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CASE REPORT

Two cases of cutaneous drug eruption associated with temozolomide therapy for glioblastoma

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ABSTRACT

Glioblastoma is the most common form of primary brain cancer. Its treatment involves surgery, radiotherapy, and chemotherapy with temozolomide (TMZ), which is an oral alkylating agent. To the best of our knowledge, few dermatologic side effects of TMZ have been described. We report two cases of cutaneous drug eruption caused by TMZ during and after radiochemotherapy treatment. In the first case, all tests were negative, but the clinical history and the time of onset supported an allergy to TMZ. In the second case, an allergy to TMZ was proved by a positive lymphocyte activation test. In this context, our study is one of a very few trying to determine dermatologic side effects by applicable tests used in routine practice.

KEY WORDS

Temozolomide, maculopapular exanthema, glioblastoma

1. INTRODUCTION

Glioblastoma is the most common form of primary brain cancer and one of the most aggressive cancers. The current standard of treatment involves maximal surgical resection followed by external-beam radiotherapy (60 Gy) and adjuvant temozolomide (TMZ), which is administered concomitantly with (75 mg/m^2 daily) and after radiotherapy (150–200 mg/m^2) for 5 days every 4 weeks[1]. An oral alkylating agent, TMZ inhibits DNA replication. To our knowledge, few reports have described dermatologic side effects such as urticaria[2]. Here, we report two cases of cutaneous drug eruption with the use of TMZ, one occurring during radiochemotherapy, and the other concomitant with and after radiochemotherapy. In one case, a delayed-type hypersensitivity to TMZ was confirmed using the lymphocyte activation test.

2. CASE DESCRIPTIONS

2.1 Case 1

A 55-year-old woman was admitted to the hospital of the University of Limoges on October 1, 2012, for atypical dizziness, which had been present for about 1 month. The patient had no particular history and took no medication. On the day of admission, the patient underwent cranial magnetic resonance imaging, which revealed a large multicentric solid necrotic tumour (48×39×39 mm) in the left frontal hemisphere. On October 12, 2012, the patient underwent an incomplete resection of the tumour and implantation of a carmustine-impregnated wafer. Definitive histologic analysis of the lesion showed a diffusely infiltrating glioblastoma.

Our patient was treated with postoperative cranial radiotherapy (total dose: 60 Gy), with concomitant temozolomide (75 mg/m^2 daily) from November 26, 2012, to January 9, 2013. During that period, antiemetic treatment with ondansetron was started. On December 17, 2012, antiepileptic treatment (levetiracetam 50 mg daily) was administered to prevent seizures. The patient tolerated treatment well, with no side effects.

After radiochemotherapy, follow-up magnetic resonance imaging revealed an intracranial mass (diameter: 16 mm). In the maintenance phase, 2 months after radiochemotherapy, TMZ was restarted at a dose of 150 mg/m^2 daily for 5 days every 4 weeks. Six cycles of TMZ therapy were initially proposed. In cycle 1 (March 14, 2013), the patient presented with generalized pruritus and erythema, with urticarial or maculopapular-type lesions. No other symptoms (fever, dyspnea, and so on) were noted.

The patient had not been exposed to new foods, drugs, or contrast media. The skin reaction occurred between days 3 and 5 of the chemotherapy cycle. A complete remission of symptoms was obtained within 24 hours with the use of antihistamines and systemic corticosteroids.

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In cycle 2, valproate was substituted for levetiracetam in an attempt to avoid a suspected drug eruption from the levetiracetam. Despite that change, lesions appeared on days 3–5 of chemotherapy. In cycle 3, metoclopramide was substituted for the ondansetron, which has been reported to cause urticaria in rare cases[3]. Nevertheless, skin lesions occurred after 72 hours of chemotherapy. In cycles 4 and 5, similar lesions were found. Cycle 6 was omitted.

2.2 Case 2

A 62-year-old woman was admitted to the hospital of the University of Limoges on May 12, 2013, for phasic disorders and deficit of the right side of the body. The phasic disorders had been present for about 2 months. The patient's only medication was clomipramine for depression. On the day of admission, the patient underwent cranial magnetic resonance imaging, which disclosed a large multicentric solid necrotic tumour (53×29×31 mm) in the left front-temporal hemisphere, associated with subfalcial and temporal herniations.

On May 17, 2013, the patient underwent complete resection of the tumour and implantation of a carmustine-impregnated wafer. Definitive histology analysis of the lesion showed a diffusely infiltrating glioblastoma. The patient was treated with postoperative cranial radiotherapy (total: 60 Gy) with concurrent TMZ (75 mg/m^2 daily). During the radiotherapy period, antiepileptic treatment (levetiracetam 50 mg daily) was introduced to prevent seizures.

At 50 Gy irradiation, the patient presented with generalized pruritus and erythema consistent with a maculopapular exanthem. No new foods, drugs, or contrast media had been given. Complete remission of symptoms was obtained within 24 hours with antihistamines and systemic corticosteroids. Two months after radiochemotherapy, TMZ was restarted at a dose of 150 mg/m^2 daily for 5 days every 4 weeks. Initially, 6 cycles of TMZ therapy were provided. During the first 2 cycles, the patient presented with the same symptoms, which were controlled with antihistamines and systemic corticosteroids.

3. SKIN TESTING

Immediate (prick and basophil) and delayed-type tests (patch and lymphocyte activation) were both performed in an attempt to confirm drug hypersensitivity to TMZ. An intradermal test was not used because a reaction occurs only with injectable drugs. Both patients stopped their antihistamines before the tests, but one patient (case 1) could not stop corticosteroid treatment.

3.1 Prick Test

One drop of each drug was applied to the patient's forearm. Patient 1 was tested for ondansetron, TMZ, levetiracetam, and potential non-medicinal allergens such as latex and lactose anhydrous (excipient of TMZ). Patient 2 was tested for TMZ, levetiracetam, latex, and lactose anhydrous. We used 10 mg/mL histamine dihydrochloride as a positive control and saline solution as a negative control. Readings were taken after 15 minutes. The skin prick tests for each substance were defined as positive if the mean wheal diameter was 3 mm or larger.

3.2 Patch Test

Appropriate concentrations of drug were applied under patches to the back of each patient. Results were analyzed at 48 hours and were confirmed definitively at 72 hours. Patient 1 was tested for ondansetron, TMZ, and levetiracetam, and patient 2 for TMZ.

3.3 Basophil and Lymphocyte Activation Tests

During these *in vitro* tests, the patient's blood is incubated with the putative drug allergen. Basophil activation indicates immediate hypersensitivity, and lymphocyte activation indicates delayed hypersensitivity.

3.4 Results

The prick, patch, and basophil tests were negative for both patients. The lymphocyte activation test was negative for patient 1 and positive for patient 2.

4. DISCUSSION AND CONCLUSIONS

Temozolomide is a reasonably well-tolerated chemotherapy. Commonly reported side effects are myelosuppression, gastrointestinal tract effects, neurotoxicity, and exhaustion[4,5]. The few dermatologic side effects that have been reported include urticarial hypersensitivity reaction, alopecia, desquamative skin rash, Stevens–Johnson syndrome, and toxic epidermal necrolysis overlap[2,4,6,7]. These effects were reported only in patients receiving radiotherapy combined with TMZ. In our patients, the dermatologic side effects were observed during and after radiochemotherapy treatment.

To the best of our knowledge, ours is one of a very few reports in which a suspected cutaneous drug eruption from TMZ was subjected to *in vivo* and *in vitro* drug hypersensitivity testing. In the first patient, all test results were negative, but clinical history and the time of onset support the likelihood of a reaction to TMZ. In the second patient, delayed hypersensitivity to TMZ was confirmed by a positive lymphocyte activation test. The timing suggests an urticarial reaction, but it could have been maculopapular exanthema instead. Patch and prick tests are a useful complement in the attempt to identify the cause of cutaneous drug eruptions, but results are not reliable in all cases[8].

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Reliable results with patch and prick tests using commercial tablet forms of medications are difficult to achieve. The TMZ (which is available only in tablet form) might have contained an insufficient concentration of the allergen. This problem is especially prevalent for non-standardized allergens and prepared products bought by patients[9].

Pothiawala *et al.*[2] suggest that the apparently low rate of cutaneous drug eruptions from TMZ can be explained by concomitant use of corticosteroids, which are a part of standard chemotherapy regimens[9,10]. Positive lymphocyte activation was observed in case 2 while the patient was under treatment with systemic corticosteroids, which were not discontinued before testing.

Adverse cutaneous reactions from TMZ are probably underestimated[6]. These eruptions can be severe and might disrupt further therapy with TMZ. Desensitization has been successfully used in some cases of exanthematous rash from TMZ[11,12]. The diagnosis of TMZ-related drug eruption is essentially clinical and based on a temporal association, but drug hypersensitivity tests can sometimes confirm the suspicion, especially in the setting of multiple concomitant medications.

5. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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