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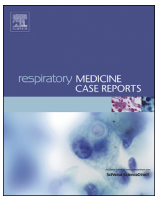

Case Report

Camrelizumab combined with chemotherapy for stage IV pulmonary sarcomatoid cancer with pancreatic metastases

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ABSTRACT

The pancreas is a rare metastatic site for lung cancer. We report the case of a 66-year-old male with pulmonary sarcomatoid carcinoma (PSC) with pancreatic and right posterior renal fascia metastases treated with immunotherapy and platinum-based chemotherapy. A pathological biopsy of the right posterior fascial mass showed lung invasive adenocarcinoma and sarcomatoid carcinoma metastasis. Immunohistochemistry staining showed that PD- L1 expression was high and next-generation sequencing revealed KRAS and TP53 mutations. Camrelizumab and chemotherapy were administered, and the metastasis disappeared. Immunotherapy combined with platinum-based chemotherapy is effective in treating PSC with pancreatic metastases.

1. Introduction

Pulmonary sarcomatoid carcinoma (PSC), a rare subtype of non-small cell lung cancer (NSCLC), is a poorly differentiated tumour characterised by sarcoma cell morphology or sarcoma-like components, representing 0.1−0.4 % of all lung malignancies. It is highly aggressive and associated with a poor prognosis [1]. Common metastatic sites include bone, lungs, brain, adrenal glands, liver, and extrathoracic lymph nodes, and the incidence of PSC with pancreatic metastases is rare [2]. There is no established standard therapy for PSC, with surgery being preferred for patients in the early stages [3]. Adjuvant chemotherapy is effective for patients with stage II and III PSC; however, overall survival remains poor [2,4]. Consequently, immunotherapy presents a promising treatment option for PSC. We report a patient with advanced pulmonary sarcoma who achieved long-term survival benefits after receiving a combination of camrelizumab immunotherapy and chemotherapy, providing a treatment plan for advanced cases and providing renewed hope.

2. Case presentation

We present a case of a patient with long-term survival who has KRAS and TP53 mutations with PSC and pancreatic metastasis and was treated with camrelizumab and platinum-based chemotherapy, offering a new promising treatment for PSC. A 66-year-old male presented with cough and haemoptysis for 1 month on July 25, 2021. Positron emission tomography-computed tomography (PET-CT) showed the presence of a mass in the right upper lobe with a size of approximately 2.3 × 2.1 cm, a mass in the right lower lobe with a size of approximately 2.0 × 3.0 cm, multiple enlarged lymph nodes in the right hilum, mediastinum, and retroperitoneum, a mass in the right posterior renal fascia (4.0 cm × 3.0 cm), and a mass in the pancreatic head (4.8 cm × 3.6 cm). Pathological biopsy of the right posterior renal fascia revealed lung invasive adenocarcinoma cancer with sarcomatoid carcinoma metastasis. Immunohistochemistry (IHC) staining showed the following tumour cell profiles: P53 (wild type), P53 (wild type), CEA (+), Napsin A (−), CKpan

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(+), CK19 (+), CK7 (+), TTF-1 (+), Villin (+), CA199 (−), CRP (−), WT-1 (−), CK5/6 (−). We performed a percutaneous lung biopsy of the mass in the right upper lobe and diagnosed it as a poorly differentiated adenocarcinoma. We also performed genetic tests on the patient's biopsy tissue from the right posterior renal fascia and peripheral blood on August 20, 2021. The results of peripheral blood next-generation sequencing (NGS), including 733 tumour-related genes, showed a mutation in Exon2 of KRAS (p.G12D Mutation Abundance 70.26 %) and a mutation in Exon5 of TP53 (p.A159Hfs*21 Mutation Abundance 53.82 %). Tumour mutational burden (TMB) was 8.38 mutations/Mb (moderate TMB), MSS was stable, and MMR, EGFR, and ALK genes did not have mutations. IHC of the right posterior fascia tumour tissue showed a tumour proportion score (TPS) of 80 % for PD-L1 expression, and the combined positive score (CPS) was 80 %. Therefore, the patient was diagnosed with stage IVb lung adenocarcinoma and sarcomatoid carcinoma (cT4N2M1c).

On August 9, 2021, a laboratory examination showed the following: alanine transferase, 159.9 U/L (0−42 U/L); alkaline phosphatase, 476 U/L (40−150U/L); γ-glutamyl transpeptidase, 754.0 U/L (11−50 U/L); total bilirubin, 84.00 μmol/L (3−20 μmol/L); direct bilirubin, 60.26 μmol/L (1.7−6.8 μmol/L); carcinoembryonic antigen CEA, 25.38 μg/L (0−4.7ug/L); and CA199, 46.25 U/mL (0−27 U/mL). Upper abdominal magnetic resonance imaging and MRCP revealed a significant dilation of the common bile duct. Following multidisciplinary consultation, bile duct stenting was performed, resulting in decreased bilirubin and liver enzyme levels. A biopsy of the pancreatic lesion was not performed at the patient's request, so it is unclear whether the pancreatic lesion was a primary tumour or a metastatic tumour. The patient was treated with camrelizumab (200 mg/body weight every 3 weeks) combined with a chemotherapy regimen including cisplatin and tegafur (50 mg, days 1–14), targeting both lung and pancreatic cancer. After one cycle, the patient experienced anorexia and neutropenia and refused to continue chemotherapy.

After two cycles of camrelizumab, CT imaging showed complete resolution of the pancreatic mass and the right posterior renal fascial mass (Fig. 1). However, a new metastasis (3.3 × 2.3 cm) was observed in the right lower lobe on November 19, 2021, after which he completed the subsequent four cycles of camrelizumab. CT re-evaluation on January 22, 2022 showed enlargement of the new lesion from 3.3 × 2.38 cm to 7.2 × 4.0 cm. The patient immediately received gemcitabine 1.6 g on days 1 and 8 and oxaliplatin 200 mg on day 1 combined with camrelizumab every 3 weeks. Partial remission (PR) was detected by CT, which showed that the new metastasis in the right lower lobe lymph nodes in the right hilum, mediastinal, and retroperitoneum were significantly shrunk after two cycles on March 28, 2022. The lymph nodes in the right hilum, mediastinal, and retroperitoneum disappeared in the third cycle of treatment on April 28, 2022. The patient continued to receive three cycles of camrelizumab combined with chemotherapy and then four cycles of camrelizumab alone. The periodic follow-up CT during treatment suggested a stable disease (SD) for efficacy (Fig. 2).

Disease progression was detected 14 months after discontinuing camrelizumab, with a new nodule in the right lung hilum identified as metastasis on October 24, 2023. After three cycles of camrelizumab, CT revealed that the lesion had shrunk significantly (Fig. 3). The patient remains in good condition and continues to receive camrelizumab. An overview of the timeline for this case is shown in Fig. 4.

3. Discussion

Lung cancer is the second most common malignant tumour and has the highest mortality rate worldwide [5]. Approximately 50 % of patients with lung cancer present with metastases at the time of diagnosis, commonly to the bone, lungs, brain, adrenal glands, liver, and extrathoracic lymph node metastasis [6,7]. Pancreatic metastasis is exceptionally rare, and more than 50 % of patients with pancreatic metastasis of lung cancer being asymptomatic, whose symptoms are similar to the symptoms of primary pancreatic cancer, including primarily weight loss, obstructive jaundice, acute pancreatitis, back pain, and other symptoms [8]. Diagnostic criteria for lung cancer with pancreatic metastasis include histopathological or cytopathological detection of pancreatic masses [9,10]. CT, endoscopic ultrasound (EUS), and PET-CT can improve diagnostic accuracy [11,12]. A small proportion of patients undergo pancreatic biopsy due to poor status or high risk. Therefore, most pancreatic metastases of lung cancer can be confirmed by imaging. If clinicians or radiologists lack a sufficient understanding of lung cancer with pancreatic metastases, pancreatic metastasis can be misdiagnosed as primary pancreatic carcinoma, leading to the selection of different adjuvant therapies.

Through a literature study, we found that the main pathological type of pancreatic metastasis of lung cancer was small cell lung cancer. Duan et al. conducted a retrospective analysis of patients with lung cancer diagnosed and treated at the Department of Cancer Hospital of the Chinese Academy of Medical Sciences. The incidence of pancreatic metastasis is approximately 0.69 %, of which small cell lung cancers account for 80 % [13]. In our case, the lung cancer was a PSC with poorly differentiated adenocarcinoma.

PSC is a rare subtype of NSCLC, characterised by poorly differentiated tumours with sarcomatous cell morphology or a sarcomatoid component. It accounts for 0.1–0.4 % of all lung malignancies and is associated with high invasiveness and poor prognosis [1]. The study found that 84 % of lung sarcomatoid carcinomas were stage IV when found, and common metastatic sites were similar to NSCLC; cases of lung sarcomatoid carcinoma with pancreatic metastasis have rarely been reported [2].

In some reports, patients with lung cancer that metastasised to the pancreas had acute pancreatitis or obstructive jaundice. Prior to antitumour treatment, biliary stenting can alleviate symptoms of obstructive jaundice [14,15]. Tanakah et al. reported that chemotherapy could relieve the symptoms of acute pancreatitis [16], while Kawaguchi et al. used pancreatic duct stents to drain the pancreatic juice and effectively control the symptoms of acute pancreatitis [17]. Surgical resection of metachronous isolated pancreatic metastases can improve long-term survival in patients who have undergone complete resection of primary NSCLC [18,19].

Systemic therapy remains the primary treatment for advanced NSCLC. Patients with EGFR and ALK mutations can be treated using chemotherapy combined with targeted therapy or immunotherapy [20]. Currently, there is no standard treatment for PSC.

Studies have shown that TMB can better predict the efficacy of combined blockade of PD-1 and CTLA-4 in the treatment of NSCLC [21]. Several studies have found that PD-L1 positive expression was observed in patients with PSC, which was higher than in patients

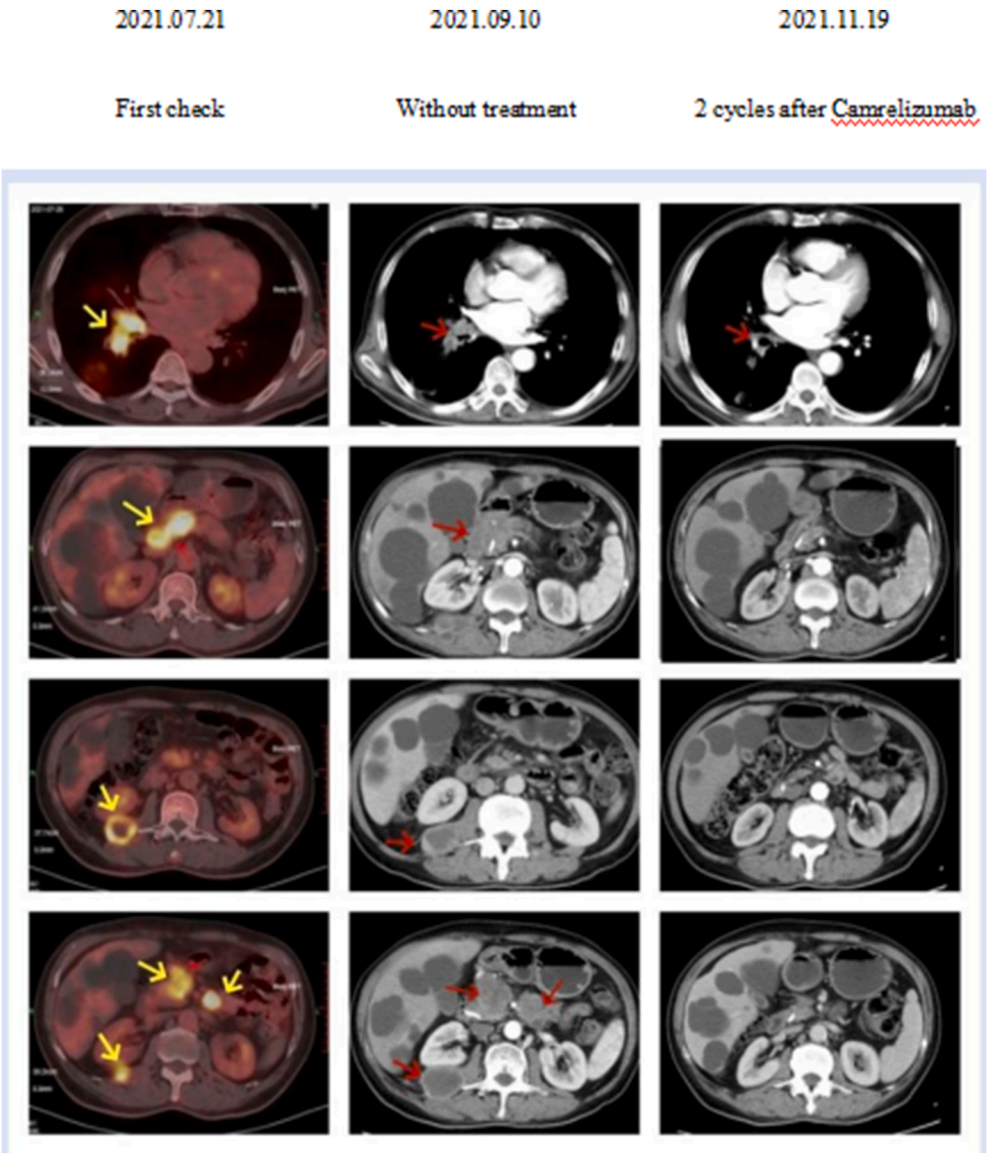

Fig. 1. Computed tomography (CT) scan shows changes in metastatic lesions after camrelizumab.

with NSCLC, and PD-L1 expression did not differ between the epithelial and sarcoma components (p = 1.0) [22–24]. Among the 37 patients with PSC evaluated in another study, 87.5 % showed high TMB (≥10 mut/Mb), suggesting that immunotherapy may play an important role in PSC [25]. In the recent research, first-line treatment with immunotherapy, immunotherapy combined with anlotinib, and immunotherapy combined with chemotherapy showed that the survival time improved significantly, and the median PFS of the three treatment regimens was 8.0, 9.4, and 9.6 months, respectively, and median OS was 19.0, 22.8 and 30.6 months, respectively, with no difference in PFS and OS [26]. NGS analysis of 32 patients with PSC revealed that TP53 (69 %), RB1 (25 %), EGFR (28 %), KRAS (22 %), and Met (16 %) were the most frequently mutated genes [27]. Studies have shown that patients with NSCLC carrying TP53 or KRAS mutations, especially those with CO mutations, are more sensitive to PD-1 inhibitor treatment [28].

NGS and immunohistochemical (IHC) detection of KRAS and TP53 mutations, no EGFR and ALK gene mutations, PD-L1 expression (TPS = 80 %, CPS = 80, and TMB = 8.38 mut/Mb) sensitive to platinum drugs. When the patient was treated with camrelizumab alone, pancreatic and prerenal fascia metastases and retroperitoneal lymph nodes disappeared, mediastinal and hilar lymph nodes were smaller than before, and primary lung lesions were smaller. However, a new lesion appeared in the right lung in a short time and continued to increase. This phenomenon, in which responding and non-responding lesions or new lesions coexist simultaneously, is considered an immunotherapy-associated dissociated response (DR). When the patient was assessed as DR, he received the second peripheral blood NGS, which showed a mutation in Exon2 of KRAS (p.G12D Mutation Abundance 1.45 %) and a mutation in Exon5 of TP53 (p.A159Hfs*21 Mutation Abundance 0.46 %).

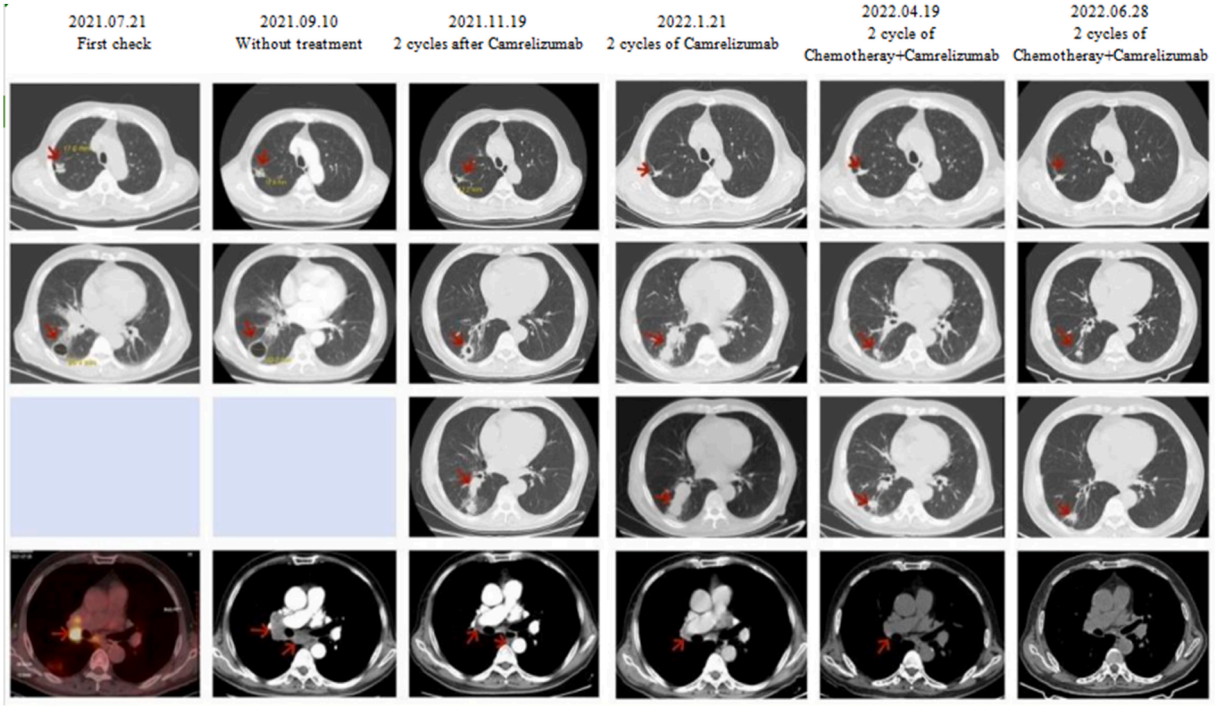

Fig. 2. Computed tomography (CT) scan shows changes in primary lesions and mediastinal lymph nodes after camrelizumab and camrelizumab + chemotherapy.

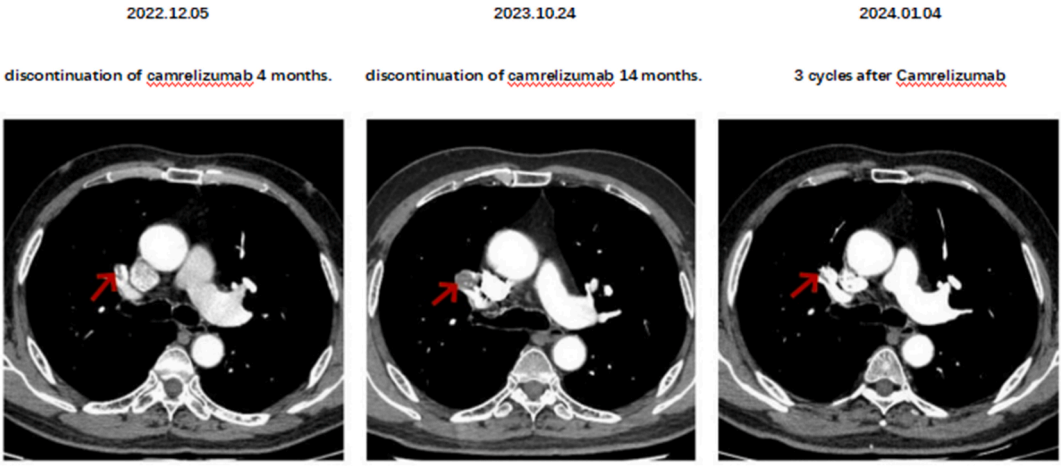

Fig. 3. Computed tomography (CT) scan shows changes in the right lung hilar lymph nodes after discontinuing camrelizumab and continuing with camrelizumab.

DR occurred between 4.7 % and 22.1 % in four retrospective and one prospective trial involving 672 patients with NSCLC from 2018 to 2021 [29–33]. Histological temporal heterogeneity between primary and metastatic lesions, differences in tumour microenvironment between primary and metastatic lesions, and differences in PD-L1 expression between different lesions may be responsible for these inconsistent responses to immunotherapy [34]. Guan advised that if a patient is initially assessed for DR, oncologists must perform the next assessment in the subsequent 4–8 weeks and continue immunotherapy due to potential good prognosis, or consider local therapy for PD lesions and proceed with treatment or move on to the next line of therapy [34]. Our patient with DR was advised to continue immunotherapy because the patient's prognosis was good. We hypothesised that patients with TP53 and KRAS gene mutations may achieve good efficacy after receiving immunotherapy due to a decrease in mutation abundance. Further studies are required to test these hypotheses.

4. Conclusions

Although the patient had multiple distant organ metastases at the time of discovery and the pathological type was poorly differentiated adenocarcinoma with sarcomatoid carcinoma with a poor prognosis, clinical treatment was guided by the results of PD-L1 IHC

The timeline of the case report, which includes the course of treatment, imaging examination and PR, partial response; PD,progressive disease;SD, stable Disease; DR，immunotherapy-associated dissociated responses； ERBD， endoscopic retrograde biliary drainage.

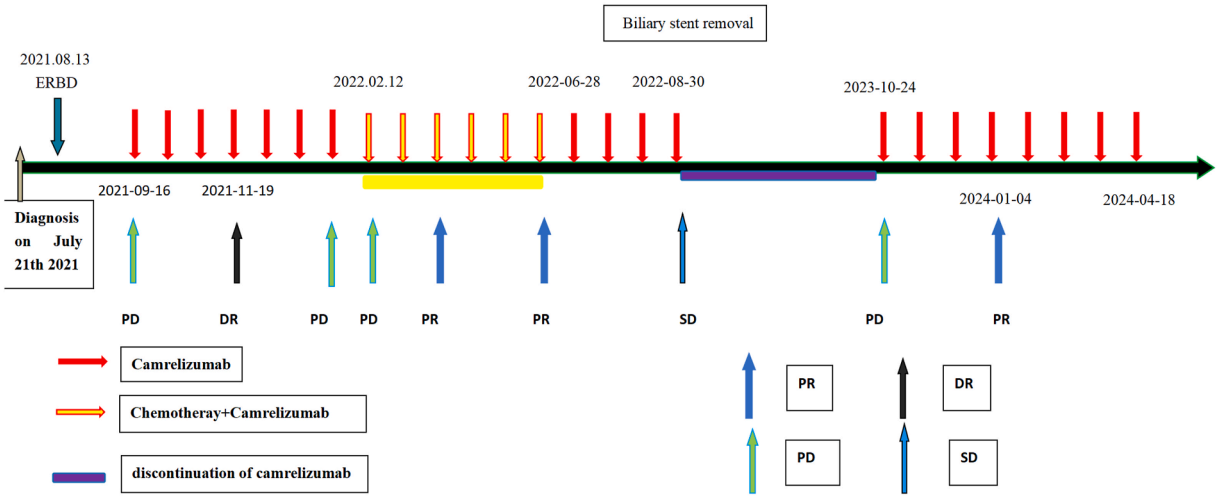

Fig. 4. Timeline of the case.

and NGS, which provided more precise and personalised treatment for the patient, and the patient achieved long-term survival. Lung sarcomatoid carcinoma has a rapid progression and poor prognosis. Camrelizumab combined with chemotherapy can effectively prevent tumour progression, improve patient survival, and bring new hope to patients.

Sarcomatoid carcinoma of the lung is a rare malignancy, and further clinical studies are needed to compare the efficacy of immunotherapy, immunotherapy combined with chemotherapy, targeted drugs, and radiotherapy to formulate the best treatment plan for patients.

- Genetic testing and PD-L1 IHC should be routinely conducted for patients with pulmonary malignancies.
- Camrelizumab, a PD-L1 blocking mAb, is well established for managing NSCLC, including histological variants of adenocarcinoma, and has demonstrated durable responses in combination with chemotherapy.
- Tumour progression following the discontinuation of immune drugs and continued use remains effective.

CRediT authorship contribution statement

Liqin Ruan: Writing – original draft, Resources. **Ningbo Fang:** Investigation. **Weili chen:** Resources. **xiaoyong Wu:** Writing – review & editing. **Xin hua Zhao:** Visualization, Conceptualization. **Lu Wang:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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