CASE REPORT OLGU SUNUMU

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Anterior Chest Wall Involvement in a Child with Familial Mediterranean Fever: A Rare Manifestation and Diagnostic Challenge

Ailesel Akdeniz Ateşi Olan Bir Çocukta Göğüs Ön Duvar Tutulumu: Nadir Bir Görünüm ve Tanı Zorluğu

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ABSTRACT Anterior chest wall involvement is frequently seen in adult patients with spondyloarthropathy and often related to advanced axial disease and rarely reported in pediatric patients. In addition, anterior chest wall involvement is frequently encountered in patients with synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome. Despite treatments of these conditions were similar, differentiation of these two diseases might be challenging due to the overlapping features. Also, several rheumatic diseases, including spondyloarthropathy, could be seen in association with familial Mediterranean fever (FMF). Additionally, treatment of cases with concomitant FMF and spondyloarthropathy might be challenging due to the different biological drug needs of the diseases. Herein, we presented a case of sternoclavicular arthritis in a pediatric FMF patient for the first time and emphasize on the challenges in differentiating SAPHO from spondyloarthropathy and difficulties in treatment.

Keywords: Acquired hyperostosis syndrome; axial spondyloarthritis; familial Mediterranean fever; sternoclavicular joint; thoracic wall

ÖZET Göğüs ön duvarı tutulumu spondiloartropatili erişkin hastalarda sıklıkla görülür ve ilerlemiş aksiyel hastalıkla ilişkili olup çocuklarda nadiren bildirilir. Ayrıca sinovit, akne, püstüloz, hiperostoz ve osteitis (SAPHO) sendromlu hastalarda göğüs ön duvarı tutulumuna sıklıkla rastlanmaktadır. Bu hastalıkların tedavileri benzer olmasına rağmen örtüşen özellikleri nedeniyle ayırt edilmesi zor olabilir. Ayrıca spondiloartropati dâhil birçok romatizmal hastalık ailesel Akdeniz ateşi (AAA) ile birlikte görülebilir. Ayrıca AAA ve spondiloartropati birlikteliği olan olguların tedavisi, hastalıkların farklı biyolojik ilaç gereksinimleri nedeniyle zorlayıcı olabilir. Burada ilk kez pediatrik bir AAA hastasında sternoklaviküler artrit olgusunu sunarak SAPHO'yu spondiloartropatiden ayırmada ve tedavideki zorluklara vurgu yaptık.

Anahtar Kelimeler: Kazanılmış hiperostozis sendromu; aksiyel spondiloartrit; ailesel Akdeniz ateşi; sternoklaviküler eklem; göğüs duvarı

Bone and joints of the anterior chest wall (ACW) could be subject to various conditions including infective, oncologic and inflammatory conditions. ACW involvement is a well-known and not an uncommon manifestation of axial spondyloarthropathy in adults. Arthritis of the ACW is often related with advanced axial disease but may be seen early in the course.[1] Apart from non-rheumatologic conditions, differential diagnosis includes synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome because of the tendency for ACW involvement.[2]

Familial Mediterranean fever (FMF) is an autoinflammatory disease with recurrent attacks of fever, serositis, and arthritis. Besides, spondyloarthropathy, manifested as sacroiliitis, is frequent in patients with FMF.[3]

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Herein, we presented a case with ACW involvement in an FMF patient with concomitant spondyloarthropathy and emphasized on the challenge of the diagnosis, whether our patient could be classified as SAPHO syndrome or FMF associated spondyloarthropathy.

CASE REPORT

Fourteen-year-old male patient presented with pain with shoulder movements and swelling in chest wall for two weeks. He did not describe any constitutional symptoms, including fever. He had exertional leg pain on the left side, but morning stiffness was not apparent. His background was complicated with multiple conditions. At 3 years of age, he was diagnosed as psoriasis treated with topical steroids, however, no findings associated with psoriasis, including finger changes, had recurred. At the age of four, he was diagnosed with FMF with recurrent episodes of fever and abdominal pain and genetic analysis revealed a homozygote M694V mutation. He was on two milligrams per day colchicine treatment. Also, at five years of age, he was diagnosed with bilateral sacroiliitis and treated with sulfasalazine. His first appearance in our clinic was at 13 years old age with low back pain and morning stiffness. Magnetic resonance imaging (MRI) revealed bilateral sacroiliitis in addition to enthesitis in bilateral trochanter major and iliac bone. HLA-B27 came out negative and he was diagnosed with seronegative spondyloarthropathy. Treatment with etanercept was initiated and, he had no complaints for 12 months until this presentation. He is the first child of consanguineous parents and family history revealed FMF and psoriasis in 2^{o} relatives. Also, there was a family history of kidney failure due to the FMF related amyloidosis. His body weight was 40 kg and height was 148 cm. Physical examination revealed a tender, erythematous, mass-like appearance overlying the left sternoclavicular joint with increased heat, and pain with shoulder movements (Figure 1). Otherwise, his physical examination was unremarkable. Laboratory evaluation revealed increased acute phase reactants (C-reactive protein: 41 mg/L, erythrocyte sedimentation rate: 24 mm/hr and serum amyloid A: 21.8 mg/dL) with normal white blood cell indices. MRI of the ACW revealed left sternoclavicular arthritis with osteomyelitis in the medial aspect of the clavicula and soft tissue inflammation extending to the mediastinum (Figure 2a, Figure 2b). Percutaneous biopsy of the lesion (bone and soft tissue) was consistent with chronic active inflammation and no microorganism was detected in cultures. Due to the bony and mediastinal involvement, bone scintigraphy was performed for suspected multifocal osteomyelitis/SAPHO syndrome. Apart from left sternoclavicular joint, no clinically relevant involvement was detected (Figure 2c). Two-weeks of low dose (0.5 mg/kg) corticosteroid treatment resulted in remission of all clinical symptoms and etanercept dose was increased to 0.9 mg/kg/week. After the sternoclavicular arthritis, increased FMF activity was observed despite

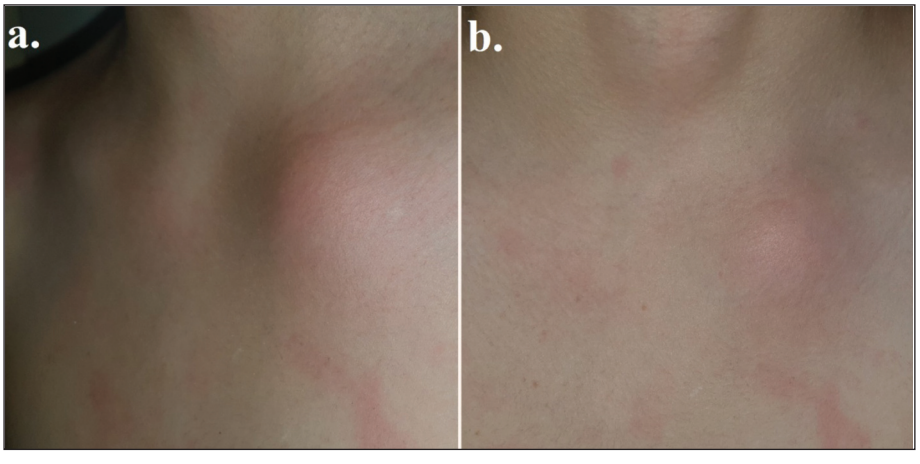

FIGURE 1: Mass like appearance overlying the left sternoclavicular joint.

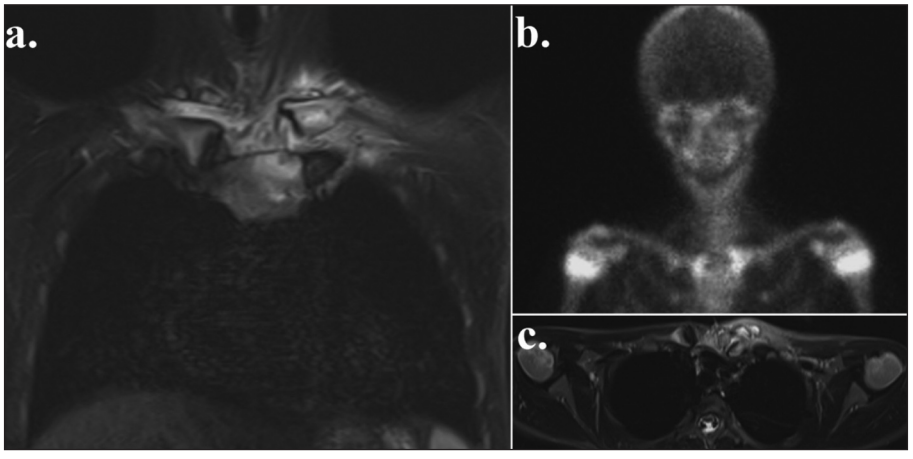

FIGURE 2: a) T2 weighted magnetic resonance images in coronal plane revealed increased synovial fluid in left sternoclavicular joint with marrow edema suggesting osteitis/osteomyelitis; **b)** fluid accumulation and synovial hypertrophy resulted in cyst like appearance anterior to the sternoclavicular joint in the horizontal plane; **c)** bone scintigraphy revealed increased activity in left sternoclavicular joint.

colchicine and anti-tumor necrosis factor (TNF) treatments. Pharmaceutical preparation of colchicine was changed and resulted in a better controlled FMF activity but, after six months of the initial sternoclavicular arthritis, patient was presented with right-sided sternoclavicular arthritis. In addition, widespread acne formation was observed in face and back of the patient. In dermatologic examination, features of the acne were not suggestive of SAPHO syndrome. Short term steroid treatment resulted with the remission of sternoclavicular arthritis but, due to the recent flare of arthritis and persistently high serum amyloid-A levels, anti-TNF treatment was switched to adalimumab.

Informed consent was obtained from the patient.

DISCUSSION

This case highlights the wide spectrum of musculoskeletal manifestations in children with FMF. Despite our case could be classified as spondyloarthropathy associated with FMF, juvenile spondyloarthropathy with sternoclavicular involvement is rarely reported. In a recent study, 13% of children with juvenile idiopathic arthritisand (JIA) had sternoclavicular involvement, mostly observed in patients with systemic JIA enthesitis related arthritis. Clinical examination is not correlated with sternoclavicular involvement and swelling was observed only in four of nine patients with synovial effusion.[4] In contrast, ACW involvement is frequently observed in adult patients with spondyloarthropathy, especially in patients with advanced disease.[1] Besides, in a prospective cohort of adult spondyloarthropathy patients, ACW pain was associated with enthesitis, sacroiliitis and more severe disease in patients with early spondyloarthropathy.[5]

Because of the bone and soft tissue involvement along with sternoclavicular arthritis, SAPHO syndrome was included in the differential diagnosis of our case. SAPHO syndrome is an auto-inflammatory bone disease with a predilection for axial skeleton involvement. Disease is more common in adults and pediatric disease is often called as chronic nonbacterial osteomyelitis (CNO) with differences in sites of involvement which is mainly peripheral in CNO.[1] Due to the occurrence of enthesitis, synovitis and association with inflammatory bowel disease, SAPHO could also be classified in the spectrum of seronegative spondyloarthropathies.[1] Bone lesions could be observed in both SAPHO/CNO and spondyloarthropathies. In a comparative study, sacroiliitis was more common in spondyloarthropathies while ACW involvement is more common in SAPHO syndrome.[6] In patients with SAPHO, bone scintigraphy may reveal characteristic “bulls head” appearance and sacroiliitis in SAPHO is usually unilateral.[2]

FMF was shown to be associated with major histocompatibility complex Class-I related diseases, including inflammatory bowel disease, psoriasis and

ankylosing spondylitis.[7] Juvenile spondyloarthropathy is frequently encountered in patients with FMF and patients with co-existent FMF were younger, had more frequent sacroiliitis, higher inflammatory markers and, less frequent enthesitis and positive HLA-B27.[3] In addition, FMF is reported in patients with CNO.[8,9] Gezgin Yildirim et al. described two patients with CNO, one with clavicular involvement, and reported a complete response with colchicine treatment.[8] Despite our case being on colchicine treatment while he developed sternoclavicular involvement, also displayed colchicine-resistant disease. Thus, uncontrolled FMF activity might be associated with CNO features in patients with FMF. Generally, it seems difficult to made diagnosis of either CNO or spondyloarthropathy in the presence of pelvic and sacral involvement but, positive HLA-B27 did not seem to be a hallmark of pediatric CNO.[10] Besides, over the long term, patients with CNO might evolve into spondyloarthropathy.[11] Also, CNO patients with a positive HLA-B27 were found to be associated with more frequent lower extremity involvement, increased number of the bone involvements and a more common diagnosis of enthesitis related arthritis in the follow-up.[12]

Despite diagnostic challenges, it is fortunate that treatment of these two diseases is similar. However, treatment of cases with co-existent spondyloarthropathy spectrum of diseases and FMF could be challenging. TNF inhibition might be required in treatment of juvenile spondyloarthropathy.[13] In contrast, colchicine intolerant or resistant FMF patients might need anti-interleukin-1 treatment.[14] In a retrospective study with colchicine refractory FMF patients, anti-TNF therapy for concomitant diseases, including ankylosing spondylitis, resulted in complete or near complete FMF response in almost half of the patients. Besides, switch of the anti-TNF treatment might be beneficial in controlling the activity of FMF.[15] However, our patient did not show a favorable response to anti-TNF treatment in regard of the FMF activity thus, we believe that the optimum treatment strategy in cases with FMF and concurrent inflammatory conditions needs to be further addressed.

In conclusion, juvenile spondyloarthropathy and CNO/SAPHO have overlapping features, which made the classification of these diseases difficult. Whether the diagnosis was SAPHO or FMF associated spondyloarthropathy, our case represents an end spectrum of spondyloarthropathy spectrum of diseases in a child with FMF. Besides, treatment of such cases could be challenging due to the need for different biologics for controlling the disease activity of these conditions.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Özge Baba, Hakan Kısaoğlu;* ***Design:*** *Hakan Kısaoğlu;* ***Control/Supervision:*** *Mukaddes Kalyoncu;* ***Data Collection and/or Processing:*** *Özge Baba, Hakan Kısaoğlu;* ***Analysis and/or Interpretation:*** *Özge Baba, Hakan Kısaoğlu, Mukaddes Kalyoncu;* ***Literature Review:*** *Hakan Kısaoğlu, Özge Baba;* ***Writing the Article:*** *Hakan Kısaoğlu;* ***Critical Review:*** *Özge Baba, Hakan Kısaoğlu, Mukaddes Kalyoncu.*

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