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PEDIATRIC ONCALL
CHILD HEALTH CARE

IMAGES IN CLINICAL PRACTICE

MULTIPLE JOINT SWELLINGS - CONSEQUENCES OF THE NATURAL HISTORY COURSE

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A 10-years-old girl, resident of Guinea-Bissau, presented to a Portuguese pediatric hospital with severe swelling of the knees, ankles, elbows, wrists, hands and feet interphalangeal (IPJ) joints for four years (Figure 1). She also had pain, joint stiffness and limited mobility of all joints, including the cervical spine, with flexion deformity of the elbows, IPJ and knees. She was not able to walk normally or perform daily activities. Family history was noncontributory. Throughout the four years of illness, she had episodes of anorexia, weight loss and intermittent episodes of fever. On investigations, she had microcytic hypochromic anemia (hemoglobin 9.4 g/dL, mean corpuscular volume 54fL, mean corpuscular hemoglobin concentration 30 g/dL) and increased inflammatory markers (leukocytes $18.43x10^9$/L, CRP 15.2 mg/dL, ESR 120 mm, platelets $612x10^9$/L). Rheumatoid factor (RF) was negative and complement and immunoglobulins were normal. Anti–citrullinated protein (CCP) and antinuclear antibodies (ANA), viral serologies and interferon-gamma release assay test (IGRA) for tuberculosis (TB) were negative (Table 1). On radiological evaluation (Figure 1), there was a severe soft tissue edema with marked joint destruction and erosions on the radius, ulna and carpal bones, as well as several metacarpophalangeal and interphalangeal joints sclerosis, ankylosis and with signs of osteopenia. She had no other systems involvement.

What is the diagnosis and how to treat this child?

When an arthritis persists for more than six weeks, especially in the absence of trauma or sepsis, juvenile idiopathic arthritis (JIA) should be considered.[1,2] In this

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Figure 1a & 2a. Swelling and deformity of the knees and hands

Figure 1b & 2b. Swelling and deformity correspondence on x-ray.

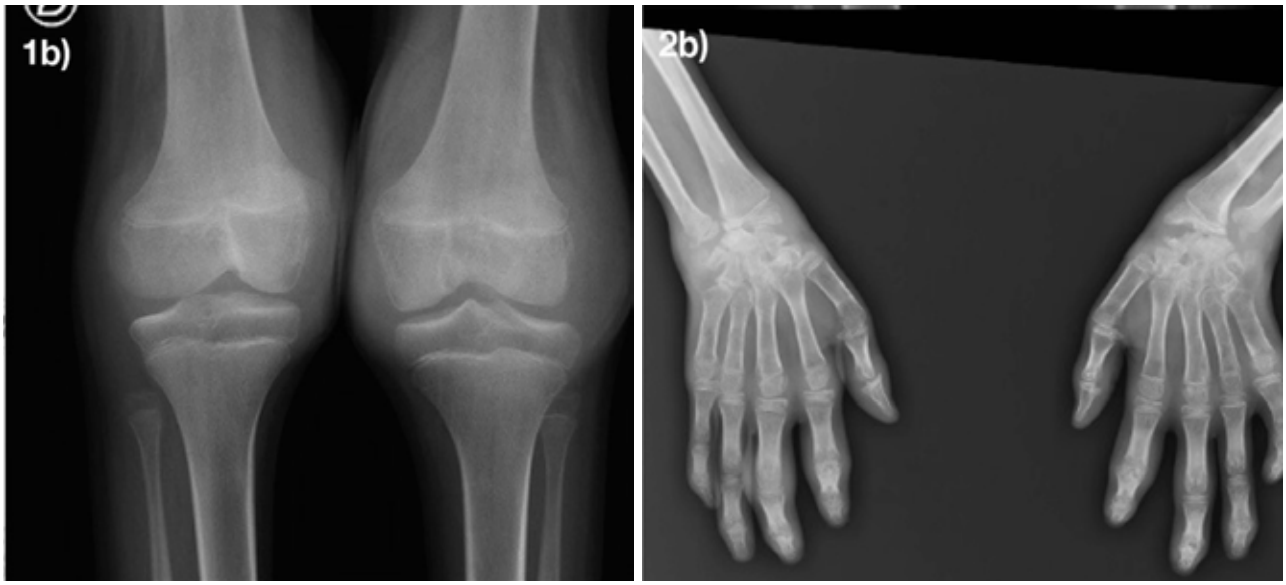


Table 1. Investigations at the time of hospitalization.

Parameter	Day 0	19th day of therapy	2 months of therapy
Complete blood count			
Hemoglobin (g/dL)	9.4	9.3	10.3
Hematocrit (%)	31.4	31.8	34.6
Mean corpuscular volume (fL)	54.0	59.6	61.3
Mean corpuscular hemoglobin concentration (g/dL)	30.0	29.2	29.8
Red cell distribution width (CV%)	17.2	23.8	19.6
Leukocytes (x10^9/L)	18.43	24.28	14.5
Neutrophils (% / x10^9/L)	70.1 / 12.9	79.8 / 19.3	78.5 / 11.38
Eosinophils (% / x10^9/L)	2.2 / 0.41	0.3 / 0.07	0.5 / 0.07
Basophils (% / x10^9/L)	0.2 / 0.04	0.1 / 0.02	0.1 / 0.01
Lymphocytes (% / x10^9/L)	24.8 / 4.57	17.8 / 4.32	18.2 / 2.64
Monocytes (% / x10^9/L)	2.7 / 0.50	2.0 / 0.49	2.7 / 0.39
Platelets (x10^9/L)	612	440	380
Erythrocyte sedimentation rate (mm/hour)	120	100	77
Biochemistry			
Urea (mg/dL)		37	28
Creatinine (mg/dL)	0.34	0.30	0.36
Sodium (mmol/L)	137	138	140
Potassium (mmol/L)	4.6		4.1
Chloride (mmol/L)	94	96	98
C reactive protein (mg/dL)	15.2	4.93	
Glucose (mg/dL)	79		86
AST(U/L)	19	22	21
ALT (U/L)	7	16	12
GGT (U/L)		49	39
Total bilirubin (mg/dL)		<0.15	
Ferritin (ug/L)	773.0		
Proteins (g/dL)	8.3		
Albumin (g/dL)	4.1		
CK (U/L)	21		
LDH (U/L)	299	288	

Parameter	Day 0	19th day of therapy	2 months of therapy
Hereditary red cells alterations			
Hb A2 (%)	2.2		
Hb F (%)	0.2		
Serologies			
HIV 1 and 2 Ab	Negative		
HBsAg	Negative		
HBsAb	Negative		
HBcAb	Negative		
VHC Ab	Negative		
CMV IgG (UI/mL)	104		
CMV IgM	Negative		
Parvovirus IgG index	Negative		
Parvovirus IgM	Negative		
Coxiella.burnetii IgG fase I and II Ab	Negative		
Coxiella.burnetii IgM fase I and II Ab	Negative		
EBV VCA IgG	Positive		
EBV VCA IgM	Negative		
EBV EBNA 1 IgG	Positive		
VZV IgG	1.17		
IGRA for TB	-		
Auto immunity			
Antinuclear Ab	Negative		
Anti-citrulline Ab	Negative		
Anti-dsDNA Ab	Negative		
ANA screening	Negative		
Immunochemistry			
Complement: C3 (mg/dL)	234		
Complement: C4 (mg/dL)	14		
Complement: CH50 (U/mL)	69.6		
Rheumatoid factor (UI/mL)	12.5		
Endocrinology			
TSH (uU/mL)	0.91		
fT4 (ng/dL)	1.49		
Vitamin D total (ng/mL)	21.6		

Note: Hb - hemoglobin; HIV - human immunodeficiency virus; Ab - antibody; Ag - antigen; HBsAg - Hepatitis B surface antigen; HBsAb - Hepatitis B surface antibody; HB Ag - Hepatitis B core antibody; HCV - Hepatitis C virus; CMV - cytomegalovirus; EBV - Epstein-Barr virus; VZV - Varicella zoster virus; IGRA - Interferon gamma release assay; TB - Tuberculosis; dsDNA - Double strain DNA; ANA - Antinuclear antibody; TSH - Thyroid-stimulating hormone; fT4 - Unbound thyroxine.

clinical case, the disease started around 6 years of age. However, it was not possible to determine exactly the number of joints affected in the first six months, thus it was not able to differentiate between oligoarticular and polyarticular arthritis. The patient also had an inconsistent history of fever, markedly increased acute phase reactants and no autoantibodies, but no other characteristics of systemic-onset JIA. However, it is not possible to guarantee that it is not a systemic arthritis with a later evolution to polyarticular. The patient also did not have characteristics of psoriatic or enthesitis-related arthritis.[3] The hypothesis of being an infectious arthritis was also considered unlikely, due to the time of the disease's evolution and negative viral serologies and TB IGRA test. Thus, diagnostic hypothesis of polyarticular JIA (polyJIA) RF(-) ANA(-) with the following scores: JADAS 37, articular JADI 26 and extra articular JADI 2 was considered in our patient.

The therapy of polyJIA should be based on an early diagnosis and allocation to specialists in pediatrics rheumatology and a rapid and effective anti-inflammatory treatment with appropriate pain and disease control.[4] None of these principles were possible to apply in our patient. Recent therapy algorithms support the initial treatment of patients with high risk polyJIA with methotrexate, non-steroidal anti-inflammatory drugs, oral prednisolone, intra-articular glucocorticoids and even biological treatment.[4,5] Concerning biologics, there are currently six approved for use in JIA patients with different modes of action: three tumor

necrosis factor inhibitors (adalimumab, etanercept and golimumab), one interleukin (IL)-1 inhibitor (canakinumab), one IL-6 inhibitor (tocilizumab) and one T-cell co-stimulation clocker (abatacept).[6] In our patient, the initial therapy was prednisolone (starting 1 mg/kg/day and decreasing until ~0.25 mg/kg/day in ~4 weeks), parenteral methotrexate (starting with ~10 mg/m^2/week and increasing until ~17.5 mg/m^2/week in ~4 weeks) and ibuprofen, with cholecalciferol, calcium and folic acid supplementation. The wrists, elbows, knees and tibiotarsal joints were injected with triamcinolone hexacetonide. During hospitalization, there was a significant improvement in disease control and functional capacity, with less active joints, besides the extensive irreversible structural damages. The patient was then referred to an inpatient urgent rehabilitation program, maintaining the treatment with subcutaneous methotrexate in increasing doses (up to ~20 mg/m^2/week), with a consequent reduction in the prednisolone dose. Despite the improvement

Table 2. Serial direct and indirect inflammatory parameters.

Parameter	**Months after hospital discharge without therapy with biologicals**		
	1	**2.5**	**4**
Leukocytes (x10^9/L)	14500	12540	16410
Neutrophils (% / x10^9/L)	11380	9960	13030
Eosinophils (% / x10^9/L)	70	30	50
Basophils (% / x10^9/L)	10	0	20
Lymphocytes (% / x10^9/L)	2640	2280	2920
Monocytes (% / x10^9/L)	390	280	390
Platelets (x10^9/L)	380000	624000	567000
C reactive protein (mg/dL)		3.82	4.02
Erythrocyte sedimentation rate (mm/hour)	77	77	87

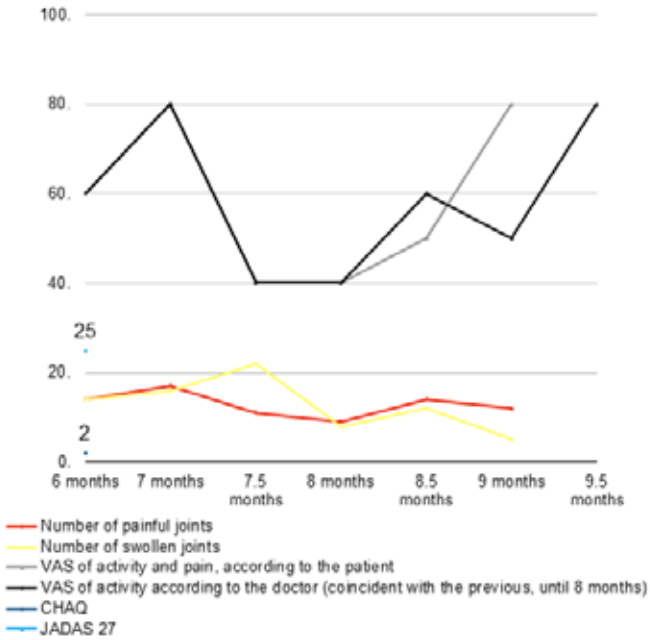
Parameter	**Months after hospital discharge, under tocilizumab**				
	6	7.5	8	8.5	9
Leukocytes (x10^9/L)				7860	
Neutrophils (% / x10^9/L)				2990	
Eosinophils (% / x10^9/L)				540	
Basophils (% / x10^9/L)				20	
Lymphocytes (% / x10^9/L)				3600	
Monocytes (% / x10^9/L)				700	
Platelets (x10^9/L)				254000	
C reactive protein (mg/dL)	3.4	0.1	0.1	0.03	0.1
Erythrocyte sedimentation rate (mm/hour)	28.7	4	3	2	4

Parameter	**Months after hospital discharge, under etanercept**					
	10	11	12	14	18	20
Leukocytes (x10^9/L)			6240		6130	7590
Neutrophils (% / x10^9/L)			3730		3680	4010
Eosinophils (% / x10^9/L)			170		200	270
Basophils (% / x10^9/L)			10		10	20
Lymphocytes (% / x10^9/L)			1820		1820	2690
Monocytes (% / x10^9/L)			510		420	610
Platelets (x10^9/L)			483000		419000	365000
C reactive protein (mg/dL)	0.1	1	3.65	5.18	2.54	1.58
Erythrocyte sedimentation rate (mm/hour)	3	13	47		52	40

in inflammatory analytical parameters (Table 2), she always presented with pain and disturbance of joint functionality. Six months later, therapy with tocilizumab (8 mg/kg/4 weeks) was started. A tocilizumab therapeutic failure was considered after 4 months (Figure 2A) and therapy was replaced by etanercept (0.8 mg/kg/week). There was an improvement in the number of painful and swollen joints (Figure 2B), and it was possible to suspend therapy with prednisolone (after one year). However, she still had increased inflammatory analytical parameters (Table 2). MRI of the knees showed moderate effusion and extensive synovitis on the right side after 4 months of etanercept, so a synovectomy was performed. After 8 months, ultrasounds still presented significant alteration of the wrists and ankles architecture, mild to moderate intra-articular effusion bilaterally in the elbows and tibiotarsic synovitis. Synovectomy was again planned for the knees and elbows. Currently, under etanercept for 10 months (~1 mg/kg/week) and methotrexate (~16 mg/m^2/week), she is able to walk, although limping, and run, despite irreversible joint structural damage.

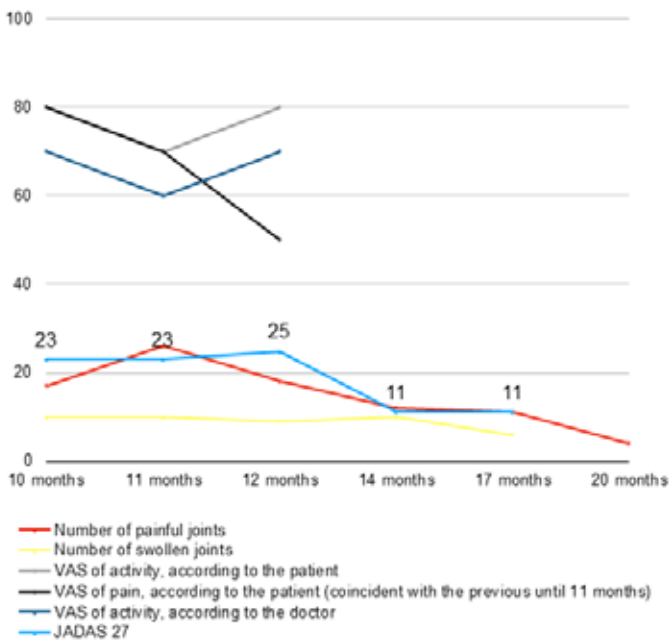
Figure 2. Evolution under tocilizumab (A) and under etanercept (B).

A)



Note: x axis: months after hospital discharge.
Abbreviations: VAS - visual analogue scale; CHAQ - The Child Health Assessment Questionnaire; JADAS: Juvenile Arthritis Disease Activity Score.

B)



Note: x axis: months after hospitalar discharge.
Abbreviations: VAS - visual analogue scale; JADAS: Juvenile Arthritis Disease Activity Score.

What we intend to alert with this case is that JIA is the most frequent cause of inflammatory arthritis in children and an early diagnosis and appropriate therapy are decisive for prognosis.[2,3,8] This clinical case is special not because of the disease itself, but for the fact that it was diagnosed at a very advanced stage, rarely seen nowadays, having exceeded all possible therapeutic windows. We will probably never be able to achieve clinical remission, but the fact that low to moderate disease activity has been achieved is very positive for the patient.

Compliance with Ethical Standards

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Conflict of Interest: None

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