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Case report

Progressive multifocal leukoencephalopathy in a patient with systemic mastocytosis treated with cladribine

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ABSTRACT

Background: Progressive multifocal leukoencephalopathy (PML) is a rare opportunistic brain infection caused by the human polyomavirus JC (JCPyV). A particular problem with the drug cladribine seems to be prolonged suppression of the CD4+ T-cells, a well-known risk factor for PML.
Case description: A 67-year-old male presented with a 3-weeks history of unsteady gait, dysarthria and a dysfunctional right arm. Seven years earlier, he had been diagnosed with urticaria pigmentosa, and 2 years later aggressive systemic mastocytosis. Cladribine treatment was initiated and regarded effective, but the course was complicated with bouts of severe anemia and recurrent episodes of salmonella associated gastroenteritis. His lymphocyte count fell to 0.1×10^9/L at its lowest level, but gradually rose. Despite this, in the 6 month wake of the last dose of cladribine given, the patient experienced herpetic stomatitis, had CMV present in blood, and ultimately developed the neurological symptoms. An MRI scan revealed a lesion in the right cerebellar hemisphere compatible with PML, and PCR analysis of the CSF showed positive for JCPyV DNA with a load of 323 950 copies/ml. No pathological cells were seen on CSF flow cytometry. The CD4/CD8-ratio was 0.45 (160 CD4+ cells/mm^3 and 360 CD8+ cells/mm^3). The patient passed away 3 weeks later.
Conclusion: PML may be the consequence of prolonged lymphopenia due to the use of cladribine.

1. Why this case is important?

Systemic mastocytosis (SM) is a disorder, defined by mast cell hyperplasia, for which no curative therapy is currently available. In a long-term follow-up study of cladribine in mastocytosis, efficacy was found significant and safety acceptable [1]. Cladribine is regarded a first-line treatment of advanced forms of SM [2]. It is a synthetic deoxyadenosine analog, activated intracellularly in certain cell types, particularly lymphocytes, inducing cell death and independently of this inhibiting cytokine secretion. Analysis of lymphocyte subsets indicates that there is a particular prolonged suppression of the CD4+ T-cells [3], a well-known risk factor for a rare brain infection with the human polyoma virus JC (JCPyV) causing progressive multifocal leukoencephalopathy (PML) [4]. In addition, cladribine has been associated with secondary malignancies, potentially caused by persistent lymphopenia and DNA-damaging properties [2]. Despite very promising efficacy against multiple sclerosis (MS) in the pivotal Phase III CLARITY study, major concerns from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) about cladribine's inherent mode of action, posing a risk of both opportunistic infections and malignancies [5], caused Merck Serono to withdraw it from the global approval process. However, based on newer data, Merck has recently received EMA acceptance for review of marketing authorization application for cladribine tablets [6].

In the absence of treatment, neither MS or SM appears to increase the risk of PML [7]. However, so far almost all the newer drugs approved for treating relapsing forms of MS, including, natalizumab, alemtuzumab, fingolimod, teriflunomide and dimethyl fumarate, have been associated with the development of PML. Herein we present a case of fatal PML in a 67-year-old man on cladribine for SM. The present case includes cladribine on the list of disease-modifying drugs for MS that may cause brain infection with the JCPyV. This adds concern that all potent agents against MS, drugs that deplete, inhibit or sequester presumed autoreactive lymphocytes, also increase the risk of PML.

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2. Case description

A 67-year-old male with no significant prior medical history, was diagnosed with urticaria pigmentosa for nearly 7 years ago. Two years thereafter he was admitted to the department of medicine with diarrhea and night sweat. Upon examination multiple lymphadenopathy, splenomegaly, ascites and scattered osteosclerotic lesions were found. Bone marrow (BM) biopsy showed multifocal dense infiltrates of mast cells (>30), in total around 5%, and the cells had aberrant expression of CD25. A stem cell factor receptor c-KIT point mutation at codon 816, characteristic of sporadic adult mastocytosis [8], was found on BM biopsy. The total serum tryptase levels were persistently higher than 20 ng/mL thereby confirming the diagnosis aggressive systemic mastocytosis (ASM) [9]. Treatment with cladribine, in repeated courses (Fig. 1) with 0.12 mg/kg/d administered over a 2-h daily intravenous infusion for 1–5 days, was initiated. Laboratory analyses prior to the first cladribine treatment showed a white blood cell count of 7.5×10^9/L (eosinophils 1.1, lymphocytes 1.1, monocytes 2.2 and neutrophils 3.0), hemoglobin level of 10.9 g/dL and platelet count of 254×10^9/L. One week after the first cladribine dose was administered, the white blood count decreased to 2.8×10^9/L (eosinophils 1.2, lymphocytes 0.6, monocytes 0.2 and neutrophils 0.9), the hemoglobin level was 9.7 g/dL and the platelet count was 294×10^9/L. In general, the treatment was regarded effective with more than 50% improvement in mast-cell infiltration-related symptoms [10]. However, the biological response experienced was only temporary. Two years after initiation of cladribine therapy he suffered recurrent bouts of severe anemia, requiring blood transfusions. He also suffered recurrent episodes of salmonella associated gastroenteritis. Consequently a colon biopsy was performed, which showed an infiltration of inflammatory cells within the lamina propria, including eosinophils and CD117 positive mast cells. In 2014 his condition was further complicated by the development of portal hypertension and esophageal varices, necessitating a one year cessation of cladribine therapy. Treatment was subsequently resumed, and after approximately 6 months he developed a burning sensation in his tongue. Upon examination of his oral cavity, confluencing white patches with small ulcerating lentil-sized vesicles on the surface of the oral mucosa and tongue were found. *Candida albicans* cultures as well as Herpes simplex virus (HSV) PCR were negative. Nevertheless treatment for both conditions was administered. Two months thereafter he was admitted with a life-threatening sepsis and neutropenic fever. Serum CMV DNA PCR analysis was positive with 150 copies/ml. His lymphocyte count fell to 0.1×10^9/L, at its lowest level. Fig. 1 shows the blood counts prior to and 1–2 weeks after each cycle of cladribine-treatment.

Five months after the last dose of cladribine he was admitted to the emergency ward with a 3-weeks history of progressive walking difficulty, reduced function in his right arm and articulation difficulty. Upon clinical examination he had a horizontal diplopia when gazing to the left and a left sided nystagmus was also observed. He had dysarthria and mild right-sided ataxia, an unsteady gait and a positive Romberg's test with a tendency to fall towards the right. An MRI scan (Fig. 2) of the brain showed a subcortical lesion within the right cerebellar hemisphere extending into the cerebellar vermis and through the middle cerebellar peduncle into the pons, with no mass effect. The lesion was hypointense on T1-weighted and hyperintense on T2-weighted/FLAIR images with no restriction on diffusion-weighted images, however slightly contrast-enhanced. The MRI findings raised suspicion of PML and therefore a lumbar puncture was performed. JCPyV PCR analysis of the CSF was positive, with a DNA load of 323 950 copies/ml. No pathological cells were seen on CSF flow cytometry. PML lesions typically do not enhance on T1-weighted contrast images. Enhancement is usually a sign of an immune response, more commonly associated with PML-IRIS. Due to this and the deteriorating clinical state of the patient the decision to administer high-dose corticosteroid treatment was taken. Subsequently his white blood cell count increased to 5.6×10^9/L (eosinophils 0.6, lymphocytes 0.6) with 1% pathological mast cells (CD25 pos) but otherwise no abnormal cells were seen. The CD4/CD8-ratio was 0.45 (160 CD4+ cells/mm^3 and 360 CD8+ cells/mm^3). In plasma the JCPyV-viral load was 150 copies/ml. HSV1 PCR from the tongue lesions was positive. Treatment with mirtazapine against the PML was initiated, but shortly thereafter the patient expressed the wish that all active, life-extending treatments, including nutrition to be discontinued. He subsequently passed away 3 weeks later, no autopsy was performed.

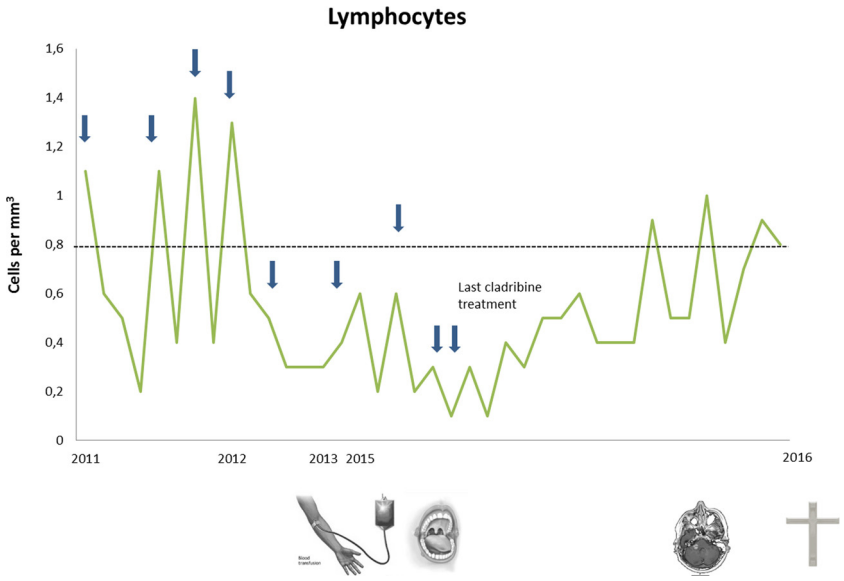

Fig. 1. Lymphocyte counts in a 67-year-old man receiving cladribine for the treatement of systemic mastocytosis. Shown are the white blood cell counts just before and 1–2 weeks after each cladribine treatment course (arrows). Indicated with a dashed line is the lower limit of the normal range. No treatment with cladribine was given in 2014 when the patient suffered from recurrent salmonella enteritis and needed several blood transfusions. Symbols on the x-axis illustrate the clinical occurrence of anemia, burning tongue syndrome, progressive multifocal leukoencephalopathy, and the death of the patient. Confer text for further information.