Juvenile Idiopathic Arthritis: Towards Improving Clinical Care

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Polyarteritis Nodosa Mimicking Juvenile Idiopathic Arthritis: A Case Report

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ABSTRACT

In this case report we present the case of a 9-year-old girl who developed myalgia after she was diagnosed with Juvenile Idiopathic Arthritis (JIA), which was treated with etanercept and methotrexate. The primary diagnosis JIA was based on symmetric polyarthritis without signs of systemic involvement. Six months later myalgia, hypertension, fever and angiographic abnormalities led to the diagnosis of juvenile systemic polyarteritis nodosa (PAN). Juvenile PAN is a rare inflammatory disease affecting small to medium-sized muscular arteries. Due to a wide range of affected organs, it causes a variable clinical presentation. Diagnosis can be difficult, because disease symptoms at the onset of disease are nonspecific and often mimic other inflammatory diseases. Even though juvenile PAN is a rare disease, it should be included in any differential diagnosis in patients with undetermined systemic symptoms or inflammatory disorders.

Key words: Polyarteritis nodosa, Juvenile Idiopathic Arthritis, Myalgia, Etanercept, Biologicals

INTRODUCTION

Polyarteritis Nodosa (PAN) is a severe inflammatory disease of insidious onset and variable clinical presentation affecting small to medium-sized muscular arteries. PAN is rare in childhood. In the general population, it has an estimated prevalence of 30.7 per 1.000.000[1]. Diagnosis is made based on the EULAR/PReS/PRINTO classification criteria for childhood Polyarteritis Nodosa, including histopathology or angiographic abnormalities plus one of five of the following symptoms: skin involvement, myalgia or muscle tenderness, hypertension, peripheral neuropathy or renal involvement[2]. In this case report we present the case of a 9-year-old girl who developed myalgia after being diagnosed with Juvenile Idiopathic Arthritis (JIA) and was treated with Etanercept and Methotrexate.

CASE PRESENTATION

A healthy 8-year-old girl was sent to our paediatric rheumatology outpatient department with chronic arthritis. One year before she had started to develop joint complaints. She went to a local hospital where she was diagnosed with post streptococcal reactive arthritis of both ankles with minor elevated antistreptolysin 200-400 U/L (<200 U/L). With the use of ibuprofen her joint complaints subsided. The NSAID was gradually tapered and stopped over the next few weeks.

A few months later joint complaints returned. The patient had difficulties walking, pain in the right shoulder and morning stiffness lasting more than 30 minutes. She was admitted to our tertiary care center. Family history revealed that her brother had one episode of reactive arthritis, and her mother mentioned several episodes of uveitis of unknown origin. On physical examination we found arthritis of the right shoulder, left wrist, metacarpophalangeal joints 2 and 3, both ankles and the right knee with flexion contracture. The patient had a severely disturbed walking pattern. Laboratory evaluation showed no presence of ANA, no IgM Rheumatoid Factor and no anti-ENA. Immunoglobulin levels were normal except for a slightly elevated IgA (2,78g/L, normal range of 0.5-2.5g/L), complement and urinary analysis were unremarkable. Based on these findings our patient was diagnosed with polyarticular JIA. Both ankles and the right knee were injected with triamcinolonhexacetonide and lidocaine, with good effect on the knee and partial effect on the ankles. Due to persistent polyarthritis she was enrolled in the BeSt for Kids study (NTR 1574). After parental consent and exclusion of mycobacterial infection, she started methotrexate and etanercept. Six months later arthritis in all joints had resolved.

When the patient returned to our outpatient department 3 months later, she was unable to walk or completely extend the right leg due to a painful, swollen right calf. There was no preceding trauma or illness. On physical examination, her right calf was painful and diffusely swollen with limited extension of at least 30 degrees, but without signs of arthritis in knee or ankle. Furthermore, she had an arthritis of the right shoulder and left wrist. She was admitted. The first differential diagnostic thoughts were deep venous thrombosis, rupture of a Baker's cyst, abscess and bony fissure, which could all be ruled out by conventional X-rays and ultrasonography. Initial laboratory testing demonstrated high acute phase reactants (CRP 70mg/L (<10mg/L), ESR 46 mm/hour (3-13mm/hour), thrombocytes 554 x109 (150-400x109)) with normal CPK. MRI of the lower legs revealed bilateral diffuse edema in the muscles of the lower legs with enhancement after intravenous gadolinium, suggestive of myositis. The neurologist reported normal muscle strength, but striking pain on stretching the lower leg muscles suggestive for fasciitis. A skin/muscle/fascia biopsy was planned and etanercept and methotrexate were stopped.

Microbiological testing revealed no evidence of viral or bacterial infection: PCR for respiratory and gastrointestinal viruses (adenovirus, enterovirus and parechovirus) was negative; IgM and IgG for Borrelia, EBV and CMV were not present. Two blood cultures and a urine culture were negative. There was no peripheral eosinophilia suggestive of eosinophilic fasciitis.

In search of a systemic inflammatory disease we evaluated organ involvement. Plain radiograph of the thorax, lung function including CO-diffusion capacity, electrocardiography, cardiac ultrasound, abdominal ultrasound and urinalysis were all unremarkable. Ophthalmologic examination revealed no signs of uveitis or vasculitis. Faeces calprotectin was low (<15µg/g) and ACE 27 U/L, ANA, anti-ds DNA, anti-ENA and ANCA were all negative, as were myositis-specific antibodies. Complement levels were normal. As a systemic inflammatory process was suspected, three methylprednisolon pulses of 30 mg/kg were administered resulting in decreased pain in the calves and a decrease of all acute phase parameters (CRP from 110 to 8 mg/L).The biopsy demonstrated no signs of myositis or fasciitis. Due to the lack of a classifying diagnosis, no oral prednisolone was started and the patient was discharged in good clinical condition and able to walk normally.

Four days following discharge the patient returned to our outpatient department in general diminished condition with constitutional symptoms of fatigue and malaise, polyarthritis and an increase in the painful swelling of the calves. The blood pressure was raised on admission (150/85mm Hg, >P95) and she developed fever (39,5 ºC) the same day. Acute phase reactants had increased (CRP 133.6 mg/L). Because of previous administration of

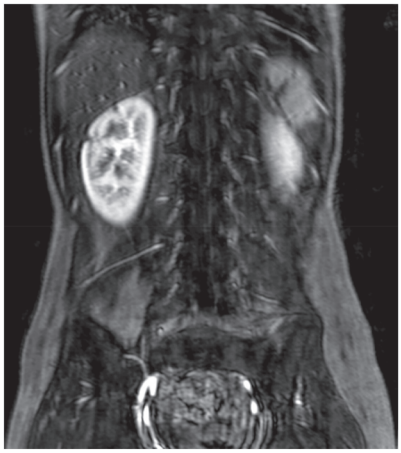

Figure 1 | MRI/MRA of the abdominal arteries showing parenchymal defects in the right kidney

immunosuppression, she was started on sepsis therapy. After 72 hours, sepsis therapy was stopped because blood and urine cultures were negative. The combination of arthritis, myalgia, fever and hypertension raised the suspicion of systemic PAN. MRI/MRA of the abdominal arteries showed no abnormalities in the large vessels but revealed parenchymal defects in the kidneys suspicious of vasculitis in smaller vessels (figure 1). A classic angiography showed subtle abnormalities in accordance with the MRI/MRA: cortical defects, irregular kidney arteries, a cut-off sign and some micro-aneurysms (figure 2).

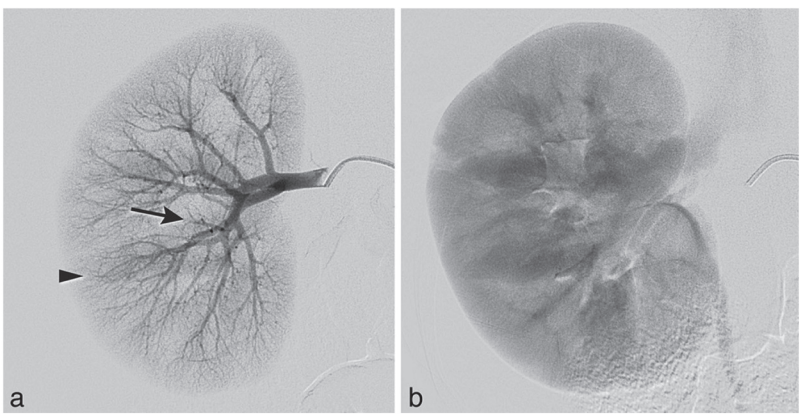

Figure 2 | Classic angiography of the kidneys. **A:** both arrows indicate cut-off signs of kidney arteries. **B:** Cortical defects in the right kidney cortex in accordance with the MRI/MRA.

According to the EULAR/Pres/PRINTO classification criteria for Polyarteritis Nodosa, the patient was diagnosed with PAN[2] with a Paediatric Vasculitis Activity Score (PVAS) of 9/64. Standard treatment for remission induction currently combines high-dose corticosteroids with cyclophosphamide[3]. If remission is achieved, treatment can be continued with azathioprine as maintenance therapy. The role of mycophenolate mofetil (MMF), instead of cyclophosphamide, in the induction of remission will be investigated in the future planned MYPAN study. Our patient received another pulse of intravenous methylprednisolone. As induction therapy oral prednisolone (2 mg/kg/day) and MMF were started ahead of the MYPAN study. The calf pain diminished, arthritis resolved and acute phase reactants dropped again. Unfortunately, after lowering prednisolone below 17,5 mg the disease flared up: acute phase reactants increased and arthritis recurred. MMF was replaced by cyclophosphamide pulse therapy (750 mg/m2 once a month IV). The prednisolone dosage was gradually tapered. To control blood pressure, amlodipine and labetolol were prescribed. Our patient returned to our tertiary care center for regular check-ups and short stay admissions for administration of the cyclophosphamide pulses. Currently in remission, she nearly finished 6 cyclophosphamide pulses combined with 12,5 mg prednisone daily and is actively involved in synchronic swimming without limitations in daily life.

DISCUSSION

This report describes a case of systemic juvenile PAN initially mimicking polyarticular JIA. JIA is the most common rheumatic disease in children and the symptoms of JIA and PAN can overlap. Early in the course of the disease both cause non-specific signs and symptoms such as myalgia, arthritis, malaise and fever. In our patient, the primary diagnosis was based on symmetric polyarthritis without any signs of systemic involvement. Later in the course of the disease myalgia, hypertension, fever and angiographic abnormalities led to the diagnosis of juvenile PAN[2].

A report from 2012 describes a similar case in which the initial diagnosis was also JIA. A few years later the patient was diagnosed with PAN because of the development of coronary artery aneurysms, fever, hypertension and myalgia[4]. Others have also pointed to the insidious onset of childhood PAN[3;5]. A recent single-center retrospective study including 69 children over 32 years concluded that many of the presenting features of PAN are non-specific and mimic other inflammatory diseases in childhood[3]. Most patients show constitutional symptoms like fatigue, weight loss, myalgia and elevated acute-phase reactants, reflecting systemic inflammation[5].

As the disease progresses and vessel damage increases, characteristic symptoms arise and PAN presents itself as a more likely cause of disease symptoms[6].

In the differential diagnosis we also considered the inflammatory process in the calf muscles as a side-effect of etanercept. Biologicals, like etanercept, antagonize immunological cytokines and receptors and might affect the quality of the immune system. This can lead to a defective immunoregulation resulting in auto-inflammation[7]. In their review, Swart et al. describe an increase in the incidence of demyelinating diseases, inflammatory bowel disease, and development of auto-immune antibodies with the use of etanercept (no cases of systemic vasculitis were described)[7]. An emerging number of autoimmune adverse events related to the use of biologics was described in another recent review article[8]. 140 cases of vasculitis were described, most commonly caused by etanercept. Ninety percent involved cases with a cutaneous form of vasculitis, glomerulonephritis or peripheral neuropathy, no systemic PAN was described. These reviews indicate that it is unlikely that our patient developed PAN because she was treated with etanercept.

CONCLUSION

This case illustrates the course of symptoms of juvenile PAN. The initial non-specific symptoms and insidious onset of disease led to the primary diagnosis of polyarticular rheumatoid factor negative JIA. During the course of disease, more specific symptoms arose and our patient was diagnosed with juvenile systemic PAN. Even though juvenile systemic PAN is a rare disease, it should be included in any differential diagnosis in patients with undetermined systemic symptoms or inflammatory disorders[9].

Consent

Informed consent was obtained from the parents of the patient for publication of this case report and any accompanying images.

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