Another Cause of Pancytopenia in a Patient Receiving Temozolomide

Yavuz Pehlivan a  Alper Sevinc b  Ibrahim Halil Turkbeyler a  Ahmet Dirier c  
Mehmet Emin Kalender b  Celalettin Camci b

Departments of a Internal Medicine, b Medical Oncology and c Radiation Oncology, School of Medicine, Gaziantep University, Gaziantep, Turkey

Key Words
Temozolomide • Myelosuppression • Pancytopenia • Vitamin B 12 deficiency • Glioblastoma multiforme

Abstract
Objective: To report pancytopenia caused by temozolomide, a second-generation alkylating agent. Clinical Presentation and Intervention: A 22-year-old patient presenting with seizures and confusion was seen in the emergency room. Cranial magnetic resonance imaging revealed a mass. After surgery, the patient was diagnosed with glioblastoma multiforme and was given temozolomide at 150 mg/m 2 on days 1 through 5 every 4 weeks. During the last cycle of temozolomide, grade 3 thrombocytopenia persisted. Possible causes of pancytopenia including vitamin B 12 deficiency were investigated. Conclusion: This case report shows that vitamin B 12 deficiency can be a potential cause of pancytopenia and it should be kept in mind for patients receiving chemotherapy.

Introduction
Temozolomide is a second-generation alkylating agent. With nearly 100% bioavailability, temozolomide is administered orally, most commonly once a day for 5 days in a 28-day cycle. It has been approved by the Food and Drug Administration for the treatment of refractory anaplastic astrocytoma and newly diagnosed glioblastoma multiforme. Clinical efficacy of temozolomide has also been demonstrated in melanoma, and a variety of other solid tumors [1]. Used as a single agent, temozolomide has also been shown to have activity against brain metastases from melanoma [2]. Three phase II trials have been reported using temozolomide in patients with brain metastases from solid tumors [3–5]. We are reporting this case in order to direct the attention of researchers to another possible cause of pancytopenia in patients receiving chemotherapy.
4 months after surgery. A second surgery was not planned. Subsequently, the patient was informed about the possible use of temozolomide, to which she assented. The patient was initially given temozolomide at 150 mg/m² on days 1 through 5 every 4 weeks. The dosage was increased to 200 mg/m² at the second cycle. After the 6th cycle, due to an abscess she was seen by a dentist who inquired about the treatment plan and laboratory findings, which were as follows: hemoglobin level: 11.2 g/dl (13.6–17.2), MCV: 100 fl (80–95), WBC: 3,120/mm³ (4,300–10,300), platelet count: 48,000/mm³ (156,000–373,000), reticulocytes: 1.4%. Grade 3 thrombocytopenia was thought to be due to temozolomide-induced myelosuppression because of the known primary toxicity associated with temozolomide treatment. Temozolomide was discontinued for 2 weeks but no improvement regarding the complete blood count values was observed. The detailed examination of the complete blood counts before and after chemotherapy is shown in table 1. Peripheral smear revealed oval macrocytosis and hypersegmented granulocytes. Serum vitamin B₁₂ level was observed to be 100 pg/ml (243–894). Bone marrow examination was compatible with megaloblastic changes. A detailed medical history revealed that the patient was on a strictly vegetarian diet. Daily intramuscular vitamin B₁₂ injection therapy was applied for 5 days. Five days after vitamin B₁₂ treatment, the patient's reticulocyte count increased to 5.3% and monthly vitamin B₁₂ injections were recommended. Her control complete blood count levels were as follows: hemoglobin: 12.5 g/dl, WBC: 5,320/mm³, and platelets: 194,000/mm³. The patient's detailed examination of the complete blood counts before and after chemotherapy was compatible with megaloblastic changes. A detailed medical history revealed that the patient was on a strictly vegetarian diet. Daily intramuscular vitamin B₁₂ injection therapy was applied for 5 days. Five days after vitamin B₁₂ treatment, the patient's reticulocyte count increased to 5.3% and monthly vitamin B₁₂ injections were recommended. Her control complete blood count levels were as follows: hemoglobin: 12.5 g/dl, WBC: 5,320/mm³, and platelets: 194,000/mm³. The patient's final control vitamin B₁₂ level was 986 pg/ml.

Temozolomide is a well-known cytotoxic agent known to cause myelosuppression. However, in the present case, vitamin B₁₂ deficiency was the triggering etiological agent causing pancytopenia. After the diagnosis of vitamin B₁₂ deficiency, 5-day vitamin B₁₂ injection therapy was applied and the blood count levels were improved. Under these circumstances vitamin B₁₂ deficiency can be another potential cause of pancytopenia.

### Discussion

Patients treated with temozolomide may experience myelosuppression, which tends to occur late in the treatment cycle and return to normal, on average, within 14 days of nadir counts. The median nadirs occurred at 26 days for platelets (range 21–40) and 28 days for neutrophils (range 1–44). In the present case, although temozolomide was discontinued for 2 weeks, pancytopenia persisted. Possible causes of pancytopenia were investigated and vitamin B₁₂ deficiency was identified.

Adverse effects of temozolomide are typical of traditional cytotoxic chemotherapy. The adverse events associated with temozolomide are mild to moderate and generally predictable; the most serious are noncumulative and reversible myelosuppression and, in particular, thrombocytopenia, which occurs in less than 5% of patients. Grade 3 and 4 hematological toxicity was documented in only 7% of patients for concurrent therapy treated prospectively in the European Organization for Research and Treatment of Cancer and National Cancer Institute of Canada landmark study [6].

Myelosuppression is the dose-limiting toxicity for temozolomide in adults and children in the postchemotherapy period. Specific guidelines regarding dose reductions based on neutrophil and platelet counts are available in the manufacturer's package insert. Geriatric patients and women, who may clear the drug more slowly than men, are at greater risk for myelosuppression [7].

Doyle et al. [8] described 3 patients who developed severe myelosuppression after low-dose temozolomide and radiotherapy. In fact 2 patients had aplastic anemia. Concurrent co-trimoxazole was given that might have con-

### Table 1. Complete blood counts before and after chemotherapy

<table>
<thead>
<tr>
<th>Cycles</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WBC/μl</td>
<td>Neu/μl</td>
</tr>
<tr>
<td>1</td>
<td>5,500</td>
<td>3,650</td>
</tr>
<tr>
<td>2</td>
<td>5,000</td>
<td>3,250</td>
</tr>
<tr>
<td>3</td>
<td>4,700</td>
<td>2,910</td>
</tr>
<tr>
<td>4</td>
<td>4,750</td>
<td>2,945</td>
</tr>
<tr>
<td>5</td>
<td>4,500</td>
<td>3,050</td>
</tr>
<tr>
<td>6</td>
<td>4,200</td>
<td>2,750</td>
</tr>
</tbody>
</table>

Normal range: white blood cells (WBC) 4,300–10,300; neutrophils (Neu) 1,800–6,400; hemoglobin (Hb) 12.3–15.3; mean corpuscular volume (MCV) 80–96; mean corpuscular hemoglobin concentration (MCHC) 32–36; platelets (Plt) 150,000–400,000.
tributed to toxicity. Another case report describes a case of aplastic anemia after the 4th cycle of adjuvant temozolomide [9]. The patient was on concomitant anticonvulsants. Moreover, Singhal et al. [10] described 2 patients who developed prolonged and severe myelosuppression after low-dose continuous temozolomide given concurrently with cranial radiotherapy. These patients did not receive any concurrent bone marrow toxic drugs such as anticonvulsants or co-trimoxazole, and vitamin B₁₂ and folate deficiency were also ruled out. Another case report described a patient with prolonged and severe thrombocytopenia with pancytopenia induced by radiation-combined temozolomide therapy. The case was investigated for a possible relationship between methylguanine-DNA methyltransferase status and pancytopenia. However, Nagane et al. [11] found out that there is not a remarkable relationship between methylguanine-DNA methyltransferase status and pancytopenia.

The principal hematologic manifestations of vitamin B₁₂ deficiency are macrocytic anemia, leukopenia, and thrombocytopenia with oval macrocytosis, anisocytosis, poikilocytosis, and hypersegmented granulocytes on blood smear. Chemotherapeutics may not be the only reason to be blamed for cytopenia in cancer patients. It should also be kept in mind that other etiological factors such as dietary factors may also cause pancytopenia in patients receiving chemotherapy.

In this case report pancytopenia was found to be associated with vitamin B₁₂ deficiency. For that reason, considering other factors can play a vital role in the treatment of pancytopenia in patients receiving chemotherapy.

**Conclusion**

Insufficient improvement in pancytopenia during the postchemotherapy period leads to the investigation of other etiologic factors. This case report showed that vitamin B₁₂ deficiency can be another potential cause of pancytopenia and it should be kept in mind for patients receiving chemotherapy.