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Sustained Immunotherapy Response in Metastatic Brain Melanoma Through 2 Pregnancies

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 39-year-old
Final Diagnosis: Metastatic brain melanoma
Symptoms: Changing mole • generalized epileptic seizure
Clinical Procedure: —
Specialty: Oncology

Objective: Unusual clinical course

Background: Metastatic brain melanoma is a deadly form of cancer with a high mortality rate and short overall survival. Immunotherapy with immune checkpoint inhibitors is the first treatment option for BRAF wild-type patients. Pregnancy is the exclusion criterion for immunotherapy and may promote the progression of melanoma. This report shows the long-lasting response of a patient with metastasis in multiple locations, including the brain, to immunotherapy and radiotherapy, who delivered 2 healthy boys during the disease.

Case Report: A 39-year-old woman was diagnosed with BRAF(-)/NRAS(+) skin melanoma, pT2bN2aM0 (IIIB). Due to pregnancy, she did not receive adjuvant therapy. Upon delivery, the disease manifested with multiple extracranial and symptomatic brain metastasis. She was treated with whole-brain radiation and immunotherapy with ipilimumab and nivolumab followed by nivolumab. A partial response of the brain metastases and an extracranial complete response were observed. During the immunotherapy, she became pregnant and the therapy was discontinued. She was under regular medical surveillance, during which she delivered a healthy boy. The last CT scan and magnetic resonance brain examination showed a maintenance response for 43 months after initiation of immunotherapy and 31 months after therapy completion.

Conclusions: A long-lasting response to radiotherapy and interrupted immunotherapy is possible in the case of symptomatic metastatic brain melanoma developing during pregnancy, and healthy deliveries are possible despite the mother's progressive melanoma or exposure of the fetus to nivolumab (first trimester).

Keywords: Brain • Immunotherapy • Melanoma • Pregnancy • Radiotherapy

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/945533

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Introduction

A combination of 2 immune checkpoint inhibitors (ICIs) – ipilimumab and nivolumab – is a preferred treatment option for patients with advanced melanoma with an Eastern Cooperative Oncology Group performance status score of 0 or 1, especially for those without mutation in the BRAF gene (BRAF proto-oncogene, serine/threonine kinase) [1]. ICIs can also provide durable clinical benefits for patients with melanoma brain metastases (MBM). However, those with leptomeningeal melanoma, neurologic symptoms, and/or requiring corticosteroids have worse median overall survival (OS) compared to patients without these factors (5.1 vs 18.5 months) [2]. In this group, durable responses can occur but are rare [3-5]. Some MBM occurs during pregnancy, since 1% of all diagnosed melanomas are associated with this physiological state (pregnancy-associated melanoma, PAM). Pregnancy is not only a contraindication to immunotherapy but also may contribute to a more aggressive course of the disease [6]. Therefore, the combination of metastatic brain melanoma and pregnancy can result in a very poor prognosis. The literature contains no data on the response of MBM to immunotherapy interrupted by pregnancy. The effect of immunotherapy on pregnancy has also been understudied. For ethical reasons, all data on this subject come only from preclinical experiments or case reports [6]. Here, we present an exceptional case of a 39-year-old woman with a massive spread of melanoma to extracranial and intracranial sites, who delivered 2 healthy babies during advanced melanoma (one during progressive disease and the other after withheld treatment). She showed a long-lasting response to interrupted immunotherapy combined with RT (radiotherapy) despite unfavorable factors such as numerous brain metastases, elevated LDH level, and use of steroids.

Case Report

A 39-year-old woman, mother of 2 children, presented to our outpatient oncology clinic 1 month after surgery for superficial spreading skin melanoma of the right breast (**Figure 1A**). There were strong indications for adjuvant systemic treatment due to postoperative pT2bN2aM0, Breslow 2 mm, IIIB stage of melanoma after dissection of the axillary lymph nodes according to the 8th Edition of the UICC TNM classification of malignant tumors (**Figure 1B**). BRAF diagnostic testing was carried out in the Department of Clinical and Molecular Genetics using the AmoyDx BRAF V600 Mutation Detection Kit (Amoy Diagnostics Co., Ltd., Xiamen, China) and was negative. Therefore, adjuvant immunotherapy was recommended. However, the patient was in the second month of her third pregnancy and did not intend to have an abortion. She was regularly monitored with ultrasound and physical examination.

Two weeks after the delivery of a healthy boy in the 36th week of pregnancy, she presented symptoms of a generalized epileptic seizure that required the intervention of emergency medical service and hospitalization. Symptoms of weakness and dizziness were noted, which disappeared after administration of 6 mg of dexamethasone per day and antiepileptic medications. Computed tomography (CT) and magnetic resonance (MR) imaging showed at least 30 brain metastases in both hemispheres and the dura mater, up to 16 mm in diameter (**Figure 2A**). Thus, the patient was not eligible for surgery or stereotactic radiosurgery (SRS) and she received whole-brain radiation, 20 Gy in 5 fractions using a 6MV energy photon beam. Meanwhile, the PET-CT examination revealed multiple liver, pancreas, small intestine, subcutaneous tissue, and lymph node metastases, and the LDH level was elevated (250 U/L). The expression of PDL-1 in the primary tumor was evaluated in the Tumor Pathology Department using PD-L1 (22C3) pharmDx antibody (cat. no. GE00621-2; Dako Omnis) and was below 5%. She was enrolled in an ongoing research

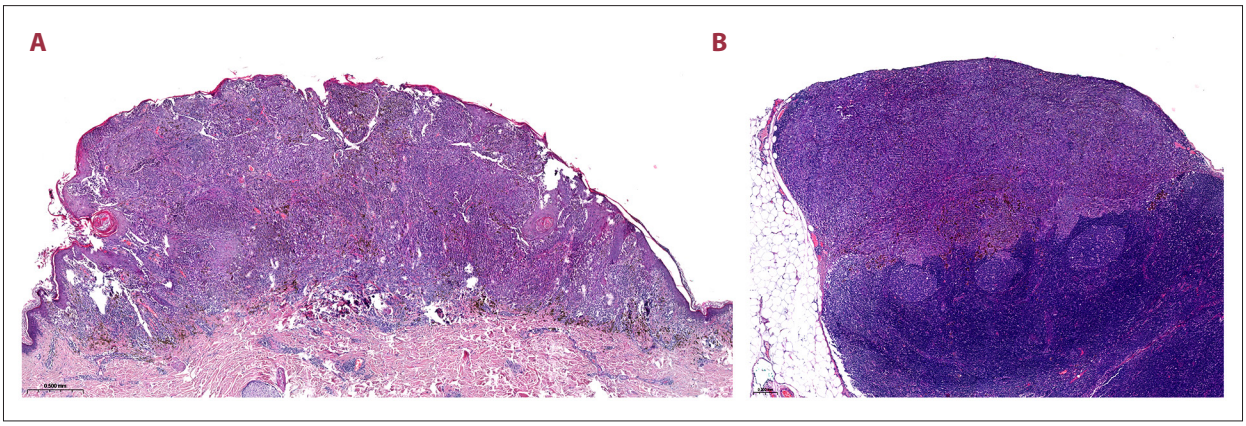

Figure 1. Superficial spreading melanoma (Breslow 2.0 mm, Clark level: III) with ulceration (H&E ×30), (**A**). Sentinel lymph node metastasis (H&E ×50), (**B**).

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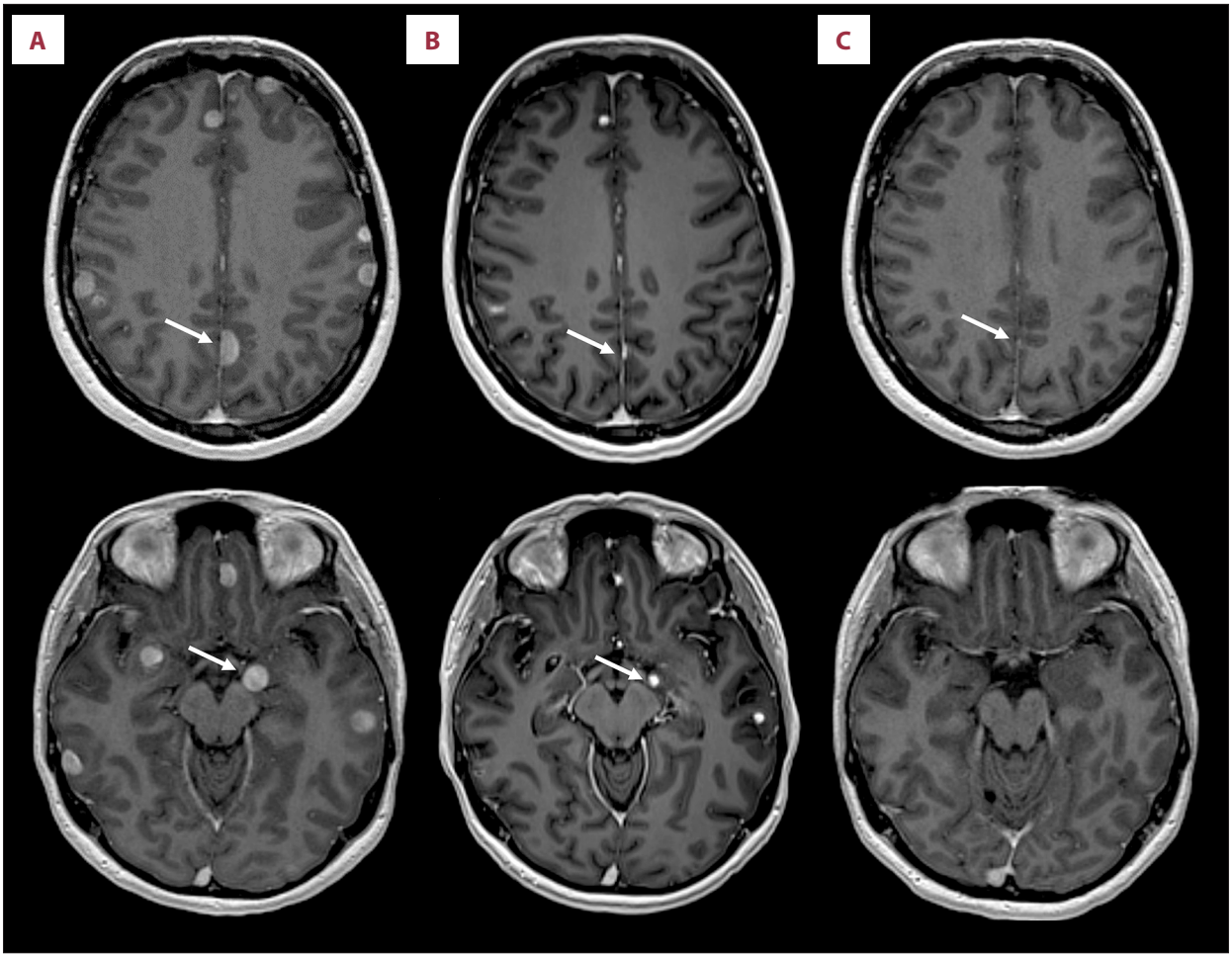

Figure 2. T1-weighted contrast-enhanced magnetic resonance imaging of the brain at 1.5 T magnetic field strength. Axial view. (**A**) Multiple brain metastases before radiotherapy and the beginning of immunotherapy. (**B**) Partial regression 3 months later. (**C**) Partial regression 3 years after the start of immunotherapy. The white arrows indicate the location of the biggest metastasis before and during therapy.

project aimed at genetic profiling of advanced melanoma using next-generation sequencing (NGS). Pretreatment samples of ctDNA (circulating tumor DNA) and DNA derived from FFPE (formalin-fixed paraffin-embedded) tissue from the primary tumor were sequenced on the Ion Torrent NGS platform using the Oncomine™ Pan-Cancer Cell-Free Assay as described in Olbryt et al (2021) [7]. The analysis revealed *NRAS* Q61K mutation in both tumor and plasma DNA, with a frequency of 40% and 8%, respectively. Furthermore, a low-frequency (0.9%) P124S mutation in the *MAP2K1* gene was detected in tumor DNA.

When the radiotherapy was started, the daily dose of dexamethasone was reduced from 6 mg to 4 mg, and then to 1 mg per day 2 weeks later. Since for patients with low expression of PDL-1, a combination of anti-CTLA-4 and anti-PD-1 is the preferred option instead of anti-PD-1 alone [8], after a negative pregnancy strip test, the patient began immunotherapy with nivolumab 1 mg/kg IV and ipilimumab 3 mg/kg IV every 3 weeks. The patient signed her consent to treatment and was informed about the necessity of contraception use, which she confirmed with her signature. Before each cycle of treatment, a denial of pregnancy was obtained during the interview. After the first cycle of treatment, she was hospitalized with a high temperature (42°C) and loss of consciousness. Following a second cycle of treatment, adverse events such as diarrhea (grade 3), and increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), grade 2 (Common Terminology Criteria of Adverse Events version – CTCAE v.5.0) were observed. HBV and HCV infection were negative. She also reported fatigue that had not been relieved by rest (grade 2 CTCAE). Immunotherapy was withheld and oral prednisone 1mg/kg/day (60 mg) and ornithine aspartate 15g PO daily were started. Two weeks later, her general condition improved. Only 2-3 bowel movements per day (grade 1 CTCAE) were reported and serum ALT/AST level was normal. Therefore, ornithine aspartate therapy was terminated and prednisone

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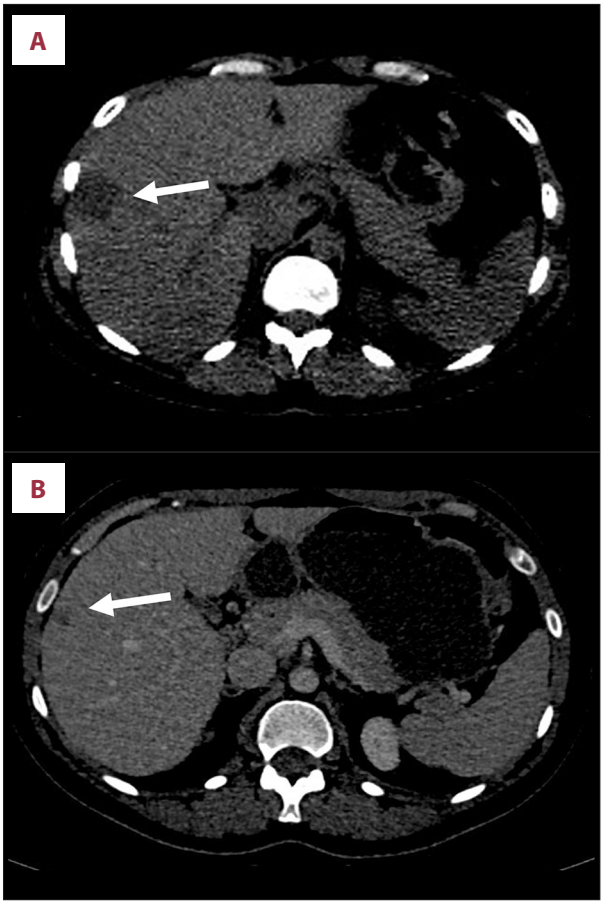

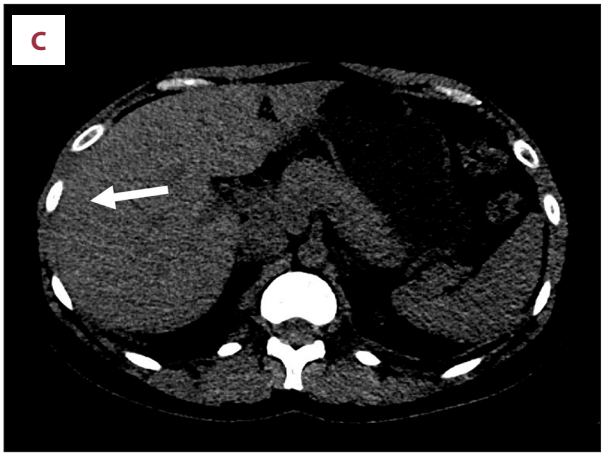

Figure 3. Abdominal CT images of liver metastasis without contrast enhancement. Axial view. (**A**) Hypodense structure in the fifth segment of the liver on positron emission tomography scan before the start of immunotherapy, (**B**) partial regression 3 months later, (**C**) complete regression 3 years after initiating immunotherapy. The white arrows indicate the location of the metastasis before and during therapy.

was reduced to 0.17 mg/kg PO (10 mg) daily. We also started nivolumab monotherapy (from the third cycle of immunotherapy) in a fixed dose of 480 mg every 4 weeks.

Three months after radiotherapy and 3 cycles of immunotherapy, a partial regression of brain metastases was observed on MRI. The largest lesion decreased from 16 mm to 6 mm (**Figure 2B**). Additionally, the dimensions of extracranial lesions also decreased; for example, in the liver from 31×27 mm (**Figure 3A**) to 13×12 mm on a CT scan (**Figure 3B**). We decided to continue nivolumab monotherapy. The favorable effect of immunotherapy was confirmed on the next CT and MR examinations every 3 months. We observed lasting metastases regression, although without complete remission. At 12 months after radiotherapy, while immunotherapy was still ongoing, the patient informed us of her fourth pregnancy at 8 weeks of gestation. We stopped immunotherapy and proceeded with physical and MR examination of the brain every 3-4 months. The pregnancy was uncomplicated. She delivered a healthy boy in the 38th week of pregnancy and no melanoma cells were detected in the placenta. Pregnancy during immunotherapy is a reason for excluding patients from reimbursement according to local regulations. Therefore, immunotherapy was not resumed and since then the patient has undergone regular CT and MR examinations. At 16 months after termination of immunotherapy, complete extracranial remission was observed (**Figure 3C**) with a partial regression of brain metastases (**Figure 2C**). The timeline of the patient's disease history is presented in **Figure 4**. The patient is still in follow-up. She is in good general condition 43 months after the start of nivolumab and ipilimumab and 31 months after the completion of immunotherapy due to pregnancy, with no signs of progression in regular CT and MR tests conducted every 3-4 months and with a normal LDH level. Her children born during the disease are healthy and developing properly. A quality of life questionnaire was not administered, but interviews every 3 or 4 weeks during treatment, and at least every 12 weeks during follow-up after discontinuation of the immunotherapy did not indicate any physical or psychological disturbances. To date, the patient has a high quality of life in terms of physical, mental, and social well-being.

Discussion

We presented a case report of a 39-year-old woman diagnosed with IIIB stage skin melanoma who, after pregnancy, progressed with multiple distant metastases, including numerous brain lesions. She was successfully treated with radiotherapy and immunotherapy. During nivolumab therapy, she became pregnant and delivered a healthy baby. Before treatment, she was recruited to an ongoing study aimed at the genetic profiling of patients with melanoma, and the *NRAS* Q61K mutation was identified in her tumor DNA. This case is exceptional

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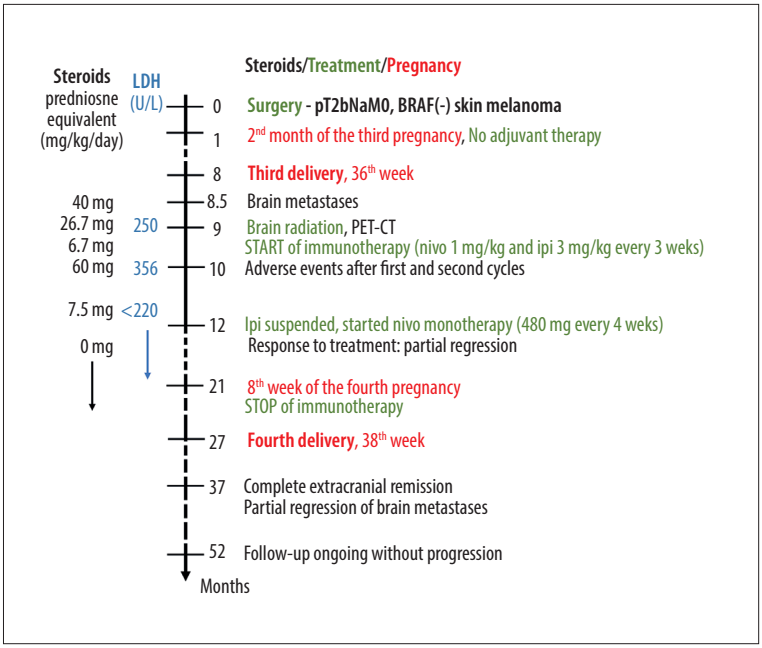

Figure 4. Timeline of the patient's disease and pregnancy history from diagnosis to date.

in 2 aspects: 2 successful pregnancies during advanced melanoma and a favorable outcome despite a poor prognosis. After delivery of the third baby and manifestation of symptomatic MBM, according to clinical trial data our patient was expected to have 2.3 months to progression [9] and approximately 13 months of survival [8-10]. The patient not only is still alive and in very good condition 43 months after MBM diagnosis, but she delivered a healthy baby boy in the meantime. Long-lasting responses of melanoma patients to immunotherapy are reported, but mainly in patients with complete response, high PDL-1 expression, and smaller tumor burden [10-12]. In MBM patients, they are more prevalent in asymptomatic cases [3] and not during steroid therapy [10]. A higher number of brain metastases [13] and elevated LDH level [5] also negatively influence the outcome. Our patient, despite many negative prognostic factors (numerous brain metastasis, low PDL-1 expression, elevated LDH, high tumor burden, and steroid treatment), had a very good treatment outcome, which has continued until now for 43 months from the start of the immunotherapy. This is significantly longer than the median PFS and OS of patients with symptomatic and/or corticosteroids-treated brain metastases (1.2 and 8.7 months, respectively [14]). It appears that the combination therapy sequence WBRT followed by ipilimumab and nivolumab treatment was successful in this case, confirming previous observations of the superiority of the RT + ICI combination over RT or ICI alone [15]. Currently, there are no known predictive markers for response to immunotherapy in melanoma. A group of potential response indicators is a genetic profile of melanoma cells [16]. Our patient's melanoma was *BRAF* wild-type and had the *NRAS* Q61K mutation. Patients with NRAS + melanoma treated with immunotherapy were reported to have a higher response and PFS compared to other cohorts [17]. On the other hand, the opposite correlation was observed in Asian patients with melanoma [18]. In our patient, potential outcome-modifying agents were administered during 2 pregnancies during disease development and treatment.

The impact of pregnancy on the progression of melanoma is not fully understood, but it can contribute to unfavorable outcomes [6]. In our patient, MBM manifested 2 weeks after the third delivery, which suggests the rapid progression of melanoma during her pregnancy. Despite the risk of transplacental metastasis in the infant [19], the baby boy, now age 3 years 10 months, is healthy and developing well, like the fourth child, who was exposed to immunotherapy during the first trimester of pregnancy. Most of our knowledge about the influence of immunotherapy on developing fetuses comes from case reports or animal studies. The data suggest that, although immunotherapy is fetotoxic, immune-related adverse effects (irAEs) depend on the trimester of pregnancy and the antigenicity of the fetus. It appears to be less toxic or nontoxic in the first trimester than subsequently [19-21], and this is in line with our case report. On the other hand, an uncomplicated pregnancy can also occur despite immunotherapy during all trimesters, as reported by Gambichler and Susok (2021) [22].

Conclusions

Long survival and response to brain radiotherapy followed by immunotherapy in patients with symptomatic MBM is possible, and pregnancy does not always have an adverse effect on the course of the disease during therapy and vice versa.

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However, pregnancy remains a contraindication to immunotherapy, and more data on pregnancy during immunotherapy are needed. This case gives hope to all oncological patients with poor prognoses.

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Declaration About Informed Consent

The authors declare that the patient provided written informed consent prior to participating in the research project.

Department and Institution Where Work Was Done

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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