

CASE REPORT

Atypical debut manifestations in juvenile idiopathic arthritis

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Abstract

Considering that destructive articular lesions may occur in the first stages of the illness, it is difficult but necessary to establish a diagnosis of Juvenile Idiopathic Arthritis (JIA) in due time. The authors present the case of a 9-year-old girl admitted to the Pediatrics Clinic of the “Filantropia” Municipal Hospital in Craiova, Romania, on November 26, 2002, for bilateral pain in the tarsometatarsal and carpometatarsal joints that had begun approximately four weeks before. After the clinical examination and paraclinical investigations, a diagnosis of unspecified arthritis is established and the adequate treatment is begun. Two months later, the patient returns to the clinic with bilateral knee pain and swelling. The results of laboratory tests indicate the persistence of anemia and of the inflammatory syndrome. The diagnosis of JIA is established. The evolution of the patient is unfavorable, both from a clinical point of view (a large number of articulations affected, a persistent rash, hepatomegaly) and a paraclinical one (increased acute phase reactants and radiological changes occurring two years after the onset of the illness).

Keywords: juvenile idiopathic arthritis, synovitis, early diagnosis, sequelae.

Introduction

Juvenile Idiopathic Arthritis (JIA) consists of a group of inflammatory processes that are characterized by the onset of arthritis before the age of 16 years, and present symptoms that last for at least six weeks, with the exclusion of other known conditions [1]. JIA is the most common rheumatic disease in children with no apparent cause [2]. However, sometimes it is difficult to establish a diagnosis without specific clinical and laboratory findings for JIA [3].

The disease develops continuously or has acute phases and remissions for several years, thus having a considerable effect on the children’s quality of life [4]. Children affected by this disease often have school attendance and socialization problems, and as adults, they are candidates for inability to work, with all the subsequent family, personal and social consequences [4, 5]. In the recent years, it has been discovered that irreversible lesions of the joints may occur early, in the first months after the onset of the disease, especially in the polyarticular and systemic forms [6]. Consequently, an idea crystallized: to establish an early diagnosis (in the first six months after the symptomatic onset of the disease), in order to initiate an aggressive and dynamic treatment and, subsequently, to prevent complications [6, 7]. An optimal pharmacologic therapy implies a correct identification of the illness subtypes that differ in etiology, prognosis and response to treatment [8]. Synovial biopsy is an invasive diagnostic procedure used in JIA when there are doubts regarding the treatment [9]. The purpose of this material is to present a case in

which synovial biopsy led to a definitive diagnosis of JIA.

Patient and Methods

The authors present the case of a 9-year-old girl admitted to the Pediatrics clinic of the “Filantropia” Municipal Hospital of Craiova, Romania, on November 26, 2002. The reason for her admission was bilateral pain in the tarsometatarsal and carpometatarsal joints that had begun approximately four weeks earlier. The patient’s family medical history shows that the maternal grandmother was diagnosed with rheumatoid polyarthritis, while the personal pathological history reveals recurrent infections of the upper respiratory tract. We carried out the usual paraclinical investigations, an eye examination in order to detect the previous uveitis, X-rays of the joints and the histopathological examination of the synovium. The articular puncture-biopsy of the left knee, under local anesthesia (Xyline) was carried out in the clinic with the consents of the patient’s parents. The histopathological examination was carried out on synovial biopsy fragments (less than 1 cm large), which were analyzed with the classical methods of paraffin inclusion and Hematoxylin–Eosin stains (Bio-Optica kit). Images were obtained using the Nikon Eclipse E600 microscope equipped with Lucia 5 software.

Results

On admission, the clinical examination revealed a patient presenting fever, pain in the tarsometatarsal and

carpometatarsal joints, with no local inflammatory changes, no functional disability, normal walk, granular pharynx. In the first 36 hours following the admission, the patient presents ephemeral rash lasting approximately 2–3 hours.

Laboratory tests reveal hypochromic anemia and increased acute phase reactants, increased values of ASLO (600 IU), absent rheumatoid factor (RF) (Table 1).

Table 1 – Evolution of the biological laboratory tests results

Date	Hb [mg/dL]	PLT	L	C-reactive protein [mg/dL]	ESR [mm]	Fb [mg%]	γ-Globulin [%]	RF	ANA	ALT [IU]
11.26.2002	10.5	480 000/mm ³	11 000/mm ³	5.4	75	450	17	negative	absent	32
01.18.2003	10.2	520 000/mm ³	12 300/mm ³	5.8	88	480	24	negative	absent	74
05.21.2004	997	650 000/mm ³	14 200/mm ³	6.2	94	510	26	negative	absent	82

Hb – Hemoglobin; PLT – Platelets count; L – Leukocytes count; ESR – Erythrocyte sedimentation rate; Fb – Fibrinogen; RF – Rheumatoid factor; ANA – Antinuclear antibodies; ALT – Alanine aminotransferase.

The left foot X-ray (Figure 1) and the eye examination were normal. Because of the clinical and paraclinical tests, a diagnosis of unspecified arthritis is established, and a treatment with non-steroidal anti-inflammatory drugs is prescribed, with favorable evolution.



Figure 1 – Left foot X-rays.

The patient returns to the clinic on January 1, 2003, presenting bilateral knee pain and swelling, with no change in the other joints. Laboratory tests results indicate the persistence of anemia and of the inflammatory syndrome (Table 1).

Histopathological appearance of synovial biopsy in serial sections indicated the proliferation of synoviocytes and a heterogeneous layered, with the presence of 2–6 rows of cells and tend to formation of synovium buds (Figure 2, A–C). The proliferation process of synoviocytes occurred in surface and also in the depth of lining layer, with hypertrophy and hyperplasia aspects. Also, under synovial lining layers we found mononuclear inflammatory infiltrate consisting mainly of lymphocytes, plasma cells and rare macrophages, with perivascular distribution, sometimes with lymphocyte clusters and the mimicry of lymphoid follicles or with diffuse distribution (Figure 2, A, B and D). The vessels located under the lining layers, in contact with inflammatory elements, presented small caliber, being slightly irregular, tortuous and suggesting a neoformation morphology (Figure 2D). Also, were present, with focal distribution areas, with mild fibroblast proliferation, with hypertrophied fibroblasts, which were increased in number and arranged in dense cellular groups (Figure 2, D and E). Although the examination also searched for the presence of fibrinoid necrosis, it was not identified in the case under analysis.

Corroborating the clinical data, the laboratory data and the result of the histopathological test, a diagnosis of “Pauciarticular Juvenile Idiopathic Arthritis” is established

and a treatment with non-steroidal and steroidal anti-inflammatory drugs is begun. The evolution is favorable, with a remission of the symptoms. The patient does not to return for follow-ups.

More than a year after the first admission (May 21, 2004), the patient goes to the “Grigore Alexandrescu” Children’s Hospital of Bucharest, Romania, for bilateral swelling and pain in the wrist and interphalangeal joints. The admission state revealed an 11-year-old girl presenting fever, bilateral swelling and pain in the wrist and interphalangeal (IP) joints, bilateral lateral cervical micropolyadenopathy, transient macular erythematous rash on her face, body and limbs, lasting for approximately one hour, usually during the evening, and accompanying the fever, as well as hepatomegaly. Laboratory tests results reveal anemia, thrombocytosis, absent RF and increased acute phase reactants (Table 1). A treatment with non-steroidal and steroidal anti-inflammatory drugs is prescribed. Diagnosis on release: “Systemic Juvenile Idiopathic Arthritis”.

Between May 2005 and December 2006, the patient has numerous admissions (21) in pediatrics clinics in Bucharest and Craiova. Considering the unfavorable evolution, both from a clinical point of view – pain, swelling and functional disability of a large number of joints, distortion of the interphalangeal joints in the shape of a suppository, and progressive mobility difficulties, the persistence of the rash on her chest and limbs, hepatomegaly, as well as the paraclinical assessment with increased acute phase reactants, and the radiological joint modifications that occurred two years after the onset, a decision is taken to introduce remissive medication. Because of prolonged treatments with corticoids, the patient develops an iatrogenic Cushing’s syndrome, characterized by overweight, typical moon facies, cortisone-impregnated abdomen, and striae. Starting with June 2006, the patient presents cortisone-induced psychotic manifestations; therefore, the administration of the cortisone therapy is interrupted.

In September 2006, the patient interrupts the recommended treatment on her own and does not return for the clinical and biologic follow-up.

In May 2008, she is admitted to the Pediatrics Clinic of the “Filantropia” Municipal Hospital of Craiova, for joint complaints: 32 affected joints, three with semi-ankylosis, one with ankylosis. Considering the unfavorable clinical and biological evolution, procedures are started for the introduction of biological medication.

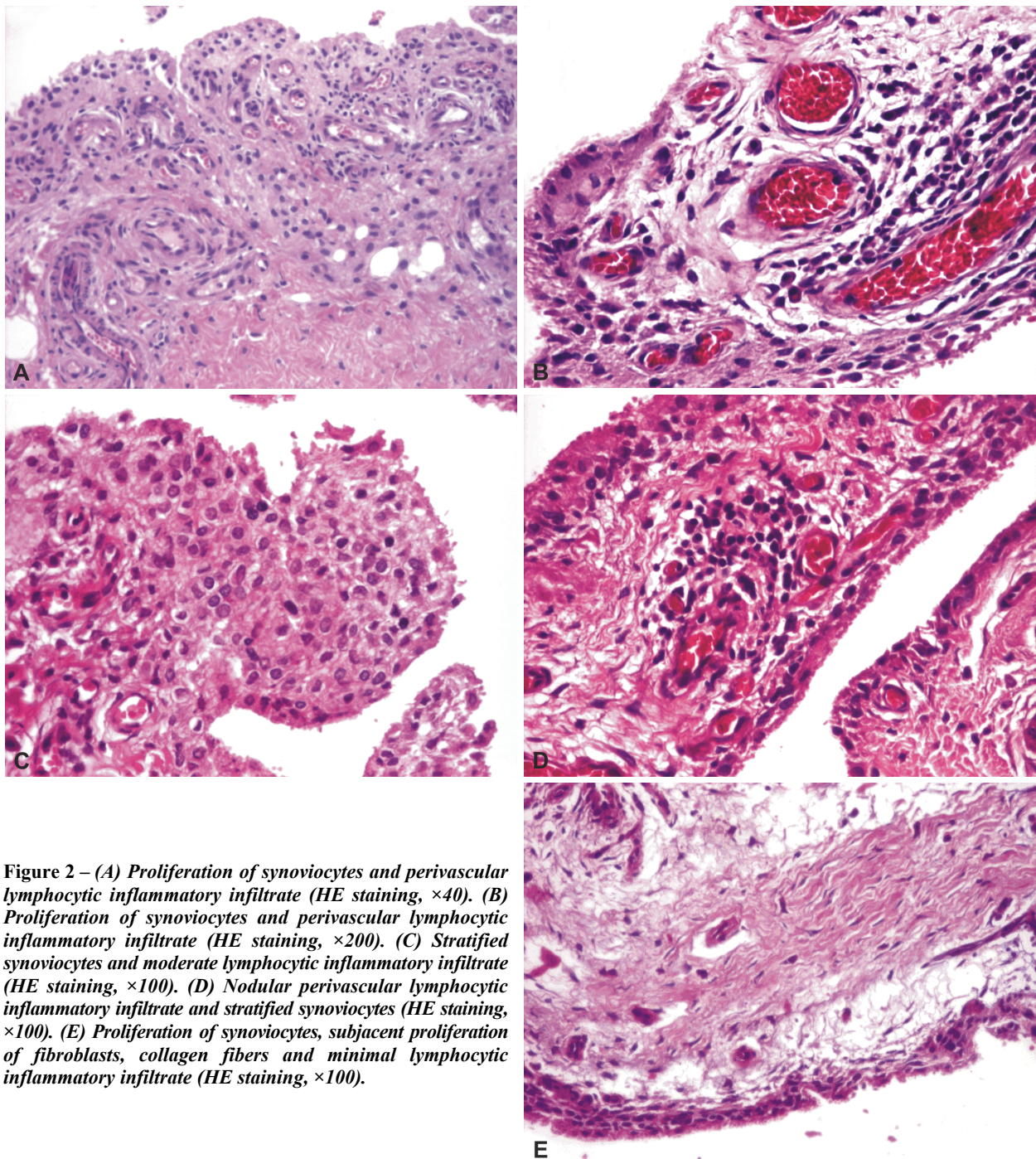


Figure 2 – (A) Proliferation of synoviocytes and perivascular lymphocytic inflammatory infiltrate (HE staining, $\times 40$). (B) Proliferation of synoviocytes and perivascular lymphocytic inflammatory infiltrate (HE staining, $\times 200$). (C) Stratified synoviocytes and moderate lymphocytic inflammatory infiltrate (HE staining, $\times 100$). (D) Nodular perivascular lymphocytic inflammatory infiltrate and stratified synoviocytes (HE staining, $\times 100$). (E) Proliferation of synoviocytes, subjacent proliferation of fibroblasts, collagen fibers and minimal lymphocytic inflammatory infiltrate (HE staining, $\times 100$).

Discussion

Systemic JIA is defined as arthritis associated with or preceded by daily fever, for at least two weeks, and by the presence of at least one of the following modifications: erythematous skin eruption; generalized adenopathies; hepatomegaly or splenomegaly; serositis [10].

Systemic arthritis represents 11–20% of JIA cases, and it may occur at any age, but with maximum occurrence between the ages of 2 and 6 years. Systemic (extra-articular) manifestations are those characteristic for this particular category of JIA. Thus, it is the only illness subtype in which fever is the main symptom [11, 12]. The rash consists in salmon-pink 2–5 mm maculae, which appear mainly on the chest, the proximal extremities

and the pressure areas [13]. Lymphadenopathy is always present in JIA [14], while hepatomegaly is almost constant, moderate in size, non-painful, with a smooth surface [15]. Myalgia, splenomegaly, involvement of the serous membranes, of the heart, of the central nervous system, of the kidneys and of the lungs complete the array of systemic manifestations [16]. Synovitis may be absent in the first days or weeks following the onset of the fever, being inconstantly preceded by arthralgias and myalgias, which makes it difficult to establish a positive diagnosis. Classically, the onset of the illness includes extra-articular manifestations, and within six months, arthritis appears and becomes the main manifestation.

The case of patient M.O.A. is a slightly atypical one for systemic JIA. The onset is late, at the age of 9 years,

and its predominant manifestation is the early, symmetrical involvement of the small joints of the hand. The JIA diagnosis was not established on the first admission.

Similar to the data from the literature, the patient presented, from a biological point of view, a moderate anemia, leukocytosis with neutrophilia, thrombocytosis during the development peaks of the disease. Signs of inflammation were also present: increase in the erythrocyte sedimentation rate (ESR), as well as increased values of fibrinogen, C-reactive protein, polyclonal hypergammaglobulinemia. The rheumatoid factor (RF) was negative, the antinuclear antibodies (ANA) were absent [14] and there were modifications of the liver tests (transaminases) [15].

The histopathological examination of the fragment obtained through articular puncture-biopsy, revealed the presence of synovitis, with the proliferation and stratification of synoviocytes and the presence of predominantly lymphocytic inflammatory infiltrate, suggestive aspects for diagnosis. The disposal predominantly perivascular of lymphocytes and neoangiogenesis aspects suggests the importance of inflammatory elements in tissue modeling and their persistence appears to be the result of imbalance between inducers and inhibitors of angiogenesis [17]. These aspects are suggested by other studies that consider juvenile arthritis as a complex process with phenomena of cell proliferation, angiogenesis, inflammation and tissue modeling [18, 19].

In this case, histopathological aspects corroborated with the clinical and paraclinical tests, determined an early diagnosis for JIA. Because the extra-articular manifestations (fever, rash) appear months after the actual onset of the disease, the first diagnosis is pauciarticular JIA, and only later is the systemic form diagnosed.

Generally, the JIA prognosis depends on the number of joints involved and on the severity of the arthritis. Thus, 50% of children show an evolution in peaks similar to the polyarticular form, with early destructive radiological lesions [20]. The remaining 50% do not have fever spikes, rash or biological inflammatory manifestations. Out of the latter group, 30% do not even present articular manifestations [20]. The major morbidity is the result of severe chronic arthropathy, which, in approximately 25% of the cases, can also persist in the adults [13]. Indicators of bad prognosis include young age at the moment of diagnosis, a disease that has been active for more than five years, persistence of systemic manifestations for more than six months, continuous corticoid treatment, thrombocytosis, elevated ESR levels, involvement of a large number of joints (especially the small joints of the hand) [21].

The evolution of our patient included polyarticular, deforming involvement, resistant to the medication used. The acute phase reactants remained increased throughout the entire monitored period, while radiological modifications appeared early, just two years after the onset of the disease. Because of the prolonged corticoid treatments, the patient develops an iatrogenic Cushing's syndrome that determines a decrease in compliance with treatment, and the interruption of the treatment for a long period of time (two years).

Conclusions

A diagnosis of JIA is often difficult to establish because of the multiple possibilities of onset and because of a lack of specific laboratory tests. The atypical onset in the case presented, raised diagnostic problems. Synovial puncture-biopsy allowed for a quick establishment of the diagnosis, but the lack of the patient's compliance with treatment has caused the appearance of sequellar lesions characteristic for the unfavorable evolution.

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