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Case report

Lyme borreliosis mimicking central nervous system malignancy: the diagnostic pitfall of cerebrospinal fluid cytology

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Abstract

We report two children with acute loss of neurological functions and signs of an increased intracranial pressure. Imaging techniques ruled out space occupying lesions, whereas CSF cytology indicated CNS involvement of a non-Hodgkin lymphoma in the form of abnormal lymphocytic pleocytosis with malignancy criteria fulfilling lymphoid cells. CSF protein electrophoresis and *Borrelia burgdorferi* serology revealed neuroborreliosis which was successfully treated with antibiotic therapy. The malignancy mimicking cytology is based on a blastoid transformation of B- and T-lymphocytes due to the antigenic stimulus of *B. burgdorferi* infection. Lymphoid cells in the CSF of a patient with acute or chronic neurological symptoms raise the differential diagnosis of inflammatory etiology versus CNS lymphoma. Monomorphism and higher quantity of the lymphoid cells point to CNS lymphoma. A lower quantity and polyclonal pattern of lymphoid cells associated with an elevated protein fraction caused by intrathecal immunoglobulin synthesis suggest an inflammatory etiology. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: *Borrelia burgdorferi*; CSF cytology; Lymphoid cells; Non-Hodgkin lymphoma

1. Introduction

The neurological symptoms of Lyme disease, caused by the spirochete *Borrelia burgdorferi*, are extremely variable and are observed in the second stage of the disease, weeks and up to months after the transmitting tick bite and a possible erythema chronicum migrans. Because of the variety and ambiguity of clinical symptoms and MRI findings, CNS malignancy is a frequent and important differential diagnosis [1,2]. Our cases describe another aspect of the malignancy mimicking nature of Lyme disease: CSF cytology can be a diagnostic pitfall suggesting CNS involvement of a non-Hodgkin lymphoma.

2. Case reports

2.1. Case 1

A previously healthy 15-year-old girl developed increasing weakness and pain in both arms over 4 weeks. In addition she had a 2 week history of cephalgia, nausea, vomiting and weight loss of 3.5 kg accompanied by a stiff neck, acute bilateral papilloedema and weakness of the left trochlear and glossopharyngeal nerves. The clinical aspect pointed to a cerebrospinal process with cervical radicular and cranial nerve IV and IX affection associated with signs of an increased intracranial pressure.

Blood count and serum inflammatory markers were negative (Table 1). Cranial and spinal MRI showed no evidence of space occupying lesions. CSF showed an increased protein fraction of 124 mg/dl and normal glucose level. The CSF cytology identified abnormal lymphocytic pleocytosis (266/μl) with 10% macrocellular and macronuclear, partially double nuclear lymphoid cells with increased basophilia frequently showing mitosis and expressing leucocyte common antigen besides mature lymphocytes and atypical

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Table 1[a]

	Patient 1		Patient 2
	Initial	*10 weeks later*	*Initial*
Blood			
ESR	25/52	10/22	4/6
Leukocytes (/μl)	4600	4500	4600
Lymphocytes (%)	42	38	37
Polymorphs (%)	52	54	63
Eosinophils (%)	2	5	
Basophils (%)	0	1	
Monocytes (%)	2	2	
Borrelia burgdorferi antibodies			
Immunoblot IgM	Positive		Positive
Immunoblot IgG	Positive		Positive
ELISA IgM			Positive
ELISA IgG			Positive
IHAT	Positive	Positive	
IFT-IgM (IE/ml)	1:40	1:40	
IFT-IgG (IE/ml)	1:160	1:80	
CSF			
Glucose (mg/dl)	49	56	49
Total protein (mg/dl)	124	22	111
Protein electrophoresis	Pathol.	Normal	Pathol.
Leukocytes (/μl)	266	14	162
Lymphocytes (%)	87	98	90
Lymphoblastoid cells (%)	10	0	5
Atypical plasma cells (%)	2	0	0
Granulocytes (%)	1	2	0
Monocytes (%)			5
Borrelia burgdorferi antibodies			
IHAT	Positive	Positive	
Immunoblot IgM	Positive		Positive
Immunoblot IgG	Positive		Positive
IFT-IgM (IE/ml)	1:40	1:2	1:2
IFT-IgG (IE/ml)	1:160	1:8	1:128

[a] Abbreviations: ELISA, enzyme-linked immunosorbent assay; IFT, immunofluorescence test; IHAT, imunohemagglutination test.

plasma cells (Table 1 and Fig. 1). The cytological findings suggested CNS involvement of a non-Hodgkin lymphoma. Bone marrow biopsy and ^{99}Tc-scintigraphy revealed no pathological findings. CSF protein electrophoresis revealed a significant disturbance of the blood brain barrier with increased albumin, alpha-, beta- and gamma-immunoglobulin fractions with positive banding indicating intrathecal immunoglobulin synthesis, suggesting an inflammatory etiology. Significant titres of *B. burgdorferi* antibodies were found, confirming Lyme disease (Table 1). Serological tests for neurotropic viruses remained negative. During 14 days of intravenous cefotaxime therapy, the neurological symptoms as well as the papilloedema normalized. Ten weeks later CSF showed a normal cytology, normal protein fractions and decreased *B. burgdorferi* antibody titres (Table 1). Two years of follow-up were uneventful.

2.2. Case 2

A previously healthy 10-year-old boy developed relapsing cephalgia, nausea, vomiting and increasing double vision for 2 months. On examination he showed convergent strabism, discrete abducens palsy and papilloedema on both sides as well as a mild ataxia. The clinical diagnosis was a cerebral process with cranial nerve VI affection and signs of increased intracranial pressure. Serum inflammatory markers were negative. CSF analysis showed an increased protein fraction of 111 mg/dl and normal glucose level.

CSF cytology identified abnormal lymphocytic pleocytosis (162/μl) with 5% macrocellular, macronuclear lymphoid cells frequently showing mitosis (Table 1, Fig. 2). Cranial MRI showed no space occupying lesion but a gadolineum enhancement in the right oculomotoric nerve. CSF protein electrophoresis showed a disturbance of the blood brain barrier with intrathecal immunoglobulin synthesis. *B. burgdorferi* serology in CSF and blood confirmed neuroborreliosis (Table 1). During 2 weeks of cefotaxime treatment the neurological symptoms improved; after 2 months follow-up they had disappeared.

3. Discussion

In both cases the cytogram showed lymphoid cells with the malignancy criteria enlarged cell volume, increased basophilia, enlarged nucleoli and frequent mitosis. This cellular pattern is usually found in primary or secondary leptomeningeal or cerebral involvement of non-Hodgkin lymphoma. The evidence of intrathecal immunoglobulin synthesis pointed to an inflammatory etiology, positive *B. burgdorferi* antibodies leaded to the diagnosis of neuroborreliosis, in case 1 meningopolyradiculitis and cranial nerve neuritis, in case 2 meningitis and cranial nerve neuritis. In both cases the clinical history concerning tick bites or skin eruptions was negative.

In neuroborreliosis blood brain barrier dysfunction and intrathecal humoral immune response in the form of IgG, IgM, IgA and oligoclonal immunoglobulin bands on isoelectric focusing are frequent but not mandatory, developing mostly during the course of the disease [3]. The same holds true for specific serological antibodies. Antibody response can be weak or absent at different stages of the disease [4]. Common CSF findings in neuroborreliosis include elevated protein fraction, normal glucose and lymphocytic pleocytosis with lymphomono-plasmacellular cytogram [5]. The occurrence of lymphoid cells suggests cerebral or cerebromeningeal involvement of a malignant non-Hodgkin lymphoma. Primary CNS non-Hodgkin lymphomas are rare, 1–2% of all brain tumors, but 10–34% of systemic non-Hodgkin lymphomas have CNS involvement [6,7]. Razavi-Encha et al. [8] described the occurrence of lymphocytic pleocytosis composed mainly of lymphoid cells and plasma cells associated with numerous foamy macrophages in four patients with *B. burgdorferi* related meningoradiculitis. Kraft et al. [9] found atypical plasma cells in seven of 2102 samples of lumbar CSF,

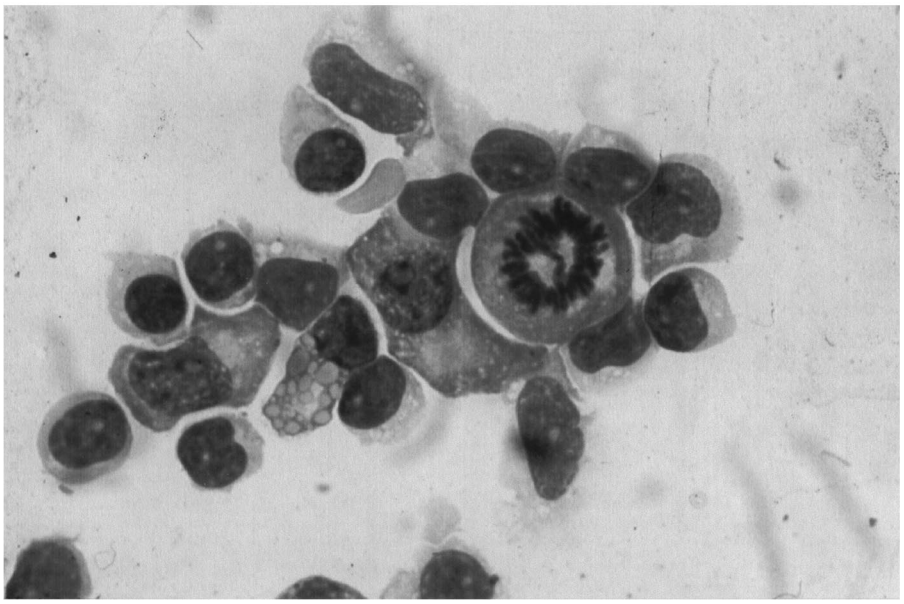

Fig. 1. Pappenheim-stained cytology of the cerebrospinal fluid (case 1). Mitotic macrocellular lymphoid cell and an atypical plasma cell with adherent lymphocytes.

four of them had neuroborreliosis, one multiple sclerosis, one herpes zoster and one a malignant non-Hodgkin lymphoma. Monomorphism, higher cellular atypia and a higher quantity of the lymphoid cells point to CNS lymphoma. A lower quantity and polyclonal pattern of the lymphoid cells associated with an elevated protein fraction caused by intrathecal immunoglobulin synthesis suggest an inflammatory etiology.

The malignant shape of the lymphoid cells is a result of activation and transformation of T-and B-lymphocytes due to the antigenic stimulus of *B. burgdorferi* [10]. An enlarged cytoplasm with increased basophilia, prominent Golgi regions, enlarged or double nuclei with loosening of the chromoplasm and visible nucleoli are the characteristic morphological changes of lymphoid cells. Furthermore they show increased mitosis and adherence and cooperation of cells, so called peripolesis [10].

Beside neuroborreliosis lymphoid cells are found more rarely in CNS herpes virus infections like cytomegaly, herpes simplex and varicella zoster [9].

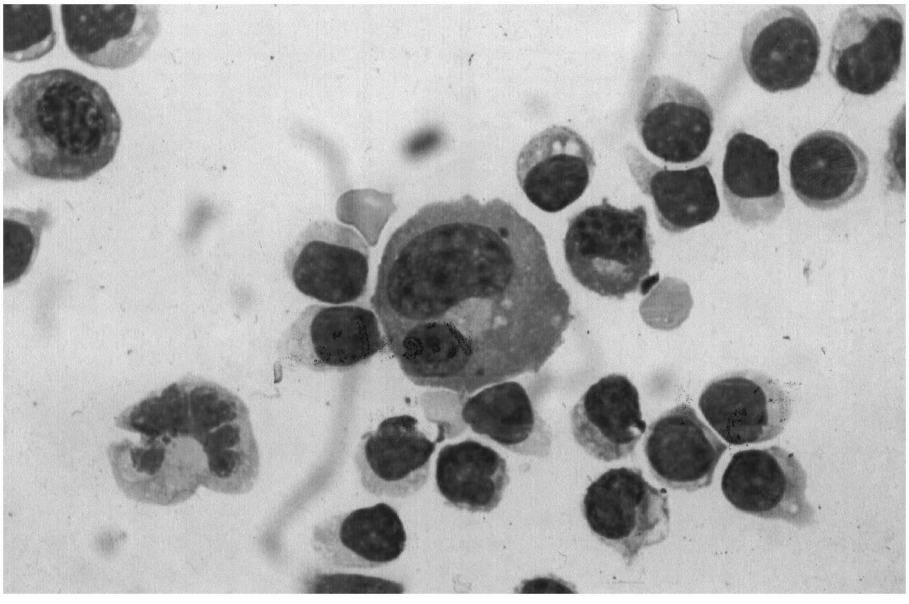

Fig. 2. Pappenheim-stained cytology of the cerebrospinal fluid (case 2). Lymphoid cell with enlarged cytoplasm, enlarged and doubled nucleus and prominent Golgi region.

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