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CASE REPORT

Severe fludarabine neurotoxicity after reduced intensity conditioning regimen to allogeneic hematopoietic stem cell transplantation: a case report

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Key Clinical Message

We present a case of severe, irreversible neurotoxicity in a 55-year-old-patient with myelofibrosis undergoing hematopoietic stem cell transplantation following a reduced intensity conditioning including fludarabine. The patient developed progressive sensory-motor, visual and consciousness disturbances, eventually leading to death. MRI imaging pattern was unique and attributable to fludarabine neurotoxicity.

Keywords

Fludarabine, hematopoietic stem cell transplantation, neurotoxicity.

Introduction

Fludarabine is a drug widely used in the treatment of hematological malignancies, representing one of the main components in the reduced intensity conditioning regimens for hematopoietic stem cell transplantation. Anemia, neutropenia, and thrombocytopenia due to myelosuppression are the major adverse effects associated with fludarabine administration [1]. Neurotoxicity is an uncommon but well-known possible adverse event during treatment with fludarabine.

Most of the published series on fludarabine neurotoxicity derive from experiences around the middle of the Eighties, where escalating doses were administered in dose-finding studies; moreover, computed tomography (CT) scans rather than magnetic resonance imaging (MRI) were available as imaging counterparts. Subsequently, standard dose fludarabine and purine analogues neurotoxicity has been seldom the matter of specific reports [2]. Only recently, clinical and MRI aspects of a possible specific neurotoxicity after standard dose fludarabine both in the treatment of hematologic malignancies and in reduced intensity allogeneic hematopoietic stem cell transplantation have been reported [3, 4]. We present an additional case of possible severe fludarabine neurotoxicity fitting with the clinical and imaging features described in the above-cited articles.

Case Presentation

A 55-year-old male patient was admitted on November 15, 2010 in our Bone Marrow Transplant Centre to undertake hematopoietic stem cell transplantation (HSCT) from a matched unrelated donor. He was affected by rapidly progressive myelofibrosis with severe pancytopenia, high transfusion requirement, and iron overload despite iron-chelating therapy. Conditioning regimen included thiotepa 5 mg/kg every 12 h for two doses and fludarabine 30 mg/m^2 per day for 6 days. Anti-thymocyte globulin 2.5 mg/kg per day, was delivered on days -3 and -2. Allogeneic hematopoietic stem cell infusion was performed on November 24, 2010. Graft versus host disease (GvHD) prophylaxis included standard dose cyclosporine and short course methotrexate.

Subsequent course was uneventful during the neutropenic phase, the patient experienced a single febrile episode rapidly resolving after starting empirical antibiotic therapy. At day +28 after transplantation, the patient was transfusion independent and chimerism analysis showed full donor engraftment. On December 25, 2010, the patient complained of bilateral symmetric proprioceptive deficit at the lower extremities. On the ensuing days, brain and spine CT scans were performed which did not show any abnormality (Fig. 1); MRI was somewhat delayed because of the mild clinical pattern and of severe claustrophobia requiring deep sedation with anesthesiologic support. Somato-sensitive evocated potentials, electroencephalogram (EEG) and electromyogram (EMG) were normal. Relying on the possibility of cyclosporine toxicity as the most probable cause, methylprednisolone and mycophenolate were provisionally substituted for cyclosporine on December 26, 2010. The clinical picture, however, continued to worsen on the following days: a proprioceptive deficit appeared also at the upper extremities while the level of leg proprioceptive deficit extended up to the knee level. Moreover, some tactile deficit was observed and the patient started to suffer from occasional confusion episodes.

Differential diagnosis, investigations, and treatment

On January 3, 2011 MRI of brain (Fig. 2) and spine was eventually performed with deep sedation. The most outstanding feature were "bilateral symmetric T2 – FLAIR hyperintense lesions involving the posterior periventricular and supraventricular white matter; the lesions demonstrated restricted diffusion suggesting cytotoxic edema without enhancement." Although primarily attributable to toxicity, the imaging pattern did not fulfill the commonly observed criteria for cyclosporine toxicity. Apart from corticosteroids, the patient received high dose immunoglobulins and hydrosoluble vitamin complex, without any benefit. To confirm the toxicity hypothesis, a Positron Emission Tomography (PET) scan was also performed, failing to show hypermetabolic areas in the brain. On the following days, the lesions became apparent also at the CT scan as hypodense ones (Fig. 3); two subsequent CT investigations showed only mild signs of worsening. The patient repeatedly refused cerebrospinal fluid examination. Blood virus monitoring was negative, with the only exception of a low number of JC and BK viruses DNA copies detected, without any tendency towards an increase.

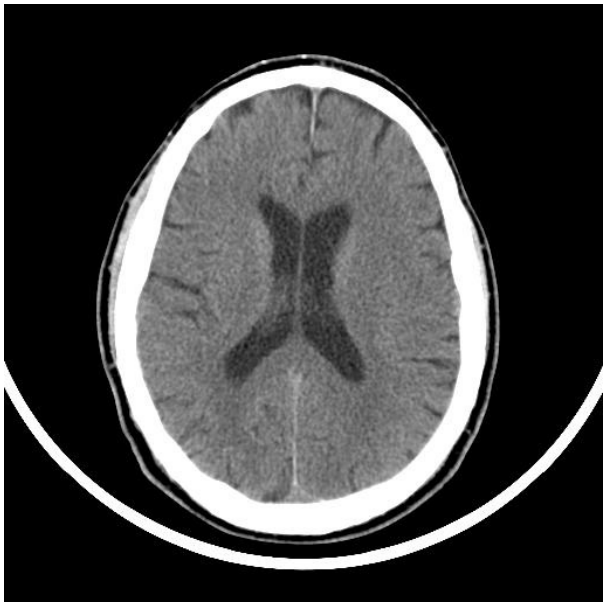

Figure 1. CT scan taken at the onset of symptoms failing to show any abnormalities.

Due to the lack of any benefit from its interruption, cyclosporine was resumed after 1 week, not hindering however the development of cutaneous, hepatic and intestinal acute GvHD. Methylprednisolone dosage was then escalated to 2 mg/kg, though allowing only cutaneous GvHD to be controlled.

Outcome and follow-up

A significant improvement in intestinal GvHD was achieved through the addition of the anti-TNF agent infliximab, whereas hepatic GvHD showed a slowly progressive, relentless course.

At the same time, the neurological picture worsened jointly at sensitive, motor and cognitive level. The patient became soon paraplegic, with sensitive deficit ostensibly sparing only pain perception; eventually, he progressively developed central blindness. At cognitive level, after a protracted phase where the patient appeared delirious and confused, he became barely contactable.

The patient died on March 12, 2011 from hepatic failure due to progressive acute GvHD.

Discussion

Fludarabine is a purine analogue, originally synthesized by Montgomery and Hewson in 1969 [5], and used primarily in the treatment of malignancies arising from the clonal expansion of lymphocytes, particularly in B-chronic lymphocytic leukemia (B-CLL) [6]; because of its potent immunosuppressive activity, it is also used in the conditioning regimens for allogeneic transplantation [7], particularly in those of reduced-intensity.

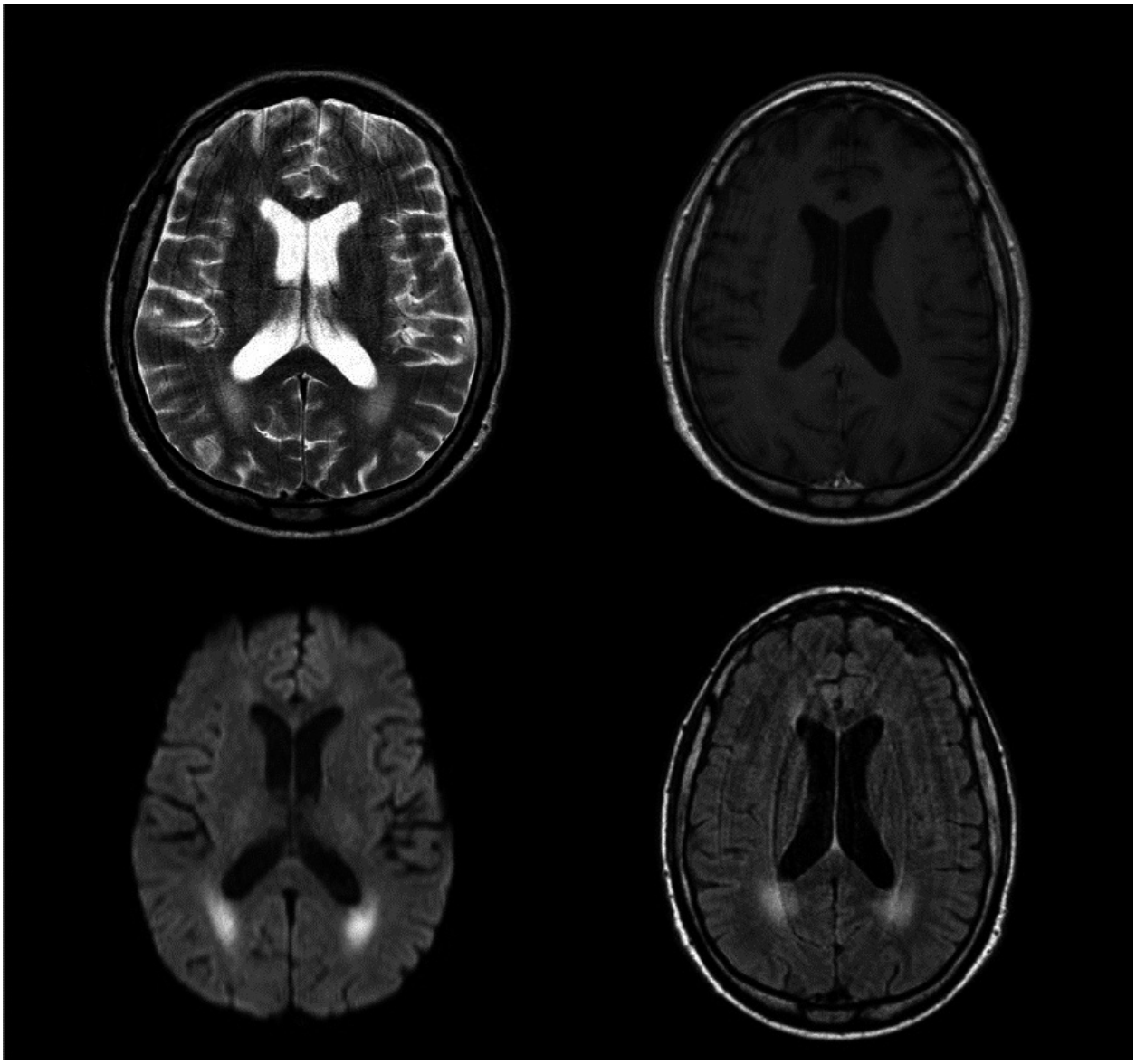

Figure 2. MRI of brain. Axial T2 (upper left), DWI (lower left), and FLAIR (lower right), showing posterior periventricular high signal areas. Axial T1 with contrast medium (upper right) showing no enhancement.

From a pharmacokinetic point of view, it acts as a "pro-drug," requiring metabolic dephosphorylation to the hydrophilic antimetabolite F-ara-A (9-beta-D-arabinosyl-2-fluoroadenine), which can enter cells only in the presence of concentrative nucleoside transporters (CNTs); within the cells, the enzyme deoxycytidine (CdR) kinase progressively re-phosphorylates F-ara-A up to fludarabine triphosphate (F-ara-ATP), the only metabolite displaying cytotoxic activity [8]. Polymorphisms in the genes codifying for CNTs or CdR kinase may cause, respectively, different uptake and conversion rate, resulting in altered fludarabine therapeutic index and risk of toxicity.

Cytotoxic activity of F-ara-ATP relays on the inactivation of DNA synthesis through the inhibition of several specific enzymes (DNA polymerase, DNA primase, DNA ligase, ribonucleotide reductase) [9]. The inactivation of DNA synthesis is followed by an initiation of an apoptotic process leading to cell death [10]. Of note, F-ara-ATP can induce death also in quiescent cells, via the activation of the mitochondrial pathway of apoptosis [11].

Anemia, neutropenia and thrombocytopenia due to myelosuppression are the main adverse effects associated with fludarabine administration [1]. Severe neurotoxicity likely related to the high activity of CdR kinase in the

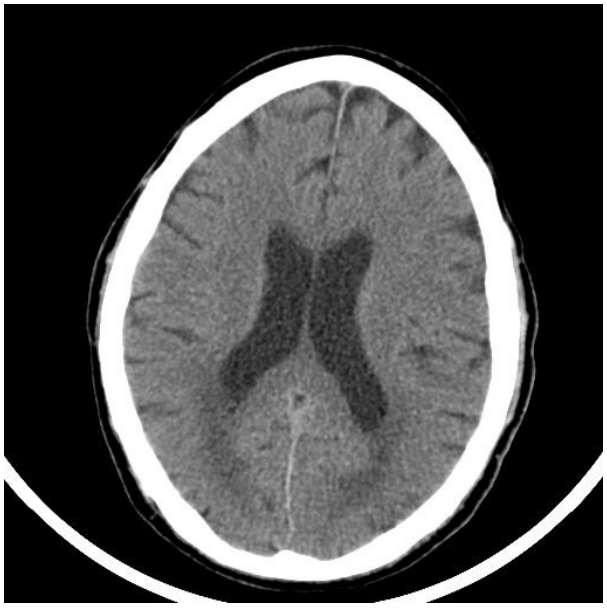

Figure 3. Subsequent CT scan showing symmetric, hypodense periventricular lesions.

brain is included among nonhematological fludarabine side effects [12, 13].

Central and peripheral nervous system toxicity [14–16] are possible side effects of several drugs, especially anticancer agents, often directing to dose reduction or drug withdrawal. Neurotoxicity may be severe and irreversible. Central nervous system (CNS) toxicity presenting as encephalopathy of different severity has been observed not only after fludarabine administration but also with other chemotherapeutic agents, such as vincristine, cisplatin, methotrexate, cytarabine, ifosfamide, 5-fluorouracil; on the other hand, peripheral neuropathy results most frequently associated with taxanes, carboplatin, vincristine, thalidomide, and bortezomib.

Several compounds have been proposed as neuroprotective agents against chemotherapy-induced neurotoxicity, but few of them have been shown to be effective [17]. In an animal model, the incidence of fludarabine neurotoxicity was reduced by the coadministration of NBMPR-P, 5′-phosphate of nitrobenzyl-thioinosine, a potent inhibitor of the nucleoside transport (NT) system. NBTGR-P, the 5′-phosphate of nitrobenzyl-thioguanosine (also a potent NT inhibitor) similarly prevented F-ara-AMP neurotoxicity in this experimental system [18].

Fludarabine is licensed and extensively used for the treatment of CLL [1]. Moreover, it is commonly used for the treatment of acute myeloid and lymphoblastic leukemia (AML/ALL) together with cytarabine and filgrastim in the setting of the "FLAG" schemes [19, 20]. More recently, it has become the reference drug for allogeneic hematopoietic stem cell transplantation following reduced intensity conditioning regimens [21, 22]. Fludarabine-related neurotoxicity was reported in up to 30–40% of patients in phase I/II studies, where the drug was frequently administered at daily doses in excess of 100 mg/m^2 for 5–7 days [13, 23–25]. High dose fludarabine neurotoxicity was frequently reported as irreversible and life-threatening, although milder cases were not infrequent [26]. Rather surprisingly, despite the extensive use of the drug, the interest on this field rapidly waned over the subsequent decades, so that rather little is known about the frequency as well as about the clinical and MRI features of standard dose fludarabine neurotoxicity. Kornblau and coworkers [27] reported 8 of 219 cases of neurotoxicity, two being severe; a neutoxicity rate of 14%, benign and reversible in most of the cases, was reported in a review by Cheson et al. dealing with standard dose purine analogues [2]. Subsequently, viral infections, including progressive multifocal leukoencephalopathy (PML) [28–30], and better established toxic events, as posterior reversible encephalopathy syndrome (PRES) [31, 32], have been the matter of reports in the field of either fludarabine therapy or reduced intensity allogeneic hematopoietic stem cell transplantation [33]. Concerning the latter, the specific role of fludarabine is hard to be distinguished from that of the well-known neurotoxic immunosuppressive agent cyclosporine-A [34], and from that of the total body irradiation (TBI), often included in the conditioning regimens.

Four years ago, Beitinjaneh and collaborators [3] reported acute toxic leukoencephalopathy (ATL) as a possible clinical and imaging counterpart of fludarabine neurotoxicity. Not unlike to previous reports [13, 23–25], the most common clinical features of ATL included cognitive impairment associated with visual and sensitive defects; the clinical outcome was frequently, but not always, irreversible and progressive; the MRI pattern was characterized by the presence of bilateral signal alterations in the deep white matter, rather distinct from PRES. The classic pattern of involvement in PRES is the presence of bilateral and symmetric lesions in the cortex and subcortical white matter of the occipital and parietal lobes [31, 32].

In the same year, Lee and colleagues [4] described in more detail the clinical and MRI features of three patients undergoing reduced intensity hematopoetic stem cell transplantation and receiving fludarabine as part of the conditioning regimen, who developed irreversible, lethal neurotoxicity. The clinical and imaging findings resembled those of ATL and were distinct from the neurological complications, of both toxic and infectious etiology. The authors concluded that these cases were tentatively attributable to fludarabine-specific neurotoxicity.

On the clinical and imaging field, the case we are here reporting bears strict resemblance to the three cases described by Lee [4]. Moreover, it shares the clinical pic-

ture with the cases reported in phase I/II studies [13, 23–25]:

(a) clinical onset occurred 1 month after the end of fludarabine administration;
(b) sensitive and cognitive impairment were the outstanding clinical features;
(c) some imbalance was evident between the polymorphic severe clinical pattern and the relatively limited extension of the white matter signal alterations;
(d) the clinical course was progressive and irreversible;
(e) the MRI pattern was indistinguishable from that reported by Lee and collaborators, [4] and strictly reminiscent of ATL;
(f) a toxic rather than inflammatory etiology was strongly suggested by the MRI findings;
(g) although the patients had refused cerebrospinal fluid examination, PET scan and virological negativity did not support an alternative etiology;
(h) the deep location of the white matter lesions was not coherent with a diagnosis of PRES as a possible alternative diagnosis.

A final matter of discussion may be the possible role of thiotepa. Thiotepa is known to pass through the blood brain barrier and to have the potential of causing neurotoxicity. Nevertheless, the available data concern either the intrathecal [35] or the high-dose administration within myeloablative conditioning regimens followed by autologous stem cell transplantation commonly used in patients with CNS malignancies, notably lymphomas [36]. In both settings, reports involved heavily pretreated patients where CNS irradiation and disease progression exerted a primary role in determining the appearance of neurological impairment [37]. Unlike fludarabine, no suggestive imaging counterpart of thiotepa neurotoxicity has been proposed thus far [36, 37]. On the clinical field, a motor impairment seems more likely attributable to direct thiotepa toxicity [38]. This reinforces the opinion that our patient did suffer of fludarabine neurotoxicity.

According to Lee and colleagues [4], after ruling out more obvious etiology of brain impairment, a fludarabine-related toxic etiology is strongly suspected for severe CNS complications and the MRI pattern defined as ATL may represent the characteristic imaging counterpart. On the other hand, Beitinjaneh and coworkers [3] suggested that fludarabine may also be involved in the pathogenesis of a proportion of more benign neurologic complications presenting as PRES at MRI; besides, ATL may also be potentially reversible in a proportion of cases. Last but not least, a 10% crude rate of neurotoxicity, mostly benign and reversible, was also reported in old series with standard dose fludarabine [2, 27], before the matter began to be somewhat overlooked.

The case of our patient reinforces the opinion that ATL may be the MRI counterpart of severe fludarabine neurotoxicity, rarely observed after standard dose treatment. Because irreversible ATL could only represent the tip of an iceberg, we suggest that fludarabine neurotoxicity should be taken into account also in cases of benign, reversible neurologic impairment.

Conflict of Interest

The authors declare that they have no competing interests.

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