CASE REPORT

Vanishing bile duct syndrome in the context of concurrent temozolomide for glioblastoma

Matthew Mason,¹ Oyedele Adeyi,² Scott Fung,³ Barbara-Ann Millar¹¹Department of Radiation Oncology, University of Toronto, Princess Margaret Cancer Centre, Toronto, Ontario, Canada²Department of Pathology, University of Toronto, Toronto, Ontario, Canada³Department of Medicine, University of Toronto, Toronto, Ontario, Canada**Correspondence to**
Dr Matthew Mason,
mmason@doctors.org.uk

Accepted 10 November 2014

SUMMARY

Temozolomide, an oral alkylating agent, is used in the treatment of glioblastoma. We describe a case of a 62-year-old woman developing jaundice with significant derangement of liver function tests on day 17 of focal radiotherapy with concomitant temozolomide. There was no structural abnormality on imaging and liver biopsy was performed. Pathology revealed absence of small terminal bile ducts affecting up to 60% of sampled portal tracts and senescence of many of the remaining small bile ducts, in keeping with a diagnosis of acute vanishing bile duct syndrome. This is a rare syndrome. It has been documented in association with Hodgkin's lymphoma and viral causes. Drugs implicated as precipitating this condition include antiepileptic medications, some antibiotics, ibuprofen and antifungals. Temozolomide was stopped. The patient received supportive care, ursodeoxycholic acid 750 mg daily and cholestyramine 4 g twice daily. She was otherwise asymptomatic and her blood results returned to normal by day 129.

BACKGROUND

Temozolomide (TMZ) is an oral alkylating agent that demonstrates central nervous system penetration.¹ For patients with newly diagnosed glioblastoma (GBM), the use of focal radiotherapy (RT) with concurrent and adjuvant TMZ has improved overall survival.² In the landmark EORTC/NCIC trial, 7% of the selected patients with GBM receiving TMZ were reported to have grade 3 or 4 haematological toxicity.² In clinical practice, nausea and vomiting are frequently associated with TMZ. Between January 1994 and March 2013, hepatic toxicity was reported in 44 patients with GBM treated with TMZ, including 19 fatal hepatic failure cases.³ Grant *et al*⁴ reported four cases of TMZ-induced liver toxicity documented by the Drug-Induced Liver Injury Network with histology demonstrating varying degrees of cholestasis, mild inflammation, focal hepatocellular injury and prominent bile duct damage or paucity. We report a case of vanishing bile duct syndrome (VBDS) in a patient receiving RT-TMZ postoperatively for GBM.

CASE PRESENTATION

A 62-year-old woman of Indian heritage, who presented with confusion, underwent surgical resection of a 4.3 × 4.2 cm enhancing left frontal lobe lesion. The pathology revealed GBM. Her medical history included type 2 diabetes for 8 years, hypertension and hyperlipidaemia. Her glycosylated haemoglobin (HbA1c) was 0.045 (recommended

level <0.7). Medications included metformin 500 mg twice daily, glimepiride 80 mg once daily, sitagliptin 100 mg once daily, rosuvastatin 5 mg once daily, ramipril 2.5 mg once daily, diamicon 60 mg once daily, pantoprazole 40 mg once daily and dexamethasone 2 mg twice daily postsurgery. No over-the-counter medications were included.

Focal RT to a dose of 60 Gy in 30 fractions with concurrent TMZ 75 mg/m² daily from the first to the last day of RT followed by adjuvant TMZ (150–200 mg/m² for 5 days during each 28-day cycle) was planned. On day 15 of concurrent treatment the patient developed mild pruritus and on day 17 she presented with marked jaundice. No other symptoms had been or were present. Clinical examination revealed scleral icterus and a soft, non-tender abdomen with neither hepatomegaly nor splenomegaly. There was neither ascites nor asterix.

INVESTIGATIONS

Routine blood test revealed a stable complete blood count, normal clotting screen (prothrombin time 12.3 sec, international normalised ratio 0.92), hyponatraemia of 130 mmol/L and deranged liver function tests (alkaline phosphatase 1402 U/L, alanine transaminase 747 U/L, aspartate transaminase 515 U/L, bilirubin 289 µmol/L and albumin 33 g/L).

The patient was admitted and while TMZ was discontinued, she continued RT to completion. Further investigations included an abdominal ultrasound and Doppler, which revealed a moderately fatty liver of 14.4 cm with no focal lesions. There were no vascular abnormalities or intraperitoneal free fluid. The gallbladder was contracted; intrahepatic bile ducts and the common bile duct were not dilated. Viral serology was negative for hepatitis A, B and C. The Monospot test was positive for Epstein-Barr virus (EBV), however, subsequent EBV DNA by PCR was negative. In addition cytomegalovirus (CMV) PCR was negative. Smooth muscle antibody, antimitochondrial antibody antinuclear antibody and anti-liver kidney microsomal antibodies were negative. Serum ferritin was elevated at 1732 µg/L (4.6–204). The patient's IgM was elevated at 7.32 g/L. Figure 1 shows the liver function tests over time with respect to the start of RT-TMZ.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included drug-induced liver injury, marker-negative autoimmune hepatitis, non-alcoholic steatohepatitis, overlap syndrome, primary sclerosing cholangitis and possibly systemic infection.

CrossMark

To cite: Mason M, Adeyi O, Fung S, *et al*. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-208117

Figure 1 Bilirubin and alanine transaminase (ALT) levels in relation to the start of the concurrent temozolomide (TMZ) (day 0). CRT, chemoradiotherapy.

TREATMENT

Owing to further deterioration of liver function tests despite TMZ having been discontinued for 13 days, a liver biopsy was performed on day 30. Pathology revealed absence of small terminal bile ducts affecting up to 60% of sampled portal tracts as well as senescence of many of the remaining small bile ducts, in keeping with a diagnosis of acute VBDS. There was associated

cholestasis and approximately 60% steatosis but no evidence of steatohepatitis or significant fibrosis (figures 2 and 3). Steatosis was believed to be related to the patient's diabetes mellitus and hyperlipidaemia, and unrelated to cholestasis and bile duct loss. The patient received supportive care and was started on ursodeoxycholic acid 750 mg daily and cholestyramine 4 g twice daily.

OUTCOME AND FOLLOW-UP

The patient completed RT and apart from mild pruritus, lasting more than 2 months, she was otherwise asymptomatic. Blood results returned to normal by day 129.

DISCUSSION

VBDS has been related to several causes. It has been documented in cases of Hodgkin's lymphoma⁵ and has been reported to be related to several infective causes including CMV,⁶ EBV⁷ and HIV in the context of highly active antiretroviral therapy.⁸ Drugs implicated as precipitating this condition include the antiepileptic medications valproic acid,⁹ carbamazepine¹⁰ and lamotrigine.¹¹ Antibiotics, such as meropenem¹² and azithromycin,¹³ as well as ibuprofen,¹⁴ have also been associated. Antifungals such as terbinafine have also been linked to this condition.

Treatment strategies for this rare condition include drug withdrawal,¹⁵ steroids,¹⁶ ursodeoxycholic acid¹⁷ and even plasmapheresis.¹⁸ Ursodeoxycholic acid, thought to have several mechanisms of action including stimulation of hepatobiliary secretion, cholangiocyte protection from hydrophobic bile acids and inhibition of apoptosis, is recommended in the treatment of similar intrahepatic and extrahepatic bile duct diseases.¹⁷

Figure 2 H&E stain showing mild-moderate steatosis and cholestasis. The cholestasis as shown in higher magnification in figure 3 results from the loss of small terminal bile ducts (original magnification $\times 100$).

Figure 3 Higher magnifications of terminal portal tracts showing absence of bile ducts by H&E stains (upper panels) and cytokeratin 7 stains (lower panels) (PV, portal vein; original magnification $\times 200$).

Learning points

- ▶ Although rare, hepatic toxicity has been related to temozolomide (TMZ) exposure.
- ▶ Vanishing bile duct syndrome is a rare condition and treatment strategies involve drug withdrawal, steroids, ursodeoxycholic acid and even plasmapheresis.
- ▶ Current recommendations for patients starting TMZ include performing liver function tests prior to treatment initiation, after each treatment cycle and midway through the cycle for patients on a 42-day treatment cycle.³

Acknowledgements The authors acknowledge Dr W Mason, neuro-oncology consultant.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Rosso L, Brock CS, Gallo JM, *et al.* A new model for prediction of drug distribution in tumor and normal tissues: pharmacokinetics of temozolomide in glioma patients. *Cancer Res* 2009;69:120–7.
- Stupp R, Mason WP, van den Bent MJ, *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352:987–96.
- Health Canada. *TEMODAL (temozolomide)—risk of liver problems—for health professionals*. 07/05/2014 Health Canada, 2014.
- Grant LM, Kleiner DE, Conjeevaram HS, *et al.* Clinical and histological features of idiosyncratic acute liver injury caused by temozolomide. *Dig Dis Sci* 2013;58:1415–21.
- Nader K, Mok S, Kalra A, *et al.* Vanishing bile duct syndrome as a manifestation of Hodgkin's lymphoma: a case report and review of the literature. *Tumori* 2013;99:e164–8.
- Tyagi I, Puri AS, Sakhuja P, *et al.* Co-occurrence of cytomegalovirus-induced vanishing bile duct syndrome with papillary stenosis in HIV infection. *Hepatol Res* 2013;43:311–14.
- Kikuchi K, Miyakawa H, Abe K, *et al.* Vanishing bile duct syndrome associated with chronic EBV infection. *Dig Dis Sci* 2000;45:160–5.
- Gnanaraj J, Fiedler P, Virata M. Vanishing bile duct syndrome in a HIV patient on HAART therapy. *BMJ Case Rep* 2011;2011:pii: bcr0620114369.
- Gokce S, Durmaz O, Celtik C, *et al.* Valproic acid-associated vanishing bile duct syndrome. *J Child Neurol* 2010;25:909–11.
- Forbes GM, Jeffrey GP, Shilkin KB, *et al.* Carbamazepine hepatotoxicity: another cause of the vanishing bile duct syndrome. *Gastroenterology* 1992;102(4 Pt 1):1385–8.
- Bhayana H, Appasani S, Thapa BR, *et al.* Lamotrigine-induced vanishing bile duct syndrome in a child. *J Pediatr Gastroenterol Nutr* 2012;55:e147–8.
- Schumaker AL, Okulicz JF. Meropenem-induced vanishing bile duct syndrome. *Pharmacotherapy* 2010;30:953.
- Juricic D, Hratic I, Radic D, *et al.* Vanishing bile duct syndrome associated with azithromycin in a 62-year-old man. *Basic Clin Pharmacol Toxicol* 2010;106:62–5.
- Alam I, Ferrell LD, Bass NM. Vanishing bile duct syndrome temporally associated with ibuprofen use. *Am J Gastroenterol* 1996;91:1626–30.
- Ramos AM, Gayotto LC, Clemente CM, *et al.* Reversible vanishing bile duct syndrome induced by carbamazepine. *Eur J Gastroenterol Hepatol* 2002;14:1019–22.
- Tajiri H, Etani Y, Mushiaki S, *et al.* A favorable response to steroid therapy in a child with drug-associated acute vanishing bile duct syndrome and skin disorder. *J Paediatr Child Health* 2008;44:234–6.
- Pusl T, Beuers U. Ursodeoxycholic acid treatment of vanishing bile duct syndromes. *World J Gastroenterol* 2006;12:3487–95.
- Kawasaki Y, Matsubara K, Hashimoto K, *et al.* Nonsteroidal anti-inflammatory drug-induced vanishing bile duct syndrome treated with plasmapheresis. *J Pediatr Gastroenterol Nutr* 2013;57:e30–1.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow