

[CASE REPORT]

Atypical Familial Mediterranean Fever Presenting with Recurrent Migratory Polyarthrititis

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Abstract:

A 38-year-old Japanese man without any significant past medical history was referred to our clinic to undergo further examination for a “refractory infection in his joints”. He suffered recurrent migratory polyarthrititis starting from bilateral knees to his right elbow. Certain antibiotic therapies appeared to improve his symptoms, but the symptoms recurred due to the migratory nature of arthritis. A diagnosis of familial Mediterranean fever (FMF) was considered and diagnostic tests were performed. Not many differential diagnoses exist for migratory polyarthrititis, particularly when it has a recurrent nature. The administration of antibiotics without sufficient diagnostic consideration can cause a delay in making an accurate diagnosis and thereby also cause a delay in administering appropriate treatment.

Key words: familial mediterranean fever, migratory polyarthrititis, fever of unknown origin

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Introduction

Many infections present with symptoms of arthritis and some become recurrent or refractory. A response to antibiotic treatment usually suggests an infectious etiology, but an apparent response to antibiotics might not be “causal”, but instead it could be a “temporal” response which may thus lead to an incorrect diagnosis.

Familial Mediterranean Fever (FMF) is an autoinflammatory disease characterized by periodic fever and serositis (1). Because conventional laboratory tests or imaging studies usually do not identify FMF, it is often mistaken as an infectious disease and patients are treated with unnecessary and often a confusing array of antibiotics. We herein present a case of atypical FMF presenting with recurrent migratory polyarthrititis.

Case Report

A 38-year-old Japanese man who did not have any significant past medical history presented in late December 2018 with repetitive episodes of arthritis and fever, which

were reported to have improved after the administration of some antibiotics. About 6 months prior to the initial visit, he started to have a fever above 39°C with bilateral knee arthritis. He was hospitalized at a different hospital and had been treated with intravenous meropenem. His symptoms did not improve with meropenem, while his fever lasted for about a week. Thereafter, the antibiotic was switched to intravenous minocycline. His symptoms improved within 24 hours after initiating minocycline, and he was thus administered antibiotics for a total of 21 days, first minocycline for week, then switched to oral doxycycline.

About 3 months before this presentation, he developed another episode of fever with right elbow swelling. He visited an orthopedic outpatient clinic. His elbow joint was swollen and the orthopedic doctor performed arthrocentesis with joint fluid drainage. The details of the nature and the amount of joint fluid are unknown, and the fluid was not sent for microbiology tests. The patient was treated with oral cefcapene pivoxil for about a week, and his condition again improved within a few days. Two months prior to our visit, he developed the same symptoms as a month before with fever and left elbow swelling, and he was treated in similar way. One month prior to our visit, he developed an-

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Table. Laboratory Results of the Patient.

Variables	Reference Ranges for Adults	On the day of the initial visit (December 2018)	Follow up visit after colchicine (March 2019)
White-cell count (per mm ³)	4,000-8,500	6,000	5,800
Hemoglobin (g/dL)	13.6-17	14.7	14.3
Platelet (per mm ³)	130,000-300,000	466,000	352,000
Sodium (mmol/L)	137-146	142	Not measured
Potassium (mmol/L)	3.5-4.7	4.1	Not measured
Chloride (mmol/L)	99-109	106	Not measured
Calcium (mg/dL)	8.8-10.1	8.8	Not measured
Phosphorus (mg/dL)	2.4-4.5	2.8	Not measured
Albumin (g/dL)	4.1-5	3.8	Not measured
Aspartate aminotransferase (AST) (U/L)	13-31	17	Not measured
Alanine aminotransferase (ALT) (U/L)	8-34	20	Not measured
Alkaline phosphatase (ALP) (U/L)	106-322	329	Not measured
Lactate dehydrogenase (LDH) (U/L)	124-222	120	Not measured
Total bilirubin (mg/dL)	0.3-1	0.5	Not measured
Blood urea nitrogen (BUN) (mg/dL)	9-22	16.7	Not measured
Creatinine (mg/dL)	0.5-1.3	0.63	Not measured
Glucose (non-fasting, mg/dL)	73-109	112	Not measured
C-reactive protein (CRP) (mg/dL)	0.00-0.14	5.20	3.09
Erythrocyte sedimentation rate (ESR) mm/hour	0-10	59	35
Complement level (CH50) (U/mL)	25-51	80.9	Not measured
C3 (mg/dL)	73-138	155	Not measured
C4 (mg/dL)	11-31	47.9	Not measured
CD4+T lymphocytes count (/mm ³)		577	Not measured
Thyroid stimulating hormone (TSH) (μIU/mL)	0.35-4.94	0.585	Not measured

other fever with bilateral knee arthritis and visited a different hospital. Based on his lengthy medical history, mero-penem refractory infections including rickettsiosis, brucellosis, mumps, or hepatitis B infection were considered, but serology tests for these infections were reportedly all negative. He was not administered any antibiotics at this time, and blood cultures were taken for the first time, which turned out to be negative. He was thereafter referred to our outpatient clinic to undergo further examinations.

He had no significant past medical history. He works for an elevator company, and he had never been exposed to sewage or any construction sites. He lives with his wife and her family and all are currently healthy. He keeps a dog and previously had a cat, who died of renal failure due to diabetes. The dog is usually taken care of by his wife and he denied any history of animal bite or exposure to any other animals or arthropods. He also reported no recent overseas travel. He reported no family history of febrile illness. Rest of his history was unremarkable.

Upon presentation, he was ambulatory and appeared well, accompanied by his wife. He was alert and oriented. By the time he visited us, his fever began to improve with minimal joint pain. His height was 168.5 cm and weight was 62.0 kg. His blood pressure was 112/79 mmHg, pulse rate was 88/minute, respiratory rate was 15/minute, and body temperature was 36.8°C at axillary measurement. He had multiple acne like skin lesions on his forehead, but there were no

other abnormalities on his head, neck, eye, ear, nose, and throat. There was no lymphadenopathies or skin lesions other than those described above. Auscultation of lungs and heart were normal. There was no arthritis, joint movement impairment, or tender muscles, joints, tendons, and ligaments. His abdomen was soft and there was no organomegaly on palpitation. The rest of his physical examination was unremarkable.

The referral letter stated that urine polymerase chain reaction (PCR) tests for *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and T-spot test for tuberculosis were negative. His antistreptolysin O (ASO) antibody level was low. We performed whole body CT scan without contrast, which did not show any abnormalities, including lymphadenopathies or serosities. A blood test showed a WBC count of 6,000/mm³ with 72.9% neutrophils, the C-reactive protein (CRP) level was 5.20 mg/dL, and the erythrocyte sedimentation rate (ESR) was 50 mm/hour. The hemoglobin level was 14.7 g/dL, but the platelet count was high (466,000/μL) (Table). Serology tests for infectious diseases causing relapsing polyarthritis were sent for analysis.

Because of the chronicity of his presentation and good general appearance, as well as the difficulty in performing a detailed fever work-up in an inpatient setting during the end of the year season, we decided to ask him to come back the following week without prescribing any specific treatment, and reminded him and his wife to call us if there was any

sudden worsening of the symptoms. Serology tests for hepatitis B, hepatitis C, human T-lymphotropic virus type (HTLV)-1, mumps, syphilis, brucellosis, tsutsugamushi disease performed at presentation all turned out to be negative a week later.

On the follow-up visit 11 days later, he stated that his fever had gone down on the day of his last visit and since had been normal without any specific treatment, and there was also no joint swelling. Due to the recurrent nature of his fever, the migrating arthritis, and the improvement of his symptoms without antibiotic therapy, FMF was thus suspected. Genetic tests of the blood were performed at the Department of Pediatrics, Graduate School of Medical Science and School of Medicine, Kanazawa University and MEFV mutations were thus identified at exon 2 (L110P and E148Q). Based on the diagnostic criteria, he was considered to clinically have atypical FMF with Mediterranean fever gene (MEFV) polymorphism.

He was prescribed oral colchicine 0.5 mg twice a day as a prophylaxis. He is currently almost symptom free except for occasional chest or abdominal pain, and his acne-like skin lesions have also disappeared. He later disclosed that he had had chest pain of a similar nature during fever and arthritis episodes.

Discussion

FMF is an autosomal recessive, inherited periodic inflammatory syndrome, characterized by self-limited recurrent attacks of fever with serositis such as peritonitis, pleuritis and arthritis (1). It is known to occur mainly among Mediterranean and Middle Eastern populations, such as non-Ashkenazi Jews, Arabs, Turks, and Armenians. Despite its name, FMF is now known to occur worldwide. In Japan, it is estimated that there are currently about 300 patients with FMF (2, 3). Although it is a relatively rare disease and one of the known intractable diseases (4), it is no longer considered to be that rare (2), and one needs to be aware of this entity as one of the periodic fever syndromes when making a differential diagnosis of a patient with fever of unknown origin.

FMF is caused by mutations in the *MEFV* on chromosome 16p13.3, which encodes a protein named pyrin. Pyrin regulates the production of interleukin (IL)-1 β and the activation of nuclear factor (NF)- κ B. The lack of normal pyrin activity in FMF is considered to be the cause of an excessive amount of cytokines and the subsequent onset of inflammatory attacks (5).

The diagnosis of FMF is usually made clinically. Genetic tests are not necessarily mandated, and they may be normal in patients with FMF.

Likewise, family history may not be detected, as in our case (1). MEFV mutations commonly seen in Japan are different from those of Mediterranean people, where M694I on exon 10 is most common for typical FMF (6). For atypical cases, mutations in exon 3 such as P369S and R408Q are

commonly seen (7). E148Q in exon 2, as was seen in our patient, is the most frequent FMF mutation in the Japanese population (40.2%) and L110P is also commonly seen (18.8%) (7). In our case, the initial fever and bilateral knee arthritis lasted for about a week, longer than that of the typical FMF diagnostic criteria, thus we considered that our case might be categorized as atypical FMF with an exon 2 mutation (4).

There are not that many differential diagnoses for migratory polyarthritis. Acute rheumatic fever secondary to streptococcal infection is a typical example, which can present with migratory polyarthritis (8). However, this has now become an extremely rare disease in the developed world where antibiotics are readily available. Other diseases known to cause migratory polyarthritis include disseminated gonococcal infection, viral arthritis such as mumps and parvovirus infection, or paraneoplastic syndrome (9-11). Arthritis can occur in patients with FMF and it is seen in about 30% of Japanese patients (3). Migratory polyarthritis is one of the known features of FMF (12). In children with FMF and arthritis in Jordan, only 4% had migratory asymmetric arthritis (13). Its incidence in Japan has never been described according to our literature search. Our patient's acne-like lesions could be associated with FMF and they improved after the administration of colchicine (14).

Septic arthritis is one of the important differential diagnoses when encountering patients with febrile arthritis. However, providing antibiotics without performing a thorough diagnostic work-up, such as blood cultures or a culture of the joint fluid will make the appropriate treatment difficult, and it can lead to an incorrect diagnosis, as occurred in our patient.

In conclusion, we herein presented a case of relapsing migratory polyarthritis caused by atypical FMF. Inappropriate antibiotic therapy usually leads to a delay in making a correct diagnosis, which is not a very rare occurrence in Japan. The atypical features of migrating polyarthritis should therefore alert clinicians about this disease entity.

The authors state that they have no Conflict of Interest (COI).

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