EXTENDED REPORT

Infectious CNS disease as a differential diagnosis in systemic rheumatic diseases: three case reports and a review of the literature

K Warnatz, H H Peter, M Schumacher, L Wiese, A Prasse, F Petschner, P Vaith, B Volk, S M Weiner

Background: Immunosuppressive treatment of rheumatic diseases may be associated with several opportunistic infections of the brain. The differentiation between primary central nervous system (CNS) involvement and CNS infection may be difficult, leading to delayed diagnosis.

Objective: To differentiate between CNS involvement and CNS infection in systemic rheumatic diseases.

Methods and results: Three patients with either longstanding or suspected systemic rheumatic diseases (systemic lupus erythematosus, Wegener's granulomatosis, and cerebral vasculitis) who presented with various neuropsychiatric symptoms are described. All three patients were pretreated with different immunosuppressive drugs (leflunomide, methotrexate, cyclophosphamide) in combination with corticosteroids. Magnetic resonance imaging of the brain was suggestive of infectious disease, which was confirmed by cerebrospinal fluid analysis or stereotactic brain biopsy (progressive multifocal leukoencephalopathy [PML] in two and nocardiosis in one patient).

Discussion: More than 20 cases of PML or cerebral nocardiosis in patients receiving corticosteroids and cytotoxic drugs for rheumatic disease have been reported. The clinical aspects of opportunistic CNS infections and the role of brain imaging, cerebrospinal fluid analysis and stereotactic brain biopsy in the differential diagnosis are reviewed.

Central nervous system (CNS) involvement may become a severe complication of several autoimmune disorders.

In systemic lupus erythematosus (SLE) between 18 and 67% of patients have CNS involvement. Symptoms include psychosis, mood disorders, seizures, acute confusional states, stroke, migraine, chorea, aseptic meningitis, transverse myelopathy, as well as subtle cognitive impairment. There are no specific laboratory or magnetic resonance imaging (MRI) findings, making a proper diagnosis often difficult. MRI may be negative despite overt neuropsychiatric symptoms. Cerebrospinal fluid (CSF) analyses may show mild lymphocytic pleocytosis. The diagnosis is made by clinical analysis often shows only a slight rise in protein and a mild increase in cell count.

Primary angitis of the CNS is a very rare disorder. Sensitivity, inflammation, and clinical manifestation are highly variable. Many cases may be missed, and the delay in diagnosis may be several weeks to months. MRI of the CNS, and histology.

Primary angiitis of the CNS: ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; CMV, cytomegalovirus; CNS, central nervous system; CRP, C reactive protein; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IV, intravenous; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy; SLE, systemic lupus erythematosus; VZV, varicella zoster virus; WG, Wegener’s granulomatosis

Abbreviations: ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; CMV, cytomegalovirus; CNS, central nervous system; CRP, C reactive protein; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IV, intravenous; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy; SLE, systemic lupus erythematosus; VZV, varicella zoster virus; WG, Wegener’s granulomatosis

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patients with pre-existing autoimmune disease and new onset of CNS disease.

CASE REPORTS

Patient 1

A 33 year old woman was admitted to our hospital with progressive personality alterations, impairment of concentration and memory, difficulties in word finding, headache, and dysarthria. Eleven years ago SLE was diagnosed by the presence of antinuclear antibodies (titre 1/6000), increased DNA binding, photosensitivity, aphthosis, Jaccoud's arthritis, anaemia, and leucopenia. She had been treated with prednisone doses adjusted to disease activity (7.5–25 mg) and various immunosuppressive drugs: initially, azathioprine; later, chloroquine, danazol, cyclosporin A; and, finally, methotrexate. Five months before admission immunosuppressive treatment was switched from methotrexate to leflunomide (20 mg/day) because of gastrointestinal symptoms and persistent arthralgias.

On admission, laboratory analysis showed a moderate leucocytopenia (3.2–4.2×10⁹/l), resulting in a slightly raised lymphocytopenia (0.7–1.0×10⁹/l). The number of CD8+ T cells was decreased (0.24×10⁹/l), an IgG index of 0.5, and positive oligoclonal bands. A stereotactic brain biopsy was performed that showed abnormal oligodendroglial cells, demyelination, and swollen astrocytes associated with inflammatory cell infiltrates, suggesting the diagnosis of progressive multifocal leucoencephalopathy (PML). The diagnosis was confirmed by electron microscopy (fig 1B) and the detection of JC virus DNA in the brain tissue (nested polymerase chain reaction (PCR)) and in CSF samples (quantitative PCR). Tests for human immunodeficiency virus (HIV), cytomegalovirus (CMV) antigen, CMV-RNA, and antitoxoplasma IgM antibodies were negative. Leflunomide was stopped and the drug elimination was hastened by a two week treatment with cholestyramine.

Within three weeks the neurological status worsened, leading to a progressive motor weakness of the right side, a central paresis of the facial nerve, and a central impairment of bladder function. An MRI follow up disclosed progressive brain lesions. Antiviral treatment was started with 5 mg/kg cidofovir every two weeks. The course of the disease was fluctuating with phases of progression followed by phases of clear improvement of the neurological deficits.

Patient 2

Four years before admission a 52 year old white man had been diagnosed with WG. After a new onset of haemoptysis, proteinuria, scleritis, and arthralgias, diagnosis was histologically proved by a necrotising, granulomatous vasculitis in a bronchial biopsy specimen and by a positive ANCA (titre 1/100, anti-PR3 positive). With oral cyclophosphamide (2 mg/kg body weight) the clinical course stabilised, except for a residual proteinuria of 0.5 g/day. After 29 months of cyclophosphamide treatment (total dose 95 g), treatment was changed to methotrexate. Two months before admission, a slight increase in arthralgias and fever had developed. Because of suspected WG relapse the treating family doctor increased the daily steroid dose to 50 mg prednisolone a day. The patient was then admitted to our hospital. Because physical examination, a computed tomography scan of the lungs, and laboratory investigations showed no signs of WG activity or of infection, the patient was discharged and tapering of prednisolone was recommended.

Three weeks later he was readmitted because of cough, fever, night sweats, and weight loss of 8 kg. Now, the C reactive protein (CRP) was raised (24 g/l) and the differential blood count showed a lymphocytopenia, with CD4+ T cell counts reduced to 0.2×10⁹/l. An initial chest x ray examination, bronchoscopy, and blood cultures failed to identify any pathogens. Subsequently, the carbon monoxide diffusion capacity was decreased and a new chest x ray examination led to a suspicion of interstitial pneumonia. A bronchoalveolar lavage was performed and showed a chronic inflammation with no signs of pulmonary haemorrhage. All bacterial cultures, PCR for tuberculosis, legionella, and chlamydia, and PCR for Herpes viruses (herpes simplex virus (HSV), CMV, Epstein-Barr virus (EBV)) were negative. Treatment with methotrexate (15 mg weekly) was stopped and a third class cephalosporin and clarithromycin were started. Because the pulmonary function deteriorated, clarithromycin was changed to intravenous co-trimoxazole for suspected Pneumocystis carinii pneumonia. Because blood cultures were positive with Staphylococcus epidermidis, cephalosporins were replaced by imipenem. With this regimen dyspnœa and CRP levels decreased slightly and improved further when three days later treatment was started with 50 mg of intravenous (IV) prednisolone/day. On the 6th day of this regimen the patient suddenly presented with a generalised seizure. An MRI scan showed numerous small hyperintense lesions disseminated all over the brain (fig 2A) with a homogeneously high signal intensity on diffusion intensity on T₂ weighted imaging. CSF analysis showed a normal cell count, an increased total protein content (652 mg/l), an IgG index of 0.5, and positive oligoclonal bands. A stereotactic brain biopsy was performed that showed abnormal oligodendroglial cells, demyelination, and swollen astrocytes associated with inflammatory cell infiltrates, suggesting the diagnosis of progressive multifocal leucoencephalopathy (PML). The diagnosis was confirmed by electron microscopy (fig 1B) and the detection of JC virus DNA in the brain tissue (nested polymerase chain reaction (PCR)) and in CSF samples (quantitative PCR). Tests for human immunodeficiency virus (HIV), cytomegalovirus (CMV) antigen, CMV-RNA, and antitoxoplasma IgM antibodies were negative. Leflunomide was stopped and the drug elimination was hastened by a two week treatment with cholestyramine.
weighted images (fig 2B). As serological tests for toxoplasma IgM, aspergillus, borrelia, varicella zoster virus (VZV) IgA, CMV IgM, HSV, HIV were still negative, a stereotactic brain biopsy was performed. Pathological examination showed non-specific inflammation, but microscopic evaluation suggested coryne-like bacteria; the culture confirmed Nocardia farcinica. Intravenous co-trimoxazole, the preferred treatment, was continued for 40 days and then switched to oral maintenance treatment. A control MRI scan of the brain showed a complete remission six months later and clinically there was no WG activity detectable despite discontinuation of methotrexate.

Unfortunately, one year later the patient presented with proteinuria (6 g/day) and histological signs of segmental glomerulonephritis. The patient was treated with mycophenolate (1000 mg/day) without recurrence of the nocardia infection during the three month follow up.

Patient 3
A 55 year old white man complained of difficulties in writing four months before admission. His previous medical history was unremarkable. As the following neurological examinations, including EEG and MRI of the brain, were without clearcut pathological findings, the initial stage of Parkinson’s disease was suspected. MRI of the brain was repeated six weeks later and clinically there was no evidence of the underlying disease.

On admission an MRI scan of the brain showed multiple confluent non-enhancing lesions of the periventricular, subcortical, and deep white matter with discrete involvement of the cortex. The diffusion weighted MRI scan showed increased diffusion of the brain lesions (fig 3B). Further examinations showed no underlying autoimmune process (negative results for rheumatoid factor, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), antiphospholipid antibodies) or embolic disease. Laboratory findings, including CRP values, were unremarkable with the exception of a steroid induced leucocytosis of 23.5 × 10^9/l (13% lymphocytes) and a mild hypogammaglobulinaemia (IgG 5.6 g/l, normal range 7–16; IgA 0.6 g/l, normal range 0.7–4). Because of the impression of an accelerated deterioration of the underlying disease cyclophosphamide pulse therapy was started. The patient felt some improvement and was discharged one week later to rehabilitation.

One month later, after the patient had received a second bolus of cyclophosphamide, he became febrile, somnolent, and tetraparetic. On readmission, an MRI scan of the brain showed progressive confluent non-enhancing subcortical white matter lesions. A spinal tap was repeated and the CSF was positive for JC viral DNA. Before treatment could be applied he died with signs of septic shock.
# Table 1 Clinical presentation of primary cerebral involvement of rheumatic diseases and opportunistic CNS infections

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>NPSLE</th>
<th>Primary CNS vasculitis</th>
<th>Wegener’s granulomatosis</th>
<th>Neuro-Behçet</th>
<th>Neurosarcoidosis</th>
<th>PML</th>
<th>HSV encephalitis</th>
<th>Bacterial meningitis</th>
<th>Brain abscess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of CNS disease</td>
<td>Acute, subacute, chronic</td>
<td>Acute, subacute, chronic</td>
<td>Subacute, chronic</td>
<td>Acute, subacute, chronic</td>
<td>Acute, subacute, chronic</td>
<td>Subacute (weeks)</td>
<td>Acute, subacute (days-weeks)</td>
<td>Acute (days)</td>
<td>Subacute (days-weeks)</td>
</tr>
<tr>
<td>Seizures</td>
<td>13–35%</td>
<td>15–20%</td>
<td>Rare</td>
<td>4%</td>
<td>10%</td>
<td>5%</td>
<td>Frequent</td>
<td>20–30%</td>
<td>20–30%</td>
</tr>
<tr>
<td>Headache</td>
<td>34–57%</td>
<td>30–64%</td>
<td>Frequent</td>
<td>95%</td>
<td>30%</td>
<td>5%</td>
<td>Frequent</td>
<td>90%</td>
<td>70–90%</td>
</tr>
<tr>
<td>Motor weakness/paresis</td>
<td>20%</td>
<td>50%</td>
<td>?</td>
<td>10–21% Paresis, 24% pyramidal signs</td>
<td>5–10%</td>
<td>33%</td>
<td>Frequent</td>
<td>10–15%</td>
<td>20–50%</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>5–10%</td>
<td>29%</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>&lt;1%</td>
<td>Frequent</td>
<td>30–50%</td>
<td>20–30%</td>
</tr>
<tr>
<td>Cognitive disorders</td>
<td>12–86%</td>
<td>40–50%</td>
<td>Rare</td>
<td>88%</td>
<td>10%</td>
<td>36%</td>
<td>Frequent</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Psychosis</td>
<td>4–6%</td>
<td>Rare</td>
<td>Rare</td>
<td>2%</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>10–30%</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Reactive</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Visual deficits</td>
<td>5% (vasculitis, neuropathy, amaurosis fugax)</td>
<td>10–15%</td>
<td>Frequent (cranial neuropathy, ocular motor deficits)</td>
<td>1% Optic neuropathy</td>
<td>5–38% Optic neuritis</td>
<td>35% e.g. homonymous hemianopsia</td>
<td>Frequent</td>
<td>Rare</td>
<td>Hemianopsia</td>
</tr>
<tr>
<td>Sensory deficits</td>
<td>6–20%</td>
<td>15–20%</td>
<td>?</td>
<td>Up to 27%</td>
<td>5–10%</td>
<td>17%</td>
<td>Rare</td>
<td>Rare</td>
<td>30%</td>
</tr>
<tr>
<td>Cerebellar disorders</td>
<td>Rare (infarction)</td>
<td>Rare</td>
<td>33%</td>
<td>Rare</td>
<td>21%</td>
<td>13–32%</td>
<td>Rare</td>
<td>Rare</td>
<td>Ataxia 10%</td>
</tr>
<tr>
<td>Cranial nerve involvement</td>
<td>5–35%</td>
<td>Frequent</td>
<td>Frequent</td>
<td>25% Ophthalmoplegia, 10–15% bulbar palsy</td>
<td>50–72% Cranial nerve palsies</td>
<td>Rare</td>
<td>Rare</td>
<td>10 (N. III, VI, VII)</td>
<td>Rare</td>
</tr>
<tr>
<td>Other</td>
<td>1% Transverse myelitis, 2–5% chorea</td>
<td>30% Aphasia</td>
<td>Chronic meningitis, myelopathy</td>
<td>8% Meningo-encephalitis, 6% movement disorders</td>
<td>5–12% Meningitis, 10–28% myelitis, 10% hypothalamic and pituitary dysesthesia</td>
<td>Impaired speech</td>
<td>Wernicke aphasia, dysphasia</td>
<td>Meningitis, fever, arthralgia</td>
<td>50% Fever, 25–30% meningitis</td>
</tr>
</tbody>
</table>

NPSLE, neuropsychiatric systemic lupus erythematosus; PML, progressive multifocal leukoencephalopathy; HSV, herpes simplex virus; ?, no data from clinical trials available.

# Table 2 MRI findings in primary cerebral involvement of rheumatic diseases and opportunistic CNS infection

<table>
<thead>
<tr>
<th>MRI findings</th>
<th>NPSLE</th>
<th>Primary CNS vasculitis</th>
<th>Wegener’s granulomatosis</th>
<th>Neuro-Behçet</th>
<th>Neurosarcoidosis</th>
<th>PML</th>
<th>HSV encephalitis</th>
<th>Bacterial meningitis</th>
<th>Brain abscess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>13–50%</td>
<td>0–50%</td>
<td>50%</td>
<td>30%</td>
<td>11%</td>
<td>Only in the early phase</td>
<td>Rare</td>
<td>?</td>
<td>Rare</td>
</tr>
<tr>
<td>Territorial infarction</td>
<td>15–30%</td>
<td>15–20%</td>
<td>18%</td>
<td>Rare</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>In T1, hyperintense lesions of the cortex</td>
<td>0–9%</td>
<td>Reversible</td>
<td>Rare</td>
<td>Cerebral granulomas (homogeneous, ring enhancement)</td>
<td>36–66% Meningoencephalitis, 26% isolated brain stem or basal ganglia</td>
<td>30% Multiple or solitary supratentorial, infratentorial, rare brain stem or cerebellum</td>
<td>56% Thalamus, 32% posterior fossa</td>
<td>Haemorrhage necrosis temporal, occipital, thalamus, hippoc., subfrontal</td>
<td>–</td>
</tr>
<tr>
<td>White matter lesions (WML)</td>
<td>30–75%</td>
<td>Subcortical &gt; deep white matter &gt; periventricular</td>
<td>Frequent infarcts in the deep white matter</td>
<td>50% Periventricular, subcortical</td>
<td>16% Para- and periventricular</td>
<td>40% Peri- and paraventricular, subcortical, confluent</td>
<td>100% Subcortical, 93% parasito-occipital, 92% bilateral, 94% confluent, no mass effect</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>GDTPA enhancement of WML or cortical lesions</td>
<td>Only active lesions</td>
<td>Active lesions</td>
<td>Active lesions</td>
<td>Often but only active lesions</td>
<td>Often nodular or annular enhancement</td>
<td>&lt;10% Enhancement of the periphery</td>
<td>Often</td>
<td>–</td>
<td>Strong contrast enhancement</td>
</tr>
<tr>
<td>Atrophy</td>
<td>10–60%</td>
<td>Chronic stage</td>
<td>42%</td>
<td>20% Brain stem</td>
<td>38–57% Nodular or diffuse meningeal/dustral thickening</td>
<td>58% Infratentorial (e.g. brain stem), no perifocal oedema</td>
<td>Often brain oedema associated with the lesions</td>
<td>Meningeal enhancement, nodular lesions</td>
<td>Mass effect</td>
</tr>
</tbody>
</table>

GDTPA, gadolinium-DTPA.
Table 3 Cerebrospinal fluid (CSF) findings in primary cerebral involvement of rheumatic diseases and opportunistic CNS infections

<table>
<thead>
<tr>
<th>CSF findings</th>
<th>NPSLE</th>
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<th>Brain abscess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal findings</td>
<td>50%</td>
<td>10-90%</td>
<td>?</td>
<td>25-30%</td>
<td>19%</td>
<td>70%</td>
<td>Only in early stages</td>
<td>–</td>
<td>20%</td>
</tr>
<tr>
<td>Pleocytosis</td>
<td>27-32%</td>
<td>20-50%</td>
<td>?</td>
<td>50-60%</td>
<td>50-70%</td>
<td>20%</td>
<td>2-200</td>
<td>&gt;1000</td>
<td>80%</td>
</tr>
<tr>
<td>Cell count</td>
<td>20-100</td>
<td>10-100</td>
<td>10-100</td>
<td>0-100 (mean 80)</td>
<td>5-200</td>
<td>20%</td>
<td>100%</td>
<td>0-1000</td>
<td>0-1000</td>
</tr>
<tr>
<td>Cell type</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
<td>Lymphocytes, initially granulocytes</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Raised protein content (mg/l)</td>
<td>30-48%</td>
<td>30%</td>
<td>?</td>
<td>60%</td>
<td>73%</td>
<td>30%</td>
<td>500-2000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>IgG index &gt;0.6</td>
<td>30%</td>
<td>190-2300</td>
<td>500-1000</td>
<td>500-1000</td>
<td>500-1000</td>
<td>500-2000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Oligoclonal bands</td>
<td>25-42%</td>
<td>16-20% Reversibility</td>
<td>16-20% Reversibility</td>
<td>18.5%</td>
<td>18.5%</td>
<td>90%</td>
<td>90%</td>
<td>7%</td>
<td>7%</td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; CSF, cerebrospinal fluid; IgG index, CSF IgG/serum IgG (normal value <0.6); protein content (normal value 180–430 mg/l); JCV, JC virus.

Raised protein content (mg/l): 500–1000; IgG index >0.6: 30%; Rare.

Among healthy volunteers, 65–90% have antibodies against and are carriers of the JC virus. One study demonstrated a correlation between anti-JCV antibody levels and brain lymphocytosis in patients with PML. Other studies have also found no relationship.

**DISCUSSION**

In recent years, mortality and morbidity of autoimmune diseases have increased due to intensive therapy. This is especially true for patients with rheumatic diseases, where secondary CNS involvement is a frequent complication. Secondary CNS involvement is often difficult to diagnose, and the signs and symptoms are non-specific. For example, patients with SLE, complement deficiency may contribute to opportunistic infections. The development of PML does not allow discrimination between primary angiitis of the CNS, and secondary CNS involvement of rheumatic diseases, and CNS infections. It is mainly associated with advanced HIV infection and is a frequent complication in patients with HIV. Reports on at least 20 cases of patients with PML receiving corticosteroids and cytotoxic drugs for other indications (Table 1) have been published. In patients with PML, the JC virus is found in the CSF and brain tissue. The JC virus is a member of the polyomavirus family and is present in the human population. The virus is normally latent in the olfactory tract and can reactivate in patients with immunosuppression. The mechanism of PML development is still unclear, but it is thought to involve the immune system. The JC virus is not specific for HIV infection and can be reactivated by other factors such as immunosuppressive therapy or viral infections. The diagnosis of PML is usually made by MRI and CSF analysis. MRI typically shows multiple, ring-enhancing lesions in the brain, which may appear as hyperintense lesions on T2-weighted imaging and hypointense on T1-weighted imaging. The lesions are usually located in the white matter, especially in the periventricular region. The lesions are often symmetrical and may expand concentrically, either at one or several sites. In later stages of the disease, MR images are strongly suggestive of the diagnosis. Typically, PML appears as bilateral, asymmetrically distributed, confluent (>90%), predominantly subcortical white matter lesions which develop close to the grey-white matter junction and in the periventricular region. They show high signal intensity on T2 weighted imaging and low signal intensity on T1 weighted imaging. They are also seen on FLAIR (Fluid Attenuated Inversion Recovery) images. They appear hypointense on T2* weighted imaging, indicating the presence of hemosiderin. They are usually not enhanced by gadolinium DTPA. Rarely, a faint peripheral enhancement is seen, which is usually related to a small number of inflammatory cells or other factors such as tumor infiltration. The lesions are often associated with the occurrence of symptoms such as headache, fever, and seizures. The clinical presentation is often nonspecific, and the diagnosis is usually made by MRI and CSF analysis. The treatment of PML is not curative and is usually supportive. The choice of therapy depends on the underlying cause of the immunosuppression and the presence of other concomitant diseases. The most effective treatment is immunosuppressive therapy, which can be used in addition to antiviral therapy. The antiviral therapy of choice is伐地那韦, which is effective against the JC virus. Other antiviral agents such as foscarnet and cidofovir have also been used. The primary prevention of PML is important and includes the use of prophylactic agents such as ganciclovir, foscarnet, and cidofovir. In addition, the prevention of secondary infections is important, as secondary infections can exacerbate the symptoms of PML. The secondary infections are often caused by opportunistic agents such as mycobacteria, fungi, and viruses. The prevention of secondary infections is important and includes the use of prophylactic agents such as aminoglycosides, macrolides, and azoles. The prevention of secondary infections is important, as secondary infections can exacerbate the symptoms of PML. The secondary infections are often caused by opportunistic agents such as mycobacteria, fungi, and viruses. The prevention of secondary infections is important and includes the use of prophylactic agents such as aminoglycosides, macrolides, and azoles. The prevention of secondary infections is important, as secondary infections can exacerbate the symptoms of PML. The secondary infections are often caused by opportunistic agents such as mycobacteria, fungi, and viruses. The prevention of secondary infections is important and includes the use of prophylactic agents such as aminoglycosides, macrolides, and azoles. The prevention of secondary infections is important, as secondary infections can exacerbate the symptoms of PML. The secondary infections are often caused by opportunistic agents such as mycobacteria, fungi, and viruses. The prevention of secondary infections is important and includes the use of prophylactic agents such as aminoglycosides, macrolides, and azoles. The prevention of secondary infections is important, as secondary infections can exacerbate the symptoms of PML.

In conclusion, the diagnosis and management of PML is challenging, and the treatment is usually supportive. The prevention of secondary infections is important, as secondary infections can exacerbate the symptoms of PML.

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**Table 3 Cerebrospinal fluid (CSF) findings in primary cerebral involvement of rheumatic diseases and opportunistic CNS infections**

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<td>10-90%</td>
<td>?</td>
<td>25-30%</td>
<td>19%</td>
<td>70%</td>
<td>Only in early stages</td>
<td>–</td>
<td>20%</td>
</tr>
<tr>
<td>Pleocytosis</td>
<td>27-32%</td>
<td>20-50%</td>
<td>?</td>
<td>50-60%</td>
<td>50-70%</td>
<td>20%</td>
<td>2-200</td>
<td>&gt;1000</td>
<td>80%</td>
</tr>
<tr>
<td>Cell count</td>
<td>20-100</td>
<td>10-100</td>
<td>10-100</td>
<td>0-100 (mean 80)</td>
<td>5-200</td>
<td>20%</td>
<td>100%</td>
<td>0-1000</td>
<td>0-1000</td>
</tr>
<tr>
<td>Cell type</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
<td>Lymphocytes, initially granulocytes</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Raised protein content (mg/l)</td>
<td>30-48%</td>
<td>30%</td>
<td>?</td>
<td>60%</td>
<td>73%</td>
<td>30%</td>
<td>500-2000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>IgG index &gt;0.6</td>
<td>30%</td>
<td>190-2300</td>
<td>500-1000</td>
<td>500-1000</td>
<td>500-1000</td>
<td>500-2000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Oligoclonal bands</td>
<td>25-42%</td>
<td>16-20% Reversibility</td>
<td>16-20% Reversibility</td>
<td>18.5%</td>
<td>18.5%</td>
<td>90%</td>
<td>90%</td>
<td>7%</td>
<td>7%</td>
</tr>
</tbody>
</table>
is interpreted as an indicator of an immune response to viral antigens in long term survivors. Despite a rather characteristic presentation of advanced PML in MRI analysis, the differential diagnosis remains a challenge, because cases of central nervous system SLE mimicking PML have been reported. Therefore, the next step in confirming a suspected diagnosis of PML must be analysis of the CSF for the presence of JC virus DNA by PCR. This test reaches a sensitivity of 93% and a specificity of 99% while PCR analysis performed in urine or blood samples was not specific for PML. Despite a rather characteristic presentation of advanced PML in MRI analysis, the differential diagnosis remains a challenge, because cases of central nervous system SLE mimicking PML have been reported. Therefore, the next step in confirming a suspected diagnosis of PML must be analysis of the CSF for the presence of JC virus DNA by PCR. This test reaches a sensitivity of 93% and a specificity of 99% while PCR analysis performed in urine or blood samples was not specific for PML. Whether the viral load correlates with the prognosis is still being debated. The firm diagnosis—unfortunately often post mortem—is made by histological examination, showing enlarged oligodendrocytes with an expanded cytoplasmic compartment and intranuclear inclusions (“ground glass”), which represent the polyoma viruses. Therefore, stereotactic brain biopsy is strongly recommended in all cases of suspected PML and negative JC virus PCR in CSF samples.

The primary differential diagnoses include other viral infections (HIV, HSV, CMV), toxoplasmosis, neuropsychiatric SLE (in patients with known SLE), lymphoma, toxic encephalitis after chemotherapy, vasculitis, and neurosarcoidosis (tables 2 and 3). Interestingly, the vascular lesions shown by cerebral angiography in patient No 3 strongly argue against PML as the cause of the primary symptoms in this patient. On the other hand, it has to be kept in mind, that several infectious agents have to be ruled out in the assessment of patients with possible cerebral vasculitis, because a variety of pathogens have a propensity to affect blood vessels—for example, aspergillus, candidiasis, coccidiomycosis, coccidioidomycosis, Strongyloides stercoralis, arbovirus, VZV, and hepatitis C virus infection.

The prognosis for PML is usually poor. No effective treatment is available at present; anecdotal reports show some efficacy of cidovir, interferon alfa, and cytosine arabinoside. Nevertheless, PML may remit if the underlying immunodeficiency improves, therefore discontinuation of immunosuppressive agents should receive a high priority. MRI findings of early white matter lesions caused by JC virus are non-specific and may be indistinguishable from early brain abscesses. However, contrast enhancement or mass effects of the lesions visualised by MRI helps to distinguish cerebral abscesses from PML and HSV encephalitis. Differential diagnosis includes primary brain tumours, metastasis, or cerebrovascular events.

Symptoms in patients with brain abscess are headache, fever, focal neurological deficits, confusion, meningitis and seizures, all of which may also occur in patients with cerebral metastasis or CNS involvement due to ANA or ANCA positive vasculitis. However, fever and meningitis are rarely seen in systemic rheumatic diseases, with the exception of WG. If a spinal tap is contraindicated owing to the mass effect of the brain abscess, the preferred diagnostic procedures are stereotactic brain biopsy followed by histological and microbiological analysis.

Typical microbes which can cause brain abscess formation are Toxoplasma gondii, fungi (aspergillus, candida, or cryptococci), mycobacteriosis, Listeria monocytogenes, and Nocardia asteroides. Thirty two cases of SLE associated nocardiosis have been reported. Lungs, skin, and brain were the organs most commonly affected. Nocardiosis of the CNS was found in up to 30% of these patients and was associated with a high mortality. Nocardia should be kept in mind as a possible pathogen in patients whose infections do not respond to third
generation cephalosporins.

Preferred antibiotics are trimethoprim-sulfamethoxazole and imipenem.

To review, the current literature to assess whether there exist specific signs to differentiate between CNS involvement of systemic rheumatic diseases and CNS infection. As shown in tables 1–3, the clinical distinction is always vague and remains difficult in certain patients because of overlapping clinical features. Differential diagnosis includes toxic leucoencephalopathy caused by therapeutic agents (for example, cyclosporin, tacrolimus, amphotericin B, antineoplastic therapeutic drugs),

hypertensive encephalopathy, and metabolic complication involving the nervous system, such as hydrolecrotic changes.

Finally, what are the lessons taught from our three cases? Firstly, in patients who are strongly immunosuppressed, the new onset or change of cerebral symptoms should alert the doctor to look carefully for opportunistic infections. Blood cultures and brain imaging (MRI) should be the first step of the clinical evaluation (fig 4). If CNS infection, especially bacterial meningitis or abscess formation, cannot be ruled out, empirical treatment should be started following the guidelines for immunosuppressed patients. In patients with mass effect of brain lesions, stereotactic brain biopsy should be started without delay, otherwise spinal tap and CSF analysis including PCR to detect JC virus, HSV, VZV, EBV, and CMV should be performed.

The diagnosis of nervous system infection may also be confirmed by the presence of antibodies to HSV, VZV, EBV or CMV in the CSF even without detectable DNA.

Secondly, in cases where the diagnosis is not clear we suggest that immunosuppression should not be intensified until an opportunistic infection has clearly been ruled out. An alternative strategy in this setting would be the treatment with intravenous immunoglobulins (IV IgG) combined with antibiotics, especially in patients who have hypogammaglobulinaemia. In several autoimmune diseases—for example, SLE and ANCA positive vasculitis, uncontrolled studies have suggested that IV IgG may be an effective therapeutic option.

IV IgG treatment has also been shown to decrease the frequency and severity of exacerbations in multiple sclerosis.

Polyvalent immunoglobulins have complex immunoregulatory effects, including the neutralisation of microbial toxins, and contain a broad range of antibodies against pathogens. Because the efficacy of IV Ig is not documented in CNS manifestations of systemic rheumatic diseases, this treatment strategy should be restricted to patients with hypogammaglobulinemia until controlled trials demonstrate a clear benefit.

Because CNS infection carries a high mortality rate and full recovery can be expected only in a small percentage of patients, multicentre studies are warranted to answer the following questions: (a) Which factors define patients at risk for opportunistic CNS infections in systemic rheumatic diseases? (b) Which imaging procedure may help to detect and distinguish CNS infection in these patients?

References


Infectious CNS disease in systemic rheumatic diseases


