Polyarthritis in a child with Rosai-Dorfman disease

F. Pessler[1], M.E. Paessler[3,4], M. Lambert[2], E. Morgan Dewitt[1,5], D.D. Sherry[1,4]

[1]Division of Rheumatology, [2]Division of Hematology and Oncology, [3]Department of Pathology, The Children's Hospital of Philadelphia; [4]University of Pennsylvania School of Medicine; [5]Present affiliation: Div. of Pediatric Rheumatology, Duke University Medical Center, Durham, NC, USA.

Frank Pessler, MD, PhD, Michele Paessler, DO; Michele Lambert, MD; Esi Morgan Dewitt, MD; David D. Sherry, MD.

F. Pessler was supported by N.I.H./N.C.I. Training Grants T32-AR 007442 and T32-CA 09140.

Publication of this case and waiver of informed consent were approved by the Institutional Review Board of the Children's Hospital of Philadelphia.

Please address correspondence to: Dr. Frank Pessler, Div. of Rheumatology, Children's Hospital of Philadelphia, 3405 Civic Center Boulevard, Philadelphia, PA 19104, USA.
E-mail: pessler@email.chop.edu

Received on June 6, 2006; accepted in revised form on January 22, 2007.

Key words: Rosai-Dorfman disease, arthritis, juvenile idiopathic arthritis, histiocytes.

Abbreviations:
ALT: alanine aminotransferase;
ANA: anti-nuclear antibodies;
AST: aspartate aminotransferase;
CRP: C-reactive protein;
ESR: erythrocyte sedimentation rate;
GGT: gamma glutamyl transferase;
RDD: Rosai-Dorfman disease;
SoJIA: systemic onset juvenile idiopathic arthritis.

Competing interests: none declared.

ABSTRACT

A 5-year-old boy presented with fever, rash, lymphadenopathy and polyarthritis. Systemic onset juvenile idiopathic arthritis was initially considered in the differential diagnosis, but lymph node biopsy established the diagnosis of Rosai-Dorfman disease (RDD). The arthritis recurred twice. Both times it correlated with the severity of the other clinical and laboratory abnormalities of RDD and responded to treatment with dexamethasone and vinblastine. This report adds inflammatory arthritis to the extranodal manifestations of RDD in children and suggests that this disorder should be considered as a rare cause of fever with rash, lymphadenopathy and arthritis.

Introduction

Rosai-Dorfman disease (RDD, sinus histiocytosis with massive lymphadenopathy) is a histiocytic disorder featuring lymphadenopathy, fever and variable extranodal manifestations, which result from histiocytic infiltration of affected organs (1, 2). The etiology is unclear, but infection with viruses including human herpes virus 6 and Epstein Barr Virus (EBV) as well as aberrant immune responses to infection have been implicated (3). Considering these potentially "reactive" aspects of RDD, joint involvement in the form of arthritis appears pathophysiologically possible. Indeed, arthralgia or arthritis were reported in 18 of the 423 RDD cases reviewed in 1990 (1). However, only two well documented cases of arthritis associated with RDD in adults have been published (4, 5). Polyarthritis was alluded to in another report (6). Here, we report a 5-year-old boy who initially presented with fever, polyarthritis, lymphadenopathy and rash, which are the typical findings of systemic onset juvenile idiopathic arthritis (SoJIA), but was subsequently found to have RDD. This report adds polyarthritis to the musculoskeletal manifestations of RDD in children. It suggests that RDD should be included in the differential diagnosis of fever with rash, lymphadenopathy and arthritis.

Case report

A 5-year-old African-American boy was hospitalized because of fever (temperature, 38.2°C), right lower extremity pain and an urticarial rash on the face. Physical exam revealed an antalgic gait and multiple joint effusions with guarding and pain of the left wrist, elbow, shoulder and the right knee. There was no history suggestive of recent infection. The infectious disease evaluation, including serologic tests for histoplasmosis and cat scratch disease, was significant only for serologic evidence of past EBV infection and a positive polymerase chain reaction test for EBV DNA, which was negative upon repeat testing 4 days later. Antinuclear antibody titers were negative. All other relevant laboratory results are summarized in the Table. The patient's symptoms improved on naproxen (10 mg/kg twice daily), and he was discharged after 3 days. The most likely diagnoses considered were a mild presentation of SoJIA or a post-infectious arthritis with liver enzyme abnormalities. Follow-up evaluation 2.5 weeks later revealed continued malaise, loss of appetite, leg and shoulder pain causing night-time awaking, and a persistent pruritic skin eruption. Temperature was 38 °C, weight 16.2 Kg (4th percentile), and height, 113.5 cm (< 3rd percentile). Physical exam revealed hepatomegaly and tender and swollen left 5th and right 3rd PIP, right knee and right ankle joints, decreased neck extension, and guarding of the left wrist, elbow and shoulder. He had an erythematous maculopapular eruption, scattered wheals with central clearing, and desquamation. Although the rash was not typical of SoJIA, this diagnosis was considered in the differential diagnosis, and he was admitted to the hospital again. Laboratory tests revealed persistent leukocytosis, elevated inflammatory markers and a further decrease in albumin and rise in GGT (Table I). Skeletal radiographs and bone scintigraphy did not reveal any bone lesions. Hepatomegaly, periportal lymphadenopathy and parenchymal hypodensities were seen by ultrasound exam of the liver. These findings were confirmed by abdominal/pelvic computed tomography (CT), which also revealed splenomegaly, lesions in both kidneys, and widespread

retroperitoneal lymphadenopathy. A bone marrow aspirate showed trilineage maturation with increased myeloid cells, but no evidence of malignancy or hemophagocytosis. Since the skin lesions had improved, liver and porta hepatis lymph nodes were biopsied. Open liver biopsy revealed mild portal expansion and acute cholangitis. Excisional biopsies of porta hepatis lymph nodes showed reactive lymphoid hyperplasia in one node. In contrast, the pathognomonic findings of RDD (diffuse infiltration of the lymphoid sinuses with $CD68^+$ and $S100^+$ histiocytes engulfing normal hematopoietic cells) were seen in another node (Fig. 1).

The patient was initially treated symptomatically for musculoskeletal complaints and pruritus. However, lymphadenopathy, arthritis, dermatitis, and laboratory abnormalities persisted six months after disease onset, and he had not gained any weight. He was therefore treated with dexamethasone (10 mg/m^2) and vinblastine (2 mg/m^2) for 6 weeks. The clinical response was excellent. The arthritis and dermatitis resolved after one week, he began to gain weight, and all abnormal laboratory values improved. However, inflammatory markers and serum protein levels did not normalize completely, thus demonstrating that systemic inflammation continued. Notably, the ESR remained relatively more abnormal than the CRP. Maintenance therapy was not initiated at this time since many cases of RDD resolve or stabilize on supportive treatment. Five months later, the dermatitis and right wrist and bilateral ankle arthritis recurred, accompanied by elevated ESR (123 mm/hr), AST and GGT, and a mild Coombs positive hemolytic anemia [a known immunologic complication of RDD (1)]. A second six-week course of dexamethasone and vinblastine was given, leading to improvement of symptoms and laboratory abnormalities within 3 days. One year later, the patient had another recurrence of dermatitis, painful swelling of one elbow and one ankle, and increase of previously involved perihepatic and mediastinal nodes. A chest CT revealed new nodules in the peripheral lung fields. Again, treatment with dexamethasone

Table I. Summary of relevant laboratory test results.

Test	Day 1	Day 18	Remission[1,2]	1st flare	Remission[2]	2nd flare
Leukocytes (per μl)	18000 (5 500-15 500)	23700	11300	13000	9600	17500
Hemoglobin (g/dL)	11.0 (11.5-13.5)	10.0	11.8	10.0	12.6	11.0
Platelets (10^3/μL)	291 (150-400)	452	344	360	210	329
ESR (mm/h)	131 (< 20)	115	48	123	57	115
CRP (mg/dL)	20 (< 1.0)	9.7	1.6	7.9	1.3	8.3
AST (U/L)	53 (15-40)	26	39	57	40	102
ALT (U/L)	76 (10-35)	66	36	33	21	169
GGT (U/L)	315 (11-21)	507	373	360	269	1220
Protein (g/dL)	8.5 (5.9-7.0)	8.3	8.0	9.1	8.2	8.8
Albumin (g/dL)	3.4 (3.5-5.2)	3.2	4.4	2.9	5.1	2.9
D-dimer (μgFEU/mL)	n/d	1.2	n/d	n/d	n/d	n/d
Fibrinogen (mg/dL)	n/d	539	n/d	n/d	n/d	n/d
Urinalysis	normal	normal	normal	normal	normal	normal

[1]After first treatment course.
[2]Values closest to normal achieved during interval.
ANA: anti-nuclear antibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transferase.

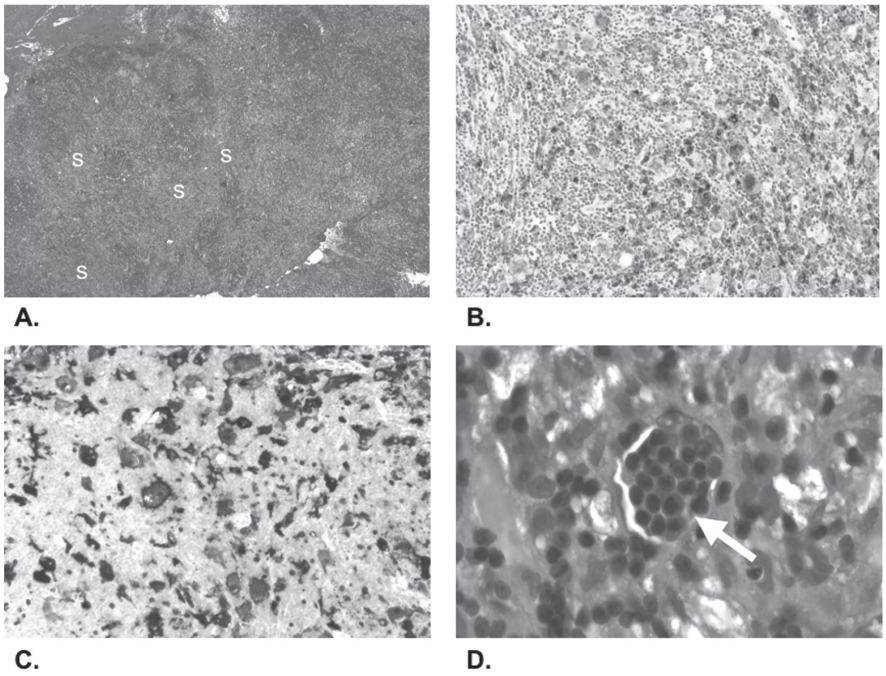

Fig. 1. Porta hepatis lymph node biopsy. **A.** The sinuses (some marked "s") are dilated and filled with histiocytes that have abundant cytoplasm (H&E stain, original magnification 40x). **B.** Immunohistochemical stain showing CD68 positive histiocytes (original magnification 200x). **C.** Immunohistochemical stain for S100 showing positive staining histiocytes (original magnification 400x). **D.** Emperipolesis, lymphocytes within the cytoplasm of a histiocyte (white arrow; H&E, oil immersion, original magnification 1000x).

and vinblastine induced resolution of skin and joint symptoms within one week. He was subsequently placed on maintenance therapy with methotrexate (60 mg/m^2) and 6-mercaptopurine (6-MP, 60 mg/m^2). He weighed 20.2 kg (6th percentile) and measured 120.6 cm (16th percentile), indicating some improvement in growth on treatment for RDD. Six months later (the time of completion of this report) a treatment course with 2-chlorodeoxyadenosine (2-CdA) was initiated because of persistent lung lesions and elevated inflammatory markers.

Discussion

Articular manifestations of Rosai-Dorfman disease

Musculoskeletal manifestations of RDD usually relate to histiocytic lesions in bone (1, 2). There are only two well documented cases of arthritis in association with RDD, both in adult patients. Gupta (5) reported a woman with chronic ankle arthritis unresponsive to TNF-α blockade with infliximab. Ankle biopsy showed synovitis with features of RDD, but extensive marrow lesions in adjacent bones suggested that the synovitis resulted from local extension of osseous lesions. Soomro (4) described a man with a chronic recurrent painful polyarthritis, with NSAID-responsive episodes lasting 3-4 days, who ultimately developed RDD with mostly skin involvement. A transient polyarthritis was mentioned in one report of RDD with unusual necrotic features in lymph node histology, but no further details of the joint involvement were given (6).

The direct association of our patient's arthritis with RDD is supported by the observations that the presence of the arthritis correlated with the other systemic manifestations (*e.g.* fever, malaise, and rash) and laboratory abnormalities such as anemia and elevated inflammatory markers and liver enzymes and that it responded to the same treatments as the RDD. An association between RDD and other rheumatologic disorders exists insofar as it has been reported in patients with primary Sjögren's syndrome (7) and systemic lupus erythematosus (8, 9). Both conditions can feature a polyarthritis similar to the one observed in our patient. However, laboratory and clinical findings ultimately did not suggest either of these disorders.

Potential mechanism of arthritis in RDD

The pathogenesis of a polyarthritis in RDD presents an intriguing question. Messenger RNAs encoding the proinflammatory cytokines TNF-α, interleukin (IL)-1 and IL-6 have been detected in RDD histiocytes and it has been suggested that cytokinemia is responsible for the systemic manifestations of RDD such as fever, which occurs in about one third of patients (10). These three cytokines, particularly TNF-α, have been implicated in the pathogenesis of inflammatory arthropathies (11). However, the one patient with RDD and arthritis who was treated with the TNF-α blocker infliximab did not improve (5). It remains to be explained why only a fraction of individuals with RDD develop synovitis. It has been suggested that chemokine receptor expression on RDD histiocytes is responsible for their migration into affected organs (12). Conceivably, accumulation of histiocytes in synovium and local cytokine production could lead to a synovitis of variable duration and severity.

Distinguishing RDD from SoJIA

This report adds polyarthritis to the musculoskeletal manifestations of RDD in children and thus suggests that RDD should be considered in the expanded differential diagnosis of patients who present with fever, rash, lymphadenopathy and arthritis. Considering that the lymphadenopathy of RDD may be absent or not apparent (1), RDD might also present with fever, rash and arthritis without lymphadenopathy.

SoJIA is most typically associated with fever, rash, lymphadenopathy and arthritis. Even though our patient did not have the classic evanescent rash and diurnal fever pattern of this disorder, SoJIA was initially suspected. Liver enzyme abnormalities have been described in SoJIA (13), but the liver lesions detected by ultrasonography were not consistent with this diagnosis. RDD was not considered early on because of the lack of arthritis in children with RDD. As this case demonstrates, clinical and routine laboratory evaluations may not differentiate adequately between SoJIA and RDD. However, clinical pre-biopsy features that should raise a suspicion of RDD instead of SoJIA are unusually large lymphadenopathy, fixed skin eruptions that do not fluctuate with fever, and absence of diurnal fever variations. If biopsy is performed, the characteristic histopathologic changes seen in skin and lymph nodes readily distinguish between the two disorders. Whereas S100$^+$ histiocytes with emperipolesis are seen in RDD skin and lymph nodes (1), minimal perivascular mononuclear infiltrates are seen in SoJIA skin lesions (14) and nonspecific follicular hyperplasia in SoJIA lymph nodes (15). In children in whom RDD is suspected, biopsy of affected skin or lymph node is therefore recommended.

Leukemia, lymphoma and macrophage activation syndrome represent other serious conditions to be considered in the extended differential diagnosis of RDD and SoJIA. In the present case, these were ruled out definitively by bone marrow aspirate and evaluation of biopsied lymph nodes by histology and flow cytometry, thus underscoring the value of these interventions in the initial evaluation of patients presenting within the spectrum of fever, rash, arthritis and lymphadenopathy.

Other uncommon features of RDD illustrated by the present case

Our patient had liver involvement, as documented by elevated transaminases and GGT and by microscopic cholangitis seen upon histologic evaluation of the liver biopsy. The gastrointestinal tract is the organ system least likely to be affected by extranodal RDD (16). In a series of 11 patients with RDD involving the GI tract, 5 (45%) had liver disease (16). As our patient, all of these also had nodal RDD and relatively severe systemic disease: Of the 4 patients with sufficient follow-up information, two died from RDD and the others had long-term disease activity.

This case also illustrates well how rare

cases of RDD require ongoing systemic medical treatment. Due to the high rate of clinically stable disease or remission, systemic medical treatment of RDD is usually reserved for patients with lesions causing significant morbidity and/or disfigurement. The primary goal of pharmacologic treatment is to induce lasting remission with a single treatment course (usually comprised of a corticosteroid with or without a cytotoxic agent) and to start maintenance treatment only if suggested by clinically significant disease flares (*e.g.*, ref. 17). In analogy to other histiocytic disorders such as Langerhans Cell Histiocytosis, maintenance therapy usually consists of methotrexate and one or more cytotoxic agents, although there are no controlled trials supporting any specific agent or combination. In our patient, systemic treatment was initiated during the first recurrence, since he had systemic symptoms, persistent failure to thrive and laboratory evidence of continuing systemic inflammation. Even though he responded well to the initial induction therapy with dexamethasone and vinblastine, he subsequently required maintenance therapy with methotrexate and 6-MP and – most recently – a course of treatment with 2-CdA.

Acknowledgements

We thank the house staff members of the Children's Hospital of Philadelphia who cared for the patient, and H. Ralph Schumacher (University of Pennsylvania) for helpful discussion and critical reading of the manuscript.

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