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ARTHROPATHY WITH RASH, CHRONIC MENINGITIS, EYE LESIONS, AND MENTAL RETARDATION

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Three unrelated children (one girl and two boys) have had since birth a syndrome characterized by a permanent skin rash which becomes more intense during flare-ups associated with fever, lymphadenopathy, splenomegaly, and arthritis symmetrically involving the large joints. In one boy, typical psoriasis was observed at age 3 years. In two patients, roentgenograms of the joints showed early patellar ossification and an abnormal epiphyseal appearance. The three children also had neurologic involvement, with mental retardation, enlarged head circumference, eye lesions, late closure of the anterior fontanel, and a chronic meningitis with infiltration by polymorphonuclear cells. No immunologic abnormalities were found, but polymorphonuclear cells infiltrated the skin, lymph nodes, synovial fluid, and CSF.

Chronic arthritides in children are most often related to juvenile rheumatoid arthritis when they meet the diagnostic criteria established by the American Rheumatism Association (1) which, in general, are not very different from those agreed upon by Europeans at the EULAR--WHO Symposium held in Oslo in 1977 (2). However, some very peculiar clinical conditions do not quite fit into any of the various classifications previously proposed. We had the opportunity to observe three unrelated patients with chronic arthritis, rash, lymphadenopathy, splenomegaly, and central nervous system involvement, including a chronic meningitis. The symptoms and findings in these children seemed very similar to that observed by Ansell et al (3) as "Familial arthropathy with rash, uveitis, and mental retardation".

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CASE REPORTS

Patient 1. This girl was born in 1963 to young, healthy, nonconsanguinous parents after normal gestation and labor (birth weight 4,150 gm). No past history of chronic inflammatory disease was found in the family, and her half-sister is healthy. A generalized maculopapular erythema, present at birth, still persists and becomes more intense during recurrent attacks of fever (38.5° C). Pruritus occurs after exposure to sunlight. In 1965, large lymph nodes and splenomegaly were detected. At age 5, the patient complained of arthralgia which progressively involved ankles, hips, knees, and wrists. The joints became red, swollen, and tender during generalized febrile and cutaneous relapses, and returned to normal during quiescent phases. Radiographs had never shown any changes in the affected joints.

Abbreviations used
CSF: cerebrospinal fluid
JRA: juvenile rheumatoid arthritis
ESR: erythrocyte sedimentation rate

Nervous system involvement appeared progressively: intermittent headaches started at 6 years and a moderate sensorineural hearing loss was detected at 7, when the head circumference was 55 cm and the IQ was 80. Skull radiographs revealed the persistence of the anterior fontanel until 9 years. Ocular examination showed intermittent papilledema and paralimbic keratitis of the lower hemicornea. At 10 years, focal seizures of the left side occurred for the first time. Cerebrospinal fluid contained 74 cells/μl with a majority of polymorphonuclears, and an elevated CSF protein concentration (140 mg/dl); it remained sterile on culture. Subsequent CSF examination revealed persistent hypercellularity (25 to 200 cells/μl) with neutrophils (28 to 65%), eosinophils (4 to 50%) and mononuclear cells (4 to 58%), and a high CSF protein concentration (90 to 165 mg/dl) containing polyclonal IgG. Electroencephalography showed the presence of slow waves. Cerebral angiography was not helpful. Computerized axial tomography revealed mild cerebral atrophy (Table I).

Five seizures occurred during the six following years, despite treatment with phenobarbital (100 mg/day) and carbamazepine (200 mg/day). No localization of neurologic signs has occurred. The girl is attending school.

Laboratory investigations showed leukocytosis (7,000 to 17,000/μl, 67 to 89% neutrophils, 0 to 6% eosinophils), high ESR 22 to 85 mm at 1 hour), and increased serum immunoglobulin values. No autoantibodies and no humoral or cellular immune deficiencies were detected. An extensive study to find a bacterial, fungal, parasitic, or viral infection (appropriate cultures; light and electron microscopy of CSF cells; serum and CSF antibody titers for mycoplasma, toxoplasmosis, *Listeria monocytogenes,* coxsackie, herpes, cytomegalovirus, Epstein Barr virus, hepatitis B, rubella, measles) failed to uncover any infection. Lymph node histology showed a nonspecific inflammatory adenitis with polymorphonuclear infiltration. Histologic study of a skin lesion revealed infiltration by polymorphonuclear cells around the blood vessels. Tissue typing was All, B7, Cve, DRW2/A32, B40, C-, DRW4.

The course of the disease, with flare-ups associated fever, increased cutaneous manifestations, arthralgia and/or arthritis, was partially responsive to systemic steroid therapy and to nonsteroidal antiinflammatory drugs. Chlorambucil (0.1 to 0.2 mg/kg/day) was given in 1973 for one year, inducing a long-term decrease in systemic relapses.

Patient 2. This boy was born to unrelated, healthy parents. A cutaneous rash developed within the first days of life, and has persisted. The child was hospitalized for the first time at 11 months for fever and exacerbation of the rash. Physical examination revealed enlargement of the lymphoid organs (lymph nodes, spleen) and liver. An elevated leukocyte (49,600 mm ^{3}) was noted at this time. At 18 months, arthritis of the knees was present. The child's course was characterized by repeated relapses, more or less influenced by systemic steroid therapy, and associated with the following features: fever (rarely above 38.5° C), a nonitching maculopapular rash persisting between the flare-ups (variable during the day, with a mild squamous appearance under the

TABLE I

MAIN MANIFESTATIONS OBSERVED IN THE PATIENTS

Symptoms	*Patient 1*	*Patient 2*	*Patient 3*
Skin lesions			
Maculopapular lesion	+	+	+
Psoriaris	−	−	+
Adenomegaly	+	+	+
Splenomegaly	+	+	+
Hepatomegaly	−	−	+
Arthritis	+	+	+
Abnormal ossification of epiphysis and patella	−	+	+
Eye lesions			
Papilloedema	+	+	+
Keratitis	+	−	−
Uveitis	−	−	+
Optical atrophy	−	−	+
Meningocerebral involvement			
Mental retardation	+	+	+
Head enlargment	+	+	+
Late closure of fontanel	+	+	+
Slow waves in EEG	+	+	+
Chronic meningitis	+	NT*	+
Cerebral atrophy	+	NT	+

* Not tested.

eyebrows and hair), hepatosplenomegaly and large lymph nodes, and progressive arthropathy involving the large joints with inflammatory flare-ups. Synovial fluid contained unaltered polymorphonuclears (30%), lymphocytes (55%), and monocytes (15%). No microorganism was detected by usual cultures. Roentgenograms of the knees showed advanced patellar ossification, and epiphyseal changes (Figure, *A*). Neurologic findings included an IQ of 80, late closure of the anterior fontanel (fourth year), enlarged head circumference (54 cm at 8 years), intermittent papilledema confirmed by fluorescent angiography, and electroencephalographic abnormalities with diffuse slow waves and instability of the tracings (Table I). CSF was not examined.

Laboratory investigations confirmed the presence of a chronic inflammatory process with leukocyte counts up to 60,000/mm^3 (65 to 75% neutrophils, 0 to 3% eosinophils), high ESR (25 to 90 mm at 1 hour), increased serum concentration of immunoglobulins IG, and elevated total hemolytic complement (CH_{50}) values. There were no detectable autoantibodies, and humoral and cellular functions were normal. No polymorphonuclear dysfunction was detected (Table II). Lymph node histology revealed follicular hypertrophy, a large medullary area, and massive infiltration by polymorphonuclear cells in the dilated sinuses. Skin biopsy showed the presence of polymorphonuclear cells in the perivascular areas. Synovial tissue was not hypertrophic and contained fibrous deposits and congested vessels. The family study revealed psoriasis in two relatives (paternal grandfather and uncle). Four other siblings are healthy. The course of the disease was characterizes by frequent exacerbations (eight to 12/year) with fever, increased rash, arthritis, and enlargement of the lymph nodes and spleen. Systemic steroid therapy seemed partially effective. Chlorambucil (0.2 mg/kg/day), started at 5 years and given for 27 months, induced a good improvement. The patient developed a fatal myelomonoblastic leukemia two years after withdrawal of chlorambucil therapy (4).

Patient 3. This boy, born in 1975, weighing 3,150 gm after a 34-week normal gestation, was the only child of nonconsanguinous, healthy parents. Two maternal aunts had cutaneous psoriasis. The labor was normal, the amniotic fluid was clear, and the Apgar score was 9 at 1 minute, but the child had a maculopapular rash, jaundice with hepatosplenomegaly, conjunctivitis, and

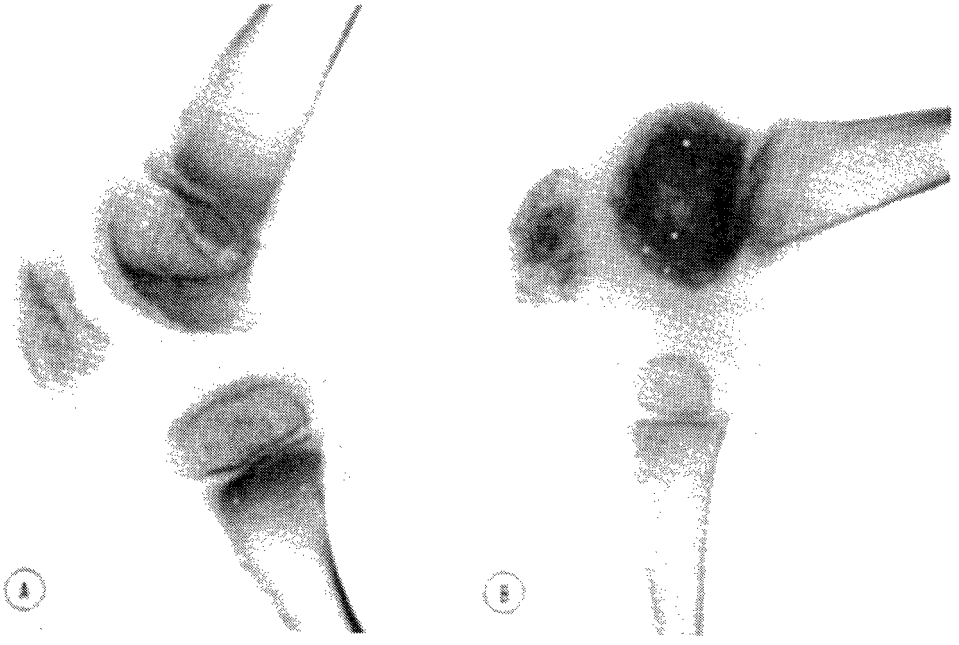

Fig. 1 — Roentgenograms of the knees at age 3 years of, *A*, Patient 2 and, *B*, Patient 3

an infected omphalocelo (*Staphylococcus epidermidis*), operated on at the sixth hour of life. Appropriate cultures from placenta, blood, urine, meconium, and from eye, ear, throat, and nose secretions remained sterile. Cerebrospinal fluid contained 8 cells/μl and 100 mg of protein/dl, and was sterile. Despite high serum values of IgA (138 mg/dl), and IgM (346 mg/dl), serologic tests for syphilis, herpes, cytomegalovirus, rubella, and toxoplasmosis were not consistent with a perinatal infection. Placental histology did not have the features of *Listeria monocytogenes* infection but showed thickened blood vessel walls with some thrombosis, and calcifications in the basal and intrachorial areas. At the time no maternal investigations were performed. The course of the disease, which was insensitive to antibiotic therapy (ampicilin 200 mg/kg/day, then cephalothin 200 mg/kg/day, and gentamicin 3 mg/kg/day) given for one month, responded to betamethasone (0.2 mg/kg/day, progressively decreased) except for the rash and the splenomegaly.

The skin lesions subsequently have been permanent, and characterized by a maculopapular rash, increasing on air exposure and during fever, itching under sunlight, and desquamating during relapses. This appearance plus the presence of nail lesions (pitting and hyperkeratosis) suggested psoriasis, which was confirmed by skin histology. Hepatosplenomegaly and lymph node enlargement were evident during flare-ups. A symmetrical polyarthritis involved the knees at the age of 3 months, and progressively affected elbows, and ankles. Affected joints were swollen, warm, and painful on motion, and residual stiffness was seen during remissions. No major synovial hypertrophy was observed, contrasting with the considerable deformation of the knee resulting from early patellar ossification. The first roentgenographic changes of the femoral epiphysis were seen at 10 months; following this, abnormal ossification rapidly involved the femoral epiphysis and patella of both knees, leading to a very peculiar radiologic appearance (Figure *B*). Humeral and radial epiphyseal changes appeared during the third year of life. The synovial fluid was cloudy, contained a majority of polymorphonuclear cells, and remained sterile.

TABLE II

IMMUNOLOGIC DATA

	Patient 1 (15 yr)	*Patient 2 (5 yr)*	*Patient 3 (4 yr)*
B-cells (%)	15	20	22
IgG (mg/dl)	2,000	2,300	1,700
IgM (mg/dl)	240	260	320
IgA (mg/dl)	664	350	520
IgD (mg/dl)	52	0	2
IgE (× N)	×2	×1	×4
Immunological complexes	—	NT*	±
Rheumatoid factors	—	—	—
Antinuclear antibodies	—	—	—
Antibody production after stimulation	Elevated	Elevated	Elevated
T-cell (%)	72	74	50
In vitro lymphocyte proliferation	Normal	Normal	Normal
Mixed lymphocyte reaction	Normal	NT	Normal
CH_{50} (units)	68	75	72
Polymorphonuclear			
N B T	NT	Normal	Normal
Chemotaxis	Normal	NT	Normal
Phagocytosis	NT	Normal	Normal
Bactericidal activity	NT	NT	Normal
Chemotactic factor	NT	NT	Normal

* Not tested.

A seizure at 3 months of age was the first manifestation of central nervous system involvement. Cerebrospinal fluid contained 25 to 200 cells/μl with neutrophils (20 to 65%) and eosinophils (0 to 13%), and 120 to 250 mg/dl protein. The CSF remained sterile. On repeated examinations clinical neurologic assessment was normal except for persistence of the anterior fontanel at 5 years. Head circumference was 49 cm at 18 months. Intelligence quotient (Brunet-Lezine test without verbal expression) was 70 at 4 years. Ocular examination showed chronic papilledema with starting optic atrophy, and some posterior synechiae without active uveitis. Electroencephalography showed bilateral slow waves without spike discharges. Computerized axial tomography revealed mild dilatation of the left ventricle, dilated cortical grooves, and enlargement of the longitudinal sulci.

A nonspecific inflammatory pattern was present in blood since birth, characterized by elevated ESR (30 to 90 mm at 1 hour) and increased WBC count (18 to 40,000/μl), with neutrophils 51 to 80%) and eosinophils (2 to 21%). Immunologic assessment at 4 years showed elevated serum immunoglobulin concentration, an elevated antibody response after vaccination, no abnormalities of cell-mediated immunity, elevated CH_{50} values, and no defect of polymorphonuclear function (Table II). The histology of a lymph node showed a nonspecific adenitis with follicular hypertrophy and a considerable infiltration by polymorphonuclear cells. Tissue typing was A1, B7, C-, DRWE/A11, B35, CW4, DRW1.

The clinical course of the disease was poorly influenced by nonsteroidal anti-inflammatory drugs, but partially responded to prednisone therapy (0.5 to 2 mg/kg in an alternate-day regimen). Treatment with D-penicillamine (10 mg/kg/day) for one year was unsuccessful.

DISCUSSION

The three patients described here had a very peculiar syndrome characterized by maculopapular skin lesions present since birth, which persisted and became more intense during acute

episodes associated with fever; enlargement of lymph nodes and spleen; and arthritis with unique abnormal epiphyseal and patellar ossification in two of them. They have neurologic involvement with mild mental retardation, head enlargement with late closure of the fontanel, eye lesions, moderate cerebral atrophy, and a chronic meningitis with infiltration by neutrophils and eosinophils. The first diagnosis considered was a condition to a systemic type of JRA (2), since a neonatal onset has been recognized by some authors (5). However, the abnormal ossification observed in two of these children seemed very unusual. The clinical and histologic findings of psoriasis in one patient, and a history of psoriasis in his family, led us to consider the relationship with this disease (6). The occurrence of psoriasis in the family of a second patient, and of eye lesions observed in two, also suggests psoriasis (7). Psoriatic arthritis is rare in childhood; a recent review estimated that only 70 cases had been described, including one of the three patients discussed here (8). However, the joint manifestations in psoriasis have never been observed before one year of age. The arthritis is generally asymmetric and often involves small joints, and joint alterations are typically erosive, quite different from those described here. Moreover, to our knowledge, no chronic central nervous system involvement has been observed in psoriasis. In fact, no satisfactory diagnosis can be proposed, including the various syndromes with hypereosinophilia described by Chusid et al. (9) The only reported cases with clinical and biologic features at all similar to those in our patients, were two siblings described by Ansell et al (3) as "Familial arthropathy with rash, uveitis, and mental retardation." These patients also had cerebral atrophy, and an elevated protein concentration in CSF was found in one of them. They did not have skin symptoms suggesting psoriasis, but their father did (B. M. Ansell, personal communication). Thus, the findings in these five patients seem to be very similar.

This condition is mainly characterized by a diffuse and chronic infiltration by neutrophils and eosinophils of blood, skin, lymph nodes, and synovial and cerebrospinal fluids, and by a chronic inflammatory process. Since the disease was present at birth, an infectious agent was considered, but extensive serologic studies, appropriate cultures, and microscopic examination of lymph nodes and of synovial and cerebrospinal fluids were not informative. On the other hand, there is no definitive argument in favour of an inherited disease except that two siblings were affected in the family described by Ansell et al. (3). There was no detectable abnormality of specific immunity, the complement system, and polymorphonuclear function, and no immune dysfunction suggesting an allergic process or an autoimmune disease.

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EDITORIAL IMPÉRIO, LDA.