Diagnostic dilemma in autoinflammatory disease in two patients: Does the name matter?

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The systemic autoinflammatory diseases are inflammatory disorders characterized by uncontrolled inflammation of the innate immune system. A common monogenic autoinflammatory disease is familial Mediterranean fever (FMF), associated with mutations in the MEFV gene. Another autoinflammatory disease group is cryopyrin-associated periodic syndromes (CAPS), which are characterized by urticarial rash and mutations of the gene NLRP. Systemic-onset juvenile idiopathic arthritis (soJIA) is classified as a multifactorial autoinflammatory disease.

We report two cases of systemic autoinflammatory disease with homozygous E148Q mutation in the FMF gene. They had unusual features, such as urticarial rash, non-erysipeloid erythema, lymphadenopathy, and hepatosplenomegaly, and neurological findings in one.

These patients met the “definition” criteria for FMF with two mutations in the MEFV gene. They fit the “description” criteria for CAPS with their fever, urticaria, and other clinical features. They also met the “classification” criteria for soJIA, with the fever, rash, arthritis, and accompanying systemic features.

Key words: autoinflammatory disease, familial Mediterranean fever, cryopyrin-associated periodic fever syndrome (CAPS), anti-interleukin (IL)-1 treatment, overlap.
Case Reports

Case 1
A 5.5-year-old boy was admitted to the hospital with daily fever, arthralgia, urticarial rash, and lymphadenopathies. His medical history was unremarkable. The examination revealed lymphadenopathies, urticarial rash, tenderness and limitation of motion on knee and ankle joints, mild hepatomegaly, and splenomegaly. His fever pattern was prolonged, raising the possibility of soJIA. Further examination for CAPS revealed apparently normal hearing and sight.

MEFV mutation screening showed him to be homozygous for the E148Q mutation. Genetic analysis of the CAPS, TRAPS and MVK (mevalonate kinase) genes did not reveal any of the known mutations. Since he did not respond to colchicines, he was started on steroids. His symptoms subsided and acute phase reactants decreased. However, his urticaria returned promptly after the cessation of steroids. He had similar prolonged episodes during the four-year follow-up. He was subsequently started on interleukin-1 (IL-1) receptor antagonist, anakinra, and at his last visit, he was well, with normal acute phase reactants.

Case 2
A 29-month-old girl presented to the department of pediatric rheumatology unit for daily fever, urticarial rash, lymphadenopathies, and a possible diagnosis of FMF resistant to colchicine treatment. She had been treated for autoimmune hemolytic anemia when she was four months old. At the age of 16 months, she was diagnosed as FMF due to arthritis, arthralgia, periodic fever, and abdominal pain. The mutations in the MEFV gene were E148Q/E148Q. She did not respond to colchicine treatment. Her weight and length percentiles were less than 3p. The physical examination revealed minimal hepatomegaly, minimal splenomegaly, lymphadenopathies, urticarial rash, and swelling of the right hand. She had mild mental retardation. No pyogenic abscesses were described. As she had urticarial rash, the gene NLRP3 was sequenced, but no mutation was identified in exon 3, where over 90% of the CAPS mutations lie. We also unsuccessfully analyzed the mutational hot spots of TNFRSF1A (exons 2, 3 and 4) for TRAPS, MVK (exons 2, 9 and 11) and the total coding sequence of IL1RN for DIRA (deficiency of IL-1 receptor antagonist). She had persistent fever and high acute phase reactants; thus, anakinra was started. She immediately responded to this treatment. At her last visit, she had grown, and had normal C-reactive protein (CRP) levels.

Comparison of the clinical characteristics of the two patients are shown in Table I.

Discussion
The systemic autoinflammatory diseases are a group of rare disorders characterized by inflammatory episodes without high-titer autoantibodies.\(^1\) FMF is the most common periodic fever syndrome and affects more than 100,000 people worldwide.\(^2\) It is most prevalent in ethnic groups of the eastern Mediterranean including Jews, Turks, Armenians, North Africans, Greeks, and Italians (south), but

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<td><strong>FMF mutation</strong></td>
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<tr>
<td>Acute phase reactants</td>
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<tr>
<td>Fever, arthralgia</td>
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<tr>
<td>Urticarial rash</td>
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<td>Lymphadenopathies</td>
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has been described in other ethnic groups, including Japanese and Ashkenazi Jews. The disease most commonly presents with 1-3-day episodes of fever, serositis, and arthralgia or arthritis. Erysipeloid erythema, particularly on the extensor surfaces of the lower extremities, may also be present; however, urticaria is not seen. The disease is associated with mutations in the Mediterranean fever (MEFV) gene that encodes pyrin. Colchicine decreases the frequency of FMF attacks. Prophylactic colchicine therapy leads to complete remission or significant improvement in 85% of patients with FMF, and it prevents amyloidosis. There is a dramatic response to colchicine, which is almost the rule, at least in the beginning of treatment. Although two mutations in the MEFV gene would lead to the diagnosis of FMF, it is not possible to explain the features of these patients with FMF. Our patients continued to have inflammatory features in spite of colchicine treatment. Furthermore, they had some clinical features that were not consistent with FMF, such as persistent urticaria and attacks exceeding three days, with lymphadenopathies and hepatosplenomegaly. These features are expected in other monogenic autoinflammatory diseases. On the other hand, while the urticaria in both patients and the growth and developmental delay in Case 2 are very typical features of CAPS, the patients lacked any known mutations for CAPS. It should be remembered that mutations in NLRP3 cannot be shown in all CAPS patients, which may be explained by rarer mutations in this or in other autoinflammatory genes. No mutation was identified in the genes for MVK, TRAPS, and DIRA.

The E148Q sequence variant carried by these two patients is controversial, since it is not always associated with the clinical phenotype of FMF. In a study from our center, the carrier frequency for E148Q was reported as 12% in the Turkish population. Some healthy individuals were found to be homozygous for E148Q. On the other hand, some studies suggested that E148Q might be a disease-causing mutation, as sometimes such patients responded successfully to colchicine treatment. However, the two patients reported here had quite a severe phenotype and were colchicine-resistant. It is tempting to speculate that these patients may well have polymorphisms or hot points associated with diseases such as soJIA. Systemic-onset juvenile idiopathic arthritis is a subtype of JIA and accounts for 10-20% of all patients. It has been long thought that soJIA might be a multifactorial autoinflammatory disease rather than a subtype of JIA. IL-1 is found to be the major cytokine that is responsible for soJIA. A multicenter collaboration is underway to delineate the hot spots in the genome for this childhood disease. Although urticaria is unlikely in soJIA, a concomitant systemic JIA may not be ruled out in the two presented patients. Interestingly, a previous study on our Turkish cohort of 35 soJIA patients demonstrated an increased frequency of MEFV mutations. In this latter paper, we suggested that mutations in a monogenic disease (FMF) represented one of the factors associated with a polygenic autoinflammatory disease (soJIA), at least in our population. In the aforementioned study, E148Q was found in three patients.

An alternative explanation for the features of these patients may have been a “digenic” inheritance. In fact, a number of digenic inheritance cases have been reported in autoinflammatory diseases with overlapping symptoms of both relevant diseases. Digenic inheritance refers to the interaction of two genes resulting in the expression of a mixed phenotype. FMF patients with only one MEFV mutation may produce a disease phenotype if there is a mutation in a gene for other known autoinflammatory diseases such as that of CAPS or HIDS. Touitou et al. described overlapping features of CAPS and TRAPS in family members carrying one of each disease-associated gene. Singh-Grewal described a FMF phenotype and deafness in a case who co-inherited MEFV and NLRP3 mutations. Examples of such synergetic effects of mutations in the genes coding for different autoinflammatory syndromes are increasing. One explanation for our patients may be the existence of a rare mutation in the CAPS gene, or that of HIDS or TRAPS, resulting in a mixed phenotype.

In fact, these patients met the “definition” criteria for FMF with two mutations in the MEFV gene. They fit the “description” criteria for CAPS with their fever, urticaria, and other clinical features. They also met the “classification” criteria for soJIA, with the
fever, rash, joint findings, lymphadenopathy, and splenomegaly. Thus, we were left with the enigma of how to diagnose these patients. A drug that works for all three disorders was thus chosen and was effective in both patients. Autoinflammatory diseases are caused by mutations in different proteins involved or regulating the IL-1 pathway. These two patients may represent yet unidentified or combined mutations in this pathway. After the description of FMF; many other autoinflammatory syndromes have been identified and many others might be in the future. On the other hand, we may simply continue to describe overlapping patients with overlapping mutations/polymorphisms. In conclusion, the collection of such cases is extremely important, since the description of different cases will shed light on future studies.

REFERENCES