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Reversible Dementia Induced by VEGFR-Tkis: A Case Report and Literature Review

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1. Abstract

1.1. Background: Vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) are widely used in patients with malignancies and common adverse events are well known by clinical oncologist. However, uncommon adverse events especially neuotoxicity are known little and there was no report of reversible dementia caused by VEGFR-TKIs to date.

1.2. Methods: A 70-year-old male was diagnosed with extensive stage small cell lung cancer in August 2019. He received six cycles of chemotherapy plus autologous cytokine-induced killer cells therapy and whole brain radiation, and complete response was got. Then he received sintilimab maintenance therapy. In August 2020 single intracranial metastasis appeared and he received stereotactic radiosurgery. Afterwards he received anlotinib therapy, three months later dementia was developed and there was no sign of positive examination. Anlotinib was discontinued and one month later the symptoms of dementia disappeared. In September 2021 the single intracranial metastasis recurred, he was administered apatinib, the symptoms of dementia reappeared five days after apatinib administration, and several days after discontinuation apatinib the symptoms disappeared gradually.

1.3. Conclusions: VEGFR-TKIs is a risk factor for the development of reversible dementia. The cognitive function should be scrutinized for the patients prescribed VEGFR-TKIs, the VEGFR-TKIs should be stopped once cognitive function impairment occurred.

2. Introduction

In the past 20 years, oral anti-angiogenesis agents targeting the vascular endothelial growth factor receptor tyrosine kinase (VEGFR-TK), such as sorafenib, axitinib, sunitinib, lenvatinib, apatinib, and anlotinib, have been introduced into clinical practice. Oral VEGF-TK inhibitors (VEGFR-TKIs) are widely used in patients with malignancies, either as monotherapy or combined with chemotherapy or anti-PD-1 antibodies [1-3]. Common adverse events (AEs) of these agents, including hypertension, hand-foot skin reactions, proteinuria, bleeding, and thrombosis, have caused widespread clinical concern. Clinicians also need to be mindful of the possibility of rare AEs during treatment with these drugs. In patients with advanced malignancies, VEGFR-TKIs are associated with a significant increase in the risk of fatal adverse events [4]. Nervous system AEs significantly influence patients' quality of life and thus warrant special attention. Rare AEs, such as reversible posterior leukoencephalopathy syndrome (RPLS), have been reported [5]; however, to date, there are no reports of reversible dementia caused by these drugs. Here, we described a case of a patient with small cell lung cancer (SCLC) with brain metastasis who developed reversible dementia after treatment with anlotinb and apatinib.

3. Methods

A 70-year-old male was diagnosed with SCLC with brain metastasis in August 2019 after presenting with a primary complaint of weakness of the right limbs. He was enrolled in a phase II study

of sintilimab maintenance therapy after etoposide/platinum plus autologous cytokine induced killer (CIK) cells in patients with extensive SCLC (NCT 03983759). He received six cycles of etoposide/platinum plus autologous CIK cells therapy and whole-brain radiotherapy (30 Gy/10f) from September 2019 to December 2019 and achieved complete response. He was subsequently treated with seven cycles of sintilimab maintenance therapy; during that time, he developed grade 3 elevated alamine aminotransferase levels (graded according to the National Cancer Institue Common Terminology Criteria for Adverse Events version 5.0), and was treated with prednisone at a starting dose of 0.5 mg/kg/d, which was then stopped gradually in six weeks.

A left frontal lobe lesion was identified on August 11, 2020 through routine follow-up, and he received stereotactic radiosurgery (SRS; 18 Gy/1f). After radiotherapy, he was administered anlotinib (10 mg) daily on a 14 days on/7 days off cycle. During the course of anlotinib therapy, grade 2 hypertension occurred, and his blood pressure was controlled to normal using nifedipine controlled-release tablets.

In November 2020, he experienced impaired orientation and memory impairment. Brain magnetic resonance imaging (MRI) showed no obvious intracranial lesions. Electroencephalogram and cerebrospinal fluid examination results were all negative, and his Mini-Mental State Examination score was 18. Compared with previous imaging results obtained on August 2020, there was evidence of atrophy of the temporal lobes and frontal lobes (Figure 1A-D). A neurologist consult was sought, and the neurologist considered that the dementia was caused by brain atrophy and prescribed oxiacetam and donepezil to improve symptoms. However, this did not result in any clinical improvement in cognitive function. Anlotinib therapy was discontinued in November 2020. A month later, the patient's orientation and memory returned to baseline status. Figure 1E and 1F (scans obtained in December 2020) demonstrate the slight improvement in atrophy of the temporal lobes.

At a routine follow-up on September 29, 2021, the left frontal lobe nodule reappeared, and there was evidence of atrophy of the temporal lobes and frontal lobes (Figure 1G and 1H). He received apatinib (250 mg) administration daily. After 5 days of apatinib therapy, the patient experienced lethargy, decreased muscle strength, and impaired memory and orientation.

Based on the temporal relationship with apatinib treatment, we suspected that his symptoms might be due to treatment with apatinib. Therefore, apatinib was discontinued, and supportive treatment was administered. From 8th to 10th october 2021, he received SRS (36 Gy/3f) for the brain metastasis. Three days after discontinuation of apatinib, lethargy and decreased muscle strength improved significantly, followed by subsequent improvements in orientation and memory. Half a month after the discontinuation of apatinib, the patient was back to his baseline state, with a Mini-Mental State Examination score of 20. In addition, he could perform activities of daily living independently. Thereafter, the patient was started on chemotherapy for the management of SCLC. Figure 2 illustrates the patient's treatment process. Written informed consent was obtained from this patient's son to publish this case report.

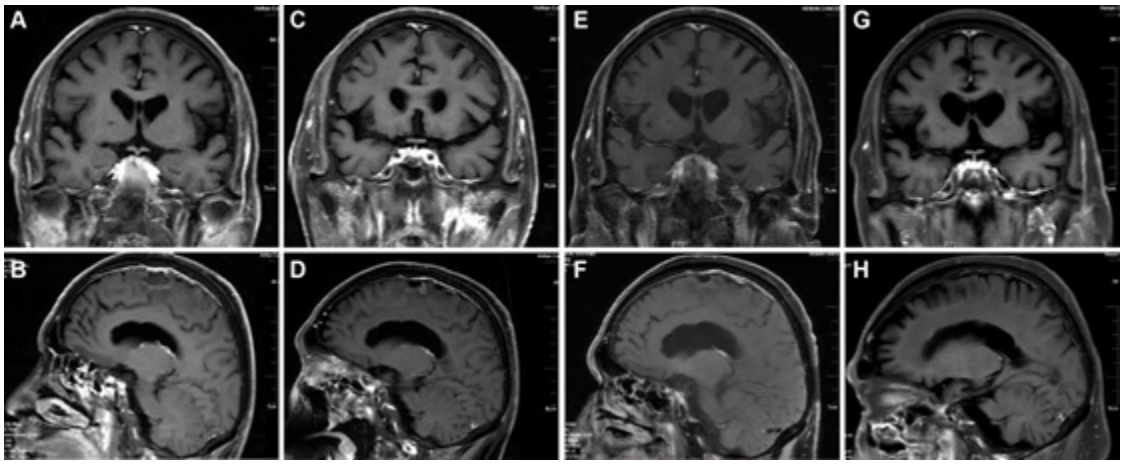

Figure 1: Magnetic resonance imaging scan of the brain. A and B show the temporal lobes and frontal lobes before anlotinib therapy. C and D show the temporal lobes and frontal lobes when dementia was detected in November 2020. D and E show the temporal lobes and frontal lobes after resolution of dementia symptoms. G and H show the temporal lobes and frontal lobes before recurrence of dementia.

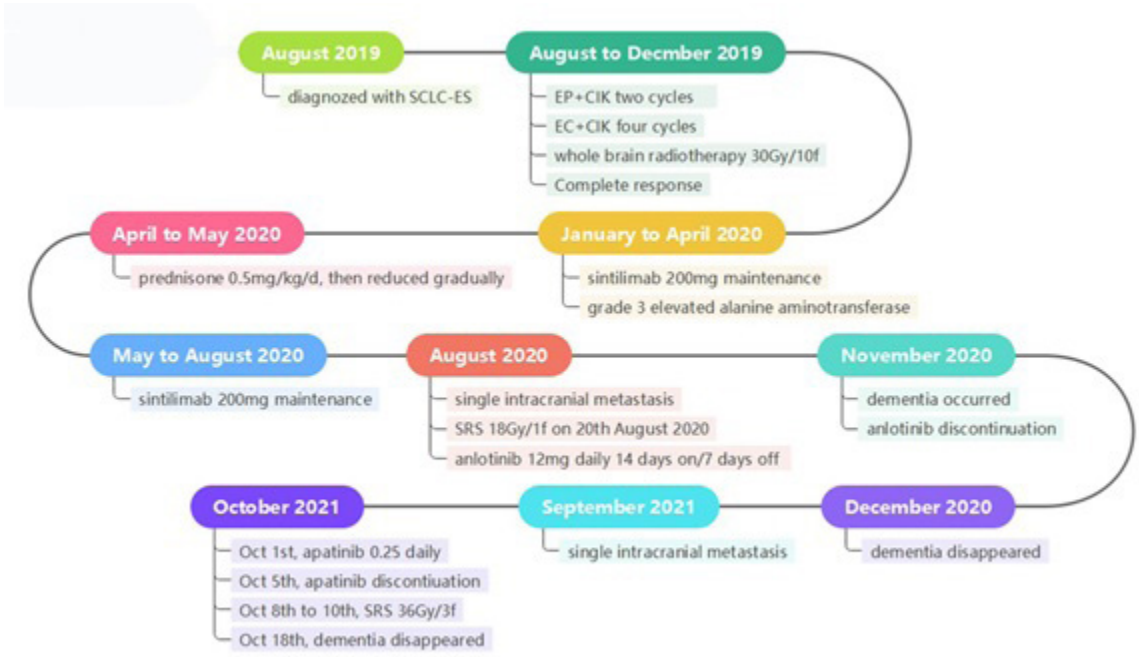

Figure 2: The treatment course of the patient. SRS: stereotactic radiosurgery.

4. Discussion

Dementia refers to a group of irreversible neuodegenerative diseases that lead to changes in cognition, communication, and function. Dementia and cognitive dysfunction lead to the loss of independence, a reduction in the quality of life, and an increase in disability, all of which adversely affect the patients, their families, and society [6]. Dementia has become a major public health problem affecting the elderly [7-8].

Given the global burden of dementia and cognitive impairment, several studies have attempted to determine the risk factors that might affect cognitive function, such as age, socio-demographic status, the presence of chronic diseases, and healthy behaviors [9-11]. To date, knowledge on the effects of prescription drugs on cognitive function is limited. Although previous studies have provided some evidence of drug-induced cognitive dysfunction, this has been mainly observed in drugs used to treat hypercholesterolemia, depression, anxiety, and cardiovascular diseases; in general, the higher the medication burden, the higher the probability of cognitive dysfunction [12].

Rapidly progressive dementia (RPD) is an emergency in cognitive neurology. It is defined as a cognitive impairment that affects activities of daily life and is characterized by rapidly progressive cognitive decline over a short period of time [13]. Secondary reversible disease is the most common cause of RPD, and the most common etiologies are infectious diseases, immune-mediated diseases, and neoplastic diseases [14].

A number of studies have explored the relationship between drug treatment and the outcome of patients with dementia and found that anticholinergic drugs increase the risk of dementia [15]. Non-steroidal antipyretic analgesics are commonly prescribed in patients with rheumatoid arthritis, and the risk of dementia in patients receiving non-steroidal antipyretic analgesics is 1.6 times higher than that in those without a history of non-steroidal antipyretic analgesic use [16]. Cardiovascular drugs, especially those with central nervous system bioavailability, such as antiarrhythmic drugs (disopyramide, quinidine), cardiotonic drugs (digoxin), and sympathetic antihypertensive drugs (clonidine, methyldopa, propranolol, reserpine), have been associated with cognitive impairment. The negative effects range from simple confusion and delirium to more chronic cognitive changes [17-20]. These drugs can cause cognitive impairment through several potential mechanisms, including decreased cardiac output leading to decreased cerebral blood flow, fluid/electolyte and/or acid–base imbalance, antagonism of central muscarinic acetylcholine receptors, neurotransmission imbalance in the central nervous system, and disruption of physiologic function of Na+/K+ ATPase in the neuronal cells [21].

In any case, drug-induced dementia is uncommon. Methotrexate is known for its central nervous system toxicity with long-term intrathecal injection, ranging from acute aseptic meningitis to delayed toxicity, including cognitive deficits and progressive dementia. However, a case of a 78-year-old man with rheumatoid arthritis who developed reversible dementia after taking oral low-dose methotrexate has been reported [22]. The exact mechanism of methotrexate-induced dementia remains unclear; however, it may involve the consumption of folic acid. Indeed, folic acid deficiency can induce some pathophysiological changes noted in Alzheimer's disease [23, 24].

To our knowledge, this is the first case of a patient diagnosed with reversible dementia due to VEGFR-TKIs. Our diagnosis was based on following evidence. First, there was a reasonable time relationship between the drug administration and the occurrence

of adverse reactions/events, and the symptoms disappeared after anlotinib withdrawal. Second, the symptoms re-appeared after initiation of apatinib administration. Although grade 2 hypertension appeared during anlotinib therapy, the blood pressure was controlled to normal after taking nifedipine controlled-release tablets, after discontinuation of anlotinib, his blood pressure backed to normal, and nifedipine controlled-release tablets was stopped. During apatinib therapy, hypertension was not noted, and no other combinational medications were administered. Third, although this patient received radiotherapy for brain metastasis, there was no time relation between dementia and radiotherapy, second RPD in this patient occurred before SRS and recovered gradually during and after SRS. Notably, most cases of dementia due to radiotherapy are irreversible. In this patient, virological indicators were all negative, and he was not taking any regular medications for chronic diseases. The symptoms of dementia disappeared in approximately one month and 10 days, which was in line with the elimination of half-lives for anlotinib and apatinib [25, 26]. Therefore, drug-induced dementia was highly suspected.

Indeed, reversible cognitive disorders after sunitinib therapy for advanced renal cell cancer has been reported in three elderly patients with pre-existing arteriosclerotic leukoencephalopathy [27]. Receiving the standard dose of sunitinib, the patients developed confusion, hallucinations, or an extrapyramidal syndrome that was rapidly reversible after sunitinib discontinuation. However, in this previous study, all patients had the comorbidity of arteriosclerotic leukoencephalopathy and hypertension. To the best of our knowledge, there has been no previous report of VEGFR-TKIs inducing RPD, which was completely reversible after stopping the drugs.

VEGFR-TKIs have been approved for the treatment of various malignant tumors. However, unexpected AEs occur occasionally in clinical practice. Thus, the diagnosis and management of these AEs are important for the development and optimal use of these agents. Neurological AEs of VEGFR-TKIs include headache, insomnia, dizziness/vertigo, sensory/motor nerve dysfunction, neuralgia, hallucinations, memory loss, ataxia/unsteadiness, syncope/lethargy/somnolence, seizures or convulsions, confusion state/cognitive impairment, toxic encephalopathy, and RPLS [5, 28-31].

Although neurotoxicity is an uncommon AE of VEGFR-TKIs, its identification is important. In one clinical study of valatinib, grades 3 and 4 neurotoxicity occurred in approximately 9% and 1% of patients, respectively [32]. Grade 3 convulsion occurred in 6% of patients in another AG-013736 study [33].

Another serious neurological adverse event associated with VEGFR-TKIs use is RPLS. RPLS refers to a group of disorders characterized by reversible subcortical angiogenic brain edema in patients with acute neurological symptoms under the conditions of renal failure, blood pressure fluctuations, and cytotoxic drug usage. It is characterized by neurological abnormalities including changes in mental function, vision loss, stupor, seizures, and white matter changes on MRI, mainly located in the posterior parietal-temporal-occipital lobes. Imaging manifestations and clinical symptoms can disappear after stopping the suspected drugs [34]. A phase II study of lenvatinib in patients with progressive, recurrent, or metastatic adenoid cystic carcinoma reported the highest incidence of RPLS (3.1%) [5].

Anlotinib and apatinib are VEGFR-TKIs that have been approved by the National Medical Products Administration for the treatment of various solid tumors, such as non-small cell lung cancer, SCLC, advanced esophageal cancer, liver cancer, gastric cancer, and thyroid cancer. Common AEs of anlotinib and apatinib include hypertension, proteinuria, hand and foot skin reactions, and delayed wound healing. Although neurological AEs are listed in the drug instructions for anlotinib and apatinib, there are currently no reports of dementia induced by these two drugs.

In contrast, dementia and Parkinson-like events induced by intravenous anti-VEGF drugs have been reported [35]. Vascular dementia has been associated with a reduced cerebral blood supply, especially in the frontal lobes [36]. It was suspected that anlotinib and apatinib could decrease cerebral blood supply by vasoconstriction.

Although the exact mechanism of neurotoxicity induced by VEGFR-TKIs remains unclear, it is speculated that neuropilin-1 (NP-1) mediates this process. NP-1 is the VEGFR-2 co-receptor of VEGF, which is expressed on axons and participates in the development of the nervous system. Furthermore, NP-1 is required for endothelial cell adhesion to soluble VEGFR-1 [37] and regulates vascular permeability signaling [38]. In addition to binding with VEGFR, VEGF can also bind with NP-1 to enhance the binding of VEGF–VEGFR2; therefore, NP-1 is used to regulate VEGF/VEGFR2 interaction rather than act as a receptor for direct cytokine transmission [39].

NP-1 binds to semaphorin and acts as a mediator in neuronal guidance, controls both axonal guidance and subcellular target recognition. Loss of semaphorin function or specific deletion of NP-1 alters the stereotyped organization of basket cell axon and impairs pinceau synapse formation[40]. Inhibition of semaphorin-NP-1 binding can lead to neuron growth inhibition and regulate axonal transport. Moreover, NP-1 plays an important role in the activation of VEGFR-2. When NP-1 is inhibited, the VEGFR-2 signaling pathway, which is very important for angiogenesis, is also inhibited [41]. Semaphorin competes with NP-1 to bind to endothelial cells to a certain extent, leading to the inhibition of endothelial cell movement and angiogenesis [42]. More recently, a genome-wide association study implicated NP-1 in the pathogenesis of severe Alzheimer disease [43]. These studies overall indicate that semaphorin could influence angiogenesis through NP-1.

Neurotoxicity related to VEGFR-TKIs use is an uncommon yet debilitating AE. At present, the only treatment for drug-induced neurotoxicity is the discontinuation of VEGFR-TKIs. In addition

to NP-1, other factors, such as the inhibition of angiogenesis by VEGFR-TKIs, which leads to the occlusion or spasm of intracranial small blood vessels and can present similarly to vascular dementia, may have contributed to the occurrence of dementia in our patient. Although brain radiotherapy and intracranial metastasis might have caused cognitive impairment in our patient, this assumption is not supported by the observation that dementia was reversed after the discontinuation of anlotinib and apatinib. Nevertheless, further studies are required to elucidate the possible mechanism.

5. Conclusions

VEGFR-TKIs administration is a risk factor for the development of reversible dementia. In older patients and those with a history of prior brain radiotherapy, the risk of dementia needs to be assessed when VEGFR-TKIs are prescribed. Furthermore, VEGFR-TKI-induced AEs should be considered in patients with cognitive impairment or Alzheimer-like events. If it is suspected, VEGFR-TKIs should be discontinued.

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