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Case Report

Progressive multifocal leukoencephalopathy in a patient with Good's syndrome

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ABSTRACT

Good's syndrome (GS) is an immunodeficiency characterized by thymoma, hypogammaglobulinemia, and impaired T-cell function. The clinical manifestations of GS include recurrent or chronic infections from common or opportunistic pathogens. Encephalitis is a rare event, with only anecdotal reports of cytomegalovirus infection. Herein we report the case of a 79-year-old woman with GS who developed subacute motor deficits and cognitive changes. Magnetic resonance imaging (MRI) of the brain disclosed white- and gray-matter lesions, mostly in the right frontal and parietal areas. Polyoma virus JC, the agent of progressive multifocal encephalopathy (PML), was identified in cerebrospinal fluid samples and brain biopsy specimens. After diagnosis, the disease had a rapid fatal course. The present case represents the first reported association between GS and PML.

1. Introduction

Good's syndrome (GS) is an adult-onset primary immunodeficiency combining hypogammaglobulinemia and thymoma, which presents in about 10% of patients prior or after thymoma resection.[1,2] Additional immunologic defects in GS may include altered T-cell function with low CD4 cells, and an inverted ratio of CD4 to CD8 cells. The humoral and cellular immunodeficiency in GS is responsible for recurrent respiratory, gastrointestinal, and urinary infections from common and opportunistic bacterial and fungal pathogens;[2,3] 40% of patients develop opportunistic viral infections, and three patients with cytomegalovirus encephalitis have been reported.[4,5] PML, an infection caused by JC virus (JCV), usually occurs in patients infected with HIV, or in patients on treatment with immunosuppressive or immunomodulatory drugs. Herein we describe the first unusual association between GS and PML.

2. Case report

A 79-year-old woman was admitted to our neurology unit because of short-lasting episodes of paresthesias and progressive weakness of the left hand. Five months earlier the patient experienced difficulties in motor planning with her left hand and attention deficits. Eight years before admission, the patient underwent resection of an epithelial thymoma, and thereafter, she developed hypogammaglobulinemia, which was treated with intravenous immunoglobulin at a dose of 400 mg/kg/day for 3 days on a bimonthly basis. On admission, her lymphocyte count was 2.14×10^9 cells/l, and lymphocyte subgroups were normal (CD4/CD8 T-cell ratio 1.5; CD4 648/mm^3; CD8 425/mm^3); B cells were absent. The total IgG level was 619 mg/dl (normal range 700–1600), the IgA level was less than 25 mg/dl (normal range 70–400), and IgM level was less than 18 mg/dl (normal range 40–250). Magnetic resonance imaging (MRI) of the brain showed bilateral flair and T2-weighted hyperintensities in the frontal and parietal cortices abutting the white matter, more on the right. No gadolinium enhancement was detected. Neuropsychological evaluation disclosed visual attention and working memory impairment, in addition to mild ideational apraxia. After a brief rehabilitation course, the patient partially recovered her arm function, and she was discharged. During the following days, she developed progressive weakness on the left side and presented visual hallucinations. On readmission, one month later, a severe left spastic hemiparesis was noted, in addition to visual agnosia for objects and faces, dyscalculia, and severe ideomotor apraxia.

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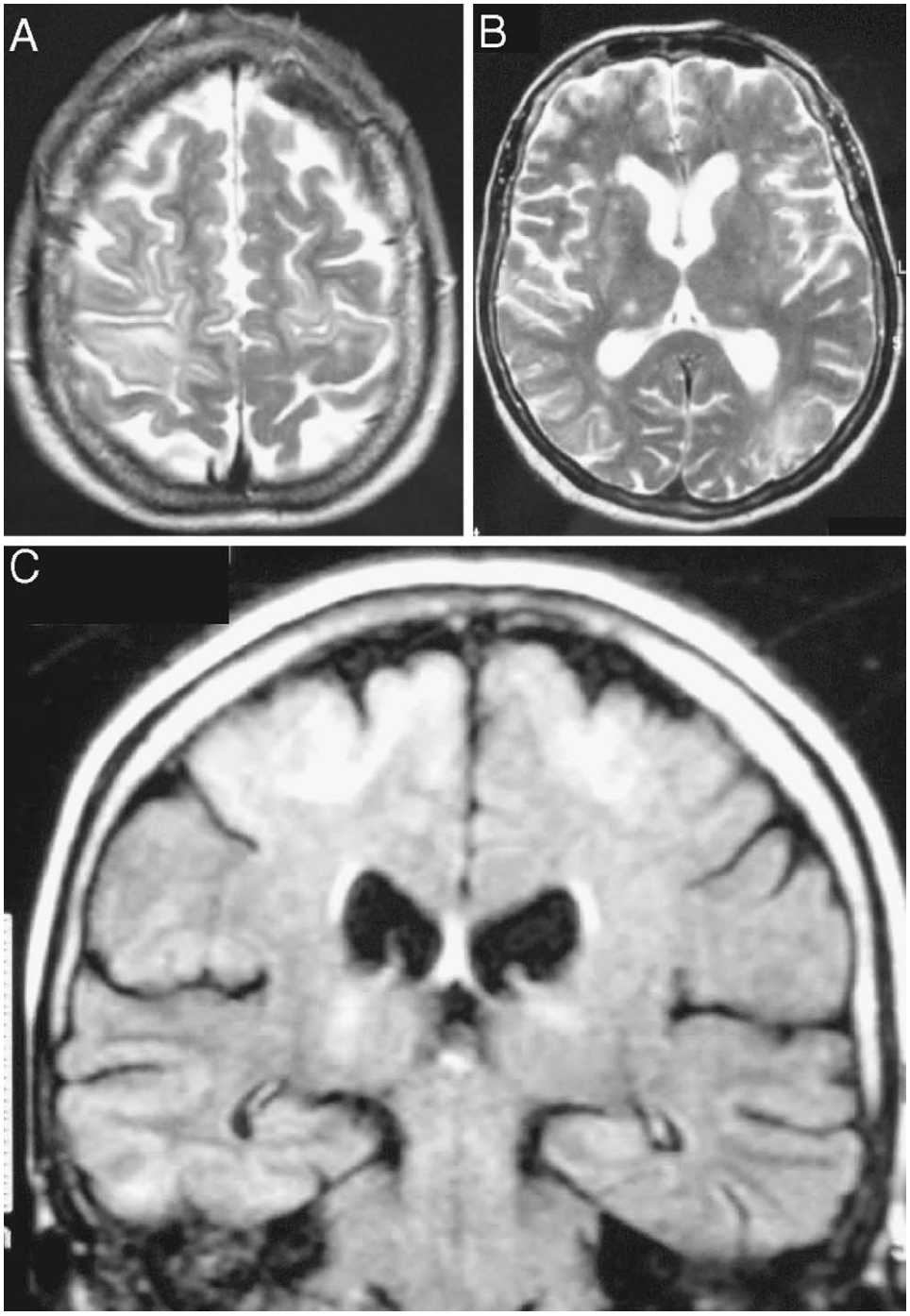

Figure 1. (A, B) Axial T2-weighted brain magnetic resonance images (MRI) showing hyperintensities in frontal and parietal subcortical areas and thalamic nuclei, bilaterally. (C) Coronal flair sequences showing hyperintensities at the level of cortical–subcortical junction and basal ganglia.

Brain MRI showed bilateral cortico-subcortical flair and T2-weighted hyperintensities in the frontal, parietal, and temporal lobes, in the thalami and in the right basal ganglia (Figure 1); there was no enhancement after the administration of gadolinium. An electroencephalogram (EEG) revealed diffuse bilateral theta–delta activity with sporadic sharp-wave prevalent in the right parietal region. Lumbar puncture yielded clear cerebrospinal fluid (CSF) with normal protein, glucose and cell count. PCR analysis for JCV in the cerebrospinal fluid was positive.

A brain biopsy specimen from the frontal lobe disclosed demyelinating lesions, bizarre astrocytes, and viral inclusions in enlarged oligodendrocyte nuclei, ultrastructurally consistent with polyomavirus particles (Figure 2). The diagnosis of JCV infection was later confirmed by quantitative real-time PCR of the CSF (9258 pairs/ml). Cidofovir (5 mg/kg/week), in association with probenecid, was administered without benefit. The patient developed cortical blindness, spastic tetraparesis, and died of *Pseudomonas aeruginosa* pneumonia five months after disease onset. Postmortem examination confirmed the diagnosis of PML and showed multiple cortico-subcortical lesions.

3. Discussion

First described by Good in 1954,[1] GS is currently classified as a distinct primary immunodeficiency syndrome. Immunologic defects in GS are not limited to hypogammaglobulinemia and

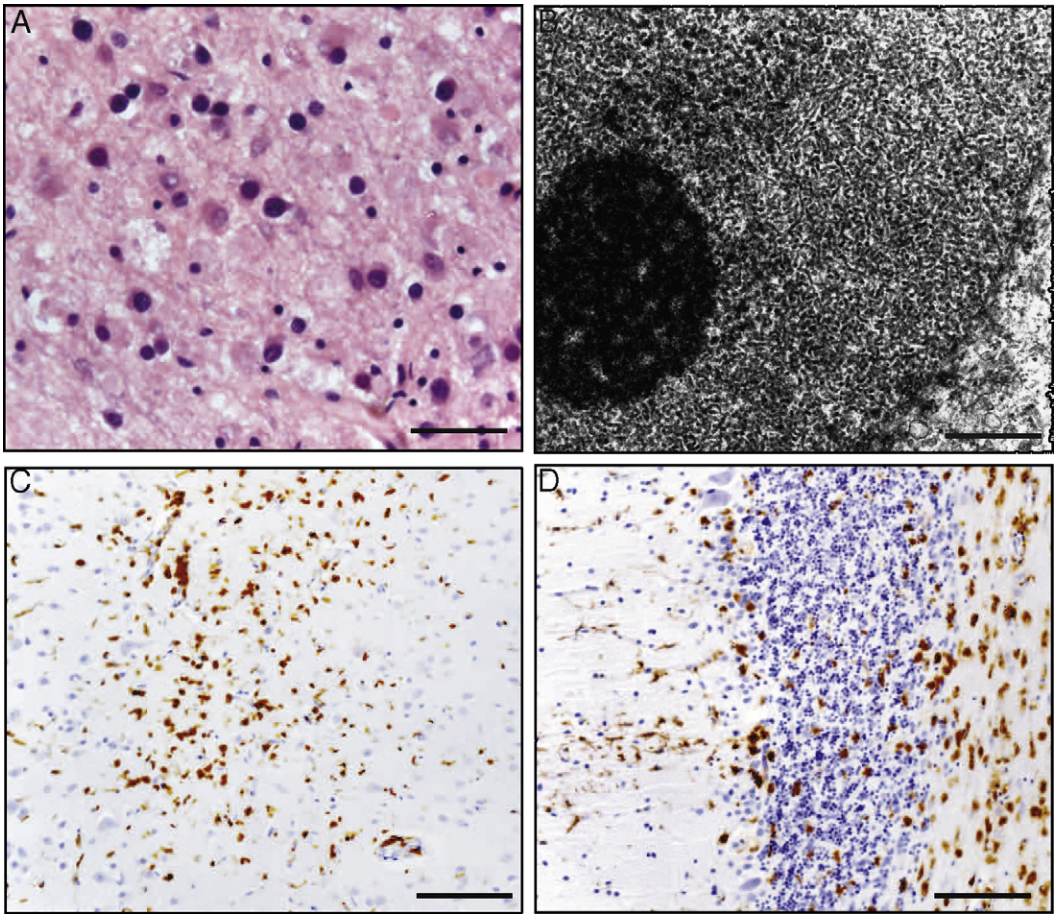

Figure 2. (A) Brain biopsy specimen showing bizarre astrocytes and abnormal oligodendrocyte nuclei (hematoxylin and eosin stain; scale bar: 50 μm). (B) Oligodendrocyte nucleus containing particles of JC virus (electron micrograph; scale bar: 0.5 μm). (C) Immunocytochemistry of the frontal cortex with monoclonal anti-CD68 antibody (Dako), recognizing cells from macrophage lineage, depicts activated microglial cell at the gray/white matter junction (scale bar: 100 μm), and (D) in the cerebellar cortex and white matter (scale bar: 100 μm).

decrease or absence of B cells, but include T-cell dysfunction with deficient CD4 lymphocytes and decreased or inverted CD4/CD8 ratio.[3] This explains the increased incidence of opportunistic infections in patients with GS, as compared to individuals with other forms of hypogammaglobulinemia. Moreover, altered T-cell function in GS is also supported by the occurrence of cutaneous anergy to test antigens, delayed rejection of skin allografts, and diminished inducible cytokine production.[3,6]

The most frequent clinical manifestations of GS include recurrent sino-pulmonary, gastrointestinal, and urinary tract bacterial infections, either from common or opportunistic pathogens, cytomegalovirus (CMV) disease, oral or esophageal candidiasis.[2] Encephalitis is very uncommon in GS, and only three patients with CMV encephalitis have been reported.[4,5] On the other hand, the association between thymoma and PML is very unusual, with only two cases described.[7,8] This index case represents the first reported association between GS and PML. PML usually occurs in patients with hematological malignancies or HIV infection, in addition to immunosuppressed individuals in treatment with methotrexate, cyclophosphamide, azathioprine, natalizumab and rituximab.

Of note, PML has also been reported in patients with defective cell-mediated immunity, and, occasionally, in subjects with impaired B-cell function, such as common variable immunodeficiency, congenital hypogammaglobulinemia, and X-linked agammaglobulinemia.[9,10] In the present case, the association between GS and PML can tentatively be explained by a coexisting T-cell functional defect, in spite of a normal lymphocyte count and lymphocyte subgroup representation.

Common manifestations of PML include subacute hemiparesis, gait or limb ataxia, hemianopsia, and cognitive impairment, as an effect of multiple lesions of the subcortical hemispheric white matter.[11] Less frequently, involvement of cortical gray matter or deep gray nuclei, such as basal ganglia and thalamus, have been reported, always in conjunction with white matter disease.[11,12] Intriguingly, in our patient gray-matter involvement occurred at the presentation, a finding which precluded an early diagnosis. The early and prevailing impairment of cerebral cortical regions was also supported by repeat neuropsychological studies showing cognitive dysfunctions, including working memory impairment, ideomotor apraxia and agnosia.[13,14] In conclusion, the present report suggests that PML should be considered in the setting of patients with GS and CNS involvement, even in cases presenting with cognitive dysfunction.

Conflict of interest: No conflict of interest to declare.

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