



CASE REPORT

A case report of simultaneous PML-IRIS during corticosteroids tapering in a patient with an anti-synthetase syndrome [v1; ref status: indexed, <http://f1000r.es/2l6>]

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Abstract

We report a case of simultaneous progressive multifocal leukoencephalopathy-associated immune reconstitution inflammatory syndrome (PML-IRIS) during corticosteroid tapering in a patient with an anti-synthetase syndrome. We describe the challenges associated with the diagnosis and the management of this emerging inflammatory neurological condition in this immunocompromised patient with a severe rheumatic disease. We highlight that, in the setting of IRIS, the low-level of the JC virus viral load requires a sensitive PCR assay before excluding PML.

Article Status Summary

Referee Responses

Referees	1	2	3
v1 published 23 Dec 2013	 report	 report	 report

1 Gabriele Arendt, University Hospital of Düsseldorf Germany

2 Joseph Berger, University of Kentucky USA

3 Xin Dang, Beth Israel Deaconess Medical Center USA

Latest Comments

No Comments Yet

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a devastating disease due to reactivation of the Polyomavirus JC virus (JCV) in immunocompromised patients¹. PML has been associated with immune reconstitution inflammatory syndrome (IRIS) during immune recovery of HIV-infected patients treated by antiretroviral therapy, or in non HIV-infected patients after the withdrawal of therapeutic monoclonal antibodies^{2,3}. Here we describe a case of simultaneous PML-IRIS during corticosteroids tapering in a patient with an antisynthetase syndrome (ASS).

Case report

A 62-year-old right-handed French Caucasian woman was diagnosed in October 2007 for an ASS and treated by corticosteroids (methylprednisolone 40 mg/week and prednisolone 20 mg/day) and mycophenolate mofetil (3 g/day). In March 2010 white blood cell count showed profound lymphopenia (486/mm³, normal range 1,500 to 4,000/mm³, Figure 1). Because the ASS was controlled, methylprednisolone was stopped and prednisolone was progressively tapered to 7.5 mg/day. In May 2010 she presented progressive cognitive impairment, followed by a brisk worsening in July 2010 with dizziness and falls. At admission on July 8th 2010 neurological

Blood lymphocyte count and immunophenotyping

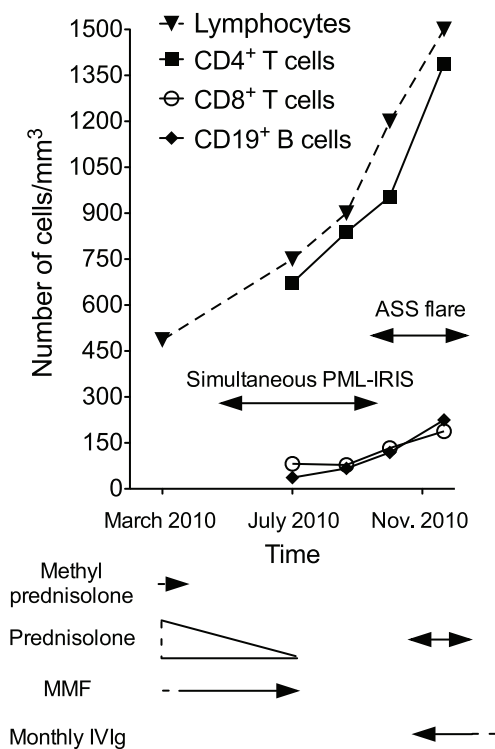


Figure 1. Course of blood lymphocytes according to symptoms and therapy. Arrows underneath the graph represent treatment periods. Single arrow heads represent treatments that were begun or stopped outside of the time period represented on the graph. ASS: Anti-synthetase syndrome; MMF: mycophenolate mofetil.

examination revealed mental slowness, attention and memory troubles, and paresis of the left lower limb. Brain axial T2-WI MRI revealed confluent subcortical white matter hyperintensities of the right frontal and parietal region (Figure 2A). Axial T1-WI MRI displayed hypointensities with multiple foci of gadolinium enhancement (Figure 2B). Prednisolone and mycophenolate mofetil were stopped. The differential diagnoses were viral encephalitis, tuberculosis, cerebral lymphoma, paraneoplastic disorder and CNS involvement of a connective tissue disorder. General examination did not demonstrate any activity of the ASS. Blood cell count showed 750 lymphocytes/mm³ (Figure 1). Cerebrospinal fluid (CSF) examination on day 2 was normal, and in-house PCR (*Herpesviridae*, enterovirus, JCV, BK virus, *Toxoplasma gondii* and *Mycobacterium tuberculosis*), and serologies (HIV, *Borrelia* and syphilis), were negative, as well as direct staining and cultures for bacteria and fungi. Blood immunophenotyping showed 673 CD4⁺ T cells/mm³ (normal range 500–1,500), 82 CD8⁺ T cells/mm³ (normal range 250–950) and 37 CD19⁺ B cells/mm³ (normal range 100–600) (Figure 1). The level of anti-Jo1 antibodies previously detected (Nov 2009, 7.4 AI (normal range 0–0.9) was decreasing (5.9 AI) and a screening for anti-neutrophil cytoplasmic and onconeural antibodies was negative. A computed tomography scan showed steady lung interstitial infiltrates, and no evidence for sarcoidosis, tuberculosis or cancer. A stereotactic brain biopsy of the right parietal lobe was performed on July 16th 2010. Neuropathological examination showed demyelinated lesions with axonal loss and a severe inflammatory reaction with a vasculitic component and endothelial damage (Figure 2D–E). Perivascular and parenchymal inflammatory infiltrates showed a pronounced CD3⁺ T cell infiltrate (Figure 2F) composed mostly by CD4⁺ T cells, in association with a few CD68⁺ macrophages/microglial cells and CD138⁺ plasma cells. Anti-Simian virus 40 (SV40) immunohistochemistry (cross-reacting with the JCV) was positive, and a second aliquot of the CSF taken on day 2, sent to Dr. Major's laboratory at the NIH, was positive for JCV by Real-time TaqMan PCR at a low level (23 copies/ml)⁴, both firmly establishing the diagnosis of PML. A diagnosis of simultaneous PML-IRIS with vasculitis was made. As in the meantime her neurological status had stabilized, the patient did not receive corticosteroids. When followed up in November 2010, mental slowness and paresis of the left lower limb had completely recovered, and repeated MRI showed improvement of previous lesions. In parallel, blood immunophenotyping showed partial normalization (Figure 1). However, concomitantly she presented with a severe flare of the ASS, with myositis, polyarthritis and active interstitial pneumonitis. A one-week course of oral corticosteroids was initiated together with monthly intravenous polyclonal immunoglobulin therapy (IVIg). By December 2012 the ASS was considered under control with IVIg alone. The patient was fully independent without any neurological abnormalities, while MRI showed sequellar lesions (Figure 2C).

Discussion

The diagnosis of PML in this immunocompromised patient is firmly established by the detection of JCV DNA in the CSF and of viral proteins on the brain biopsy sample, and by the exclusion of alternative infections or tumors¹.

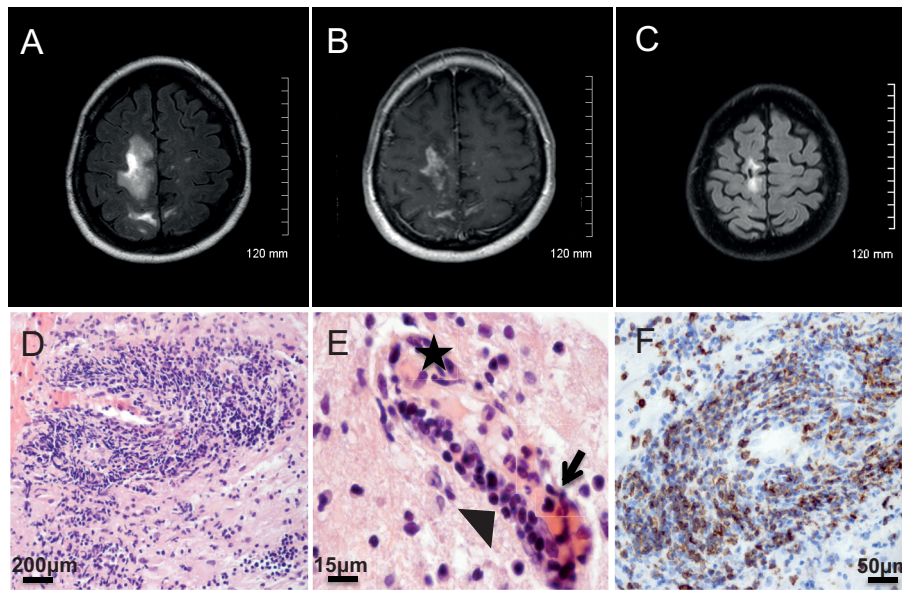


Figure 2. Brain MRI and histopathology. **A–B:** Brain MRI at the onset of the simultaneous PML-IRIS showing white matter hyperintensities of the right frontal and parietal region (A, axial T2-WI) with multiple foci of gadolinium enhancement (B, axial T1-WI). **C:** Brain MRI nine months after the onset of PML-IRIS showing sequelae lesions (axial T2-WI). **D–E:** Histopathology showing severe perivascular infiltrates (D, H&E \times 200) with a vasculitic component (E, H&E \times 630, star: fibrin deposit, arrow: neutrophils and serohematic material, arrowhead: lymphocytes infiltrating vessel wall). **F:** Immunohistochemistry analysis (\times 400) showing perivascular inflammatory infiltrates positive for CD3 antibody (clone F7.2.38, DAKO).

However, this PML case is associated with very unusual inflammatory features, as attested by contrast enhancement on brain MRI and T cell infiltrates with a vasculitic component on brain biopsy. Because the level of immunosuppression was recently alleviated in this patient, as suggested by the increase of the blood lymphocyte count at admission, we believe that this patient developed a simultaneous PML-IRIS. The development of neurologic abnormalities due to an unusual inflammatory form of PML in the setting of immune recovery is consistent with the definition of simultaneous IRIS⁵. IRIS results from the restoration of an antimicrobial immune response that causes disproportionate tissue damage in infected organs⁶. In this case, the corticosteroid tapering, by restoring partially immune surveillance, might have unleashed the T-cell mediated immune response underlying PML-IRIS. The subsequent control of the viral replication might explain the low-level of the CSF viral load in this patient, highlighting that a sensitive PCR assay is required to exclude PML in the setting of IRIS.

Brain infiltrates were mainly composed of CD4⁺ T cells, which is another unusual feature of this case. Indeed, a clear dominance of CD8⁺ T cells in infiltrates has been observed in natalizumab-associated PML-IRIS in patients with multiple sclerosis (MS)⁷, and in PML-IRIS in HIV-infected patients⁸. Nevertheless, a recent case report suggested a central role for CD4⁺ T cells in natalizumab-associated PML-IRIS in a patient with MS⁹. The fact that lymphopenia in our patient mainly relies on CD8⁺ T cells, and not on CD4⁺ T cells, conversely to the situation in HIV-infected patients, might in part explain this phenomenon.

Despite severe neurological deterioration, this PML correlates with favorable outcome without corticosteroid treatment. The inflammatory reaction associated with IRIS is often self-limited and does not seem to alter survival of patients with PML¹⁰. A better control of viral replication might also have contributed to this positive outcome. Because corticosteroids have a profound impact on the JCV-specific T-cell response, they should be reserved for life-threatening PML-IRIS¹¹. Finally when the ASS relapsed, the IVIg therapy was a suitable way to manage the risks of immunosuppression¹².

In conclusion, PML-IRIS might occur in patients with rheumatic diseases not receiving therapeutic monoclonal antibodies when immunosuppression is alleviated. PML presentation is unusual in this setting, and diagnosis requires a sensitive PCR assay, and/or brain biopsy.

Consent

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

Author contributions

G. Martin-Blondel: Drafting/revising the manuscript for content, including medical writing for content, Study concept or design, acquisition of data, analysis and interpretation of data, study coordination. D. Brassat: Drafting/revising the manuscript for content, acquisition of data, analysis and interpretation of data. H. Dumas: Revising the manuscript for content, neuroradiological analysis.

E. Uro-Coste: Revising the manuscript for content, pathological analysis. D. Adoue: Revising the manuscript for content, acquisition of data. H. Lassmann: Revising the manuscript for content, pathological analysis. M. Clanet: Drafting/revising the manuscript for content, acquisition of data, analysis and interpretation of data.

Competing interests

No competing interests were disclosed.

Grant information

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[PubMed Abstract](#) | [Publisher Full Text](#)

Current Referee Status:

Referee Responses for Version 1



Xin Dang

Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Approved: 07 March 2014

Referee Report: 07 March 2014

The presence of JCV genomic DNA in CSF is the key evidence for making a diagnosis of PML. However, from time to time in our research, CSF samples from diagnosed PML patients could be JCV negative in conventional PCR; only the most sensitive real time PCR can detect the extremely low JC viral load in these CSF samples. For this reason, I suspect that some PML patients may be misdiagnosed. The remarkable work of Dr. Martin-Blondel's group will encourage other clinicians to look into a possible PML diagnosis in some neural ataxia cases when occurring in immunosuppressed patients.

I have two suggestions that will improve this work:

1. Based on my own experience, JC viral load may increase to a higher level after the PML lesions become visible. If post PML diagnosis CSF samples are available, the data of the JC viral replication kinetic in this patient will help readers gain a better understanding of how JCV replicates in this PML-IRIS patient.
2. This patient also shows cognitive dysfunction, which I suspect may be the symptom of a newly defined JCV associated cerebellar disease called JCV Granule Cell Neuronopathy (JCVGCN). Unfortunately, the MRI of the cerebellum is not available in this paper and the authors didn't look into the presence of GCN type JCV strains. However this won't hurt the integrity of this paper.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.



Joseph Berger

Department of Neurology, University of Kentucky, Lexington, KY, USA

Approved with reservations: 03 March 2014

Referee Report: 03 March 2014

The authors describe a fascinating patient with ASS and PML-IRIS. The latter appeared to develop concomitant with tapering of corticosteroid therapy. I would suggest the following to improve the manuscript:

1. The focus of the paper should be expanded or modified. The occurrence of PML-IRIS at the time of the initial diagnosis of PML is a well-described phenomenon in patients being treated with natalizumab. In fact, as many as 40% of the them have IRIS concomitant with their PML. This literature should be cited. More importantly, this appears to be the first case of ASS and PML.

There is at least one case report of polymyositis and PML, but I could not find another of ASS and PML and I think that is probably more important than the concomitant appearance of PML and PML-IRIS.

2. The figures should include some histopathological sections to demonstrate the demyelination and the SV40 staining. Were bizarre astrocytes and enlarged oligodendroglial nuclei not observed? If so, it should be described.
3. Does ASS ever occur with vasculitis or brain disease? A discussion of this aspect of the differential diagnosis would be helpful to the reader.
4. The authors reserve comment on the specific clinical features of the rheumatological condition to the very end of their case description. I think it would be more useful to incorporate it earlier in their description. When did it develop, what were the clinical features, etc?
5. Do the authors think that the mycophenolate mofetil contributed to the PML? After all, it carries a black box warning in the U.S. for PML.
6. Change the wording from "mainly relies on CD8" to "mainly characterized by CD8" or something similar.
7. This patient had resolution of the IRIS in the absence of corticosteroid treatment. This is another important point as the neurological community has widely embraced employment of steroids at the outset of the disorder. A discussion of this dilemma can be found in [Berger, JR \(2009\)](#).

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.



Gabriele Arendt

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Approved: 10 February 2014

Referee Report: 10 February 2014

The authors present an article on a patient with an antisynthetase syndrome developing progressive multifocal leucoencephalopathy = PML-IRIS under cortisone tapering. The case is interesting, well presented and important, because it shows that IRIS-PML might occur also when a relatively mild immunosuppression is reduced.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.
