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Case Report

The Differential Diagnosis of Spondiloarthritis in Adolescence: the Critical Reasoning Originating by A Clinical Case

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Abstract

Background: Spondyloarthritis (SpA) are chronic inflammatory diseases characterized by axial and peripheral arthritis, enthesitis, dactylitis, uveitis, psoriasis, inflammatory bowel disease and association with HLA-B27. Teenagers present more frequently with peripheral or root arthritis than adults and differential diagnosis can be challenging. The category juvenile SpA is not universally accepted by pediatric rheumatologists and patients younger than 16 years with features of SpA are classified, according to International League of Associations for Rheumatology (ILAR) into three of the six categories of JIA: enthesitis-related arthritis, psoriatic arthritis and undifferentiated arthritis.

Case report: Here we describe the case of a 16 years old boy with right coxalgia and pubalgia who was wrongly diagnosed as affected by SpA. Lack of improvement under treatment with anti-TNF leads us to revalue the diagnosis. Hip MR and CT, as well as a skeletal scintigraphy showed findings consistent with a Osteoid Osteoma (OO) of the right hip. The lesion was successfully treated with radiofrequency ablation (RFA).

Conclusions: SpA may mimic an OO since in both conditions pain gets worse during the night, is relived by Nonsteroidal Anti-Inflammatory Drugs (NSAID), patients may have limp and imaging may show a synovitis. Other diseases that should be considered in the differential diagnosis of SpA in a teenagers are rheumatoid arthritis, subsets of JIA other than enthesitis-related arthritis and psoriatic arthritis, septic arthritis, spondylodiscitis, proximal femoral epiphysiolysis, Legg-Calvé-Perthes Disease, brucellosis, osteosarcoma, Ewing sarcoma, leukemia, primary non-Hodgkin lymphoma of the bone, hypoparathyroidism, hypophosphatemia, osteomalacia, Paget's disease and Klippel Feil syndrome.

Introduction

Spondyloarthritis (SpA) encompasses a group of chronic inflammatory diseases that share common clinical and genetic features: axial and peripheral arthritis, enthesitis, dactylitis, uveitis, psoriasis, inflammatory bowel disease and association with the HLA-B27 gene [1]. SpA includes the following conditions: Aankylosing spondylitis (AS), psoriatic arthritis (PA), arthritis/spondylitis with inflammatory bowel disease (IBD), reactive arthritis and undifferentiated SpA [2]. However in the domain of pediatric rheumatology the category juvenile SpA is not universally accepted and diagnosis of SpA is performed according to the classification of Juvenile Idiopathic Arthritis (JIA) of the International League of Associations for Rheumatology (ILAR) which includes SpA into three of the six JIA categories: enthesitis-related arthritis, psoriatic arthritis and undifferentiated arthritis [3]. JIA is a broad term used to describe all forms of arthritis of unknown origin arising before 16 years of age [3]. Multiple studies reported that SpA presenting in juvenile age is more frequently associated with peripheral arthritis, root arthritis, and rarely with axial symptoms [4,5]. We report the case of a male adolescent misdiagnosed as SpA with the aim to discuss the broad spectrum of the differential diagnoses.

Case Report

A 16 years old boy began to complain about right coxalgia and pubalgia worsening during the movements and in the night. He denied any preceding trauma or infection. Family history was negative for rheumatic or autoimmune diseases and his recent and past medical history did not report fever, oral aphtae, skin lesions or uveitis, enthesitis and dactylitis He was first visited at an Orthopedic Unit and underwent a right and left hip magnetic resonance (MR), which showed a right hip effusion, a small area of edema of the femural neck and an initial osteophytosis of the acetabular margin compatible with an acetabular femoral impingement. A spine and pelvis X-ray was normal. The laboratory findings including Complete Blood Count (CBC), CRP (C-reactive protein), ESR (erythrocyte sedimentation rate), Antinuclear Antibodies (ANA), RF (rheumatoid factor), anti-cyclic citrullinated peptide (anti-CCP) were all within the normal range. HLA-B27 was negative. The patient reported a remarkable improvement of pain in taking nonsteroidal anti-inflammatory drugs (NSAIDs), but without resolution. Due to the persistence of the painful symptoms and despite the beginning of the physical therapy, he underwent a synovectomy and received an osteoplasty for acetabular femoral impingement. Sinovial biopsy showed a chronic inflammatory infiltrate. After one year he was visited by a rheumatologist, receiving the diagnosis of "undifferentiated SpA". A treatment with salazopyrin was started at the dose of 2 grams a day. Nevertheless the pain persisted affecting the quality of life: daily activities and sleep, leading to the addition to the treatment of a biological drug (anti TNF-alfa, etanercept biosimilar). Three months after the beginning of this therapy, the boy was referred to our Rheumatology Unit for consultation. He reported no improvement of the coxalgia and the need to take NSAIDs for the pain control. On physical examination the right hip was limited and painful in every movement with a consequent lameness. Therefore we decided to perform a new right hip and sacroiliac joints MR, which showed a focal intracortical area (12 mm) at the femural head-neck passage, which was hyperintense in T1 weighted images (Figure 1). A concomitant bone edema was reported. These findings were strongly suggestive for osteoid osteoma (OO). We referred the patient to the Orthopedic Unit where he underwent a skeletal scintigraphy with technetium 99m-HDP (Figure 2) and a right hip Computed Tomography (CT), which showed "the nidus" as a low-density area of 11x7 mm within a halo of bone sclerosis (Figure 3). The diagnosis of OO was confirmed. Therefore, we interrupted the medical treatment with etanercept biosimilar and salazopyrin and the lesion was successfully treated trough radiofrequency ablation (RFA) under CT guidance (Figure 4). One month after the procedure, the boy was fully weight bearing, without the need of support and without experiencing any pain.

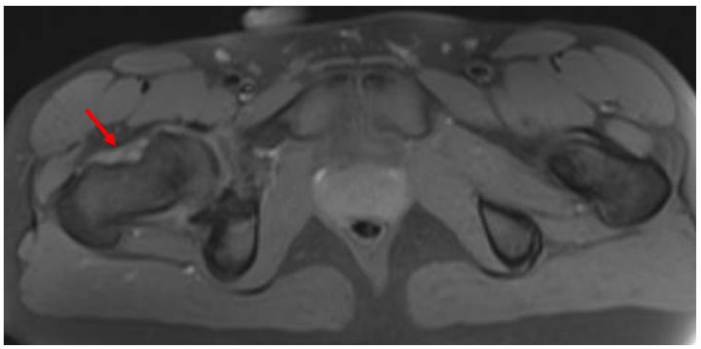

Figure 1: MR: Focal intracortical area (12 mm), hyperintense in T1 weighted images (arrow), at the femural head-neck passage with concomitant bone edema.

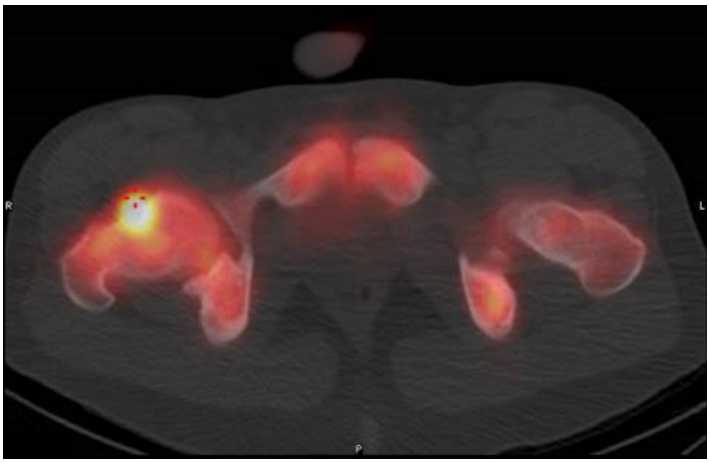

Figure 2: Skeletal scintigraphy with technetium 99m-HDP: Increased bone uptake at the femural head-neck passage

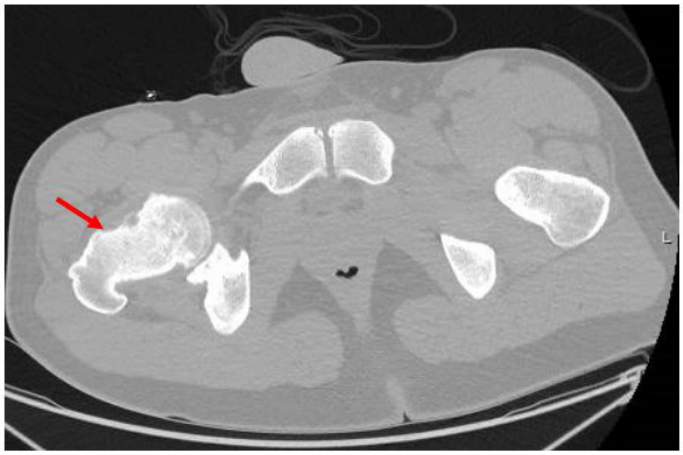

Figure 3: CT: "The nidus" a low-density area of 11x7 mm within a halo of bone sclerosis (arrow).

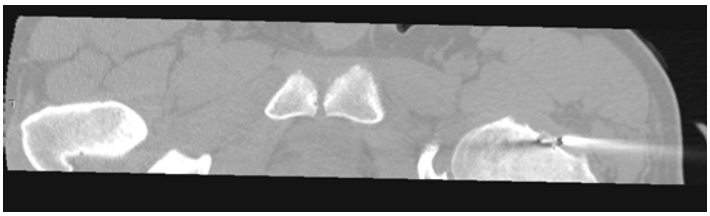

Figure 4: Radiofrequency ablation (RFA) under CT guidance of the osteoma osteoide lesion.

Discussion

The presented case reveals that the diagnostic approach to SpA diagnosis in childhood, particularly in the period of adolescence, is more difficult than in adulthood, since spine is less frequent involved in juvenile age. In an attempt to understand the clinical reasoning that led to the misdiagnosis of SpA in our patient at the first presentation, we think that the finding of hip synovitis with the negativity of anti CCP and RF, though the spondyloarthritis international society classification criteria (ASAS criteria) [2] were not satisfied, may have oriented towards the diagnosis of undifferentiated SpA. The initial good response to NSAID also favored this diagnosis. Furthermore, the lack of improvement after a 3-months course of treatment with etanercept biosimilar, whose effectiveness in Spa patient is demonstrated [6,7], led us to question this diagnosis. Many pathologic conditions should be considered in the differential diagnosis of SpA in an adolescent patient: osteoid osteoma (OO), rheumatoid arthritis (RA) (in patients older than 16 years), subsets of JIA other than enthesitis-related arthritis and psoriatic arthritis (in patients younger than 16 years), septic arthritis, epiphysiolysis of the femoral head, Legg-Calvé-Perthes disease (LCPD), brucellosis, osteosarcoma, Ewing sarcoma, leukemia, primary Non-Hodgkin lymphoma of the bone (PNLB), hypoparathyroidism (HP), hypophosphatemia (HYP), osteomalacia, Paget's disease (PD) and Klippel Feil syndrome (KFS) (Table 1). Osteoid Osteoma (OO) is the third most common benign tumor. It has a strong male predilection (male to female ratio 3:1) and usually affects patients aged between 10 and 20 years [8]. Any bone can be affected, but the most common sites are the proximal femur and tibia. Approximately 12% of all OO are intra-articular; in this case they are more likely to occur in the hip [9]. Intra-articular or juxta-articular OO is typically associated with non-specific and misleading symptoms such as joint effusions and synovitis; in these cases the differential diagnosis with an arthritis must be carried out [10]. The typical presentation of OO includes increasing pain worsening at night and responsive to NSAID. OO of the lower extremities is often associated with limp and weakness [8]. Histological picture is characterized by a network of dilated vessels, osteoblasts, osteoid and woven bone which includes a central nidus surrounded by a rim of reactive osteosclerosis, which represents the characteristic "mark" of the disease [11]. Plain radiograph is the first imaging that should be performed, but, since not all the lesions can be visualized, supportive imaging is required. Computed tomography (CT) is the imaging method of choice showing the characteristic image: a radiolucent nidus surrounded by an area of reactive bone sclerosis. The effectiveness of MR in diagnosing of OO is controversial. The appearance of the lesion may be highly variable, and the presence of associated soft-tissue changes and bone marrow edema may result in diagnostic errors. Bone scan shows high uptake, representing a sensitive method to localize the lesion [9]. OO should be considered in the differential diagnosis of SpA because in both conditions patients may present with limp, pain worsening during the night and relieved by NSAID; imaging may reveal synovitis. The elevation of inflammatory markers and HLA-B27 positivity that can be found in SpA and the typical imaging findings of OO can be of help in the differential diagnosis. Radiofrequency ablation (RFA) is currently the treatment of choice in both adult and pediatric patients, being minimally invasive, safe and effective [12]. Open excision is reserved for the cases of localization in areas not accessible to RFA [12]. In a patient over 16 years of age presenting with arthritis, RA should be considered in the differential diagnosis with SpA. Unlike SpA, RA preferably affects the female gender. It is a chronic systemic autoimmune, inflammatory disease characterized by symmetrical swelling and tenderness of the joints. Usually the small joints of hands and feet are the first to be involved; the spine is spared (with exception of atlanto-occipital joint occasionally involved) and no enthesitis, dactylitis and psoriasis are observed in these patients. 75-80% of RA patients are RF positive and 70% have anti-CCP antibodies, whose specificity is higher (95%) than that of RF [13]. HLA-B27 antigen is negative. The above mentioned clinical phenotype and laboratory tests can help in differentiating the two conditions. The first DMARD to be

used in patients with RA is methotrexate which on the contrary does not improve the SpA axial involvement. Both patients suffering from RA and SpA are responsive to steroids, NSAID and anti-TNFα. Juvenile idiopathic arthritis (JIA) is not a single disease, as encompasses all forms of arthritis of unknown origin, arising under the age of 16 years and persisting for more than 6 weeks [3]. In the case of our patient, the finding of hip arthritis (besides enthesitis-related arthritis and psoriatic arthritis that are considered by some authors as part of juvenile SpA) [14,15], the diagnosis of oligoarthritis should be ruled out, even if hip is rarely affected in JIA. Oligoarthritis is defined as an arthritis that affects four or fewer joints during the first 6 months of disease. It is characterized by asymmetric arthritis, early onset (before 6 years of age), female predilection, high frequency of positive ANAs and high risk of iridocyclitis. Oligoarthritis preferably involves the legs, being the knee joint mostly affected, followed by the ankles. Acute-phase reactants are often normal or moderately increased. The differential diagnosis between oligoarthritis and other musculoskeletal pathologic conditions is mainly based on the ANA positivity, found in 60-70% of patients, on the rarity of enthesitis, the absence of psoriatic rash, family history of psoriasis, spine involvement and HLA-B27 positivity . NSAID and intra-articular steroid injections with triamcinolone hexacetonide are the first line therapies. Patients who do not reach the remission are addressed to the treatment with of methotrexate, a biologic response modifier. Anti TNFα represent the therapeutic option for patients who are resistant or intolerant to conventional antirheumatic agents [16]. Septic arthritis and infectious spondylodiscitis represent an urgent condition and their diagnosis must be promplty excluded. Septic arthritis is more often monoarticular (80-90%), prefers a single joint, typically the knee. Arthrocentesis and the consequent synovial fluid analysis are the cornerstones of the diagnosis. Synovial fluid must be analyzed for cell count, gram stain and culture; leukocytes are generally extremely high with preponderance of polymorphonuclear cells. Blood culture are positive in approximately 50% of patients, being S.aureus the most common microorganism involved. Once septic arthritis or spondylodiscitis is suspected and the proper samples for microbiologic studies are collected, antibiotic treatment should started immediately [17,18]. Patients with spondylodiscitis experience back pain, abdominal pain, fever and malaise. Characteristic X-ray features of spondylodiscitis are disc space narrowing and irregularity of the adjacent vertebral end plates. The clinical picture of septic arthritis or a spondylodiscitis: involvement of just one joint or of a defined spine segment, presence of fever, deterioration of general condition, marked increase of inflammatory indices may help to differentiate these conditions from SpA. Proximal femoral epiphysiolysis is the most common adolescent hip disorder with a peak age between 10 and 14 years [19]. It occurs when the femoral epiphysis displaces posteriorly on the femoral neck at the level of the growth plate. The most likely mechanism for this slippage is rotation of the epiphysis on the metaphysis, as a result of torque force. Weakness in the proximal femoral growth plate can be caused by a variety of factors such as stress on the growth plate due to obesity, endocrine disorders (panhypopituitarism, hypothyroidism and renal osteodystrophy) and rapid growth spurt during adolescence. Patients affected are generally overweight adolescents. It is bilateral in 10% to 20% of affected cases. Pain in the hip and/or knee region of the affected side and limp are the most common symptoms. On physical examination a limited internal rotation is observed. The involved hip typically will go into obligatory external rotation if passively flexed up to 90°. A pelvis X-ray generally allows the diagnosis. Surgical treatment is always needed [19,20]. Legg-Calvé-Perthes Disease (LCPD) is a hip disorder of unknown etiology that result from temporary interruption of the blood supply to proximal femoral epiphysis leading to osteonecrosis and femoral head deformity. Patients classically are between 4 and 8 years of age but LCPD can present from 18 months of age to skeletal maturity. Males are 4-5 times more likely to be involved than females and bilateral disease occurs in 10% to 15% of patients [19]. The most common presenting symptom is a limp of varying duration. Pain, if present, is, unlike in SpA, activity related and may be localized in the groin or referred to the anteromedial thigh, knee region or buttock. Hip motion, primarily internal rotation and abduction, is limited. Pelvis and hip X-ray are the primary diagnostic tools for LCPD diagnosis. In the absence of changes on plain radiographs, particularly in the early stages of the disease, MR is useful to show early infarction. The treatment of early disease includes the use of NSAD, protected weight bearing, limited physical activity, and physical therapy for range of motion. Surgery to contain the femoral head is the next option for the patients who does not improve with these initial conservative measures [19,21].

Peripheral involvement	Axial involvement
Osteoid osteoma	Infectious spondylodiscitis
Rheumatoid arthritis	Brucellosis
Juvenile idiopathic arthritis	Leukemia
Septic arthritis	Hypoparathyroidism
Proximal femoral epiphysiolysis	Hypophosphatemia
Legg-Calvé-Perthes Disease	Osteomalacia
Brucellosis	Paget disease
Osteosarcoma	Klippel-Feil syndrome
Ewing sarcoma	
Leukemia	
Primary Non-Hodgkin lymphoma of the bone	
Paget disease	

Table 1: Differential diagnosis of Spondiloarthritis.

Brucellosis is a systemic infectious disease, transmitted to man by ingestion of unpasteurized milk and its products or contact with infected animals, by inhalation or through abraded skin and conjunctiva. Fever, sweating and constitutional symptoms including fatigue, malaise, anorexia and asthenia are observed in most patients [22]. The most frequent complications of brucellosis is osteoarticular involvement, with 10 to 85% of patients affected [23]. The sacroliac (up to 80%) and the spinal joints (up to 54%) are the most common affected sites. Spondylitis and spondylodiscitis are the most frequent complications of brucellar spinal involvement. Brucellosis with peripheral skeleton involvement is less prevalent compared with vertebral features. It can manifest as arthralgia, enthesopathy, osteomyelitis, arthritis, bursitis, tendonitis and tenosynovitis. [23,24]. Peripheral arthritis occurs in 14-26% of the patients suffering from acute, subacute or chronic brucellosis. Knee, hip and ankle are the most common affected joints. In children monoarticular arthritis (usually of the knee or the hip) is more common than spine involvement [23,24] On physical examination, hepatomegaly and splenomegaly occur in about one-third of patients. Lymphadenopathy is seen in about 10% of patients. Genitourinary complications (orchiepididymitis, glomerulonephritis and renal abscesses) can be found in around 10% of patients [22]. Neurological findings are reported in 5-10% of patients with brucellosis and include: peripheral neuropathies, chorea, meningoencephalitis, transient ischaemic attacks, psychiatric manifestations and cranial nerve involvement [25,26]. The diagnosis of brucellosis traditionally relies on serological testing. The Widal-Wright test, which is a standard agglutination test (SAT),measures the total amount of IgM and IgG antibodies, and the 2–ME (2-mercaptoethanol) test measures IgG antibody. In the endemic regions, a SAT titer≥1:160 and a 2-ME titer≥1:80 is in favor a brucellosis diagnosis [27]. Enzyme-linked immunoasorbent assay (ELISA) can detect both IgM and IgG antibodies but has less specificity than agglutination test [26,27]. Polymerase chain reaction is a molecular method which can be very useful due to its quick procedure and high sensitivity and specificity [26]. In the differential diagnosis between patients with brucellosis and spondiloarthritis the following features should be considered: disease duration, low back pain, contact history of livestock, myalgia, fever and HLA-B27. Patients with brucellosis are suffering from fever and myalgia more often than SpA patients [28]; their back pain does not improve with exercise and the disease has a shorter duration. The antimicrobial medication of brucellosis is necessary either to treat or to prevent the relapse. The WHO oral regimen consists of 200 mg doxycycline plus 600–900 mg rifampicin daily for a minimum of 6 weeks, whereas the alternative oral/parenteral consists in the administration of 200 mg doxycycline for a minimum of 6 weeks associated with 15 mg/kg daily for the first 2–3 weeks of streptomycin intramuscular therapy. Treatment should be prolonged in complicated cases [26]. A coxalgia may also be due to a malignant bone tumor such as an osteosarcoma or an Ewing sarcoma. The highest risk period for developing both conditions is the second decade, and in both tumors males are affected 1,5 times more frequently than females. Local pain followed by localized swelling and limitation of range of motion are typical signs and symptoms. In a patient with these symptoms a pelvis X-Ray should be performed. The lesion of osteosarcoma may appear as a coexistence of lytic and blastic images and new bone formation is usually visible. The classic radiographic appearance of osteosarcoma is the “sunburst” pattern. Ewing sarcoma indeed appears as a lytic bone lesion with periosteal reaction, the characteristic “onion skinning”. X-Ray should be followed by MR, bone scan and a biopsy of the lesion to confirm the diagnosis. In both diseases an elevated lactate dehydrogenase can be found and may be associated with a worst prognosis [29,30]. Patients with leukemia, in particular acute lymphoblastic leukemia, may also complain about musculoskeletal symptoms. They may present with peripheral or axial arthralgias but also with arthritis. Bone pain, significant nocturnal pain, pain out of proportion to joint involvement, prominent systemic features (fever, weight loss, night sweats), absence of morning stiffness may be early clues to the diagnosis of underlying malignancy. Hematological abnormalities are found in many patients with leukemia. Both patients with SpA and leukemia may have elevated inflammatory markers, but an LDH increased should orient towards a malignancy. Bone marrow examination should always be performed in doubtful cases even if blood count is normal [31,32]. Primary Non-Hodgkin lymphoma of the bone (PLB) has been defined as a single bony lesion with or without involvement of regional lymphnodes or multiple bony lesions but without lymphnode or visceral disease. It represents about 2-9% of non-Hodgkin lymphomas in children, with a mean age at diagnosis of 11.3 years and a male to female ratio of 1.65:1 [33]. Non traumatic pain is the main symptom and, similarly to SpA pain, can be present also at night. In patients with SpA, pain occurs mainly in the second half of the night and it is associated with stiffness, while in PLB pain can be associated with swelling or mass, fever, pathological fractures and irritability [34]. However, the low specificity of such symptoms may lead to misdiagnosis. In particular, when pain is located on buttocks or low back, the differential diagnosis between the two disorders may be difficult at the first observation [35]. Therefore radiological investigations are fundamental either to solve the dilemmas, but also for staging and assessing the treatment response [34,36]. At this regard, plain radiographs, whole-body PET/CT imaging and tissue biopsy are used for pretreatment staging for most patients with PLB, beyond their importance in differentiating from other diseases such as osteomyelitis, Ewing sarcoma, and osteosarcoma. As regard prognosis, pediatric PLB is less aggressive than the adult variants [36]. Nevertheless, children often show a systemic disease, thus needing of combination chemotherapy regime, even in patients with localized lesions [34]. Hypoparathyroidism (HP) is a disease characterized by absence or inappropriately low

concentrations of Parathyroid Hormone (PTH) [37], that is critical for maintaining the level of circulating calcium within a narrow normal range through its actions on bone, kidney, and intestine [38]. HP can be transient, inherited, or acquired, and it is caused by inability to synthesize or secrete PTH, abnormal parathyroid gland development, destruction of parathyroid tissue, or peripheral resistance to PTH [39]. Anterior neck surgery is the most common cause of the rare endocrine disorder of HP [40]. On the other hand, activating mutations in the calcium-sensing receptor (CaSR), that cause Familial hypercalciuric hypocalcemia, are the most common genetic cause of HP. HP may also be a component of some genetic syndromes like Di George syndrome (22q11 deletion, velocardiofacial syndrome), Kenney-Caffey syndrome and Sanjad-Sakati syndrome [41]. Other genetic causes include absence of parathyroid glands and rare mutations in the PTH gene [42]. The appropriate differential diagnosis is a complex process: skeletal abnormalities of HP, caused by calcifications, and the related stiffness and changes in gait and posture can simulate some forms of SpA [43,44]. In this case it is useful to perform an X-ray: in HP the radiographic findings in the sacroiliac joint are predominant in the lower portion with ossification of the iliolumbar ligament, whereas the involvement of the upper region of the joint is more common in SpA. In addition, the evident ossification at the hip joint with preserved joint space is not characteristic of SpA, but has been reported in HP. Sacroiliitis is not usually observed while it is the earliest manifestation in most AS patients. The patterns of syndesmophytes in patients with HP can resemble those of AS with origin from the vertebral margin and preserved disc space, but more often an involvement of the posterior longitudinal ligament is also observed [44]. Moreover, the lack of HLA-B27 expression may reduce the likelihood of SpA diagnosis as over 90% of AS and about 50% of PA patients are positive for this allele. A correct differential diagnosis between HP and SpA is important to set the specific therapy; standard therapy of HP is oral calcium and vitamin D supplementation at varying doses, based on clinical judgment [45]. The pain in HP is not responsive to immunosuppressive agents and non-steroidal anti-inflammatory drugs, but can resolve completely with calcitriol therapy [43,46,47]. Hypophosphatemia (HYP) is defined as an adult serum phosphate level of less than 2.5 mg/dL. The normal serum phosphate in children is considerably higher and levels < 4 mg/dl are considered low. Hypophosphatemia is a relatively common laboratory abnormality and is often an incidental finding [48-51]. Phosphate is critically important in childhood for a variety of physiologic processes such as skeletal growth, development and mineralization. Children with chronic hypophosphatemia may develop rickets and impaired growth. Generalized muscle weakness and fatigue are the most common symptoms of hypophosphatemia [52-54]; they can mimic low back pain and morning stiffness that are typical for SpA. Patients with chronic hypophosphatemia also develop osteomalacia and resultant bone pain that can be confused with other musculoskeletal disorders such as SpA. Radiological changes of the sacroiliac joint of patients with HYP can be wrongly described as inflammatory sacroiliitis. Non-mineralized osteoid accumulation in the subchondral bone results in enlarged view of the sacroiliac joint and can mimic the early stages of sacroiliitis. Ossification of the anterior sacroiliac ligaments or intraarticular bone formation can be confused with the last stage of sacroiliitis or ankyloses. The differential diagnosis is mandatory also to establish the correct therapy. It has been shown that in HYP, early initiation of treatment with a combination of phosphate supplements and vitamin D analogs during childhood progressively makes it possible to correct the leg deformation [51].

Osteomalacia is a metabolic disorder characterized by impairment of bone mineralization, sparing bone volume. It leads to accumulation of unmineralized matrix (or osteoid) in the skeleton and to reduced bone density [55,56]. Worldwide, the main cause of osteomalacia is alteration of Vitamin D (VitD) metabolism, in particular its deficiency, which can lead to rickets in children because of poor cartilage mineralization in their epiphyseal growth plates [54]. Osteomalacia can also be a rare paraneoplastic syndrome (the so-called tumor-induced osteomalacia). In this case it is a consequence of HYP induced by mesenchymal tumor releasing fibroblast growth factor 23 (FGF23) [57,58]. Clinical manifestations of osteomalacia involve rest muscoloskeletal pain (mostly localized in the pelvis), which can mimic inflammatory back and buttocks pain of SpA; furthermore it is often associated with bone fractures, skeletal deformities, muscle weakness and, sometimes, symptomatic hypocalcaemia [56]. Laboratory and imaging findings may be of help in differential diagnosis: high level of ALP, low level of sera calcium or phosfate, high level of FGF23 and PTH are suggestive of osteomalacia, as well as typical radiological images (e.g. pseudofractures called Looser's zone) [54]. Etiological treatments are advised in patients with osteomalacia: VitD supplementation is recommended in patients with VitD deficiency; phosphate administration in hypophosphatemic forms without hypercalciuria; surgical treatments for tumor related forms [59].Paget's disease (PD) is a chronic focal disorder of bone remodelling, leading to changes in the architecture and overall appearance of the bone; it usually involves middle aged males [60]. Nevertheless, the familial forms of PD are characterized by an early clinical presentation, even after birth, often with a severe course. Various mutations in the genetic region codifying for Osteoprotegerin (OPG, a bone resorption-regulating protein, mainly expressed by osteoclasts) have been reported, associated with variable phenotypical expression [61]. Bone pain at rest is the leading symptom of PD, typically occurring at night-time or early after getting up and relieved by movement [62]. In the case of pain localized in the pelvic region or in the lumbar spine, it might mimic the inflammatory back and buttocks pain of SpA [63]. Differential elements between these

disorders are represented by skeletal deformities, bone expansions, hearing loss or retinal lesions that can be found in PD, while enthesitis, uveitis or psoriasis and inflammatory bowel disease are associated with SpA [60,63]. HLA-B27 positivity is another helpful parameter to discriminate these different clinical entities, being present in a high percentage of patients with SpA [64], but never described in PD. In terms of biomarkers, bone remodelling in PD leads to increased concentration of alkaline phosphatase (ALP), bone-ALP, procollagen type 1 amino-terminal pro-peptide (P1NP); conversely, markers of inflammation are elevated in 50-70% of patients with SpA [65]. Radiological investigations such as multi-sites X-Ray and bone scintigraphy detect up to 93% of PD lesions, whereas a single sacroiliac X-Ray or MRI can be strongly indicative for the diagnosis of SpA [60,63].

Moreover a correct differential diagnosis between PD and SpA is of fundamental importance because the therapeutic approach to PD (consisting in antiresorptive medications) is not useful in patients with SpA [60,63].

Klippel-Feil syndrome (KFS) is a heterogeneous highly complex skeletal disorder, characterized by congenital fusion of two or more cervical vertebrae [66]. The prevalence of KFS is about every 40000 newborns worldwide, mainly in females (60% of cases). The etiology of KFS is not completely elucidated: several studies reported that vascular disruption, global fetal insult, primary neural tube complications, or genetic related factors may be implicated in the development of KFS [67-70]. The clinical phenotype includes skeletal anomalies and organ involvement [71], requiring a complex workup to diagnose KFS [70]. Skeletal abnormalities can misdiagnose with other diseases, particularly SpA, but some clinical and radiological differences orient towards the correct diagnosis. At first, low back pain and stiffness are the predominant features of SpA, in contrast to KSF patients, in whom these symptoms are not usually present. Moreover, there are two sagittal compensatory patterns for kyphosis that are differently associated with these pathologic conditons: in SpA patients, with the loss of lumbar lordosis, the extension of the hips and flexion of the knees create a typical posture to compensate for thoracic kyphosis; conversely, KSF patients can increase lumbar lordosis to compensate for the increase in thoracic kyphosis. KSF patients may present multi-organ involvement represented by auditory abnormalities, lung defects, congenital anomalies of the heart and the urinary tract [71,72], instead, SpA is associated with uveitis, psoriasis, inflammatory bowel disease and HLA-B27 positivity. The diagnosis of KSF is traditionally based on radiological evaluation of cervical spine; X-ray is commonly performed to illustrate fusion of vertebral bodies as well as facets and even spinous processes and MR is useful in assessing the integrity of the spinal cord, disc space, nerve rootlets, ligaments, and rest of the soft tissue structures. Among KFS patients, only those ones with persistent neurological pain, myelopathy, new onset muscle groups weakness, and documented spinal instability are considered to be candidates for surgery [73].

Conclusions

The examination of a patient with coxalgia and evidence of sinovitis with effusion needs an extensive diagnostic work up for an appropriate differential diagnosis, particularly if the case examined is suggestive of SpA. A wide spectrum of pathologic conditions must be considered, including orthopedic, infective diseases, malignancies and disorders of calcium-phosphate metabolism. A careful medical history and physical examination are the fundamental first steps to correctly start the diagnostic process. In addition the lack of response to a targeted therapy may induce to revaluate the diagnosis.

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