Familial arthropathy with camptodactyly: reports of two families

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SUMMARY: Soylu A, Türkmen M, Kavukçu S, Özer E, Canda T. Familial arthropathy with camptodactyly: reports of two families. Turk J Pediatr 2001; 43: 356-361.

Familial association of congenital camptodactyly and arthropathy without evidence of concurrent inflammation has an autosomal recessive pattern of inheritance. We describe four children born to consanguineous parents in two families with congenital camptodactyly and polyarthropathy which were misdiagnosed and treated as juvenile rheumatoid arthritis (JRA) for some time. The siblings in the second family also had fibrosing pleuritis. Histopathological examination of the synovial tissues of the children in the first family revealed synovial hypertrophy and presence of multinucleated giant cells with minimal inflammation and vasculitis. On the other hand, prominent fibrosis with no inflammation was present in the synovial tissue of the elder boy in the second family. Thus, while the children in the first family had the phenotypic characteristics of congenital familial hypertrophic synovitis, the latter siblings probably represent a form of the familial fibrosing serositis.

Key words: camptodactyly, childhood, familial arthropathy, familial fibrosing serositis, juvenile rheumatoid arthritis.

Camptodactyly is used to describe nontraumatic flexion deformity of the proximal interphalangeal joints[1]. After the first description of familial association of congenital camptodactyly and arthropathy in 1965, additional cases of camptodactyly associated with noninflammatory arthropathy have been reported[2]. Characteristic features of the syndrome are its familial nature, congenital or early-onset camptodactyly and polyarthropathy associated with synovial hyperplasia but without evidence of concurrent inflammation[2,3]. An autosomal recessive pattern of inheritance has been proposed for this condition[4]. Presence of additional features has led to various acronyms for the syndrome as CAP (camptodactyly-arthropathy-pericarditis) or CAC (camptodactyly-arthropathy-coxa vara). However, genetic evaluation of the families with different manifestations has led to the localization of the gene to chromosome 1, thus the combined term CACP (camptodactyly-arthropathy-coxa vara-pericarditis) was suggested for this entity[2]. In addition, progressive fibrosing pleuritis has recently been described as a component manifestation of this familial syndrome, and the term familial fibrosing serositis was proposed for this distinct condition[3].

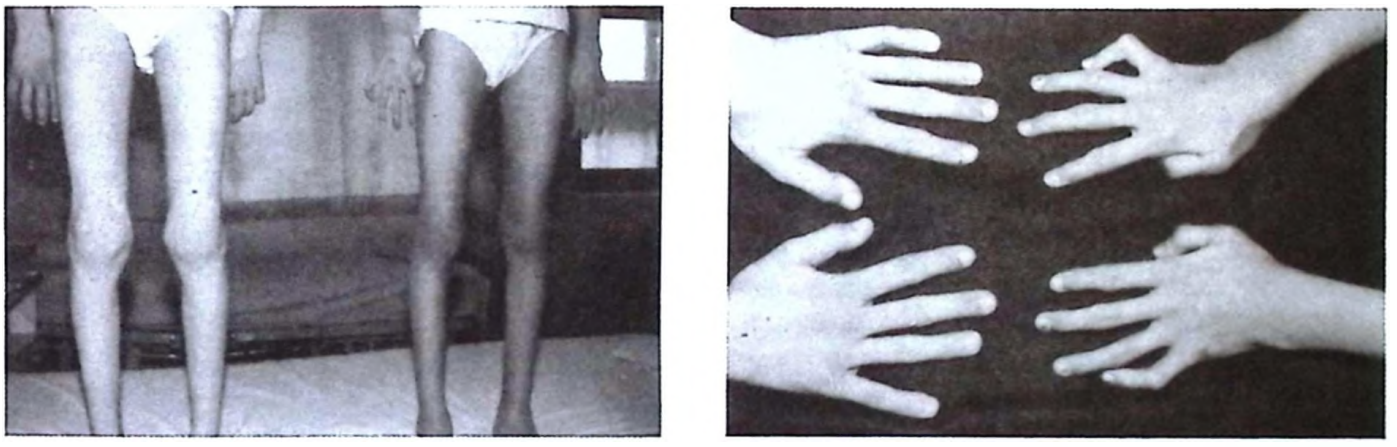
We describe four children in two families with congenital camptodactyly and polyarthropathy which were misdiagnosed and treated as juvenile rheumatoid arthritis (JRA) for some time. The siblings in the second family also had pleuritis as a component of the syndrome.

Case Reports

Family 1
Case 1

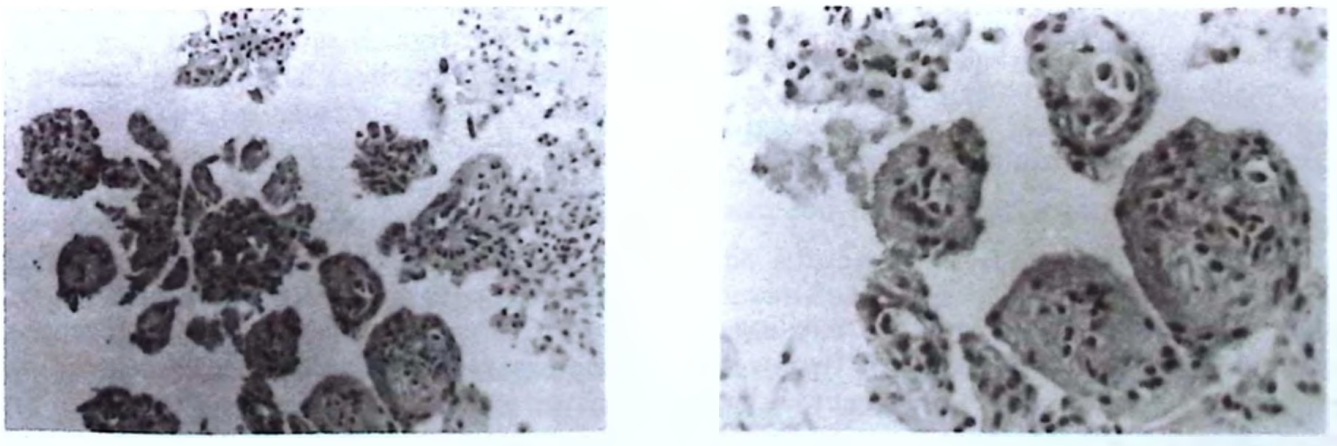
A six-year-old girl presented with the complaints of swelling in both knees for two years. Her past history was marked by congenital flexion contractures in both thumbs, difficulty for two years in squatting and an operation performed due to a bent thumb. Her parents were first-degree relatives; however, there was no history of a similarly affected relative other than her brother. Physical examination revealed bilateral swelling in her wrists, knees, ankles, and proximal and distal interphalangeal joints (PIP and DIP), bilateral hallux valgus deformity, and bilateral flexion contractures in her fingers, most prominent in the first and fifth fingers. No erythema, tendemess or warmth was present over the involved joints. Ophthalmologic examination was normal.

Laboratory analyses were characterized by normal complete blood count and erythrocyte sedimentation rate (ESR) and negative C-reactive protein (CRP), antinuclear antibody (ANA) and rheumatoid factor (RF) tests. Joint X-rays demonstrated only soft tissue swelling. She was treated with indomethacin as polyarticular JRA at that point. However, this therapy was stopped after six months by the parents due to its ineffectiveness. When she presented the second time approximately three years later, in addition to her previous complaints, growth failure and swelling and flexion contractures in both elbows and knees were determined (Fig. 1a). Laboratory analyses were normal again. At that time, she was treated with deflazacort (0.5 mg/kg/day) and methotrexate (10 mg/m^2/week) for one year with no benefit. After that, she was followed by another physician team and congenital familial hypertrophic synovitis (FHS) was suspected on the basis of history and clinical examination. Thus, a biopsy was undertaken to obtain synovial tissue and synovial fluid from her right knee. Synovial fluid analysis revealed reactive synovial cells and multinucleated giant cells with no inflammatory cells. In histopathological examination, synovial tissue was fragmented and there were papillary buds of synovial cells over fibrocollagenous stroma (Figs. 2a and 2b). These findings were compatible with congenital FHS variant of familial arthropathies[3]. The medications were stopped, and physiotherapy was instituted.



(a) (b)

Fig. 1a. Swelling in both knees. b) swelling and flexion contractures in the fingers of both siblings (female on the right).



(a) (b)

Fig. 2a. Hyperplastic synovial cells with papillary appearance (H and E x 40), and b) synovial cells, minimal mononuclear infiltrate and lack of vascular proliferation (H & E x 100) in the synovial biopsy specimen of Case 1.

Case 2

An eight-year-old male sibling of the previous case presented with the complaint of swelling in both knees and wrists with no pain, erythema or warmth. Past history was marked by an operation involving both knees performed due to swelling. On physical examination, swelling in his shoulders, elbows, wrists and knees and limitation in the range of motion of his elbows were determined. In addition, there was mild flexion contractures of PIP joints in his fifth fingers bilaterally. There was no tenderness, erythema or warmth over his joints. Laboratory analyses demonstrated normal complete blood count and ESR and negative CRP, ANA and RF tests. Joint X-rays were normal other than soft tissue swelling. He was also diagnosed as polyarticular JRA and given indomethacin like with his sister. This treatment was continued for six months with no benefit. Three years later, he presented with growth failure, bilateral flexion contractures in his knees and elbows, and swelling and limitation in the range of motion in his ankles, in addition to the previous findings (Fig. 1b). Laboratory analyses were normal again. At that point, he was treated with deflazacort and methotrexate for one year, again like his sister. After that, he was followed by another physician team and the diagnosis of congenital FHS was made on the basis of history and clinical examination. Synovial biopsy from his right knee was performed which revealed papillary buds of synovial cells and areas of hyalinization with minimal inflammatory cell infiltration and vascular proliferation (Fig. 3). Synovial fluid analysis revealed only reactive synovial cells and multinuclear giant cells. His medications were stopped, and physiotherapy was instituted as with his sister.

Cross-examination of the biopsy materials of the siblings obtained in another hospital six years ago revealed similar histopathological characteristics with minimal inflammation.

Family 2

Case 3

A four-year-old boy presented with swelling of both knees and wrists for the last two years. He had been given salicylate treatment with no benefit. The parents were second-degree cousins. On examination, his height and weight were in 25th and 75th percentiles, respectively. Examination of joints revealed swelling and

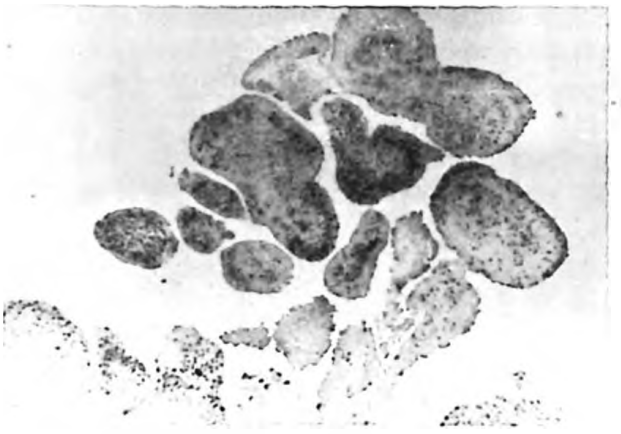
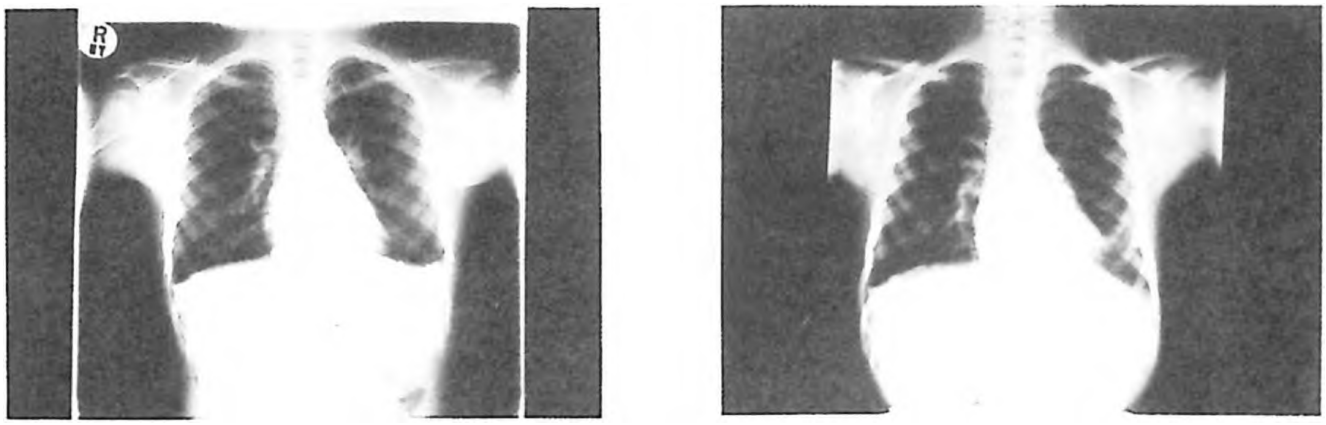


Fig. 3. Papillary buds of synovial tissue in the synovial biopsy specimen of Case 2 (H and E x 40).

limitation of motion in both knees with fluctuation on the left. PIP joints had fusiform swelling and contractures. He also had flexion contractures at elbows, synovial cysts at wrists and ankles, and bilateral hallux valgus deformity. The rest of the physical examination including ophthalmologic examination was normal. Complete blood count and ESR were normal, and CRP, ANA and RF were negative. Joint X-rays revealed widened joint spaces, osteoporosis and soft tissue swelling. Magnetic resonance (MR) evaluation of the cervical vertebrae and ophthalmologic examination were normal. He was diagnosed as JRA and given naproxen with no improvement in his complaints. Methotrexate was instituted at fourth year of follow-up due to worsening of complaints and physical signs. However, no improvement in the clinical course was noted. MR evaluation of the knees demonstrated intraarticular collection of viscous fluid and diffuse synovial proliferation with normal menisci. Vertebral X-ray revealed osteopenia, and fissuritis of the left lung was noticed in addition. Chest X-ray showed blunting of the costophrenic sinuses bilaterally (Fig. 4a). Ultrasound examination revealed only pleural thickening without effusion. White blood cell count and ESR were normal. PPD caused an induration with a diameter of 10 mm (he had two BCG scars). He had no respiratory symptom, but was given a macrolide antibiotic for two weeks. Repeat chest x-ray after one month was similar to the previous one. Echocardiography was normal. Synovial biopsy showed profuse fibroadipose tissue without inflammatory cell infiltration (Fig. 5)



(a) (b)

Figs. 4a and b. Chest x-rays of the siblings in the second family demonstrating pleuritis manifested by blunted costophrenic sinuses bilaterally.

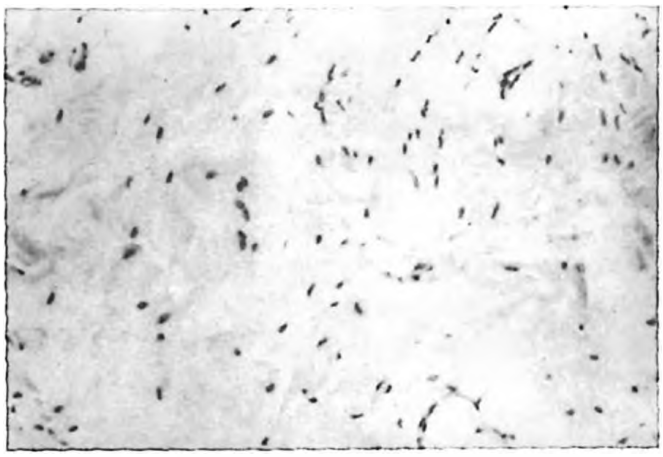


Fig. 5. Prominent fibrous tissue in the synovial biopsy specimen of Case 3 (H&E x 100).

Case 4

The younger brother of the propositus was three years old at presentation. He had had swelling without any other complaint in both knees for one year. Physical examination was characterized by normal anthropometric features (height and weight at 50th percentiles), swelling and palpable effusion in both knee joints, and swelling and contractures in PIP joints. Ophthalmologic examination was normal. Laboratory analyses including complete blood count, differential white blood cell count, ESR, CRP, ANA and RF were normal or negative. X-rays of the knees revealed minimal joint effusion along with normal bony structures. He was diagnosed as JRA, and given nonsteroidal antiinflammatory drugs with no improvement in his complaints. MRI of the knees performed one year later demonstrated increased joint fluid and synovial proliferation. Chest X-ray, obtained after demonstration of pleuritis in his brother, revealed that his costophrenic sinuses were also blunted (Fig. 4b). Ultrasound examination showed pleural thickening and no fluid. Echocardiography was normal. PPD was negative, and ESR was within normal ranges.

Discussion

The major differential diagnosis of arthritis in childhood includes JRA and its clinical subgroups. Although our patients met some of the criteria of the American College of Rheumatology necessary for the diagnosis of JRA[5], none of them had tenderness, pain on motion or increased heat on the involved joints. In addition, none of them had any sign of systemic inflammation. Furthermore, MR evaluation of the knee joints of the siblings in the second family did not show the features described in patients with JRA other than increased joint fluid[6]. Finally, none of the cases showed any improvement of disease symptoms and signs despite long-term treatment with adequate doses of various drugs used in the treatment of JRA.

The siblings in the second family also had serositis with polyarthritis which are also seen in familial Mediterranean fever (FMF) and systemic lupus erythematosus (SLE)[7,8]. However, absence of recurrent febrile episodes and signs of serosal inflammation, presence of many joint deformities starting from early infancy, and persistence of pleural reaction for the last six months in our cases excluded FMF

as a possible diagnosis. Absence of systemic inflammatory signs and ANA, presence of joint deformities, and familial nature of the disease also ruled out SLE in these cases.

The first case in the second family had a PPD reaction of 10 mm in addition to chest X-ray findings. However, the size of this reaction was within the normal limits described in children with two BCG scars[9]. In addition, absence of systemic inflammatory findings and familial nature of the disease were not compatible with tuberculosis in this patient.

The main features of our patients were camptodactyly associated with polyarthropathy presenting at young age, absence of local and systemic signs of inflammation, and the familial nature of these complaints (Table I). Thus, our patients fulfilled the criteria to be categorized as "familial arthropathy and camptodactyly" that has four subgroups: 1) Congenital FHS which is characterized by nonimflammatory arthropathy, congenital flexion contractures of the fingers, and synovial hyperplasia with a large number of multinucleated giant cells. 2) Familial arthritis and camptodactyly: Here the patients have inflammatory changes in the synovial biopsy specimens, later onset of camptodactyly, iridocyclitis, elevated ESR, and erosive changes. 3) Blau syndrome which is a familial granulomatous arthritis, uveitis, rash and camptodactyly. 4) CAP syndrome in which the patients have additional findings of constrictive pericarditis with effusion and prominent fibrosis with mild inflammatory cell infiltration of the synovium and the pericardium[3].

The first two cases described here had the clinical and histopathological features of the first subgroup, and they were categorized as congenital FHS. On the other hand, the siblings in the second family had additional findings of bilateral pleural thickening and, for Case 3, prominent fibrosis in the synovial biopsy specimen. Although pericarditis has been described relatively frequently and accepted as a phenotypic variant of this syndrome[2,3,10,11], pleuritis was reported first in 1995[3]. However, the patients described in the latter paper also had pericardial effusion, and prominent fibrosis with minimal inflammation was reported to be present in the synovium/pericardium/pleura. The authors proposed the term "familial fibrosing serositis" for this entity. Echocardiography of our patients were normal. In addition, we did not perform pleural biopsy. However,

Table I. Clinical and Laboratory Features of the Cases

	Family 1		Family 2	
Characteristics	Case 1	Case 2	Case 3	Case 4
Camptodactyly	+	+	+	+
Arthropathy-large joints[1]	+	+	+	+
Coxa vara	–	–	–	
Sex	F	M	M	M
Age at onset of camptodactyly (year)	Birth	Birth	Birth	Birth
Age at evaluation (year)	6	8	4	3
Response to therapy[2]	–	–	–	–
Signs of systemic inflammation[3]	–	–	–	–
Signs of local inflammation[4]	–	–	–	–
Uveitis	–	–	–	–
Synovial biopsy	Synovial hyperplasia with giant cells	Synovial hyperplasia with giant cells	Prominent fibrosis	Not performed
Pericarditis	–	–	–	–
Pleuritis	–	–	+	+

[1] Bilateral wrists, elbows, ankles and knees.
[2] Salicylates, nonsteroidal antiinflammatory drugs, steroids and methotrexate.
[3] Fever, rash, malaise, increased erythrocyte sedimentation rate.
[4] Heat, tenderness or pain on motion.

presence of prominent fibrosis in the absence of inflammation in the synovium along with pleural reaction not responding to antibiotic and nonsteroidal antiinflammatory therapy and the familial nature of the disorder suggest that these two siblings are more like the patients described by Verma et al[3].

Camptodactyly with arthropathy has been proposed to result from a regulatory dysfunction in the proliferation of synovial and serosal cells[2]. Autosomal recessive inheritance was suggested on the basis of parental consanguinity in many affected families[4], and the genetic locus has been localized to chromosome 1q25-31[2]. Our patients were also products of consanguineous parents, and no other affected family member was reported.

In summary, the two families described in this report represent two different phenotypic variants of congenital camptodactyly associated with arthropathy. While the siblings in the first family could easily be subclassified as congenital FHS, those in the second family probably represent a variant of familial fibrosing serositis. Furthermore, the siblings in the second family are the first cases, to our knowledge, to have pleural involvement without pericarditis. Whatever the subtype, these cases demonstrate that familial arthropathies should be included in the differential diagnosis of childhood arthritides, especially if more than one family member is affected. Otherwise, these children might be unnecessarily treated with drugs having many side effects for long periods.

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