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# Temozolomide-induced aplastic anaemia: Case report and review of the literature

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## Abstract

**Introduction:** Temozolomide (TMZ) is an oral alkylating agent principally indicated for neurological malignancies including glioblastoma (GBM) and astrocytoma. Most common side effects are mild to moderate, and include fatigue, nausea, vomiting, thrombocytopenia and neutropenia. Severe or prolonged myelosuppression, causing delayed treatment or discontinuation, is uncommon. Major haematological adverse effects such as myelodysplastic syndrome or aplastic anaemia (AA) have rarely been reported.

**Case report:** We report a 68-year old female with GBM treated at a tertiary hospital with short-course radiotherapy and concurrent temozolomide following craniotomy. On treatment completion she was transferred to our hospital for rehabilitation. She was thrombocytopenic on admission. Platelets continued falling with significant pancytopenia developing over the next two weeks. Blood parameters and a markedly hypocellular bone marrow confirmed the diagnosis of very severe AA, probably due to TMZ.

**Management and outcome:** Treatment consisted of repeated platelet transfusions, intravenous antibiotics, antiviral and antifungal prophylaxis, and G-CSF 300 mcg daily. Platelet and neutrophil counts had returned to normal at 38 days following the completion of TMZ treatment.

**Discussion:** Whilst most cases of AA are idiopathic, a careful drug, occupational exposure and family history should be obtained, as acquired AA may result from viruses, chemical exposure, radiation and medications. Temozolomide-induced AA is well documented, though only 12 cases have been described in detail. Other potential causes were eliminated in our patient. Physicians should be aware of this rare and potentially fatal toxicity when prescribing. Frequent blood tests should be performed, during and following TMZ treatment, to enable early detection.

## Keywords

Aplastic anaemia, glioblastoma, temozolomide

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## Introduction

Glioblastoma (GBM), the most aggressive type of diffuse glioma, is the commonest brain and central nervous system (CNS) malignancy, accounting for 45.2% of malignant primary brain and CNS tumours and 54% of all gliomas.[1] It remains an incurable disease, with a median survival of 15 months. The current standard of care for newly diagnosed GBM is complex and initially consists of maximal safe surgical resection followed by radiotherapy (RT) {2 Gy given daily on 5 days per week for 6 weeks – total of 60 Gy} with concurrent temozolomide (TMZ) {75 mg/m$^2$ oral daily for 6 weeks} chemotherapy followed by 6 cycles of adjuvant TMZ monotherapy {150–200 mg/m$^2$ oral daily for 5 days each 28 day cycle}.[2] With this approach, Stupp and colleagues demonstrated a two-year survival rate

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of 26.5% with concomitant RT plus TMZ compared with 10.4% with RT alone. Combined treatment resulted in grade 3 or 4 haematological toxicity in 7% of patients.[2]

Temozolomide (TMZ), an oral alkylating agent, which has been in clinical use for over 20 years, is indicated in the treatment of several cancers, principally neurological malignancies such as GBM and astrocytoma. It causes DNA methylation, subsequent DNA breakage and apoptosis of cancer cells. The most common side effects of TMZ are mild to moderate, and include fatigue, nausea, vomiting, thrombocytopenia and neutropenia.[3] Myelosuppression is the major dose-limiting toxicity, occurring late in the treatment cycle and primarily affects platelets and white blood cells. However, myelosuppression is a non-cumulative and reversible effect, with bone marrow recovery usually occurring within 28 days.[3] Severe or prolonged myelosuppression, resulting in treatment delays or discontinuation, is a relatively uncommon adverse effect of TMZ. Major haematological adverse effects such as myelodysplastic syndrome, leukaemia, agranulocytosis and aplastic anaemia (AA) have rarely been reported.[3–5]

We wish to report a case of AA presenting in a female patient with GBM treated with surgical resection followed by concomitant TMZ and RT. Patient consent has been obtained and approval for publication granted.

## Case presentation

A 68-year-old Caucasian woman presented to her general practitioner with urinary incontinence and changes in memory and personality in late August 2019. Computed tomography (CT) showed a right frontal lesion and she was immediately referred to a private metropolitan tertiary treatment centre. Magnetic resonance imaging (MRI) demonstrated a likely GBM and she was commenced on dexamethasone and levetiracetam. On the 28th August 2019, a craniotomy and resection of the right frontal tumour was performed. Surgery was uncomplicated and dexamethasone was weaned without any issues. Histology demonstrated glioblastoma (World Health Organisation grade IV) which was p53 mutated, IDH1-R132H wild-type, and exhibited EGFR protein overexpression. The tumour was negative for 1p/19q codeletion and EGFR gene amplification.

On Day 6 post-surgery she had a mild aphasia and had difficulty in following commands. The next day impairment in cognition was noted with a Montreal Cognitive Assessment score of 7/30. An increase in confusion necessitated re-instigation of dexamethasone which led to symptom improvement. Prior to surgery she was a fit and active woman who was independent in all activities of daily living. Past medical history included depression and osteoporosis for which she had been prescribed raloxifene. Due to her age, she commenced short-course radiation (40 Gy in 15 fractions over 3 weeks) plus concurrent temozolomide at a dose of 75 mg/m$^2$ for 21 consecutive days.[6] Treatment with temozolomide started at a dose of 100 mg on the 19th September. Chemoradiotherapy was completed on the 9th October and was well tolerated. Platelet count on that day was $128 \times 10^9$/L (Range (115–400). As her recovery was slow arrangements were made to relocate the patient closer to her family.

On the 9th October 2019, the patient was transferred to Toowoomba Hospital for rehabilitation. Medications on admission were oral dexamethasone, esmeprazole, levetiracetam, paracetamol and raloxifene, and subcutaneous enoxaparin. On admission to the rehabilitation unit she had ongoing issues with mobility requiring a two-person assist. Platelets were $83 \times 10^9$/L. Over the next 7 days function only minimally improved but platelets continued to fall. She was transferred to Medical Oncology on the 17th October with platelets of $11 \times 10^9$/L. Five days later she was pancytopenic with neutrophils $0.03 \times 10^9$/L (Range 2.00–8.00), haemoglobin 108 g/L (Range 115–160) and platelets $1 \times 10^9$/L. She was treated with repeated platelet transfusions, intravenous antibiotics, antiviral and antifungal prophylaxis, and granulocyte-colony stimulating factor (G-CSF) 300 mcg subcutaneously daily.

Haematology consultation on 25th October suggested aplastic anaemia likely induced by temozolomide, Counts were neutrophils $0.00 \times 10^9$/L, haemoglobin 77 g/L, platelets $5 \times 10^9$/L and reticulocytes $8 \times 10^9$/L (Range 10–100), which fulfills the definition of very severe AA.[6] A bone marrow aspirate and trephine was markedly hypocellular (10% cellularity) confirming the diagnosis. Parvovirus B19 DNA was not detected. Testing for cytomegalovirus, human immunodeficiency virus, hepatitis B and hepatitis C were all negative. Anti-nuclear antibody testing was negative. Nothing was found on CT scanning that might explain her presentation. Platelet transfusions and G-CSF continued and over the next few weeks blood parameters gradually improved. Counts on 16th November (38 days after temozolomide cessation), were neutrophils of $3.42 \times 10^9$/L and platelets of $156 \times 10^9$/L. She was readmitted for rehabilitation on the 4th December with transfer to a nursing home completed 9 days later. Counts on the 7th December were neutrophils of $5.32 \times 10^9$/L and platelets of $240 \times 10^9$/L. Due to her diagnosis, adjuvant treatment with temozolomide was not commenced.

## Discussion

Aplastic anaemia is a rare and heterogeneous disorder. It is defined as pancytopenia with a hypocellular bone marrow in the absence of an abnormal infiltrate or marrow fibrosis.[7] Severe AA is defined as marrow cellularity <25% (or 25–50% with <30% residual haematopoietic cells), plus at least 2 of: (i) neutrophils $<0.5 \times 10^9$/l, (ii) platelets $<20 \times 10^9$/l, and (iii) reticulocyte count $<20 \times 10^9$/l. Very severe AA is the same as above but with a neutrophil count of $<0.2\ 10^9$/l.[7] Patients commonly present with symptoms of anaemia and thrombocytopenia. Whilst the majority of cases are idiopathic, a careful drug, occupational exposure and family history should be obtained, as acquired AA may result from viruses, chemical exposure, radiation and drugs.[7,8] In drug-induced AA, multipotent haematopoietic stem cells undergo damage before differentiation to committed stem cells. Therefore, the number of circulating neutrophils, platelets and erythrocytes are reduced.[8,9] Symptoms of drug-induced AA are variable in onset and may present from days to months after the commencement of therapy with the causative drug. These may include fatigue, pallor, weakness, fever, chills and pharyngitis. Several drug classes have been implicated and include anticonvulsants (carbamazepine, phenytoin) and anti-infectives (sulphonamides), that may be prescribed in patients undergoing treatment for brain tumours.[8]

The prompt diagnosis of drug-induced AA is crucial as it is associated with high morbidity and mortality. The first step in management should be the immediate discontinuation of any potential causative medications. Regular blood product support with transfusions of red blood cells and platelets are essential to maintain safe blood counts, correct symptoms of anaemia and thrombocytopenia and improve quality of life.[7] Infection is the major cause of death in AA and patients who are severely neutropenic should be treated with prophylactic antibiotic and antifungal therapy.[6] Haemopoietic growth factors, such as erythropoiesis-stimulating agents and granulocyte-colony stimulating factor (G-CSF), can be used but may be ineffective in supporting blood counts in AA patients.[7] Encouraging preliminary results have been reported with the thrombopoietin-mimetic agent, eltrombopag.[7] Commonly, immunosuppressive therapy has been employed in the treatment of AA, especially in patents deemed unsuitable for transplantation. Standard first line immunosuppressive therapy is the combination of horse antithymocyte globulin (ATG) and cyclosporine.[7,10] Allogeneic haemopoietic stem cell transplantation, either from a human leucocyte antigen (HLA) matched sibling or unrelated donor, can be curative. However, serious, and potentially lethal, complications can occur.[7,9]

In 2005, a phase II trial described, in limited detail, what was possibly the first presentation of TMZ-induced AA.[10] This patient was concomitantly taking trimethoprim plus sulphamethoxazole (TMP-SMX) with TMZ, and therefore causality could not be determined. Villano et al., in 2006, reported the first, well documented case of a 45-year old male with GBM, who, following surgical debulking, underwent fractionated RT with concurrent TMZ.[11] Following his fourth cycle of 4-weekly adjuvant TMZ monotherapy he developed profound pancytopenia. A bone marrow biopsy showed AA. In addition to TMZ, phenytoin and carbamazepine had been prescribed so causality was not definitively determined. Haematological toxicity from anticonvulsants typically presents as agranulocytosis rather than pancytopenia and this subsequently recovers following drug cessation. However, as discontinuation of the drugs did not lead to marrow recovery, the authors proposed that TMZ was the likely culprit.

In 2007, a drug safety newsletter was published by the FDA.[12] From 1999 to 2006, the FDA received 18 reports of AA among patients receiving TMZ, of which 11 were confirmed by biopsy. Six cases reported had prior concurrent exposure to medications that have been associated with AA, including alkylating agents, anticonvulsants and antibiotics. Five patients experienced marrow recovery within one to four months following the cessation of TMZ, however, five others died from complications of AA or complications of treatment of AA with allogeneic transplantation. The FDA MedWatch database was searched for reports on TMZ from November 1997 to September 2008 to identify cases of major haematologic adverse effects.[4] From 5,127 reports, 39 cases of AA were identified. Most of the 11 deaths attributed to AA were due to infection. The mediation duration of TMZ therapy was 6 weeks, while the median onset of clinical findings was 4 weeks. A systematic review of TMZ-related idiosyncratic and other uncommon toxicities was undertaken in 2012.[5] From 73 cases, 21 idiosyncratic haematologic adverse effects were analysed. Eleven patients had histopathologically proven evidence of AA, with all receiving TMZ in association with RT. Female gender was also identified as a risk factor. In 2015, the Mayo Clinic performed a cohort study with patients treated with TMZ from 2003 to 2014 developing prolonged bone marrow suppression of at least 28 days.[13] Bone marrow suppression was defined along similar lines as AA. Of 2356 successive patients treated with TMZ during the specified timeframe, only 15 (0.6%) developed bone marrow suppression. A female predominance was also reported.

Following the initial report of TMZ-induced AA by Villano et al.,[11] eleven additional cases have been described in detail.[14–24] Comprehensive information on these cases is provided in Table 1, with potential

**Table 1.** Case reports of temozolomide-induced aplastic anaemia.

| Cases | Age years | Sex | Diagnosis | Time course of AA development | Potential contributing medications[7] | Treatment given | Outcome At time of report |
|---|---|---|---|---|---|---|---|
| Villano et al.[10] | 45 | M | GBM | After 4th cycle of temozolomide monotherapy | Carbamazepine, phenytoin | D/C, AI, G-CSF, Epo, PT, allogeneic SCT | Died, 4 months after SCT |
| Jalali et al.[13] | 30 | F | GBM | After completing concurrent RT/TMZ | Phenytoin, TMP-SMX | D/C, AI, G-CSF, BP | Died, rapid deterioration |
| Morris et al.[14] | 16 | F | GBM | Day 24 of RT/TMZ (90 mg/m$^2$), RT only completed | None | D/C, G-CSF, BP, ATG, cyclosporin, corticosteroids, BMT | Alive |
| George et al.[15] | 65 | F | GBM | Day 14 of 1st cycle of temozolomide monotherapy | None | D/C, BP | Alive, declined therapy, hospice |
| Oh et al.[16] | 63 | F | GBM | Day 18 of RT/TMZ, RT only completed | TMP-SMX | D/C, AI, BP, G-CSF, Epo, | Alive, palliative care |
| Kopecky et al.[17] | 61 | F | GBM | Day 23 of RT/TMZ, RT only completed | TMP-SMX | D/C, AI, BP, G-CSF | Died, sepsis |
| Comez et al.[18] | 31 | F | GBM | After 3$^{rd}$ cycle of temozolomide monotherapy | Phenytoin | D/C, AI, BP, G-CSF | Died, sepsis |
| Lam et al.[19] | 21 | F | Anaplastic astrocytoma | Day 39 of RT/TMZ, RT only completed | Dapsone | D/C, AI, BP, G-CSF | Alive, 4 years post TMZ |
| Vandrass et al.[20] | 69 | M | GBM | Day 24 of RT/TMZ, RT only completed | None | D/C, AI, BP, G-CSF, romiplostim | Died, 12 months post TMZ |
| Hanna et al.[21] | 36 | F | Anaplastic oligodendroglioma | Day 28 of RT/TMZ, RT only completed | TMP-SMX | D/C, BP, G-CSF, Epo | NR |
| Newton et al.[22] | 51 | F | GBM | Day 54 from initial TMZ dose, after completing 5 weeks of RT/TMZ (initial week – RT alone) | TMP-SMX | D/C, AI, BP, G-CSF, Eltrombopag | Died, 16 months post diagnosis |
| Batalini et al.[23] | 89 | M | GBM | Day 22 of 1st cycle of temozolomide monotherapy | None | D/C, AI, BP, G-CSF | Died, hospice |
| Gilbar et al. | 68 | F | GBM | Day 15 of RT/TMZ | None | D/C, AI, G-CSF, PT | Died, 9 months post diagnosis |

AA: aplastic anaemia; AI: anti-infective agents; ATG: antithymocyte globulin; BP: Blood products; BMT: bone marrow transplantation; D/C: discontinuation of medications; Epo: erythropoietin; F: female; GBM: glioblastoma multiforme; G-CSF: granulocyte colony stimulating factor; M: male; NR: not reported; PT: platelet transfusion; SCT: stem-cell transplantation; TMZ: temozolomide; TMP-SMX: trimethoprim/sulphamethoxazole.

contributing medications only included if they had been previously reported as causing AA.[8] Other alkylating agents, including dacarbazine and lomustine, have been reported to cause AA.[3] The mechanism of TMZ-related AA is uncertain,[5] but is thought to differ from other alkylating agents.[22]

A model to predict the likelihood of developing severe myelosuppression following TMZ treatment has been proposed by Armstrong et al.[25] A retrospective review of 680 malignant glioma patients treated with TMZ without RT was used to develop a clinical risk formula for myelotoxicity for each gender by logistic regression. An increased incidence of myelotoxicity was seen in women ($p = 0.015$). For males, risk factors included body surface (BSA) $\geq 2\,m^2$, taking laxatives and not on steroids. For females, risk factors included BSA $< 2\,m^2$, no prior chemotherapy, higher pretreatment creatinine levels, lower pretreatment platelet counts, on analgesics and not on medications for gastroesophageal reflux disease. Genetic polymorphisms related to the development of myelotoxicity have been investigated in an attempt to individualised TMZ dosing for affected patients.[25–27] The $O^6$-methylguanine-DNA methyltransferase (MGMT) gene has been most studied as silencing of the MGMT promoter has been associated with increased TMZ toxicity.[22] Prediction of who may experience an increased risk of myelotoxicity remains difficult though further studies may prove a genetic susceptibility.

Our patient seems to have no likely causative factors for the development of AA other than TMZ. There was no family history, exposure to environmental factors or possible medication causes. Prior to starting TMZ she was only on raloxifene, which has not been implicated in causing AA. Levetiracetum was commenced at the time of diagnosis. While some anticonvulsants have been associated rarely with AA, no cases of levetiracetum-induced AA have been reported.[22] She was not prescribed prophylactic TMP-SMX during treatment. The possibility of AA resulting from RT to her right frontal lobe is considered improbable given the narrow field. The probability of the adverse drug reaction (ADR) being related to TMZ was assessed using the Naranjo algorithm.[28] We obtained a score of +6 which indicates a probable ADR.

In conclusion, although TMZ is considered a relatively safe drug, many cases of bone marrow suppression and AA have been reported. Definitive causality for TMZ has been difficult to determine as other agents, such as prophylactic anti-infectives and anticonvulsants, that are commonly prescribed during treatment have also been implicated in inducing AA. However, several cases of AA have been documented in patients on TMZ monotherapy. The optimal strategy for managing TMZ-induced AA has yet to be determined due to the infrequency of cases and the differing presentations and responses of affected patients. Physicians should be aware of this rare and potentially fatal toxicity associated with TMZ when prescribing. Frequent blood tests should be performed, during and immediately following treatment, to enable early detection and treatment of this life-threatening complication.

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