CASE REPORT

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IRIS without PML in MS patients – a case report of IRIS after past alemtuzumab therapy with subsequent oral cladribine treatment and review of the literature

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Abstract

Alemtuzumab is a high-efficacy drug for relapsing-remitting multiple sclerosis (MS), leading to non-selective reconstitution of the immune system. Immune reconstitution inflammatory syndrome (IRIS) develops due to reconstruction of cellular immunity and inflammation in the CNS, mostly after progressive multifocal leukoencephalopathy (PML). A case of a 42-year-old patient is presented treated in the past with alemtuzumab because of highly active MS. He was admitted after 8 years of remission because of aphasia, bulbar syndrome and severe agitation. MRI of the brain showed multiple big confluencing lesions supra- and infratentorially, with mass effect and contrast enhancement. IRIS was diagnosed. Prolonged steroids therapy and plasma exchange were used with success. IRIS can also be a complication of natalizumab or fingolimod withdrawal and arise from the restoration of the previously suppressed immune response. Other cases of IRIS in MS patients without preceding PML are also reviewed.

Key words

immune reconstitution inflammatory syndrome (IRIS), alemtuzumab, highly-active multiple sclerosis, oral cladribine

INTRODUCTION

Alemtuzumab is a recombinant humanised monoclonal antibody (immunoglobulin G1, IgG1) directed against the CD52 (cluster of differentiation 52) surface antigen that is expressed on cells of the immune system (i.e. on membrane of the mature lymphocytes T and B, and in lower levels – on natural killer cells – NK, monocytes, macrophages, eosinophils and monocytes derived from peripheral blood dendritic cells – DC). It depletes T and B cells through complement mediated cytotoxicity (CDC) and antibody dependent cellular cytotoxicity (ADCC), resulting in repopulation and production of new T and B cells originating from stem cells or by homeostatic proliferation of lymphocytes that escape depletion. In neurology, it is used as a high-efficacy drug in the treatment of highly active relapsing-remitting multiple sclerosis (MS) leading to non-selective reconstitution of the immune system [1, 2, 3].

Immune reconstitution inflammatory syndrome (IRIS) develops due to the reconstruction of cellular immunity and inflammation in the central nervous system (CNS), in most cases after progressive multifocal leukoencephalopathy (PML) [4]. PML is a disease of the white matter caused by the reactivation of opportunistic infection by polyoma virus called the John Cunningham virus (JCV, from the name of the first patient diagnosed with PML). PML usually develops in patients with immunodeficiency, e.g. in human immunodeficiency virus (HIV) infection, or in the course of treatment with drugs causing immunosuppression. IRIS can sometimes also occur in the absence of PML [5].

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OBJECTIVE

The aim of this Case Report was to present the first case of an MS patient treated with alemtuzumab 8 years earlier in whom IRIS without preceding PML developed (with introduction of follow-up successive treatment with oral cladribine), and to review similar cases of IRIS without PML in MS patients.

CASE REPORT

A 42-year-old male patient was treated in 2011 and 2012 with alemtuzumab because of highly active MS and initially treated with interferon beta; however, due to severe relapses requiring steroid therapy, the treatment was switched to highly-active treatment with alemtuzumab. During the following 8 years a remission was observed, and the clinical and radiological picture remained stable. In February 2020, the patient was admitted to the Department of Neurology because of rapidly progressing aphasia, bulbar syndrome and severe agitation. MRI of the brain showed multiple, big confluencing lesions hyperintense in T2-weighted images, in

the white matter, both supra- and infratentorially, associated with mass effect and contrast enhancement (Fig. 1). Lumbar puncture was performed. Analysis of the cerebro-spinal fluid (CSF) was normal, JCV-DNA was negative in the CSF. However, due to doubts as to the final diagnosis (MS relapse, PML and IRIS were considered), prolonged intravenous steroids therapy (methylprednisolone: 1 × 1000 mg during 5 days, then 1 × 500 mg during 3 days, then dexamethasone: 1 × 8 mg during 5 days, then 1 × 4 mg during 3 days) and plasma exchange were used. Mirtazapine in tablets at a dose 30 mg once daily was also introduced in the treatment. The results of examinations and clinical improvement allowed the final diagnosis of IRIS. During a series of control MRI gradual regression of lesions was observed (Fig. 1). Partial neurological improvement occurred during the next 3 weeks and the patient was discharged.

Five months later, the patient was qualified to treatment with oral cladribine, with the first dose of the drug given in July 2020. Standard regimen of cladribine was used with doses given in the first and the second year of therapy (in agreement with Summary of Product Characteristics). Since then, the patient's neurological state and radiological picture of the brain have been stable and undergoing gradual improvement in comparison to pictures from February 2020 (Fig. 1).

Four years after administration of the first dose of cladribine, reactivation of disease activity occurred and in June 2023 the patient was hospitalized and treated with i.v. steroids because of a relapse of MS with right-sided hemiparesis. An MRI made in June 2023 revealed new lesions infratentorially and better visible lesions in the spinal cord at the level of C2/C3. In July and August 2023, a booster dose (the third dose) of oral cladribine was administered according to recommendations [6]. Since then, the patient has been stable.

DISCUSSION

Discussion and review of other cases of IRIS without preceding PML. PML is a subacute, progressive disease of the brain characterized by steadily increasing demyelination. It is often fatal and develops in the case of an immunocompromised state, usually in HIV-positive patients or in patients with diseases such as lymphoma, leukaemia, systemic lupus erythematosus (SLE) or after organ transplantation, as a result of reactivation of latent infection with neurotropic virus, JCV [5, 7]. In neurological patients it can develop in the case of treatment with agents that cause immunosuppression in the brain, most commonly with natalizumab, but also fingolimod, dimethyl fumarate and ocrelizumab [5, 7, 8]. So far, only one case of PML in an MS patient after alemtuzumab has been reported, that of a 31-year-old female, 2 months after the second cycle of alemtuzumab, generalised tonic-clonic seizures occurred and PML was diagnosed [9]. There were cases of PML after alemtuzumab in patients with other diseases and after treatment of graft versus host disease [10, 11].

Clinically in PML, the following symptoms are observed: altered mental status, motor deficits, ataxia, visual disturbances (e.g. diplopia and hemianopia) and seizures. PML is fatal in 22% (in MS patients treated with natalizumab) to 50 % (all PML cases). Prognosis of PML is generally poor with a relentless neurological decline leading to coma and death occurring in the majority of patients with PML. If untreated, PML is usually fatal within one year, often during 2 – 6 months [5, 7].

IRIS can develop as a result of the treatment of PML. It arises from the restoration of the previously suppressed inflammatory immune response, in the absence of active infection, due to reactivation of memory cells that had previously been activated by antigen exposure. IRIS causes neurological deterioration, but prognosis is better

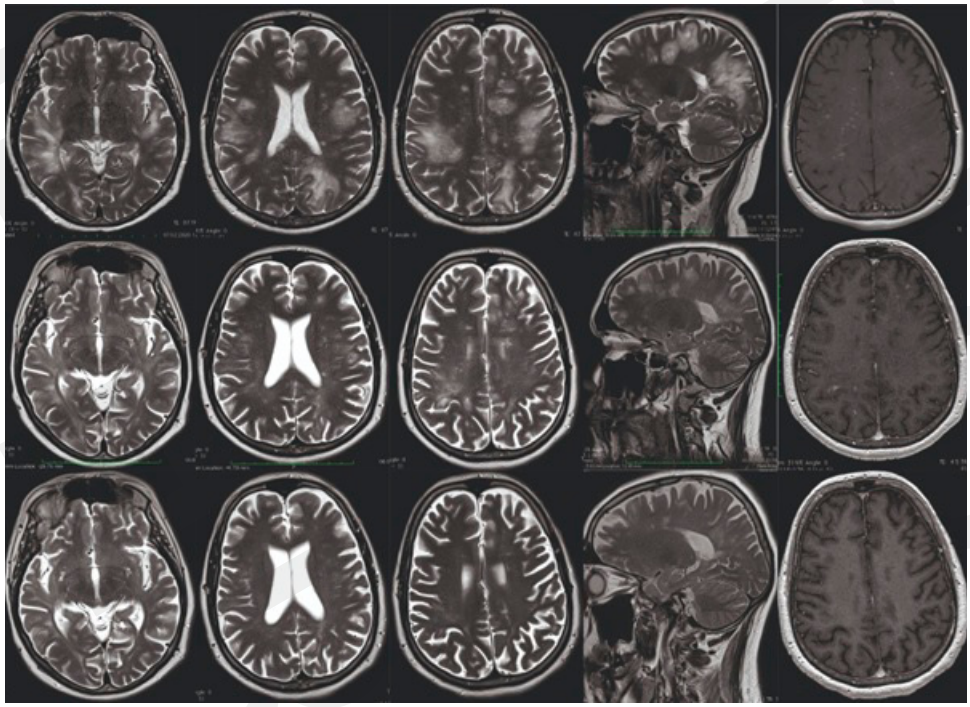

Figure 1. MRI of the brain, axial and sagittal view, T2-weighted images and T1-weighted images with contrast (last column), February 2020 – upper row, June 2020 – middle row, and June 2021 – bottom row

than in PML as fatal cases occur in less than 5%. IRIS is often observed in patients with AIDS after introduction of antiretroviral therapy when paradoxically neurological deterioration occurs. Although IRIS can also develop in MS patients with PML after natalizumab treatment [5], it rarely develops without preceding PML as a result of restoration of the previously suppressed immune response, in the absence of active infection, i.e. PML.

In the literature from the last 10 years [12–19], there are only 6 published cases of IRIS without PML in MS patients after cessation of natalizumab treatment, and 2 after cessation of fingolimod (Tab. 1). Discontinuation of fingolimod may lead to an abrupt rise in the lymphocyte count within 1–2 months, which could be implicated in fingolimod-associated IRIS [14]. Discontinuation of natalizumab leads to rise in autoimmune lymphocyte count directly in the CNS, which could be responsible for natalizumab-associated IRIS [19].

So far, no cases of IRIS without PML after previous alemtuzumab treatment have been reported in the literature [5, 9].

Differentiating PML and IRIS MRI is helpful. In PML, imaging reveals characteristic multifocal lesions in the subcortical hemispheric white matter or the cerebellar peduncles. PML lesions also occur in grey-matter areas, such as the basal ganglia or thalamus. Lesions are asymmetric with periventricular and subcortical involvement, most often seen in the parieto-occipital and frontal lobes. There is little, or no mass effect nor contrast enhancement. Characteristic hyperintense, multiple punctate high T2-signal lesions surrounding the main area (called milky way sign) and parieto-occipital signal abnormality crossing the splenium (called barbell sign) are often visualised.

In contrast, in IRIS on MRI there are multifocal T2-hyperintensive enhancing masses that gain mass effect rapidly; enhancement is variable and appears bizarre or wild.

Table 1. Literature review of cases of IRIS without preceding PML in MS patients during the last 10 years

Study	Age -years/gender	Earlier treatment and course of IRIS (without preceding PML)	Treatment	Outcome
1. N'gbo N'gbo Ikazabo R et. al., 2016 [12]	24/male	IRIS developed after cessation of natalizumab, therapy was switched to fingolimod	plasmapheresis, corticosteroids	fatal
2. Cuascut FX et al., 2021 [13]	48/female	Fingolimod (during 7.6 years) and abatacept (for rheumatoid arthritis); fingolimod-related cryptococcal meningoencephalitis and IRIS developed 73 days after drug discontinuation	oral prednisone	recovery
3. Gundacker ND et al., 2016 [14]	46/male	IRIS and cryptococcal meningitis developed after 2-year therapy with natalizumab	corticosteroids, amphotericin B lipid complex and flucytosine	fatal
4. Mulero P et al., 2014 [15]	22/female	After the patient's fifth natalizumab infusion, aggressive radiological and clinical evolution occurred – due to the appearance of natalizumab antibodies that triggered lymphocyte migration to the CNS in a rebound phenomenon	changing the patient's treatment to fingolimod	recovery
5. Evangelopoulos et al., 2015 [16]	47/female	After 44 months, natalizumab treatment was discontinued due to clinical and radiological activity, with severe neurological and radiological signs 4 months later	corticosteroids i.v. for 5 days, then monthly corticosteroid treatment for 12 months	recovery
6. Mickeviciene D et al., 2022 [17]	35/female	A few months after fingolimod withdrawal patient developed severe clinical decline (global aphasia, an altered mental status, left hemiparesis; was unresponsive and bedridden with complete incontinence) and MRI lesions, IRIS was diagnosed	several pulsed methylprednisolone infusions, plasmapheresis, i.v. dexamethasone, oral mirtazapine	gradual recovery on ocrelizumab
7. Holmøy T et al., 2016 [18]	50/female	A LHON-MS patient developed severe MS activity peaking 14 months after discontinuation of natalizumab, with extensive inflammatory lesions throughout the brain and the spinal cord – IRIS was diagnosed	high dose methylprednisolone for 5 days, later alemtuzumab	improvement
8. Sepúlveda M et al., 2015 [19]	43/female	After 42 natalizumab infusions, due to positive JCV antibodies, the patient discontinued therapy. Thirteen weeks later she developed a severe visuospatial deficit and cognitive impairment, then – hemiparesis and hemineglect. Patient's condition worsened leading to tetraparesis with EDSS=9, IRIS was diagnosed	corticosteroids iv., 6 cycles of plasma exchange, 1 g of IV cyclophosphamide followed by a cycle of rituximab (1 g administered 2 weeks apart)	gradual improvement; after 16 months resumed glatiramer acetate therapy
9. Alroughani R et al., 2014 [20]	36/female	On completion of 24 infusions of natalizumab, due to JC seropositive status, she elected to switch to fingolimod after a washout period of 2 months. Because of severe lymphopaenia of 0.1×10^9/L fingolimod was discontinued. Natalizumab was resumed after the normalisation of lymphocyte count. Three days later severe reactivation of disease occurred, within 7 weeks of fingolimod's withdrawal (despite the absence of breakthrough disease during the 8-week natalizumab washout period previously).	plasma exchange (6 cycles), a course of i.v. methylprednisolone, followed by oral prednisone (1 mg/kg)	partial improvement
10. Massey TH et al., 2017 [21]	22/female	Natalizumab was discontinued on 15th infusion because the patient reported 8 weeks of pregnancy. At 16 weeks' gestation (3 months after her last natalizumab infusion), the patient developed rapidly progressive weakness of all 4 limbs over a week, then deteriorated further, becoming encephalopathic and quadriparetic, with a complex ophthalmoplegia and gross ataxia (EDSS 9.5). Restarted monthly natalizumab infusions at 24 weeks' gestation.	corticosteroids i.v. and continued enteral prednisolone	recovery; gave birth to a healthy baby girl by elective caesarean section at 40 weeks' gestation

EDSS – Expanded Disability Status Scale; IRIS – Immune reconstitution inflammatory syndrome; i.v. – intravenous; LHON – Leber hereditary optic neuritis; MS – multiple sclerosis

Examination of the CSF is necessary for the differential diagnosis. DNA of JCV is detected with polymerase-chain reaction (PCR) in the case of PML, which is absent in the case of IRIS [4, 5, 7].

In the presented Case Report, IRIS was diagnosed after taking into account the negative result of JCV DNA in the CSF, and characteristic MRI lesions with contrast enhancement. However, due to doubts about the final diagnosis, both steroids and plasma exchange were used in the treatment. In general, steroids are also recommended in IRIS treatment [4, 5, 7]. Mirtazapine is suggested in the case of suspicion of PML as it might be beneficial in its treatment by preventing the spread of virus [16].

When the neurological condition of the patient was stable and MRI of the brain showed regression of lesions, treatment with the drug causing selective immunosuppression was introduced. In total, the patient received 3 courses of oral cladribine, first in 2020 and 2021, and then again in 2023, because of a relapse and new lesions on MRI. Due to the active disease in his case, a highly-active therapy was considered, with low risk of PML [20, 21]. For this reason, cladribine was chosen, with apparent good results. After the first dose of cladribine in 2020 up to June 2023, the patient remained stable and there were no new lesions on MRI. In the fourth year of treatment, the disease reactivated, and the third course of cladribine – a booster dose – was applied in July 2023. The standard regimen of cladribine in tablets given in the first and the second years of therapy, and the booster dose given in case of disease reactivation, was justified and has been recommended [6].

CONCLUSIONS

IRIS can be a complication of alemtuzumab treatment and arises from the restoration of the previously-suppressed immune response, in the absence of active infection, i.e. PML. The absence of JCV-DNA in the CSF of the presented patient, mass effect and bizarre contrast enhancement of lesions on brain MRI and clinical improvement, suggested IRIS, for the patient who had undergone treatment with alemtuzumab 8 years earlier. Alemtuzumab therapy in the past (many years earlier), as well as the recent discontinuation of natalizumab or fingolimod can result in IRIS without preceding PML [12–19]. Oral cladribine treatment in the patient after IRIS stabilised his neurological condition [6, 21].

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