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Juvenile spondyloarthritis and chronic recurrent multifocal osteomyelitis overlap syndrome in a 16-year-old adolescent. A case report and literature review

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Abstract

The authors present a very rare case of juvenile spondyloarthritis and chronic recurrent multifocal osteomyelitis overlap syndrome in a 16-year-old girl and discuss diagnostic difficulties associated with this case. Juvenile spondyloarthropathies are a type of rheumatic diseases characterized by non-symmetrical peripheral arthritis and enthesitis as well as by spondylitis. Chronic recurrent multifocal osteomyelitis is a rare, possibly autoimmune disease found primarily in children and adolescents. The disease is characterized by bone marrow inflammation and the presence of lytic and sclerotic lesions. Diagnostic imaging plays a key role in the identification of both diseases. The primary modality is X-ray; however, currently, magnetic resonance imaging and ultrasound are increasingly important. A correct early diagnosis allows one to start appropriate treatment to reduce the consequences of these diseases.

Case report

A 16-year-old patient with juvenile spondyloarthritis and chronic recurrent multifocal osteomyelitis (CRMO) overlap syndrome was admitted to our department for follow-up examinations. She had been hospitalized at the department a few times before.

The patient had a history of joint and back pain and pain in the left buttock and the left thigh when walking since 2011. Physical examination revealed abnormal gait with sparing of the left leg and signs of peripheral arthritis. On ultrasound, peripheral arthritis, including in the left ankle (Fig. 1), left

knee, the first metatarsophalangeal joint of the left foot and the right sternoclavicular joint was confirmed. On X-ray of the spine, rotoscoliosis of the thoracic and lumbar spine was found. Laboratory tests revealed moderately elevated inflammatory markers and the presence of the HLA-B27 antigen.

In December 2012, whole-body MRI revealed bone marrow edema in C7, Th5 and Th6 vertebral bodies, Th6 endplate damage, reduction of Th6 body height and bone marrow edema in the sternoclavicular joint, in the left sacroiliac joint, in the diaphyses of both ilia, in the right navicular bone (Fig. 2) with associated edema of soft tissues and of the left lateral malleolus.

On chest X-ray, the following abnormalities were found: pleuro-diaphragmatic adhesions in the left dome of the diaphragm, significant right thoracic scoliosis, irregular contours and subchondral sclerosis of the edge of the sternal end of the right clavicle (Fig. 3). On X-ray of sacroiliac joints bilateral grade 2 inflammation was found.

At the time, the diagnosis of enthesitis-related juvenile idiopathic arthritis (ERA-JIA) was made, i.e. a form of juvenile idiopathic arthritis (JIA) which also belongs to the category of juvenile spondyloarthropathies (diseases in which peripheral arthritis is combined with spondylitis).

Non-steroid anti-inflammatory drug and sulfasalazine therapy was administered (November–December 2012) and pain was reduced. However, due to the patient's parents' failure to report to the department with their child, consecutive stages of treatment were discontinued. In addition, due to a positive result of a tuberculin test, the girl was hospitalized three times (in 2012, 2013 and 2016) at a respiratory disease and tuberculosis treatment center. Latent tuberculosis was diagnosed.

Further in the disease process (2013–2015) the patient had periods of active peripheral arthritis, sacroiliitis and spondylitis.

Further MRI examinations (2015, 2016) revealed a significant progression of the lesions: vertebral body fractures, bone marrow edema in multiple additional locations: in the right iliac bone body, the right iliac acetabulum, the right pubic bone, the left femoral neck and greater trochanter, the head of the right fibula and the first metatarsal bone of the right foot, massive bone marrow edema in both sacroiliac joints (Fig. 4) and soft-tissue edema at the level of the affected joints.

On MRI, chronic recurrent multifocal osteomyelitis (CRMO) associated with JIA was diagnosed, i.e. an overlap syndrome was present.

On ultrasound of the right foot the following abnormalities were noted: a thickened, intensively vascularized synovial membrane in the first metatarsophalangeal joint, a large erosion filled with vascularized synovial membrane on the medial surface of the first metatarsal bone head (Fig. 5), a small effusion under the fifth metatarsal bone head and a thickened synovial membrane of the bursa (submetatarsal bursitis). On left knee ultrasound effusion in the joint cavity was revealed.

Combined Metex + adalimumab therapy was applied and clinical symptoms resolved and inflammation markers returned to normal.

Since April 2017 the parents did not report with the child to the department again and they discontinued the treatment.

In September 2017 the girl was readmitted to the department due to pain recurrence, particularly in the

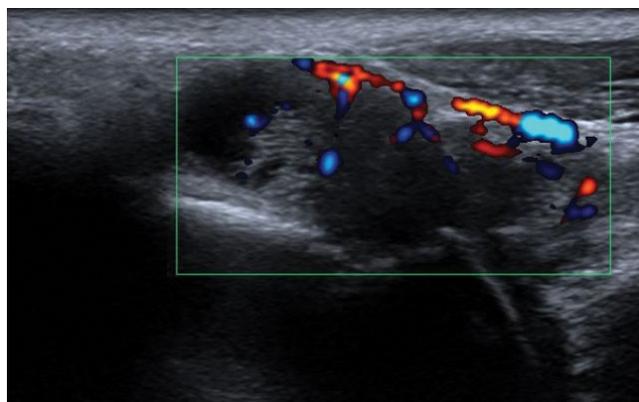


Fig. 1. Developing erosion filled with a hypertrophic synovial membrane with increased vascularization and effusion on ultrasound

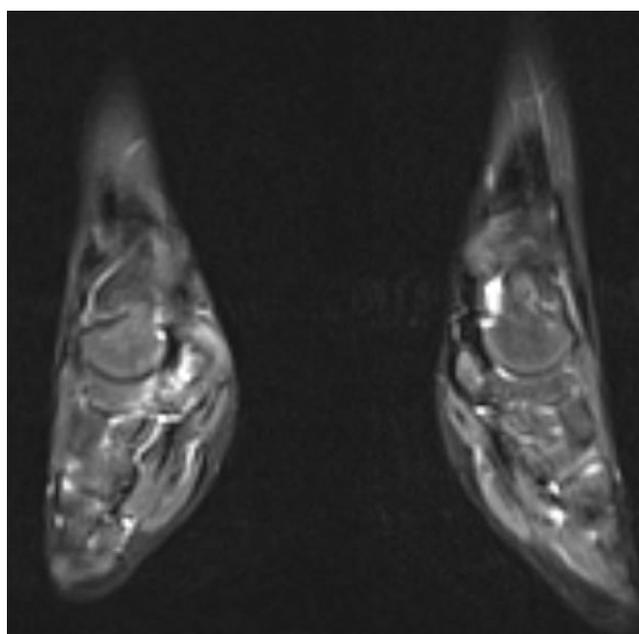


Fig. 2. Bone marrow edema in the right navicular bone on whole-body MRI, the high signal intensity on the left is consistent with visualized vessels

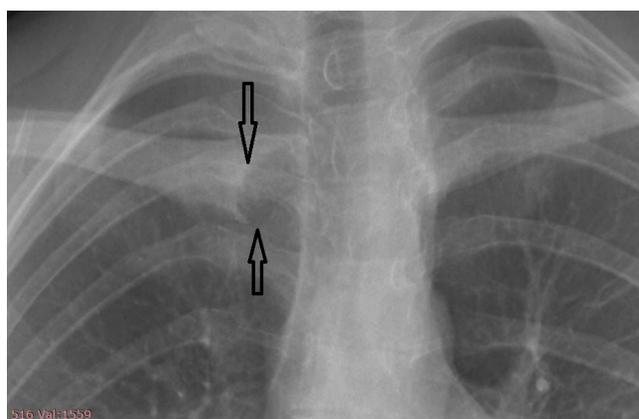


Fig. 3. Areas of bone loss, irregular contours surrounded by a sclerotic margin in the lower central part of the sternal end of the right clavicle

left leg. Diagnostic imaging revealed further progression of the lesions, including multilevel vertebral body fractures and syndesmophytes in the lumbar spine on X-ray (Fig. 6).

Discussion

Juvenile spondyloarthropathies and CRMO are rare childhood disorders and their identification is often very difficult. This paper presents an even rarer case of an overlap syndrome involving the coexistence of juvenile spondyloarthropathy and CRMO. A dramatic course of the disease is described which is primarily due to the non-compliance of the sick child's parents.

According to the International League of Associations for Rheumatology (ILAR), juvenile spondyloarthropathies (JSpA) belong to the subtype of JIA called enthesitis-related arthritis (ERA)⁽¹⁻³⁾. However, the European Spondyloarthropathy Study Group (ESSG) treats JSpA as a separate group of conditions divided further into a few entities, as in adults. In our department the ILAR definition of the disease has been adopted.

ERA accounts for approximately 5–10% of all forms of JIA. The criteria for the diagnosis of this condition include the presence of arthritis and enthesitis or arthritis or enthesitis alone and the presence of at least two characteristics below:

- sacroiliac tenderness or inflammation-related sacral pain;
- the presence of the HLA-B27 antigen;
- family history of at least one first- or second degree relative with a disease associated with the presence of the HLA-B27 antigen;
- anterior uveitis; arthritis in a boy after 8 years of age.

In addition, excluding psoriasis in the patient or a first- or second degree relative and finding the presence of systemic arthritis are a prerequisite for the diagnosis.

The most common manifestations are enthesitis and clinical signs of oligo- and polyarthritis, predominantly in the joints of the legs (most commonly the knee, the hip, the ankle, the metatarsophalangeal joint and interphalangeal joint of the hallux)⁽⁴⁻⁶⁾. In approximately 30–40% of children the disease progresses and the spinal and sacroiliac joints become involved, which, unlike in adults, are usually not affected by inflammation at the initial stage of the disease (spondylitis, sacroiliitis)⁽⁶⁻⁸⁾. The case presented in our study shows the involvement of multiple joints and a significant disease progression.

The primary method of ERA (JSpA) diagnosis is radiographs^(7,9,10) of the peripheral and spinal joints. The limitation of radiographs is their ability to detect only advanced inflammatory and destructive lesions. Early stages of the disease are diagnosed using MRI and ultrasound.



Fig. 4. Bone marrow edema in both sacroiliac joints on whole-body MRI

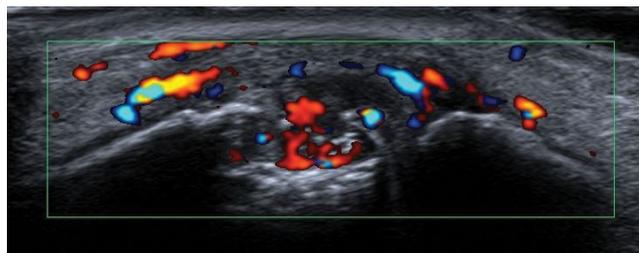


Fig. 5. Large erosion filled with vascularized synovial membrane on the medial surface of the head of the first metatarsal bone



Fig. 6. Multilevel vertebral body fractures in the cervical spine

X-ray

Sacroiliitis can be unilateral at the initial stage of the disease. The stage of the disease is assessed in the same way as in adults on the basis of the New York criteria (Tab. 1)^(8,7,11). The end stage of the disease is the fusion of the iliac and sacral bones (ankylosis), which is, however, extremely rarely observed in children.

In addition, radiographs show enthesopathic lesions (ossifications and erosions in the osseous part of the enthesis) and lesions in peripheral joints (manifesting as soft tissue shadow widening, osteoporosis, cysts and, less commonly, erosions). In children, unlike in adults, vertebral rigidity (bamboo spine sign) does not occur. Square vertebral bodies and syndesmophytes, which were found in our patient, are evident only after many years of disease⁽⁸⁾. There is characteristic, although very rarely diagnosed, vertebral body destruction with osseous reconstruction, usually in the cervical spine. We report it in the present case.

Ultrasound

Peripheral joints, synovial bursae, tendons, tendon sheaths and entheses are subject to evaluation^(10,12). At the initial stage of the disease, the thickening of the synovial membrane and, subsequently, its increased vascularization and effusion are observed. Further lesions include geodes and erosions of the articular surfaces of bones as well as damage to the hyaline cartilage, often beginning with an increased echogenicity, which is probably a sign of biochemical disturbances in the cartilage. The appropriate response to treatment is the disappearance of increased vascularization in the synovial membrane and the lack of disease progression and signs of destruction.

Inflammatory lesions in the entheses manifest as thickening and decreased echogenicity, disturbed filamentous echostructure, often increased vascularization and lesions in the osseous part of the enthesis (irregularities, erosions, geodes)⁽¹³⁾.

Magnetic resonance imaging

Apart from lesions evident on ultrasound, MRI also makes it possible to assess^(10,14) edema in the bone marrow (the earliest sign of inflammation), in the spine and in the spinal

cord, articular cartilage in its entirety as well as the level of activity of a synovial membrane affected with inflammation and subchondral bone tissue following the administration of a contrast agent. Magnetic resonance imaging is considered to be a more sensitive procedure to evaluate inflammatory and destructive lesions associated with JSpA and JIA than physical examination, ultrasound scan or X-ray^(15,2).

CRMO

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare form of osteitis of a possible autoimmune origin, found mainly in children and young adults, primarily in females. Localized bone and joint pain, often occurring at night, joint edema and tenderness are characteristic of the disease. General symptoms of inflammation such as fever, weakness and weight loss can occur and laboratory signs such as slightly elevated ESR, CRP, leukocytosis and the TNF- α cytokine can be present. The course of the disease is usually recurrent with periods of exacerbations and remissions, less commonly chronic⁽¹⁶⁻¹⁹⁾. The most common locations of abnormalities include the epiphyses and metaphyses of long bones (the femur, the tibia, the fibula), the clavicle, the thoracic wall, vertebral bodies, the mandible and pelvic bones. There can be single or multiple inflammatory foci, which are often distributed symmetrically. The disease starts with bone marrow inflammation which is readily visible on MRI before lytic and sclerotic lesions develop that will be evident on radiography⁽²⁰⁻²³⁾. Approximately 25% of patients develop skin lesions: pustulosis of the palms and feet, generalized pustulosis, psoriasis and acne^(24,25).

Currently, the Bristol diagnostic criteria of 2016 are applied⁽²⁶⁾:

1. the presence of typical clinical findings (bone pain \pm localized swelling, without local or systemic features of inflammation or infection);
2. typical radiological findings: X-ray (lytic and sclerotic lesions, new bone formation), MRI (bone marrow edema \pm lytic areas, periosteal reaction).

With the following conditions being met:

1. lesions in more than one bone (or a single lesion in the clavicle), moderately increased CRP (< 30 g/l);
2. if the disease is unifocal (in a location other than the clavicle) or CRP is > 30 g/l: bone biopsy showing inflammatory changes (plasma cells, osteoclasts, fibrosis, sclerosis) with no bacterial growth while not on antibiotic therapy.

Tab. 1. The New York diagnostic criteria for sacroiliitis

Grade 0	No abnormalities (normal sacroiliac joints)
Grade 1	Suspected abnormalities (blurred joint margins)
Grade 2	Minimal abnormalities (single erosions and juxta-articular sclerosis)
Grade 3	Advanced abnormalities (distinct juxta-articular sclerosis, multiple erosions with widening of the joint space, possible partial ankylosis)
Grade 4	Complete ankylosis

In our patient, the diagnosis was made using MRI based on the presence of multiple sites of bone marrow edema, lytic areas and sclerotic lesions in locations typical for both JIA and CRMO. The abnormalities found correlated with clinical symptoms: bone and muscle pain and edema. Moreover, laboratory tests revealed a moderately increased CRP level and the presence of the HLA-B27 antigen.

The case discussed in this study shows that the differential diagnosis of JSpa should not only take into account the presence of CRMO, which was indicated by Robertson *et al.*⁽²⁷⁾, among others, but also the coexistence of JSpa and CRMO. The case of the 16-year-old girl with an overlap syndrome presented in this study, which was diagnosed after a few years of delay, is not an isolated one: there are cases reported in medical literature in which both conditions were not diagnosed at the same time^(28–31). However, in the cases described in the literature CRMO was diagnosed first and then JIA was identified^(28–32), while our case is the first one in which JIA was diagnosed before CRMO.

In our patient, a more than 4-year delay in the diagnosis of the overlap syndrome was due to a non-specific clinical and radiological presentation, the need to exclude other diseases, the lack of close disease

monitoring and treatment discontinuation, which led to spinal fractures.

Summary

The diagnosis of rheumatic arthritis in children is often difficult and overlapping syndromes are particularly difficult to identify. It is essential for clinicians and radiologists to cooperate closely, however, even if they do, the diagnosis is still often delayed due to the lack of specific symptoms and the need to exclude other arthropathies one by one and perform further diagnostic procedures. Consequently, the patient does not receive optimal treatment until later in the disease, which results in progression. A lack of improvement may also discourage parents from continuing the treatment, which happened in the present case. These difficulties lead to disease progression and advanced lesions.

Conflict of interest

The authors do not report any financial or personal affiliations to persons or organizations that could negatively affect the content of or claim to have rights to this publication.

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