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Sinushistiocytosis With Massive Lymphadenopathy (Rosai-Dorfman Disease): Response to Methotrexate and Mercaptopurine

Gerd Horneff, MD, Heribert Jürgens, MD, Waldemar Hort, MD, Dietrich Karitzky, MD, and Ulrich Göbel, MD

We report a 3-year-old girl presenting with bilateral cervical lymph node enlargement persisting for > 3 months. Leukocytosis, elevated erythrocyte sedimentation rate, a marked hypergammaglobulinemia, and a moderate hepatosplenomegaly were also found. The diagnosis of sinushistiocytosis with massive lymphadenopathy (SHML), also known as Rosai-Dorfman disease, was established histologically by the demonstration of characteristic sinushistiocytosis with lymphocytophagocytosis. Treatment was started with high dose steroids, and a decline of lymph node size and a normalization of laboratory parameters occurred. However, when steroids were tapered, lymph node size rapidly reincreased. Chemotherapeutic treatment was started using etoposide, which was completely ineffective. Therefore, treatment was changed to a combinatory low dose methotrexate therapy and 6-mercaptopurine for 4 months. Whereas a prompt and complete remission was reached, single 6-mercaptopurine therapy was maintained and treatment has been discontinued after a total of 2 years. The child has remained healthy for 7 years. This case would recommend the use of methotrexate and 6-mercaptopurine for treatment of complicated SHML.

Key words: sinushistocytosis, Rosai-Dorfman disease, Methotrexate, Mercaptopurine

INTRODUCTION

The sinushistiocytosis with massive lymphadenopathy (SHML), also known as Rosai-Dorfman disease, has to be considered in the differential diagnosis of cervical lymphadenopathy. SHML is a benign condition that usually affects children and usually presents with enlarged bilateral tenderless cervical lymphadenopathy [1]. In 1969 and in 1972, Rosai and Dorfman described 34 cases [2,3]. Since then, numerous cases have been reported [1,4–8]. Fever, leukocytosis with neutrophilia, an elevated erythrocyte sedimentation rate, and polyclonal hypergammaglobulinemia are common accompanying features. Although the etiology remains unknown, the disease is thought to be a disorder of immune regulation or a response to a presumed infection with major manifestations in the lymph nodes [8]. Associated infectious agents include Klebsiella, Brucella, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, and Herpes type 6 virus [9,10]. The affected lymph nodes show a distinct histologic morphology with pericapsular fibrosis, dilated sinus, which are filled with numerous histiocytes showing large clear cytoplasm, and a marked hemophagocytosis with a prominent lymphocytophagocytosis [11,12]. Using immunohistochemical methods, the histiocytic cells show a typical profile and stain positive for the S-100 antigen and α-1-antichymotrypsine [7,13]. In the majority of cases, the course of the disease is benign and self-limiting but prolonged. Some cases show intermitting exacerbations. Patients with extranodal involvement, which is uncommon, an underlying immunocompromizing illness, or concomitant viral infections may have a fatal prognosis [8,14]. Massive enlargement of lymph nodes may result in upper airway obstruction. However, there are no concrete therapeutic recommendations. Frequently corticosteroids are used for therapy. Other therapeutic strategies included chemotherapy using vinca alkaloides, alkylating agents, but also surgical procedures, radiation, and treatment using tuberculostatic and virustatic agents were reported [15].

CASE REPORT

The 3-year-old girl was first seen in 1987 because of a progressing bilateral cervical lymph node enlargement.

From the Division of Pediatric Oncology, Department of Pediatrics, (G.H., U.G.), and Institute of Pathology (W.H.), University of Duesseldorf, Duesseldorf, Department of Pediatrics, University of Muenster, Muenster (H.J.), Division of Pediatrics, City Hospital Leverkusen, Leverkusen (D.K.), Germany.

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Address reprint requests to G. Horneff, M.D., Department of Pediatrics, University of Duesseldorf, Moorenstr. 5, 40225 Duesseldorf, Germany.

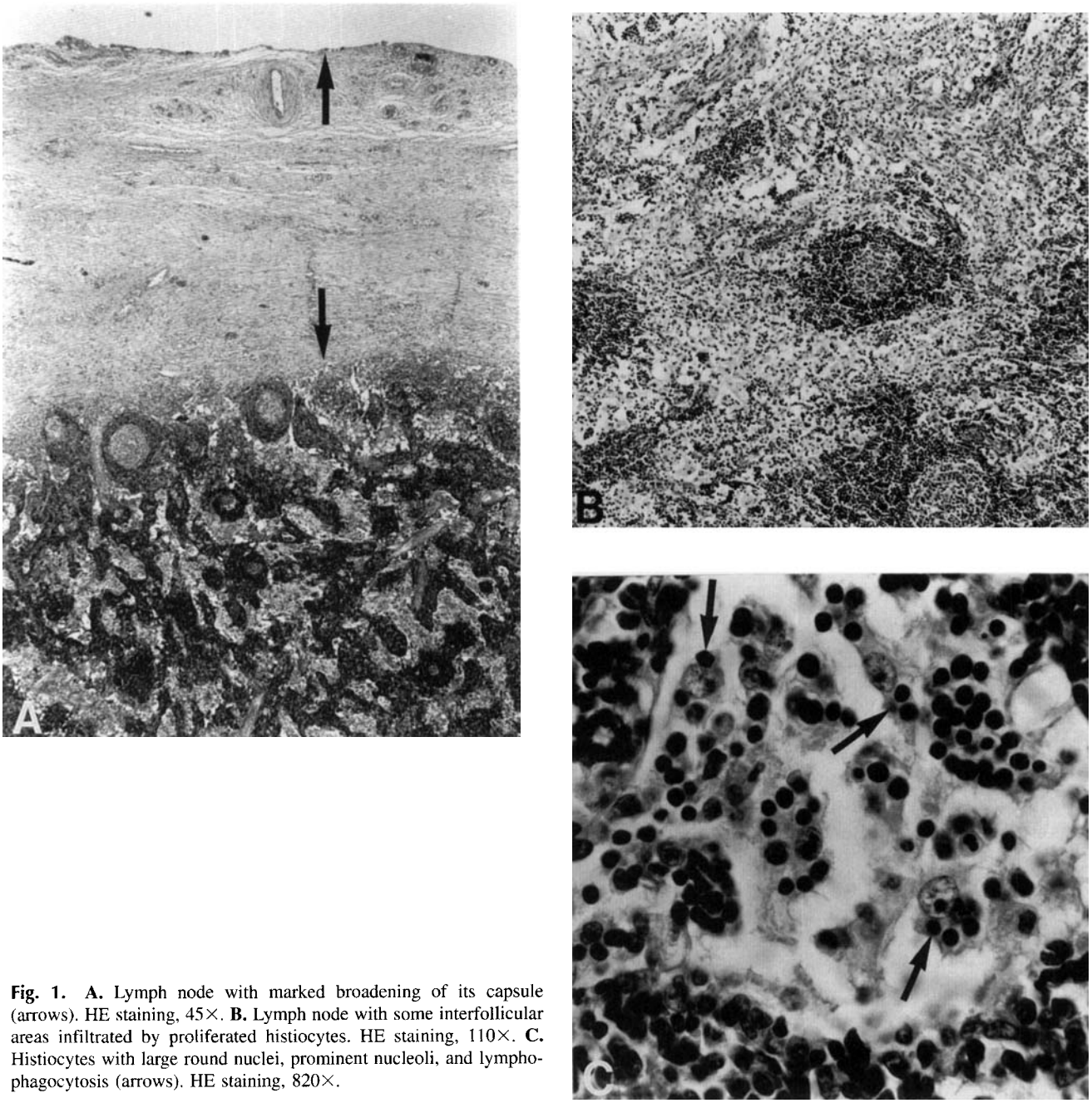

Fig. 1. **A.** Lymph node with marked broadening of its capsule (arrows). HE staining, 45×. **B.** Lymph node with some interfollicular areas infiltrated by proliferated histiocytes. HE staining, 110×. **C.** Histiocytes with large round nuclei, prominent nucleoli, and lymphophagocytosis (arrows). HE staining, 820×.

Her medical history was unremarkable except for several upper airway infections, otitis, and recurrent conjunctivitis. Sinusitis of the ethmoid cells and maxillary sinus has been treated successfully. On physical examination, bilateral enlarged submandibular lymph nodes of up to 4 cm and a moderate hepatosplenomegaly (liver 3 cm above normal range, spleen at the upper limit) were found. Laboratory examination revealed a leukocytosis of 14,500 μl with a relative lymphopenia of 10%, an increased ESR of up to 132 mm/h, a serum level of CRP of 62 mg/l, and a hypergammaglobulinemia with an elevation of all classes (IgG 26.4 g/l, IgM 3.0 g/l, IgA 3.3 g/l). All serological tests for infections carried out were negative. Chest roentgenograms, radionucleide bone scan, and bone marrow aspirate showed no abnormalities. Histopathological examination of an extirpated lymph node of the left submandibular region was performed. The lymph node architecture appeared not to be destroyed, but there was a marked fibrous thickening of the capsule (Fig. 1A). Lymphoid follicles and germinal centers were present. The interfollicular regions and the sinuses (Fig. 1B) were expanded by an infiltration of large histiocytic cells. These contain large round vesicular nuclei with one or more distinct nucleoli and an abundant pale-staining cyto-

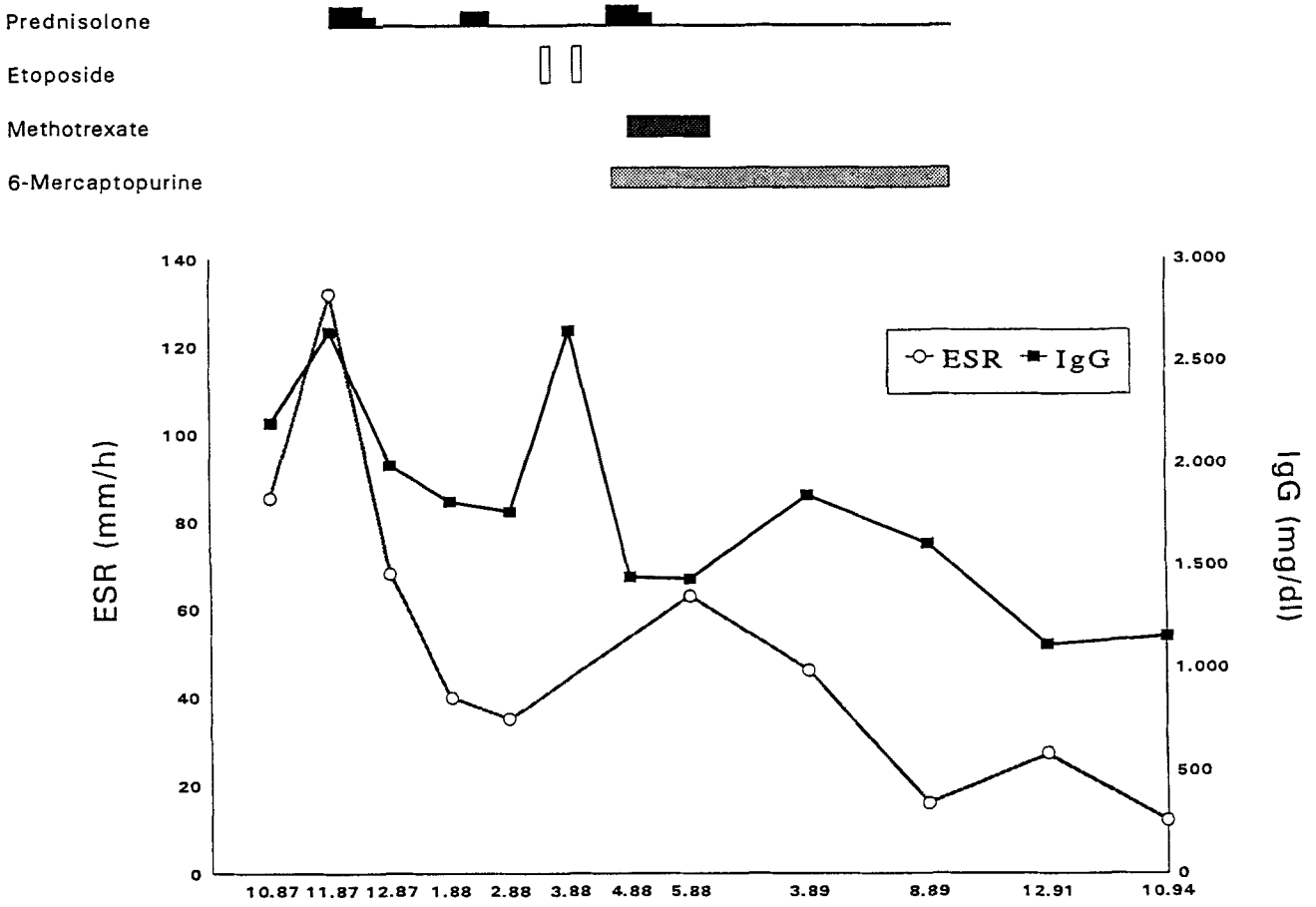

Fig. 2. Treatment and kinetics of ESR and level of immunoglobulin G in the course of the patient.

plasm frequently containing lymphocytes and plasma cells (Fig. 1C). Additionally, plasma cells were prominent in the medullary lymphoid cords and are often seen around vessels. Similar infiltrations were also seen in the cortical and paracortical region. These histological features are characteristic for the SHML.

During the following 4 months, lymph nodes increased in size. Repeated biopsy was performed, which confirmed the diagnosis. After treatment with prednisolone (2 mg/kg body weight), rapid regression of the lymph nodes sizes was observed and hepatosplenomegaly disappeared; however, when corticosteroids were tapered, lymph node size increased again, reaching pretreatment level. A second course of high dosage corticosteroids was given followed by etoposide, frequently used for treatment of malignant histiocytosis (2×160 mg/m^2 body surface followed by 3×160 mg/m^2 3 weeks later). However, this treatment did not alter lymph node size or laboratory abnormalities. Consequently, a third prednisolone treatment was instituted together with a combinatory chemotherapy using 6-mercaptopurine (60 mg/m^2 per day) and methotrexate (12 mg/m^2 weekly). Treatment and the course of laboratory parameters are outlined in Figure 2. When a prompt and complete remission was obtained, methotrexate was stopped after 4 months and therapy with 6-mercaptopurine and low dose oral corticosteroids (5 mg/m^2 every 48 hours) was maintained. Laboratory parameters normalized during the second year of treatment. After a total of 2 years, treatment was discontinued. There were no side effects observed, and the child has showed no further complications for 7 years.

DISCUSSION

SMHL is a histologically well defined disorder usually affecting cervical lymph nodes of children and adolescents. Adults and elderly people are rarely affected. The clinical presentation usually consists of massive, bilateral painless lymphadenopathy simulating a malignant process. Other lymph node regions are occasionally involved clinically or more frequently by microscopic changes only [12].

The etiology remains unknown, and the course of SMHL is often self-limiting and benign, but cases with a remitting course have been described. Since malignant transformation seems not to occur in SMHL, a fatal out-

TABLE I. Case Reports of the Literature: Indication and Response to Treatment

First author, year	Number	Treatment	Indication[a]	Response
Rosai, 1972	34	antibiotics antituberculostatics, corticosteroids		15 × healthy, 9 × persisting disease, 8 unknown
		4 × radiation		
		4 × chemotherapy	1 × amyloidosis	1 death (renal insufficiency)
			1 × malignant transformation	1 death (infection during therapy)
Lampert, 1976	15	none or antibiotics or corticosteroids	generalized LAP in the fatal course	6 healthy, 1 persisting disease
				1 death, 8 unknown
Ngendohayo, 1982	8	1 × surgery	LAP	1 unknown, 1 healthy
		2 × tuberculostatic	LAP	5 persisting disease
		5 × none		1 death, 1 death unrelated to SHML
Miettinen, 1987	4	2 × none		both healthy
		1 × surgery	bone involvement	healthy
		1 × corticosteroids	skin involvement	persisting disease
Nawroz, 1988	1	surgery	bone involvement	healthy
McAlister, 1989	7	5 × none		spontaneous resolution
		1 × radiation and corticosteroids	eye involvement	alive
		1 × vincristine, then chlorambucil, then methotrexate	kidney infiltration, anemia hypergammaglobuliemia	complete response to methotrexate
Layfield, 1989	1	none		healthy
Pettino, 1990	1	none		persisting disease
Philipp, 1991	1	corticosteroids	generalized LAP and skin infiltrates	complete remission
Chu, 1992	5	3 × none		1 healthy, 2 persisting disease
		1 × surgery		unknown
		1 × chlorambucil	salivary gland infiltration, fatigue, polyarthralgias	persisting disease
Wenig, 1992	14	5 × surgery only	all patients	5 × complete remission
		7 × surgery, corticosteroids and radiation	recurrence/persisting disease	1 died, 2 persisting disease
		cytoxan and etoposide	progression, orbital infiltration recurrence and sinsus involvement	1 complete remission, 1 persisting disease
Baildam, 1992	1	aciclovir	preceding varicella infection	healthy
Paulli, 1992	1	radiation	LAP, fever, hypergammaglobulinemia	persisting disease
Afzal, 1992	1	surgery	renal infiltration	healthy
Perrin, 1993	1	corticosteroids, cyclophosphamide	uveitis, fatigue, fever	persisting disease
Shaver, 1993	1	corticosteroids	intracerebral infiltrates	complete remission
Levine, 1994	1	surgery and radiation	soft tissue infiltration	healthy
Foucar, 1984	14 deaths	radiation 3 ×	5 × extranodal disease (skin,	cause of death:
		corticosteroids 8 ×	mucosa, bone)	SHML in 2, persisting disease in 4,
		tuberculostatics 1 ×	6 × generalized LAP	immunoregulatory abnormalities in 5,
		chemotherapy 4 ×	cervical and axillar LAP	unusual infection in 3 patients
Total	111			45 (40%) healthy/complete remission
				27 (24%) persisting disease
				20 (18%) deaths (1 unrelated to SHML)
				18 (16%) unknown

[a]LAP = lymphadenopathy.
[b]Only fatal courses reported, no. agents unknown.

come was associated with extranodal infiltration of brain and kidney, immune dysfunction, or unusual infections [16,17]. Extranodal involvement occurred not rarely and was observed in up to 40% [11,12]. In addition, cervical obstruction by massive lymphoma may occur.

In our patient, SHML was present for 7 months before treatment was considered because of increasing lymph node size. Treatment with prednisolone results into a marked but transient clinical response. Treatment with etoposide was started because of its effectiveness in ma-

lignant childhood histiocytosis, but it was totally ineffective. A combination therapy using corticosteroids and the antimetabolits methotrexate and 6-mercaptopurine proofed to be effective. Since thereafter the child remained healthy, there is no hint for an underlying immunodeficiency of an immunoregulatory disorder, which has been observed in other patients with complicated or recurrent disease.

SHML generally does not by itself require chemotherapeutic treatment as shown by numerous published cases [4,5,7,12]. However, there is no information about indication for treatment and there is no study of treatment efficacy available. Table I summarizes several reports in which treatment of SHML with or without extranodal manifestations has been performed. In most cases localized extranodal disease prompted to a primarily surgical therapy or to radiation. In several cases antibiotics or tuberculostatic agents were given without a significant response [4,5]. Corticosteroids have been tried successfully in generalized lymphadenopathy or in a case with intracranial infiltrations [16–18]. Whereas the course of SHML can be fatal or because of organ involvement or systemic manifestations, treatment with chemotherapeutics may be indicated and had been tried [1,8,11,12,14]. However, four patients died despite chemotherapy [14]. In three of them (treated with either immuran, cytoxan, or methotrexate), autopsy showed ongoing SHML. One patient treated with cyclophosphamide died after an aspiration pneumonia, but no autopsy was performed. Cytoxan and etoposide were used for treatment in two other patients, which was successful in one of them [1]. Chlorambucil and cyclophosphamide have been tried without success in two other patients [8,11]. In a case reported by McAlister et al. [12], vincristin and chlorambucil had been tried, but disease recurred. Thereafter, methotrexate was successfully used. The analysis of 111 cases in the literature revealed as many patients with a complete remission as with persisting disease or a fatal course. Excluding the data of Foucar et al. [14], who reported fatal courses only, about the half of the patients had been cured, 30% had persisting disease when reported, and 6% died; history is unknown for the remaining others.

In summary, there is only little information available to answer the question when and how patients should be treated. In extranodal or generalized manifestation or persistent disease, treatment using cytotoxic agents may be indicated when corticosteroids failed. In this case, antimetabolites should be the drug of first choice before alkylating agents or radiation are considered.

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