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CASE REPORT

**D. Behringer · A. Spyridonidis · S. Fetscher
A. Schmitt-Gräff · S. Högerle · R. Kaiser**

# Paraneoplastic polyneuropathy preceding the diagnosis of Hodgkin's disease and non-small cell lung cancer in a patient with concomitant *Borrelia burgdorferi* infection

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**Abstract** A patient with painful peripheral neuropathy is presented, whose symptoms were thought to result from an infection with *Borrelia burgdorferi* sensu lato. Investigations of the cerebrospinal fluid for signs of inflammation and borrelial antibodies were negative, and the patient did not benefit from repeated antibiotic treatment. Electrophysiologic studies and sural nerve biopsy showed axonal neuropathy consistent with a paraneoplastic syndrome. Further workup revealed mediastinal Hodgkin's disease (HD; nodular sclerosing subtype) Ann Arbor stage II and non-small cell cancer of the lung (stage T1N0M0). Surgical resection of the lung cancer and combined chemo- and radiotherapy for HD resulted in complete remission of both malignancies. While the preexisting neurologic symptoms persisted during treatment, neurography showed some improvement of the distal nerves. During radiation therapy the patient developed transient left-sided brachial plexopathy. This case illustrates that the diagnosis of borreliosis in patients with isolated painful peripheral neuritis cannot be based solely upon positive IgG titers and supports the requirement for a thorough workup for an underlying – potentially curable – disease. In addition, singular pulmonary lesions in the setting of HD should be suspected to have a separate cause.

D. Behringer (✉) · A. Spyridonidis · S. Fetscher
Department of Hematology/Oncology, University of Freiburg, Hugstetterstrasse 55, 79106 Freiburg, Germany
e-mail: behringer@mm11.ukl.uni-freiburg.de
Fax: +49-761-2703684

A. Schmitt-Gräff
Department of Pathology, University of Freiburg, Germany

S. Högerle
Department of Nuclear Medicine, University of Freiburg, Germany

R. Kaiser
Department of Neurology, Städtische Kliniken, Pforzheim, Germany

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## Introduction

In Europe, infection of the nervous system with *Borrelia burgdorferi* sensu lato (B.B.) most often presents as painful radiculitis with lymphocytic pleocytosis, impairment of the blood–CSF barrier and intrathecal immunoglobulin synthesis. Peripheral neuritis is a rare manifestation of B.B. infection and is frequently associated with acrodermatitis chronica atrophicans [1, 2]. The prevalence of elevated serum IgG titers for B.B. amounts to 5–25% of occupationally exposed persons in certain geographic areas [3], thus increasing the risk of an erroneous interpretation of positive IgG titers in patients with neurologic symptoms, as presented in this report. The presence of serum IgG antibodies against B.B. in patients with painful polyneuropathy (PNP; without acrodermatitis chronica atrophicans) does not justify extensive antibiotic treatment but requires an extensive workup including biopsy of a peripheral nerve in order to identify underlying diseases.

## Case report

In March 1997 a 44-year-old white man, living in an area in which B.B was endemic [4], noted tingling and painful dysesthesias of both forearms and hands. The symptoms persisted, and he went to see a general physician 4 months later. His past history was unremarkable except for meningitis as a child and a 10×6 $cm^2$ hemangioma of the right thoracic wall since birth. A primary workup, including a white blood count and blood chemistry within normal limits (WNL), was remarkable for an elevated IgG titer to B.B. and an equivocal IgM titer (IgM IFT 1:10, IgG 1:640 normal <1:40). The physical examination was reported normal. The patient was treated with doxycycline (200 mg per day) for 2 weeks. Neither this treatment nor another 3 weeks of doxycycline 3 months later alleviated the symptoms.

In October 1997 the patient recognized a general loss of strength, bilateral dysesthesias of the feet and an increase in the

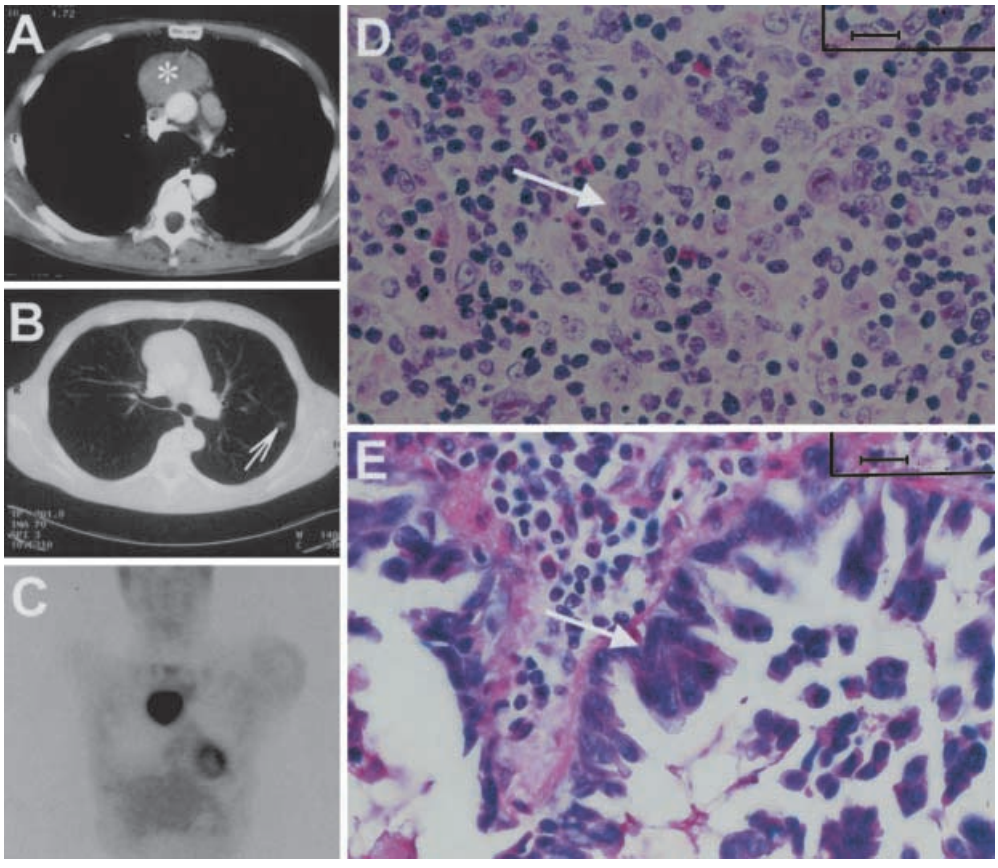


**Fig. 1** Computed tomography of the chest (**A**) revealed a large mediastinal mass (*) and with contrast enhancement an additional isolated lesion of segment 3 (*arrow* in **B**). The mediastinal mass was visualized as a hypermetabolic lesion by positron emission tomography with 18-FDG (**C**); however, the parenchymal lesion of the left lung did not show enhanced uptake (note physiologic uptake of 18-FDG in the heart). Histology of the mediastinal mass (**D**) was consistent with classical Hodgkin's disease. Diagnostic multinucleated Reed-Sternberg cells with prominent nucleoli (*arrow*) and background cells consisting of small lymphocytes with scattered eosinophils are seen throughout the field (Giemsa stain; *bar*: 50 µm). Microscopic analysis of the pulmonary lesion (**E**) showed a papillary proliferation of columnar epithelial cells with nuclear atypia (*arrow*) (PAS stain; *bar*: 32 µm)

burning pain of both hands and feet. The neurologic examination and a laboratory workup (serum protein, serum immunoelectrophoresis, rheumatoid factor, liver enzymes) were considered unremarkable; however, the neurographic evaluation was consistent with a PNP [moderate impairment of nerve conduction velocity (NCV) of the right sural nerve]. The IgG titer for B.B. was unchanged and IgM was not detectable. Treatment with clarithromycin (600 mg/day) for 4 months resulted in only transient symptomatic improvement.

Because of persisting symptoms, in March 1998 the patient went to see his neurologist. Neurography now showed deterioration of the right tibial nerve (NCV 36 m/s, normal 41 m/s; NAP 4 mV, normal 5 mV) compared with October 1997; lumbar puncture revealed borderline pleocytosis (8/µl, normal <5/µl; 90% lymphocytes, 10% monocytes), an intact blood–brain barrier (CSF protein WNL), and no evidence of intrathecal immunoglobulin synthesis or B.B.-specific antibodies.

Because of the persisting symptoms the patient was referred to the neurology outpatient clinic of the university hospital in July 1998. The pertinent neurologic findings at that time included absence of left knee reflexes and bilateral ankle reflexes and glove-like dysesthesia of the left hand and the ulnar aspect of the right hand. Although a causal relationship between the patient's complaints and the borrelial infection was considered unlikely, intravenous administration of a third-generation cephalosporin (ceftriaxone 2 g/day for 2 weeks) was performed.

Two months later the patient was admitted to the neurology department with progressive symptoms. In addition to absent knee and ankle jerks, the physical examination now revealed hypesthesia and hypalgesia of both hands and distal lower legs with normal pallesthesia and positional sense of both feet. Sensory stimulation of the median and tibial nerve for somatosensory evoked potentials and nerve conduction studies revealed a severe sensory, predominantly axonal neuropathy with absent cortical signals. The following laboratory investigations were unremarkable: WBC, liver enzymes, creatinine, antinuclear and anti-neutrophil-cytoplasmic antibodies (ANA, ANCA), complement components, cryoglobulin, angiotensin-converting enzyme, vitamin $B_{12}$ and folic acid serum levels, cerebrospinal fluid (cell count, differential, protein, glucose, oligoclonal bands), and screening for IgG antibodies to Hu, Yo and Ri proteins in CSF and serum by immunoblotting. Borrelial serology remained unchanged. The histopathologic examination of a sural nerve biopsy including electron-microscopic studies showed primary axonal degeneration with secondary demyelination and an absence of inflammatory cellular infiltration and was considered consistent with a paraneoplastic neuropathy. There was no evidence of a cellular infiltration.

A chest X-ray revealed a mediastinal mass of 6×5×8.5 $cm^3$ in addition to a 2-cm parenchymal lesion in the third left pulmonary segment. Biopsy of the mediastinal mass was consistent with the nodular-sclerosing subtype of Hodgkin's disease (HD, Fig. 1D). While the left pulmonary lesion was considered as a manifestation of Hodgkin's disease on chest CT (Fig. 1A, B), positron emission tomography (PET) failed to show signal enhancement of the corresponding pulmonary site compared to the bright signal elicited in the mediastinal mass (Fig. 1C). An open lung biopsy revealed an adeno-papillary carcinoma (pT1G2, Fig. 1E). Since the tumor reached the resection borders, the upper lobe of the left lung was resected and the mediastinal lymph nodes were explored. The final pathologic stage of the adenocarcinoma was pT1N0M0, and the HD was Ann Arbor stage IIA. The latter disease was treated with a modified combination chemotherapy (bleomycin, etoposide, doxorubicin, prednisone, cyclophosphamide, procarbazine; no vincristine because of the preexisting PNP). Staging after completion of chemotherapy revealed a reduction of the mediastinal mass by 80%. During the first week of radiation therapy (mantle field, 45 Gy) the patient developed a progressive sensory and motor deficit of the left upper extremity. Neurologic evaluation at that time indicated a diffuse brachial plexus lesion, whereas neurography of the distal nerves showed an improvement compared with the previous

examinations. As the radiation was considered a likely cause for the plexopathy, the radiation field was modified and excluded the left upper thoracic area until completion of the radiation therapy.

As of April 2000, 9 months after completion of therapy, the patient still suffers from painful PNP; with respect to the two malignancies there is no evidence of active disease. The symptoms related to the left brachial plexus have considerably improved.

## Discussion

Painful neuropathy most frequently occurs in the presence of alcohol abuse, diabetes mellitus or vitamin deficiency. Multiple other rare conditions (e.g., arsenic poisoning, cryoglobulinemia, vasculitis of the vasa nervorum, infectious causes, paraneoplastic mechanisms) may also lead to this condition [5].

The patient described here presented with three conditions that might have caused the painful PNP. The finding of an equivocal B.B. serology was considered sufficient to submit the patient to four different antibiotic regimens, which all failed to improve his symptoms. There are few reports considering distal PNP as a manifestation of B.B. infection [6, 7]. Since the prevalence of positive IgG titers against B.B. may range between 5% and 25% in endemic areas such as the Black Forest, where the patient lived, the risk of an erroneous interpretation of this serologic finding is considerable. Unfortunately, neuropathies with a predominantly distal distribution are typically associated with inconspicuous CSF findings with regard to inflammation or intrathecal synthesis of agent-specific antibodies [1, 6, 7, 8]. Therefore, more extensive evaluation including nerve biopsy has to be carried out in order to exclude potentially curable underlying conditions. Nerve biopsy findings of patients with distal painful polyneuropathy – suspected to result from B.B. infection – have shown axonal degeneration with dense peri- and intravascular lymphoid cell infiltration, in contrast to the findings here, with only sparse cellular infiltration [1, 8, 9]. In one patient the identification of DNA of B.B. in the sural nerve was reported [10]. Interestingly, the serology of that patient was ambiguous: two assays for the detection of serum antibodies to B.B. (ELISA and immunoblotting) were negative and one (immunofluorescence assay) was marginally positive (titer 1:100, normal ≤1:50). Lumbar puncture revealed an elevated protein level and oligoclonal bands. In addition, the patient's symptoms improved considerably after 4 weeks of intravenous ceftriaxone. These findings do not correspond to those obtained in our patient. Therefore it is unlikely that the PNP presented here was a manifestation of B.B. infection.

Among malignant conditions, lung cancer has most often been associated with paraneoplastic PNP [11]; however, there are reports of subacute sensory neuropathy in the setting of HD [12]. On the basis of our investigations no definitive conclusion can be drawn as to what may have caused the PNP in this patient [12, 13, 14]. The failure to detect Hu- or Ri-specific antibodies in immunoblotting does not exclude the possibility of a paraneoplastic syndrome, as the sensitivity of these antibodies is only about 30–40% [15]. Unfortunately, no chest imaging studies were performed during the first 18 months of the PNP manifestation, which could have provided more conclusive information as to which malignancy had occurred first.

While the risk of a second malignancy in patients treated for HD has been estimated at 17.6% [16], the synchronous manifestation of HD and a nonhematologic primary malignancy in patients who have not received prior radio- or chemotherapy is exceedingly rare [17, 18, 19]. No obvious genetic or environmental causes have been identified in such patients. The atypical manifestation of a solitary pulmonary lesion in our patient with mediastinal HD [20], together with the lack of signal enhancement of this tumor by PET in contrast to the bright signal of the primary mediastinal mass, raised the suspicion of a different etiology of the pulmonary lesion. This finding allowed for curative therapy with surgical resection of the lung cancer and combined chemo- and radiotherapy for stage II HD.

We conclude that patients with a distal painful PNP in the setting of an isolated borrelial serology (positive IgG) and lack of other manifestations indicative of an active borrelial infection should not be submitted to repeated antibiotic treatments without thorough investigation for other – potentially curable – underlying diseases.

An atypical pattern of HD otherwise limited to the mediastinum mandates exclusion of a second malignancy by histopathologic evaluation to allow for appropriate staging and therapy.

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