CSS were the eosinophilic fasciitis (Shulman syndrome), focal eosinophilic myositis (calpainopathy), eosinophilic polymyositis, eosinophilia-myalgia syndrome due to ingestion of L-tryptophan, and the toxic oil syndrome due to ingestion of adulterated oil containing aniline [11]. These differentials were excluded upon the history, and clinical

and muscle biopsy findings. Eosinophilic polymyositis was additionally excluded upon normal creatine-kinase and absent myopathic pattern of the motor unit action potentials on needle electromyography. Idiopathic hypereosinophilic syndrome, characterised by chronic hypereosinophilia for at least six months leading to tissue damage and polyneuropathy [12,13], was excluded since hypereosinophilia never lasted >6 months and since there was no tissue damage. Other differentials of eosinophilia were excluded upon the history and appropriate laboratory tests [5]. Corticosteroids were excluded as the cause of the skeletal muscle abnormalities upon the histological findings on muscle biopsy, the eosinophilia, and the electromyographic findings.

In conclusion, this case shows that mitochondrial disease may go along with marked eosinophilia and manifestations mimicking CSS. Steroids may be useful to resolve episodic eosinophilia in mitochondrial disease but may be ineffective and contraindicated for mitochondrial myopathy.

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Table 1. Laboratory findings in the described patient over 13 years

Parameter	RL	4/94	12/00	12/00	1/01	1/00	2/00	na/02	12/04	1/05	2/05	3/05	5/05	6/05	7/05	8/05	5/07
Leukocyte count	4-10G/l	na	11.2	9.4	14.9	10.9	16.0	na	9.9	8.0	6.9	9.0	6.2	9.6	5.0	8.5	10.0
Eosinophil count	2-4%	40.0	8.5	24.2	44.1	32.9	na	30.0	3	1.6	3	0.8	4	1.4	7.7	2.7	na
Thrombocytes	150-300G/l	na	168	na	132	na	na	na	146	206	168	164	133	172	138	164	154
GOT	<31U/l	na	na	na	na	na	na	na	na	72	45	28	27	27	na	14	na
GPT	<34U/l	na	na	na	na	na	na	na	na	54	33	10	9	10	na	29	na
CK	<145U/l	na	na	na	na	na	na	na	na	102	53	90	85	89	na	89	144

GOT: glutamate-oxalate transaminase, GPT: glutamate-pyruvate transaminase, CK: creatine-kinase, na: not available

Figure 1. Muscle biopsy showing single ragged red fibres on the haematoxylin-eosin stain (a) and the Gomori-trichrome stain (b), and single COX negative fibres (c). Additionally, myoadenilat-deaminase deficiency was observed (d. Inset: normal MAD activity). (a, b, and c: original magnification x400; d and inset: x200)

