Author’s response to reviews

Title: Progressive multifocal leukoencephalopathy associated with thymoma with immunodeficiency: a case report and literature review

Authors:

Tatsuya Ueno (lacote19thg@gmail.com)

Nobuyuki Sato (nobuyuki_sato@med.pref.aomori.jp)

Tomoya Kon (tk10608pc@nifty.com)

Rie Haga (rie_haga@med.pref.aomori.jp)

Jin-ichi Nunomura (Jin-ichi_Nunomura@med.pref.aomori.jp)

Kazuo Nakamichi (nakamich@nih.go.jp)

Masayuki Saijo (msaijo@nih.go.jp)

Masahiko Tomiyama (masahiko_tomiyama@med.pref.aomori.jp)

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Author’s response to reviews:

Reviewer reports:

Jin Nakahara (Reviewer 1): This paper describes an important case of PML occurrence in a patient with MG, concomitantly with the development of GS.

1) The authors' suggestion that "neurologists should keep in mind the risk of development of PML in MG patients with thymoma, even if MG symptoms are in remission, and evaluate the immunological status of the patients" provide a particularly important insight into daily clinical management of MG patients. However, it is unclear to this reviewer whether if PML could have been avoided in this case when immunological status was regularly evaluated as the authors suggest. How often GS occurs in MG patients, and when GS was diagnosed what should we do to avoid PML? Should immunological surveillance be considered even in MG patients without thymoma? What kind of immunological evaluations are necessary to avoid PML; I understood that "the incidence of hypogammaglobulinemia in patients with thymoma is 6-11%," but could this also be a risk for PML in addition to GS and if so what should we do?

Thank you very much for your constructive comments. Revisions to the manuscript in response to the recommendations of Reviewer #1 are shown in blue font.
To the best of our knowledge, there are no epidemiological data showing the prevalence of Good’s syndrome (GS) among myasthenia gravis (MG) patients. However, Kelesidis et al. reported MG in 14 (15.7%) of 89 GS patients [1], while Jansen et al. also found that three (9.1%) of 47 GS patients also had MG [2]. This suggests that the prevalence of GS among MG patients may be very low, because GS is a rare autoimmune disease. We have added this information to the manuscript (lines 98–99).

We need to treat GS-related immunodeficiency to prevent the development of progressive multifocal leukoencephalopathy (PML). However, this problem is challenging for physicians, because there is currently no established treatment for GS [3]. Thymectomy is recommended in patients with thymoma without previous thymectomy [1, 3], while other options include radiotherapy, combination chemotherapy, immunosuppressive therapy, plasmapheresis, and/or splenectomy [1]. Immunoglobulin replacement treatment may also be considered, as noted below [4]. We have added this information to the revised manuscript (lines 233–243).

Patients with MG usually require immunosuppressive therapy, but long-term immunosuppressive therapy may induce immunodeficiency. Thus even though no thymoma may be detected at the initial evaluation, it may be found subsequently [5], associated with a deterioration of neurological MG symptoms and elevated anti-acetylcholine receptor (AchR) antibodies. The main immunological findings in patients with GS are hypogammaglobulinemia, low or absent B cells, CD4+ lymphopenia, and reversal of the CD4/CD8 ratio [1, 2]. MG patients with or without thymoma should thus receive an immunological assessment including complete blood count, quantitative immunoglobulins, and B cell/T cell subsets. Alternatively, clinicians should consider evaluating the immunological status of MG patients without thymoma if their neurological symptoms or anti-AchR antibody values deteriorate. We have added this information to the revised manuscript (lines 227–232).

Because the development of PML is associated with severe cellular immunosuppression [6], hypogammaglobulinemia itself does not usually cause reactivation of JCV. However, immunodeficiency associated with GS increases the risk of bacterial, viral, and fungal infections [1, 2], with encapsulated bacteria such as Haemophilus influenzae and Streptococcus pneumoniae, being the most common pathogens [3]. Opportunistic infections associated with disorders of cell-mediated immunity are common in patients with GS compared with X-linked agammaglobulinemia and common variable immune deficiency [3]. However, Squintani et al. reported a patient with PML who had normal CD4+ T and CD8+ T cells and decreased gammaglobulins, indicating humoral but not cellular immunodeficiency [4]. Although this patient could potentially also have had cellular immunodeficiency, immunoglobulin replacement treatment for hypogammaglobulinemia due to GS could be considered for PML prevention. We have added this information to the manuscript (lines 236–243).

2) Were there any (clinical or radiological) signs of IRIS in this patient?

The patient’s neurological symptoms did not deteriorate after treatment with mirtazapine and mefloquine. We planned a follow-up brain MRI but the patient unfortunately died before this could be performed, and we were therefore unable to determine if there were any radiological
signs of immune reconstitution inflammatory syndrome (IRIS). We have added this information to the manuscript (lines 170–171).

Kazuo Fujihara (Reviewer 2): This is a 47 year-old woman with a history of invasive thymoma and myasthenia gravis who developed aphasia and gait disturbance and was diagnosed with progressive multifocal leukoencephalopathy (PML) based on clinical and MRI findings and detection of JCV DNA in the cerebrospinal fluid by PCR (Human immunodeficiency virus (HIV) was negative.). The patient had received chemotherapy for intractable invasive thymoma and was found to have severe cellular and humoral immunodeficiency (severe lymphopenia, very low numbers of CD4+ and CD8+ T cells and CD19+B cells and hypoimmunoglobulinemia of all subclasses). Authors concluded that that this is the first case of non-HIV-related PML associated with Good syndrome, a disease characterized by thymoma and immunodeficiency.

There is no doubt that the patient developed PML in the context of profound humoral and cellular immunodeficiency, and this is potentially an interesting case. However, as authors discussed, the main problem with this case is whether the immunodeficiency was induced by chemotherapy or linked to Good syndrome. The patient had invasive thymoma for more than 20 years and received multiple chemotherapy which could induce the prolonged immunosuppressive state. Thus, it is difficult to make a definitive diagnosis of Good syndrome in the present case. It would be desirable to provide data of genetic alterations or other biomarkers specifically associated with Good syndrome to confirm the diagnosis.

We are grateful for your comments and useful suggestions. Revisions to the manuscript in response to the recommendations of Reviewer #2 are shown in red font.

We agree that determining the cause of the immunodeficiency leading to PML in this case was complicated because of the possible influences of the chemotherapy and Good’s syndrome (GS). Unfortunately, there are no established diagnostic criteria for GS, and it is therefore diagnosed of the basis of thymoma, hypogammaglobulinemia, low or absent B cells, CD4+ lymphopenia, and reversal of the CD4/CD8 ratio [1]; to the best of our knowledge, no characteristic genetic alterations or other biomarkers specific for GS have been reported. We therefore judged the causes of the changes in immunity according to the time since chemotherapy and the type of chemotherapy, and concluded that the patient was likely to have had both GS and chemotherapy-induced immunodeficiency. We have added this explanation to the revised manuscript (lines 206–209).

Other points

1. Line 83, "fatal", "potentially-fatal" would be more precise.

Thank you for your suggestion. We have revised the manuscript accordingly (line 83).
2. Line 87, "including monoclonal antibodies", should be replace by "including natalizumab and other monoclonal antibodies"

Thank you for your suggestion. We have revised the manuscript accordingly (line 87).

3. English editing is needed.

The revised manuscript has been edited by a native English speaker from a commercial editing service (Edanz).

References


