JBACHS
Journal of Basic and Clinical Health Sciences

J Basic Clin Health Sci 2022; 6: 928-930
https://doi.org/10.30621/jbachs.1053935
CASE REPORT

FAMILIAL MEDITERRANEAN FEVER AND PAGET'S DISEASE: INCIDENTAL OR ASSOCIATED?

Betul Sargin[1]

[1]Adnan Menderes University, Medical Faculty, Department of Physical Medicine and Rehabilitation, Division of Rheumatology, Aydin, Turkey

ORCID: B.S. 0000-0002-9463-8413

Corresponding author: Betul Sargin, **E-mail:** betulsargin83@hotmail.com
Received: 05.01.2022; **Accepted:** 10.04.2022; **Available Online Date:** 29.09.2022

Cite this article as: Sargin B. Familial mediterranean fever and paget's disease: incidental or associated? J Basic Clin Health Sci 2022; 6: 928-930.

ABSTRACT

Co-existence of Familial Mediterranean Fever (FMF) and Paget's disease (PD) is very rare. In this paper, we aimed to present a case of FMF patient presenting with PD. A 62-year old male patient admitted with complaint of chronic low back pain and weight loss. An increased uptake at pelvis which was reported as paget metabolic bone disease was identified in bone scintigraphy. An infusion of 5 mg of zoledronic acid, calcium and Vitamin D treatments were administered. Paget's disease (PD) is a rare condition in patients with FMF. The co-existence of FMF and PD should not be forgotten.

Keywords: Familial Mediterranean Fever, Paget's disease, incidental, associated

INTRODUCTION

Familial Mediterranean Fever (FMF) is a monogenic autoinflammatory disease and the most seen of this diseases (1). It is associated with gene mutations on chromosome 16p13.3. As a result abnormal pyrin (marenostrin) is encoded. Pyrin (marenostrin) is responsible of the caspase-1 activation and releasing of the pro-inflammatory cytokine Interleukin-1β (IL-1β) (2).

Whereas Paget's disease (PD) etiology includes viral and genetic factors (3-5). A slow virus of paramyxovirus family (e.g.,measles virus, respiratory syncytial virus, canine distemper virus) are of these viral causes (3). In first degree relatives of PD patients PD is seen 7-10 times higher when they are compared with age and sex-matched controls (4). In familial PD patients SQSTM1 gene mutations have been identified. These mutations have important role in NFkB signalling pathway (5). In here, we presented a 62 years old man who had FMF presented with PD.

CASE REPORT

A 62-year-old male patient was admitted to the rheumatology outpatient clinic with complaints of chronic low back pain and weight loss. He had diagnosed as FMF due to recurrent (periodic) fever and abdominal pain complaints forty-seven years ago. He was receiving colchicine (1.0 mg / day) for FMF. His general condition was moderate, oriented, and cooperated. The sacroiliac region was tender to palpation. Hemoglobin was 12.0 gr/dL, leucocyte count was 7.10 µl/L, thrombocyte count was 238.000 µl/L in laboratory test performed at patient admission. The other laboratory tests were as follows: Urea nitrogen was 40 mg/dL, creatinine was 0.72 mg/dL, alkaline phosphatase (ALP) was 300 U/L, erythrocyte sedimentation rate (ESR) was 22 mm/h, C-reactive protein (CRP) level was 0,5 mg/L, prostate specific antigen (PSA) was 3,15 ng/mL, free PSA was 0,94 ng/mL. On the other hand tumor marker results were as follows: Alfa-fetoprotein (AFP) was 0.0 ng/ml,

cancer antigen-125 (CA-125) was 2.0 U/mL, CA-15-3 was 12.0 U/mL, CA-19-9 was 11.96 U/mL and carcinoembryonic antigen (CEA) was 1.59 ng/ml. Urine analysis findings are as following : Leukocyte esterase, 0, Nitrite Pos; 0; pH; 5,0; Protein Normal; Blood Neg; Sp Gr 1.025; Ketones 0 , Glucose 0 ; Bilirubin Neg. No proteinuria was detected in 24-hour urine analysis. Human Leucocyte Antigen (HLA)- B27 test was negative and FMF mutation analysis was positive with R202 heterozigot. A suprapubic pelvis anterior-posterior radiography was performed due to his chronic low back pain. Suprapubic pelvis anterior-posterior radiography showed diffuse sclerosis in the pelvic bones (Figure 1). In the sacroiliac magnetic resonance imaging (MRI) bilateral active sacroiliitis was detected (Figure 2). A bone scintigraphy was performed due to his complaints weight loss and laboratory analysis such as elevated serum ALP.

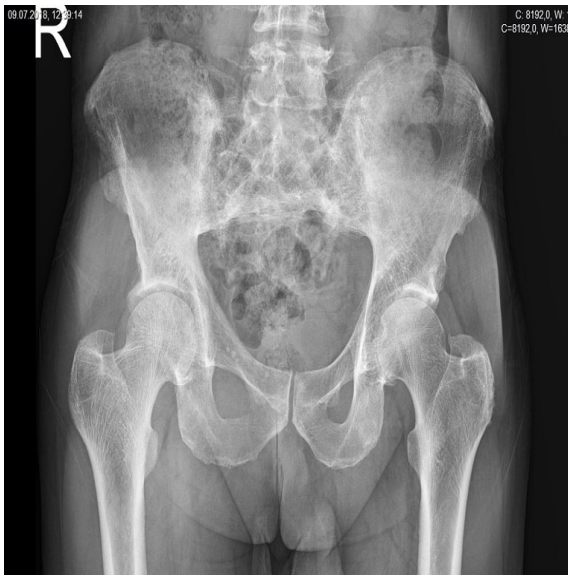

Figure 1. X-ray of the sacroiliac joint shows diffuse sclerosis in the pelvic bones

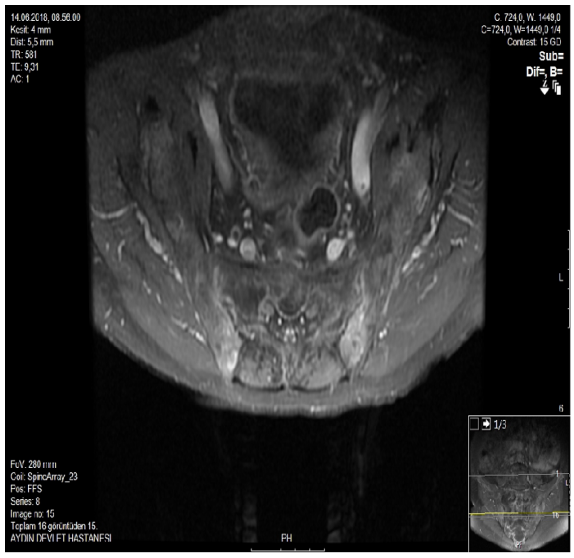

Figure 2. MRI of the sacroiliac joint shows bilateral active sacroiliitis

In the bone scintigraphy report an increased uptake at pelvis which was reported as paget metabolic bone disease was obtained. The clinical, laboratory, and radiographic findings were consistent with the co-existence of FMF and PD. 5 mg zoledronic acid infusion, calcium and Vitamin D treatments were started. With this treatment the ALP level decreased from 300 U/L to 110 U/L at two months following the start of treatment. And he noted a decrease in his back pain. The patient is currently under clinical control.

DISCUSSION

Recurrent episodes of fever, leukocitosis, serositis, myalgia, erysipelas-like skin lesions, lasting in 12-72 hours are seen in FMF patients (2). It is diagnosed according to the Tel-Hashomer criteria (6). The patient had diagnosed as FMF 47 years ago according to this criteria. In symptomatic FMF patients colchicine treatment is used. Nonsteroideal antinflammatory drugs (NSAIDs) and corticosteroids are adjunctive symptomatic therapies. In colchicine-intolerant or resistant FMF patients, biologic agents (etanercept, infliximab), IL-1 trap (Rilonacept), IL-1 inhibitors (Anakinra, Canakinumab), IL-6 receptor antibody (Tocilizumab), Interferon-α and thalidomide are used (2). PD patients are frequently asymptomatic (7). Bone lesions in PD occur in three phases. Early changes are predominantly lytic. The second phase is a mixed osteolytic and osteoblastic process. In final phase bone formation becomes dominant. Abnormal bone expansion is seen in multiple areas commonly in pelvis, vertebral bodies, skull, femur, and tibia (8). The main complaint is pain in symptomatic patients. Headache, spinal stenosis, compression of the brain stem and cerebellar system, hydrocephalus and cranial neuropathies and irreversible hearing loss which is the most common neurological complication are seen as neurological complications (7). PD diagnosis is based on clinical assessments (pain, deformity, complication), biochemistry examinations (bone turnover markers:ALP), skull X-ray and total body bone scan (9). Intravenous infusion of zolendronic acid 5 mg is currently considered as the first step treatment (7). It

induces biochemical remission, improves quality of life and it's effect persists for many years (10). The most useful biochemical marker for PD is total ALP level (11).

Our patient was diagnosed with FMF 47 years ago due to recurrent (periodic) fever, abdominal pain and R202 heterozigot mutation positivity (6). Also, he was diagnosed as PD according to the unexplained elevation of ALP activity, diffuse sclerosis in the pelvic bones at the suprapubic pelvis anterior-posterior radiography and increased uptake at pelvis at the bone scintigraphy. He was diagnosed as a case of co-existence of FMF and PD.

FMF is caused by mutations in MEFV gene. MEFV gene encodes a 781-amino acid protein defined as pyrin (marenostrin). Pyrin regulates caspase-1 activation and IL-1β production through interaction of it's N-terminal pyrin. The interaction of N-terminal pyrin with IκB-α induced calpain-mediated degradation of IκB-α potentiates NF-κB activation (12). In familial PD patients SQSTM1 gene mutations can be seen. These mutations have important role in signalling pathways including the NFkB pathway (5). The co-existence of FMF and PD can be explained by this common pathophysiology.

As we discussed before in FMF abnormal pyrin (marenostrin) is encoded (2). The interaction of N-terminal pyrin activates NF-κB pathway (12). In familial PD patients SQSTM1 gene mutations can be seen. These mutations have important role in signalling pathways including the NFkB pathway (5). The co-existence of FMF and PD can be explained by this common pathophysiology.

CONCLUSION

In conclusion, we aimed to report a case with FMF and PD. The clinic findings such as bone pain and weight loss should be carefully followed until a final diagnosis can be clearly made.

Acknowledgments: None.

Author contribution: Concept - BS; Design - BS; Supervision - BS; Fundings - BS; Materials -BS; Data Collection and/or Processing - BS; Analysis and/or Interpretation - BS; Literature Search -BS; Writing Manuscript - BS; Critical Review -BS.

Conflict of interests: The authors have no conflicts of interest to declare.

Ethical approval: None.

Funding: The authors declared that this study received no financial support.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Almeida de Jesus A, Goldbach-Mansky R. Monogenic autoinflammatory diseases: concept and clinical manifestations. Clin. Immunol 2013;147:155-174.
2. Portincasa P. Colchicine, Biologic Agents and More for the Treatment of Familial Mediterranean Fever. The Old, the New, and the Rare. Curr Med Chem 2016;23:60-86.
3. Galson DL, Roodman GD. Pathobiology of Paget's disease of bone. J Bone Metabol 2014;21:85-98.
4. Eekhoff EW, Karperien M, Houtsma D, et al. Familial Paget's disease in The Netherlands: occurrence, identification of new mutations in the sequestosome 1 gene, and their clinical associations. Arthritis Rheum 2004;50:1650-1654.
5. Albagha OM. Genetics of Paget's disease of bone. Bonekey Rep 2015;4:756.
6. Mor A, Shinar Y, Zaks N, et al. Evaluation of disease severity in familial Mediterranean fever. Semin Arthritis Rheum 2005;35:57-64.
7. Appelman-Dijkstra NM, Papapoulos SE. Paget's disease of bone. Best Pract Res Clin Endocrinol Metab 2018;32:657-668.
8. Singer FR, Bone HG, Hosking DJ, et al. Paget's disease of bone: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2014;99:4408-4422.
9. Josse RB, Hanley DA, Kendler D, et al. Diagnosis and treatment of Paget's disease of bone. Clin Invest Med 2007;30:E210-E223.
10. Cundy T, Maslowski K, Grey A, et al. Durability of response to zoledronate treatment and competing mortality in Paget's disease of bone. J Bone Miner Res 2017; 32:753-756.
11. Walsh JP: Paget's disease of bone. Med J Aust 2004;181:262-265.
12. Chae JJ, Wood G, Richard K, et al. The familial Mediterranean fever protein, pyrin, is cleaved by caspase-1 and activates NF-kappaB through its N-terminal fragment. Blood 2008;112:1794-1803.