CASE REPORT

Progressive multifocal leukoencephalopathy in a patient with Good's syndrome

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SUMMARY

Good's syndrome (GS) is an immunodeficiency characterised by thymoma, hypogammaglobulinemia and impaired T-cell function. The clinical symptoms are recurrent or chronic infections from common or opportunistic pathogens and diarrhoea. Encephalitis is rare, mostly associated to cytomegalovirus. We present a 65-year-old woman who developed blindness, motor deficits and cognitive changes over a 4-month period. MRI of the brain showed symmetric subcortical white matter changes in the occipital lobes, first thought to correspond to posterior reversible encephalopathy syndrome. A thymoma was found and operated. The patient had no B cells, low immunoglobulins and an inverted CD4/CD8 ratio. GS was diagnosed. In the cerebrospinal fluid >1 million JC virus copies/mL were found and a repeat MRI now showed a picture compatible with progressive multifocal leukoencephalopathy (PML). Her disease had a fatal outcome. The present case is the second reported association between GS and PML.

BACKGROUND

- This is the second description of Good's syndrome (GS) and progressive multifocal leukoencephalopathy (PML) in the literature, but the first description where the immunodeficiency (GC) was not known beforehand.
- It was an unusually prolonged course of PML, clinically as well as radiologically.

It was very difficult to differentiate the condition from posterior reversible encephalopathy syndrome (PRES), the diagnosis of which is much discussed in the neurological literature today. This underscores the importance of paying attention to the following:

- A. When a presumed cause (PRES in this case) is not running its normal course, think of another possible cause.
- B. When patients have recurrent infections, think of immunodeficiency.
- C. Consider the possibility of GS and PML in an immunodeficient patient presenting with progressive neurological deterioration and brain white matter changes.

CASE PRESENTATION

Clinical details

A 65-year-old woman came to our emergency department (ED) with progressive worsening of visual functions and reading ability over 4 months. She also had headaches, difficulty in finding words and memory problems. Her medical history

contained hypertension treated with candesartan and hyperlipidemia treated with simvastatin and ezetimibe. In the past years, she had suffered from recurrent sinus infections. At the ED she had a generalised seizure. On admission, her blood pressure was 155/100 mm Hg. CT and MRI of the brain showed changes compatible with PRES (figure 1); the treatment was focused on reducing the raised blood pressure. CT cerebral angiography, 24 h ECG, transesophageal echocardiogram as well as cerebrospinal fluid (CSF) analyses were all normal. The blood pressure was normalised without additional pharmacological treatments. Her visual acuity was 20/200 bilaterally but peripheral vision with Goldmann perimetry was normal. The neuro-ophthalmologist suggested that her symptoms could be due to alexia without agraphia and possibly Balint's syndrome with simultanagnosia and oculomotor dyspraxia. She did not deteriorate further and was discharged for rehabilitation, but returned to the ED after 2 weeks with dizziness and worsening of her vision. On admission, the blood pressure was high (220/94 mm Hg) but normalised spontaneously. MRI of the brain showed no progress. The patient was discharged again but returned 6 weeks later because of sudden headache and unsteadiness. At the ED she was disorientated and had a new left-sided weakness. MRI showed mild progress of white matter hyperintensities subcortically in the occipital lobes. CT of the thorax showed a well-defined tumour (5 cm in diameter)

Figure 1 Axial MRI scan with mild white matter changes in a subcortical distribution in the occipital lobe bilaterally.

To cite: Sveinsson O, Matell H, Herrman L. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009763

in the anterior mediastinum, compatible with a thymoma. She deteriorated further, with vision loss, cognitive difficulties and became wheel chair bound. Now she could not recognise her husband visually. All paraneoplastic antibody analyses in serum were negative. She received a 3-day course of high-dose steroids (methyl prednisolone 1 g daily intravenously) resulting in a slight improvement of her headache. However, a new CT showed further progress of the white matter changes with extension into the temporal lobe on the right side and parietal lobe on both sides. Thymectomy was performed. She became hemiplegic on the right side, totally blind and aphasic. In the CSF >1 million JC virus copies/mL were found. The protein levels and white cell count remained normal in CSF. The patient had no detectable CD19-positive B lymphocytes in blood by flow cytometry ($<0.01 \times 10^9/L$; normal ref $0.09\text{--}0.40 \times 10^9/L$). The CD4/CD8 T-cell ratio was 0.66 (1.13–3.93). Natural killer cells were also low; $0.05 \times 10^9/L$ ($0.07\text{--}0.42 \times 10^9/L$). All immunoglobulin levels were low. The IgG level was 5.7 g/L (6.7–14.5 g/L), the IgA level was 0.22 g/L (0.88–4.50 g/L) and IgM level 0.22 g/L (0.27–2.10). The microscopic investigation of the thymoma showed a type AB thymoma according to the WHO classification. A diagnosis of GS was made (the combination of lymphocyte derangement and thymoma). An MRI of the brain verified progression of white matter signal changes extending into temporal, parietal and frontal lobes bilaterally with involvement of splenium of the corpus callosum. The changes involved the juxtacortical fibres and diffusion-weighted images showed restricted diffusion at the leading edges but without enhancement; thus, compatible with PML (figure 2). She was started on mirtazapine and mefloquine to try to halt further progression of PML, but without effect. She finally became tetraplegic, comatose and died at a hospice clinic a few weeks later.

DIFFERENTIAL DIAGNOSIS

Posterior reversible encephalopathy syndrome.

DISCUSSION

GS is a rare primary immunodeficiency syndrome first described by Good in 1954.¹ This syndrome is the underlying cause of immunodeficiency in 1–2% of patients with primary antibody deficiency who are on immunoglobulin replacement therapies. In contrast to most other primary immunodeficiency states, GS usually presents in the fourth or fifth decade of life.² It is not only defined by a decrease or absence of B cells and hypogammaglobulinaemia, but also T-cell dysfunction with deficient CD4 lymphocytes and a decreased or inverted CD4/CD8 ratio.³ This likely explains why opportunistic infections are more common in patients with GS than other B-cells immunodeficiencies, and also why the prognosis is worse in GS.² The altered T-cell function in GS can be seen in a range of functional tests, such as cutaneous anergy to test antigens, delayed rejection of skin allografts, diminished inducible cytokine production and reduced T-cell mitogen proliferative responses.^{2,3}

The pathogenesis of the immunodeficiency in GS remains elusive. The presence of B-cell and T-cell lymphopenia, pre-B cell arrest, impaired maturation of erythroid and myeloid precursors, pure red cell aplasia, neutropenia and eosinopenia in many cases of GS, may suggest that the basic defect may be in the bone marrow.

To the best of our knowledge this is the second case of PML associated with GS.⁴ PML is most commonly seen in connection with AIDS, haematological malignances and patients treated with immunosuppressive drugs (such as natalizumab for multiple sclerosis).

The clinical presentation was initially thought to be caused by PRES due to the presence of clinical (seizures, high blood pressure, headache, vision disturbances) as well as radiological signs compatible with this disease. The clinical symptoms of PML and PRES are non-specific and can be quite identical with seizures, visual disturbance, headache and confusion. The radiological signs can also be quite similar. Both diseases have subcortical

Figure 2 (A) Axial MRI scan showing progress of white matter changes into parietal and frontal lobes with involvement of juxtacortical fibres. (B) Diffusion-weighted image showing restricted diffusion of leading edges relating to active demyelination, a pattern typical of progressive multifocal leucoencephalopathy.

involvement most often in the parieto-occipital white matter.⁵ PML most often has a subacute presentation, but our patient had symptoms over 8 months. Interestingly, a similar course was also present in the other recently reported case of PML in association with GS.⁴ That patient, like ours, presented mainly with apraxia. In our patient, we initially missed paying attention to her prior history of recurrent sinus infections. However, she had no history of other recurrent infections or diarrhea, which is commonly seen in GS.

These two cases underscore the importance of considering the possibility of GS and PML in patients presenting with a progressive neurological deterioration and brain white matter changes, not the least when there is a history of recurrent infections or immunosuppression.

Learning points

- ▶ Posterior reversible encephalopathy syndrome (PRES) is a new and mostly a radiological diagnosis.
- ▶ Be ready to review the PRES diagnosis if it is not running its natural course. By definition it should be reversible.
- ▶ In the beginning, PRES can present exactly like progressive multifocal leukoencephalopathy (PML).
- ▶ If patients have a decrease or absence of B cells, inverted CD4/CD8 ratio and hypogammaglobulinemia, think of Good's syndrome and examine the thymus gland.
- ▶ PML usually runs a subacute course but in this case the time period from first symptoms to death was 8 months.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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