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Letter to the editor

Valproic acid related idiosyncratic drug induced hepatotoxicity in a glioblastoma patient treated with temozolomide

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Abstract

Glioblastoma patients undergoing treatment with surgery followed by radiation and temozolomide chemotherapy often develop a state of immunosuppression and are at risk for opportunistic infections and reactivation of hepatitis and herpes viruses. We report the case of a 48-year-old glioblastoma patient who developed acute cholestatic hepatitis with hepatic failure during adjuvant treatment with temozolomide and the integrin inhibitor cilengitide. A viral hepatitis was excluded and valproic acid treatment was stopped. Upon normalisation of the liver tests, temozolomide treatment was resumed without perturbation of the liver tests. Valproic acid related idiosyncratic drug induced hepatotoxicity should be considered as a differential diagnosis in glioblastoma patients undergoing adjuvant therapy.

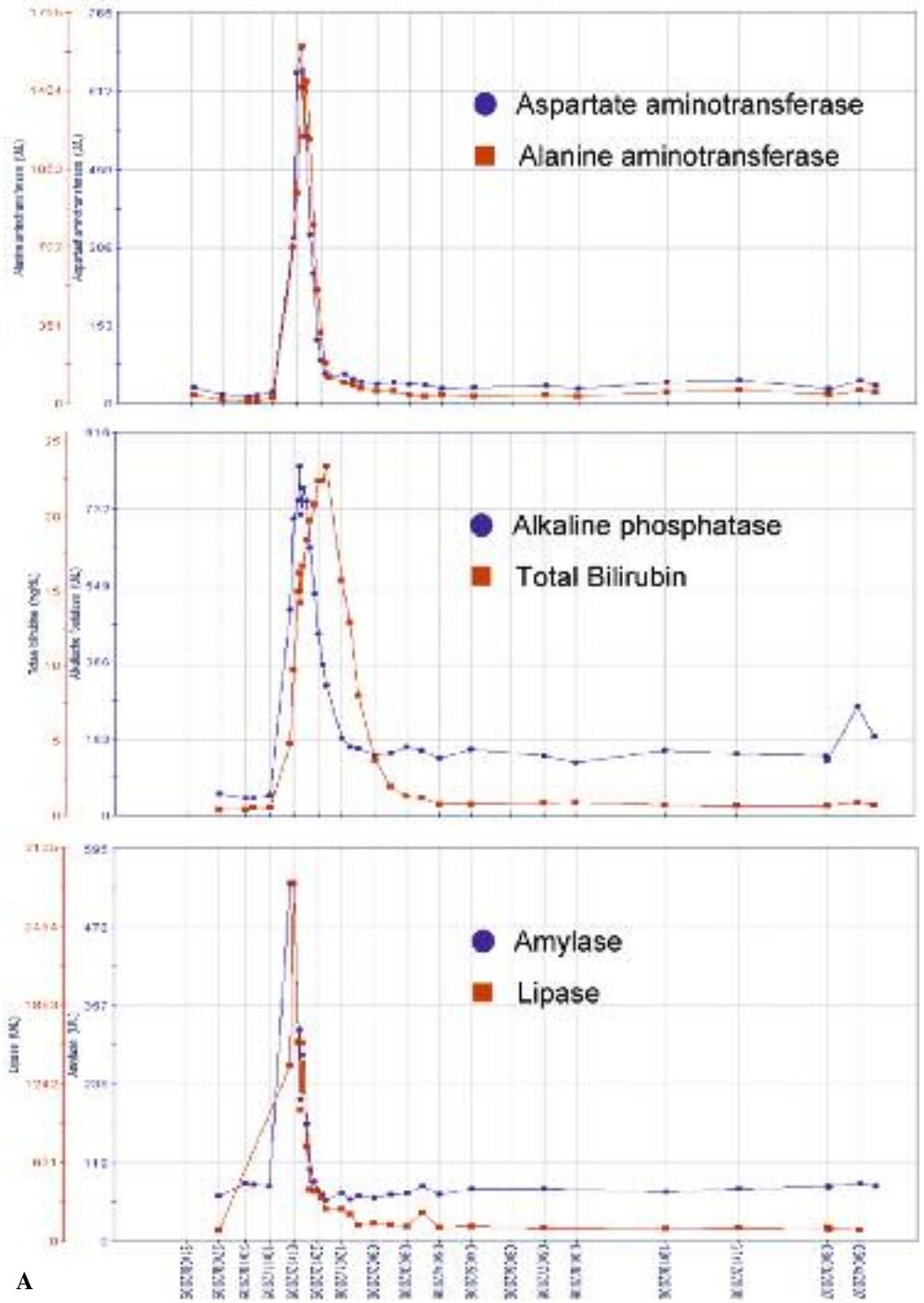
Key words : Glioblastoma ; temozolomide ; valproic acid ; idiosyncratic ; hepatotoxicity.

To the Editor,

Two case reports have recently been published on the reactivation of hepatitis B virus (HBV) infection in glioblastoma patients who were treated with corticosteroids and temozolomide chemotherapy (1, 2). Hepatic failure, attributed to HBV reactivation by the authors, was fatal in one of these two patients while in the second patient infection was controlled with antiviral treatment.

We encountered in our clinical practice a 48-year-old Caucasian man without any prior history of hepatitis, blood transfusions, IV drug abuse or other health problem who underwent a subtotal surgical resection of a left-sided temporo-insular glioblastoma. He was treated within a prospective phase II study with standard radiation therapy (30×2 Gy/d) with concomitant daily temozolomide (75 mg/m² of body-surface area per day, PO during RT) and a novel integrin inhibitor cilengitide (500 mg i.v. twice weekly throughout the study) (3). He was taking valproic acid as seizure prophylaxis and 16 mg of methylprednisolone for control of peritumoral brain edema. He reported no use of alcohol or herbal remedies. Two days after the end of radiation therapy and temozolomide the patient complained about fatigue. Liver tests and bilirubin had been in the normal range up to the latest control 14 days before and blood counts had remained normal up to that day. Three days later jaundice developed and a sharp increase in liver enzymes, bilirubin and to a lesser extend pancreatic enzymes was documented (Fig. 1A). Administration of Cilengitide was discontinued and valproic acid was substituted by levetiracetam. Viral serology revealed immunity for the CMV and EBV viruses. Hepatitis serology for HBVsAg and anti-HCV were negative before the initiation of protocol therapy, and all serology (hepatitis A, B and C) remained negative at the onset and after the incidence of jaundice and liver enzymes elevation. MRI of the liver and pancreas revealed no abnormality. The liver enzymes reached a peak elevation after 9 days and returned to normal after 8 weeks. Bilirubin reached its peak after 4 weeks and returned to normal after 10 weeks. Amonia levels remained below the upper normal limit and there were no clinical signs of encephalopathy. Blood coagulation deteriorated with an international normalized ratio of 1.8 after 2 weeks. A liver biopsy performed on day 9 following the rise in liver enzymes and bilirubin revealed a cholestatic hepatitis with discrete signs of periportal hepatitis and very discrete intralobular hepatitis. There was clear damage to the epithelium of the bile ducts (Fig. 1B arrowhead indicating damaged bile duct, arrow indicating bile plug, at 40× magnification). There was no positivity on immunohistochemistry against CMV.

Fourteen weeks after the initial rise in bilirubin and after the normalization of liver enzymes and bilirubin, standard therapy with maintenance temozolomide (150 mg per square meter for the first cycle and 200 mg per square meter on days 1 through 5 of a 28-day cycle) was resumed. No significant increase in liver enzymes or bilirubin occurred besides a slight elevation in GGT ($< 5 \times$ UNL) during a total of 6 adjuvant cycles and up to present. We did not


Aspartate aminotransferase
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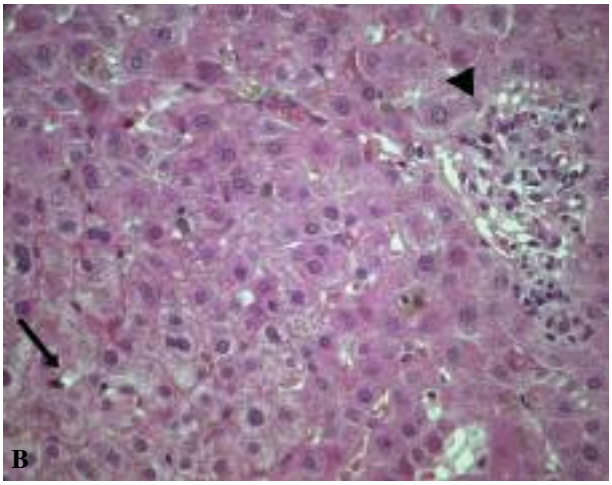
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FIG. 1. —

re-expose the patient to the investigational agent cilengitide. Although we can not definitively rule out a causative role of cilengitide, liver toxicity has to date not been observed with this agent. Occasional increase in liver enzymes with temozolomide has been described (4). However, in large clinical studies no clinically significant liver abnormalities have been observed (5). The clinical presentation of our patient is most consistent with an idiosyncratic drug-induced hepatotoxicity. Valproic acid has been associated with fulminant hepatotoxicity, which is usually fatal, and believed to be idiosyncratic without an immunologic basis (6, 7). While limited elevation of liver enzymes (CTCAE grade 1) during treatment with valproic acid is common and clinically not relevant, life-threatening idiosyncratic hepatotoxicity is a rare event. Risk factors for valproate hepatotoxicity are a young age, polypharmacy, and high VPA serum level. Rare but potentially serious side effects should be taken into consideration when prescribing prophylactic antiepileptic treatment with valproic acid in brain tumor patients. A recently published systematic review by the Cochrane Database provided no evidence in favor of prophylactic treatment with the antiepileptic drugs phenytoin, phenobarbital, and divalproex sodium in patients with brain tumors (8).

The case described by Grewal and colleagues also received antiepileptic therapy with valproic acid (1). Although reactivation of HBV was demonstrated in this patient by serology and circulating viral titers, we believe that in the absence of histopathologic proof of fatal liver destruction trough viral infection the differential diagnosis with an idiosyncratic druginduced hepatotoxicity needs to be considered. We believe that the fatal outcome of this patient may have been related to a similar idiosyncratic drug reaction on top of a compromised hepatic function due to chronic HBV infection. Glioblastoma patients who undergo combined radiation therapy with concomitant daily temozolomide or who are treated with dose intense extended dosing regimens often develop profound lymphocytopenia (with CD4 T-cells below 200/mm3 seen in over half of the patients). This state of immunosuppression, frequently exacerbated by the need for corticosteroids, results in the susceptibility for opportunistic infections such as pneumocystis pneumonia, fungal pneumonia and herpes virus reactivation (9-12). Similar observations of lymphocytopenia and associated opportunistic infections during temozolomide treatment have been made in patients with melanoma and neuroendocrine tumors (13, 14). Likewise we should be aware that there is a risk for reactivation of latent hepatitis virus infections (HBV and HCV). Therefore, documentation of HBV and HCV serology before the initiation of temozolomide and monitoring of hematological and biochemical blood values during treatment may be appropriate. Nevertheless, the experience of a large phase III study conducted buy the EORTC and NCIC demonstrated that the absolute risk for severe complications of this nature is very low (5). Besides pneumocystis pneumonia prophylaxis, we should consider the use of additional anti-viral, -fungal and/or -bacterial prophylaxis on an individualized basis until evidence based guidelines are established.

Disclosure

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