Progressive multifocal leukoencephalopathy in a patient with undifferentiated systemic vasculitis and bilateral acute retinal necrosis

Sirs,

Progressive multifocal leukencephalopathy (PML) is a generally fatal demyelinating disease of the central nervous system affecting predominantly immunocompromised individuals, *e.g.* AIDS patients, cancer patients and allograft recipients receiving strong immunosuppressive therapy. Here, we describe a case of PML in a patient with hypogammaglobulinemia, undifferentiated systemic vasculitis and bilateral acute retinal necrosis.

A 52-year-old woman complained of sudden onset of blurred vision in November 1994. Ophthalmological findings were typical for bilateral acute retinal necrosis and vasculitis with sheathing, paravascular hemorrhages and terminal obliteration of arterioles (Fig. 1). In laboratory analyses, an increased ESR of 72 mm within the first hour and a C-reactive protein of 3 mg/dl (normal <0.5) as well as a strongly elevated factor VIII (>200%) were detected. Apart from a positive PCR results for CMV matrix protein pp-65 in the aequeous humor and blood samples, there was no clear evidence of a viral or bacterial infection. Autoantibodies including ANA and ANCA as well as cryoglobulins were negative.

In January 1995, an acute exacerbation of retinal vasculitis of both eyes occurred with complete optic atrophy. Moreover, bronchopulmonal symptoms were accompanied by fever. X-ray examination revealed fine granular and reticular shadowed lung structure, while high-resolution CT disclosed circumscript infiltrations consistent with vasculitis.

The inflammatory process was initially stabilized by a treatment with high dose prednisolone (starting with 250 mg/d in November 1994 and reduction to 50 mg/d in January 1995) in combination with ganciclovir and foscarnet (repeated courses from November 1994 to February 1995). In February 1995, leukocytopenia (1.8 x10^3/μl) with a marked lymphocytopenia (0.27 x10^3/µl) was noted with decreased of B- (CD19+ 0.0 x10^3/µl) and T-cell (CD4+ 0.58 x10^3/µl, CD8+ 0.22 x10^3/µl) numbers. Subsequently hypogammaglobulinemia with deficiency for all IgG-subclasses was observed (IgG total 2.7 g/l, IgG_1 1.83 g/l; IgG_2 0.605 g/l; IgG_3 0.267 g/l; IgG_4 <0.06 g/l). Since immune electrophoresis revealed a monoclonal gammopathy (IgM/kappa), a systemic hematologic disease was excluded by bone marrow analysis showing reduction of erythro- and lymphopoiesis most likely due to drug toxicity. Whereas blood cellular counts were normalized after discontinuation of the antiviral drugs in April 1995, a mild lymphocytopenia was detectable in the follow-up. Hypogammaglobulinemia remained as a persistent finding and was only temporarily normalized by substitution of immunoglobulins. After excluding other causative agents (including negative CMV PCR) by bronchoalveolar lavage, undifferentiated systemic vasculitis with retinal and pulmonal involvement was diagnosed.

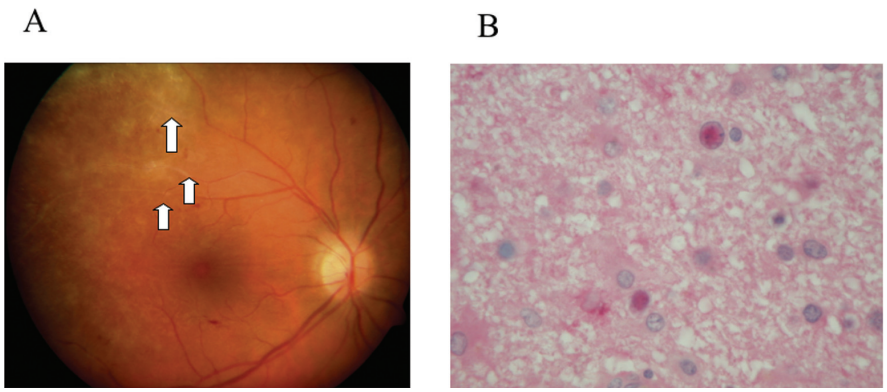

Fig. 1A: Fundus photograph of the patient indicating acute retinal necrosis syndrome of the right eye with well demarcated peripheral retina lesion. Several occluded retinal vessels are indicated by arrows.
B: Oligodendrocytes present with enlarged nuclei containing amphophilic viral inclusions containing JC-virus as shown by immunohistochemistry (peptideantibody against JVC kindly provided by Rönspek PEPSCAN, Berlin).

In March 1995, immunosuppressive therapy was intensified with high dose glucocorticoids (starting with methyl-prednisolone 500 mg i.v. tapered down to prednisolone 30 mg p.o. within one month) in combination with cyclosporine A (100 mg daily) and plasmapheresis (with substitution of immunoglobulins 25g after each session) especially to reduce monoclonal paraproteins, which are known to be implicated in the development of certain neuropathies and vasculitides (1, 2). In the follow-up, remission of disease was achieved (ESR 5 mm within the first hour, C-reactive protein 0.47 mg/dl). In May 1995, cyclosporine A was ceased because of recurrent herpes zoster infections by maintaining clinical remission under low-dose prednisolone (5 mg/d). Unpredictably, a progressive frontal lobe syndrome occurred with disorientation in time and place in November 1996. Neurological examination and cerebral CT-scan as well as MRI were suspicious for PML showing severe subcortical lesions in the frontal lobe. Cerebral angiography revealed an occlusion of both ophthalmic arteries consistent with vasculitis. JC-virus infection was confirmed by positive PCR-liquor result and by immunochemistry post-mortem in December 1996.

In our case, it remained unclear, whether humoral and cellular immunodeficiency or the underlying risk of the autoimmune disease itself had a significant influence on activation of JC virus. Of note, immunodeficiency syndromes including cellular abnormalities were described to be associated with the development of PML (3) and, a coincidence was also described for immunodeficiency syndromes and ARN (4). PML has been reported also in patients with SLE and systemic vasculitis receiving different immunosuppressive drugs as well as in phases of clinical remission (5, 6). Moreover, reactivation of JC virus and development of PML had occurred in patients treated with the alpha4beta1-integrin inhibitor natalizumab (7). Recently, PML has been reported in two patients with SLE, one patient with vasculitis and one patient with rheumatoid arthritis undergoing anti-CD20 therapy (8). However, the underlying risk of the autoimmune disease itself to develop PML versus the risk by an immunosuppressive therapy has not been clarified yet. Therefore, activation of JC polyomavirus should be considered as a long-term risk in patients with systemic autoimmune disorders especially in coincident immunocompromised conditions.

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References

1. KYLE RA: Monoclonal proteins in neuropathy. *Neurol Clin* 1992; 10: 713-34.
2. ROLLINO C, COPPO R, MAZZUCCO G *et al.*: Monoclonal gammopathy and glomerulonephritis with organized microtubular deposits. *Am J Kidney Dis* 1990; 15: 276-80.
3. NARULA S, LAROSA DF, KAMOUN M, DALMAU J, LEVINSON AI: Progressive multifocal leukoencephalopathy in a patient with common variable

immunodeficiency and abnormal CD8+ T-cell subset distribution. *Ann Allergy Asthma Immunol* 2007; 98: 483-9.
4. GARTRY DS, SPALTON DJ, TILZEY A, HYKIN PG: Acute retinal necrosis syndrome. *Br J Ophthalmol* 1991; 75: 292-7.
5. GOVINDAPPA V, HICKS S, WICHTER M, JOLLY M: Progressive multifocal leukoencephalopathy in systemic lupus erythematosus. *Arthritis Rheum* 2007; 57: 352-4.
6. PAGNOUX C, HAYEM G, ROUX F *et al.*: JC virus leukoencephalopathy complicating Wegener's granulomatosis. *Joint Bone Spine* 2003; 70: 376-9
7. STÜVE O: Alpha4-integrin antagonism with natalizumab: effects and adverse effects. *J Neurol* 2008; 255 (Suppl. 6): 58-65.
8. FDA PUBLIC HEALTH ADVISORY: Life-threatening brain infection in patients with systemic lupus erythematosus after Rituxan (Rituximab) treatment (press release). Rockville, Maryland:US Food and Drug Administration; December 18, 2006

Early diagnosis of pediatric Takayasu arteritis (TA) not fullfiling the ACR criteria

Sirs,

TA is a chronic vasculitis of unknown etiology characterized by granulomatous inflammation of large and medium-sized vessels that affects the aorta, its main branches and the pulmonary arteries (1). Onset is most common during the third decade of life, but childhood disease has been reported.

Angiography has been the standard imaging tool for the diagnosis and follow-up of TA (2), but less invasive techniques, such as computed tomography (CT) and magnetic resonance angiography (MRA), can visualize early changes (vessel wall thickening without stenosis or dilatations, mural edema, increased mural vascularity) not detectable by conventional angiography, and may lead to earlier diagnosis (3-4).

In 1990, the American College of Rheumatology (ACR) defined specific diagnostic criteria for TA (5), and diagnosis is confirmed by the presence of at least three of the six criteria, but most of these are clinical features of the disease's late fibrotic phase and thus may not be fulfilled in the early inflammatory stage.

In this report we describe a case of TA the diagnosis of which was established by CT and MRA imaging, even though the ACR criteria were not met.

A 16-year-old girl was admitted to the Rheumatology Department of the Children's Hospital in Rome because of malaise and fever of unknown origin for several days which was unresponsive to antipyretics. She complained of sharp dorsal pain for two months that worsened with fever. Cardiac murmur was detected out but no other bruit. She did not present decreased pulsation of any peripheral pulse or significant difference in systolic pressure in the arms. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and complement were repeatedly elevated, normocitic anemia was also detected, and ANA were negative. Echocardiography revealed a bicuspid shaped aortic valve with regurgitation and aortic root dilatation. Chest and abdominal CT revealed wall thickening of the aortic arch, of its primary branches and of the entire thoracic and abdominal aorta. MRA revealed a marked dilatation of both the ascending and descending aorta with valve strip immobility and valve regurgitation during the diastolic phase. Although our patient had just one of the clinical ACR criteria, TA with bicuspid aortic valve regurgitation was diagnosed on the basis of the MRA. The patient started oral prednisone at 2 mg/kg/dose. Steroid therapy was quickly effective but methotrexate was also added at 15 mg/m^2/dose for disease control. She quickly recovered, her pain improved and she had no fever for 3 months. However, she then relapsed with fever and marked increase of acute phase reactants. Infliximab was started (5 mg/kg at time 0, 2, 4 and 8 weeks and then every 8 weeks) with prompt and persistent remission.

Although less invasive cross-sectional methods such as CT and MRA can effectively demonstrate thickening of vessel walls, which may be the earliest manifestation of the disease, the arteriogram abnormality is still one of the diagnostic criterion of TA. The Pres Vasculitis study group is now working to change the classification criteria for vasculitis in children (6). For the diagnosis of TA, angiographic abnormalities detected by conventional, CT or MR angiography could be accepted (3-4).

The early diagnosis of TA may be difficult since early symptoms such as fatigue, malaise, joint pain and fever are nonspecific. When our patient was hospitalized she had no claudication, decreased pulsation, remarkable difference in systolic pressure or arterial bruits, but only a cardiac murmur. Because of that, we performed an echocardiogram that revealed the dilatation of the aortic root and subsequent imaging studies which led to the diagnosis.

Our patient did not meet the ACR 1990 criteria for TA, probably because of the early stage of the disease. With our case we want to point out the accuracy of the new imaging methods to identify very early disease manifestation.

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References

1. LUPI-HERRERA E, SANCHEZ-TORRES G, MARCUSHAMER J, MISPIRETA J, HOROWITZ S, VELA JE: Takayasu's arteritis : clinical study of 107 cases. *Am Heart J* 1977; 93: 94-103.
2. YAMATO M, LECKY JW, HIRAMATSU K, KOHDA E: Takayasu arteritis: radiographic and angiographic findings in 59 patients. *Radiology* 1986; 161: 329-34.
3. YAMAZAKI M, TAKANO H, MIYAUCHI H *et al.*: Detection of Takayasu arteritis in early stage by computed tomography. *Int J Cardiol* 2002; 85: 305-7.
4. ALUQUIN VPR, ALBANO SA, CHAN F, SANDBORG C, PITLICK PT: Magnetic resonance imaging in the diagnosis and follow-up of Takayasu's arteritis in children. *Ann Rheum Dis* 2002; 61: 526-9.
5. AREND WP, MICHEL BA, BLOCH DA *et al.*: The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. *Arthritis Rheum* 1990; 33: 1129-34.
6. OZEN S, RUPERTO N, DILLON MJ *et al.*: EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. *Ann Rheum Dis* 2006; 65; 936-41.