Seminars in Arthritis and Rheumatism 46 (2016) 367–371

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Autoinflammatory associated vasculitis

Shira Ginsberg, MD*, Itzhak Rosner, MD, Michel Rozenbaum, MD, Gleb Slobodin, MD, Karina Zilber, MD, Nina Boulman, MD, Lisa Kaly, MD, Abid Awisat, MD, Nizar Jiries, MD, Ofrat Beyar-Katz, MD, Doron Rimar, MD

Rheumatology Unit, Bnai-Zion Medical Center, 47 Eliyahu Golomb St, Haifa, 33048 Israel

ARTICLE INFO

Keywords:
Autoinflammatory diseases
Leukocytoclastic vasculitis

ABSTRACT

Autoinflammatory diseases are characterized by recurrent episodes of fever and localized or systemic inflammation and are caused by monogenic defects of innate immunity.

The skin is commonly involved with various manifestations including erysipelas like rash and urticaria. Although vasculitis has been described in many autoinflammatory diseases, it has not been recognized as a characteristic feature of these diseases and autoinflammatory diseases are not listed as an etiology for vasculitis associated with a systemic disease in the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides.

We describe herein 3 patients with different autoinflammatory diseases in whom leukocytoclastic vasculitis was one of the major and presenting symptoms. A review of the vast evidence in the literature for vasculitis in the spectrum of autoinflammatory diseases and a suggested pathophysiology is presented.

We suggest the term autoinflammatory associated vasculitis to describe vasculitis associated with autoinflammatory diseases. Autoinflammatory diseases should be considered within the differential diagnosis of vasculitis.

Introduction

The hereditary periodic fever syndromes (HPFS) or "monogenic autoinflammatory diseases" are caused by monogenic defects of innate immunity and are characterized by recurrent episodes of fever and localized inflammation [1,2].

Major progress in this field was obtained in 1997 with the description of the mutations in the Mediterranean fever (MEFV) gene which cause the Familial Mediterranean Fever (FMF)—the most common monogenic autoinflammatory disease [3].

Recurrent fever is the predominant symptom in HPFS accompanied by variable organ involvement such as eyes, bones, joints, gastrointestinal tract, CNS, serous membranes, and skin [1].

Leukocytoclastic vasculitis is not described as one of these presenting symptoms.

In this case series, we describe 3 patients with different autoinflammatory conditions who presented to our ward with leukocytoclastic vasculitis as one of their major manifestations and review the literature of vasculitis throughout the spectrum of autoinflammatory diseases.

Case 1

A 24-year-old man of Moslem Arab origin was admitted to our department with fever up to 40°C of 2 days duration. On examination, erythematous erysipelas like rash was evident on his right malleolus and tender enlarged right posterior cervical lymph node (3 × 8 cm) was noted. Laboratory results demonstrated leukocytosis −12 × 10^3 cells/μl (nl: 4–11 × 10^3 cells/μl), with 80% neutrophils, elevated C-reactive protein (CRP) 222 mg/dl (normal: 0–6), positive antinuclear antibody (ANA) with nucleolar pattern borderline staining, positive cytoplasmic anti-neutrophil cytoplasmic antibodies (C-ANCA), and IgG anticardiolipin antibody 20 IU (normal to 10 IU). Anti-double stranded DNA (anti-dsDNA), proteinase-3, and myeloperoxidase were negative. (His clinical presentation were not consistent with systemic lupus erythematosus nor with ANCA associated vasculitis.) Urinalysis and complement concentrations were normal. Viral and bacterial serologies were negative, with sterile cultures. Neck, lungs, and abdomen computed tomography (CT) revealed cervical lymphadenopathy and hepatosplenomegaly. A skin biopsy showed mild perivascular mononuclear infiltrate of the superficial dermis.

Review of his past medical history revealed 8 hospital admissions since the age of 19 with episodes of fever, abdominal pain, rash, diarrhea, pleuritis, and lymphadenopathy.

In view of this history, a lymph node biopsy, bone marrow, and repeat skin biopsies were undertaken, revealing a lymph node

* Corresponding author.
E-mail address: shiragins@gmail.com (S. Ginsberg).

http://dx.doi.org/10.1016/j.semarthrit.2016.07.007
0049-0172/

with reactive pattern, normal bone marrow, and leukocytoclastic vasculitis on the skin biopsy from his left leg.

The patient was treated with diclofenac, with gradual clinical improvement within 7 days including resolution of fever, rash, and lymphadenopathy. For HPFS assessment, immunoglobulins levels were measured and elevated IgD, 150 mg/ml (normal range: 0–8 mg/ml) and IgA, 7.54 mg/ml (normal range: 0.9–3.2 mg/ml) found.

Gene mutation analysis of MV444K revealed a single V377I mutation in exon 11 and no MEFV and TNF receptor mutations. Urine mevalonic acid was undetectable during the attack.

A diagnosis of variant hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) was made as the patient had typical features of HIDS including episodic fever, diarrhea, rash, lymphadenopathy, hepatosplenomegaly, elevated IgD level, leukocytosis, and elevated CRP concentration, which supported the diagnosis.

The patient was treated with canakinumab with good response.

Case 2

A 53-year-old male, Christian Arab from North Israel, experienced an unclassified multisystem inflammatory disorder for the previous 2 years. Main features were weight loss, fever, maculopapular skin eruption, arthritis, lymph node enlargement, hepatosplenomegaly, and periosteal bone reaction, all associated with a major acute phase response. He was treated solely with alternating acetaminophen as needed during his prior 2 years of illness, but did not take any drug before hospitalization. Skin biopsy revealed perivascular and intravascular inflammatory infiltration containing neutrophils and some eosinophils, characteristic of small vessel vasculitis. (Fig. 1).

High dose corticosteroids induced a favorable response yet recurrent bouts were evident after tapering down of steroids, in spite of the use of immunosuppressive agents including disease–modifying antirheumatic drugs (DMARDs), anti-TNF agents, rituximab, and tocilizumab. Subsequently, he developed a motor–sensory peripheral neuropathy of the legs and sensorineural deafness. There was no evidence of amyloidosis in rectal biopsy nor was there a relevant family history.

Gene analysis from peripheral blood cells and buccal mucosa revealed a somatic mutation in NRLP3, Tyr570Cys that has been recently described in late onset cryopyrin-associated periodic syndromes (CAPS) [4]. Other mutations in MEFV, TRAPS, and MVK genes were not detected.

The patient was treated with anti-interleukin-1 (IL-1) agents. Anakinra was poorly tolerated and then changed to canakinumab

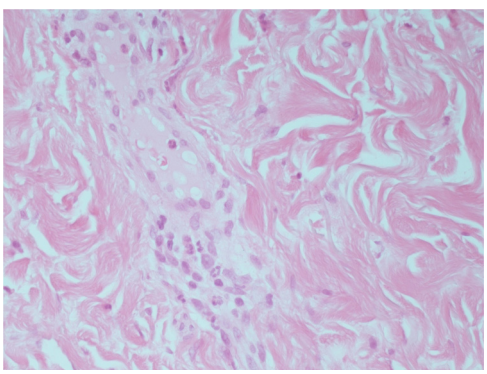

Fig. 1. Skin biopsy of patient no. 2 revealing perivascular and intravascular inflammatory infiltration containing neutrophils—characteristic of small vessel vasculitis.

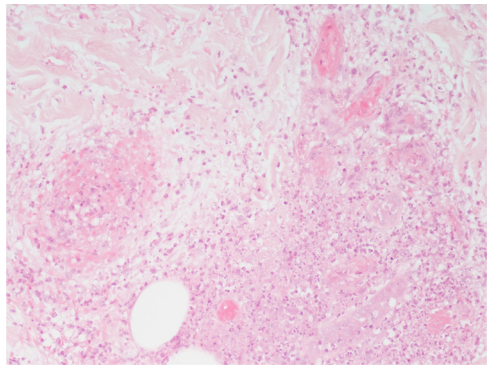

Fig. 2. Skin biopsy of patient no. 3 revealing severe leukocytoclastic vasculitis with neutrophil infiltration, fibrinoid necrosis, and nuclear dust.

300 mg/4 weeks SC with complete remission of all symptoms aside from the sensorineural deafness and peripheral neuropathy.

Based on the inflammatory clinical syndrome that included bouts of fever, skin rash, arthritis, lymphadenopathy, hepatosplenomeagly, sensory neural hearing loss, and peripheral neuropathy, the gene mutation in the NLRP3 and the favorable response to IL-1 antagonist, he was diagnosed with variant CAPS.

Case 3

A 44-year-old woman of Ukrainian origin was admitted to our medical center for assessment of longstanding relapsing remitting febrile illness.

For 10 years prior her admission, she had experienced recurrent bouts of fever lasting 4–5 days (up to 38.5°C), arthritis, sore throat, hepatosplenomegaly, and maculopapular rash on her legs. Two skin biopsies were inconclusive. Tongue biopsy from an ulcer showed active eosinophilic inflammation.

The patient was initially treated with DMARDs (methotrexate, leflunomide, and azathioprine) with poor response. Subsequently, anti-TNF agents, rituximab, abatacept, and tofacitinib failed to achieve a remission. Anakinra resulted in a local allergic reaction at injection sites and was discontinued due to intolerance. Intravenous immunoglobulin (IVIG) was complicated by aseptic meningitis. On her current hospitalization, the patient was on Tocilizumab for 4 months and MTX for a few years.

On admission, the patient was alert and oriented. Vital signs were within normal limits, except for fever 38.5°C.

On physical examination, diffuse synovitis was present in her right metacarpophalangeal joints, proximal interphalangeal joints of the hands, knees, and ankles bilaterally in addition to maculopapular rash on her legs—consistent with previous exacerbations of her baseline inflammatory disease

Laboratory tests were remarkable for the following: CRP = 110 mg/dl (nl: 0–6), ESR = 100 mm/h, white blood cell count: 12.3 $\times$ 10^3 cells/μl (4–11 $\times$ 10^3 cells/μl), and platelets 420 $\times$ 10^3 cells/μl (150–400 cells/μl). Serological tests were negative for antinuclear antibody, rheumatoid factor, and anti-cyclic citrullinated peptide antibody. Skin biopsy from her right leg revealed small vessel vasculitis (Fig. 2).

Genetic tests revealed a gene mutation in the MVK gene (a single Arg121Trp variant in exon 4) and a gene mutation in NLRP3 (a single Gln703Lys variant). No mutations were found in MEFV or Tumor necrosis factor Receptor Associated Periodic Syndrome (TRAPS) genes.

Favorable response was demonstrated to high dose methylprednisolone 1 g per day for 5 days—with improvement of her