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Case Report

Explosive Progression of Brain Metastases from Lung Adenocarcinoma after Radiotherapy and Significant Reversal after Inhalation of Hydrogen-Oxygen Gas: A Case Report

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Abstract

Rationale: For multiple brain metastases complicated by Non-Small Cell Lung Cancer (NSCLC), Whole Brain Irradiation Therapy (WBRT) is the first choice for treatment. But little is known about the explosive progression of brain metastases caused by radiotherapy and the reversal of hydrogen gas inhalation.

Patient concerns: A 51-year-old female patient was diagnosed with NSCLC with multiple brain metastases. After receiving Gefitinib and Osimertinib without clinical response, she received 28 days of WBRT.

Diagnosis: One week after the end of WBRT, the patient's general condition suddenly worsened, with severe headache, vomiting, confusion, and incontinence. MRI showed that the number and size of brain metastases increased explosively.

Interventions and outcomes: In the absence of any special "anti-cancer" treatment available, the patient only receives hydrogen gas inhalation therapy, inhaling a mixture of hydrogen and oxygen (66% H_2 and 34% O_2), 3000 ml/min, at least 6 hours a day. The patient's condition began to improve after a week, and markedly improved after one month. A reexamination of MRI showed that more than 90% of brain metastases disappeared.

Lessons: Radiotherapy is a double-edged sword. Doctors should pay attention to the adverse effects of radiotherapy, especially for brain metastases complicated by lung cancer. Molecular hydrogen is a therapeutic gas that can selectively scavenge toxic free radicals, its role in cancer treatment is worthy of attention and further research.

Keywords: Lung cancer; Radiotherapy; Hydrogen gas; Inhalation

Introduction

Non Small Cell Lung Cancer (NSCLC) is the one of leading causes of cancer-related death in the China. Adenocarcinoma is the most common subtype of NSCLC. Up to 50% of pulmonary carcinoma patients would develop brain metastases throughout their clinical courses, and 10% to 25% of them have Brain Metastases (BMs) at the time of initial diagnosis [1]. With the discovery of targetable molecular drivers and the development of an astonishing number of Tyrosine Kinase Inhibitors (TKI), the treatments for NSCLC, especially lung adenocarcinoma have significant advancement. Unfortunately, most of these drugs are difficult to penetrate the blood-brain barrier, so that the effect on brain metastasis is limited. Surgical resection, Stereotactic Radio Surgery (SRS) and Whole Brain Radiation Therapy (WBRT) are still the main treatments for BMs caused by lung cancer [2].

But for NSCLC, radiation therapy is a double-edged sword. In some cases, radiation therapy can promote and exacerbate metastasis [3]. Here, we introduce a female patient with advanced lung adenocarcinoma with multiple brain metastases confirmed pathologically, after receiving WBRT, her brain lesions progressed explosively and were miraculously reversed after inhalation of hydrogen.

Case Presentation

A 51-year-old woman was admitted to one hospital in Beijing, China in October 2019 due to left arm pain for one month, and the chest Computed Tomography (CT) showed irregular solid mass lesions in the left lower lung, with small cavities, multiple small lesions in both lungs, with mediastinal lymph node metastasis and rib bone metastasis (Figure 1), which was pathologically confirmed by the percutaneous lung biopsy as lung adenocarcinoma. Then head Magnetic Resonance Imaging (MRI) showed multiple abnormal nodular enhancements in the two cerebral hemispheres, which was diagnosed as brain metastases (Figure 2).

The tumor was classified as stage IV-B (cT4N1M1) lung adenocarcinoma. Genetic testing showed EGFR exon 21 L858R

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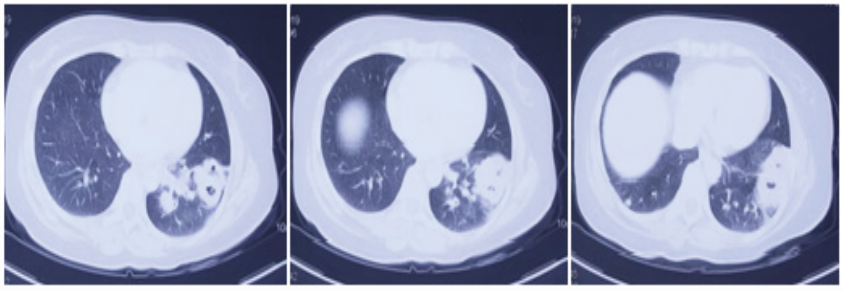

Figure 1: Chest Computed Tomography (CT) showed irregular solid mass lesions in the left lower lung, with small cavities, multiple small lesions in both lungs, with mediastinal lymph node metastasis.

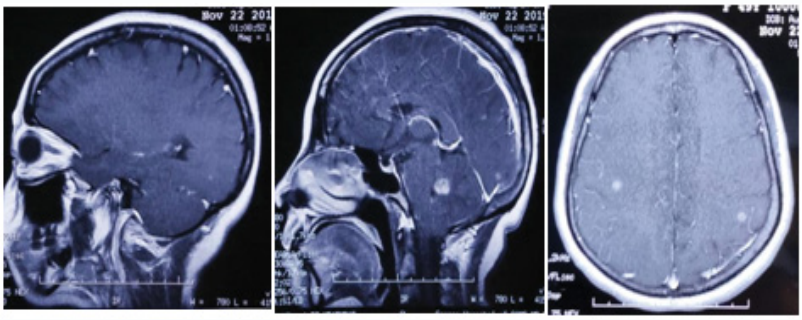

Figure 2: Head Magnetic Resonance Imaging (MRI) showed multiple abnormal nodular enhancements in the two cerebral hemispheres.

mutation. The patient began taking Gefitinib (250 mg/d) since December 25, 2019. In April 2020, nearly three-month treatment later, the patient complained of worsening headaches, reevaluation showed progression in both lung and brain lesions. Repeated genetic sequencing of tumors performed twice in different centers showed that the original EGFR exon 21 L858R mutations turned negative. From April 23, the patient stopped taking Gefitinib, changed to take Osimertinib. From May 2 until May 29, the patient received WBRT with an intensity of Dt50Gy/25f, at a frequency of 5 days per week. One week after the radiotherapy, the patient suddenly had difficulty walking, severe headache, vomiting followed by confusion and incontinence. Re-examination of MRI on June 3 showed that the number and size of metastases in the brain increased explosively, covering the entire brain (Figure 3). In the following month, the patient did not receive any special "anti-cancer" therapy except for symptomatic and supportive treatment. On July 16, the patient began to receive hydrogen inhalation therapy by using a hydrogen-oxygen nebulizer (AMS-H-01, Asclepius, Shanghai, China, SFDA registration No. 20203080066) and inhaling a mixture of hydrogen and oxygen (66% H_2 and 34% O_2) with a gas flow rate of 3,000 ml/ml through a nasal cannula for a total of at least 6 hours per day, intermittently or continuously inhaling. After half a month inhalation, the patient's self-feeling began to improve. One month later, the patient's headache disappeared; she was able to walk on the ground, and her eating, consciousness, urination and bowel movement return to normal. Re-examination of MRI showed that more than 90% of the brain metastases disappeared (Figure 4).

Since then, the patient successfully received treatments such as Sintilimab (PD-1 inhibitor), Carboplatin, and Bevacizumab. On October 22, 2021, 15 months after the start of hydrogen inhalation, the follow-up found that the patient felt good about herself and was able to perform light physical labor, the lung lesions were further improved, and the brain metastases were still stable and in further improvement (Figure 5).

Discussion

The NSCLC patient stated above has very special and thought-provoking clinical features. First, in view of the EGFR mutation, the patient first received the first-generation TKI Gefitinib treatment, but there was no clinical response and the recheck genetic sequencing showed that the original EGFR exon 21 L858R mutations disappeared. The patient changed to receive the third-generation TKI Osimertinib, which did not show clinical effects, but progressed to lung lesion and brain metastasis. Secondly, after receiving whole brain irradiation for BMs, the whole body condition deteriorated sharply, life was in a critical state, and brain metastases, both in number and size, showed an explosive increase. Third, given that no special treatment was available, the patient received hydrogen (mixed hydrogen and oxygen) inhalation. The magic is that only relying on this simple therapy, the patient's general state and brain metastasis have been significantly improved and reversed. It has been 15 months since hydrogen inhalation, and the patient's lung damage and brain metastasis are still stable and in further improvement.

BMs are the main complication of EGFR-positive NSCLC. Chemotherapy-based treatment is generally not used to treat BM, mainly because the blood-brain barrier prevents the penetration of chemotherapy drugs into the brain, resulting in limited efficacy [5]. The first-generation TKI has a low brain penetration rate and a low response rate to the treatment of BMs. Compared with the first-generation TKI, Osimertinib has become the first-line TKI of choice for the treatment of NSCLC with BMs due to its tolerability, prolonged Progression-Free Survival (PFS) and higher brain penetration [6]. A group of multi-center clinical trials showed that the clinical response rate and disease control rate of Osimertinib in the treatment of NSCLC with BMs reached 91% and 95%, respectively [7]. Unfortunately, in the patient reported now, neither the Gefitinib nor the Osimertinib have been able to prevent disease progression. This may be related to the heterogeneity of lung cancer and genetic

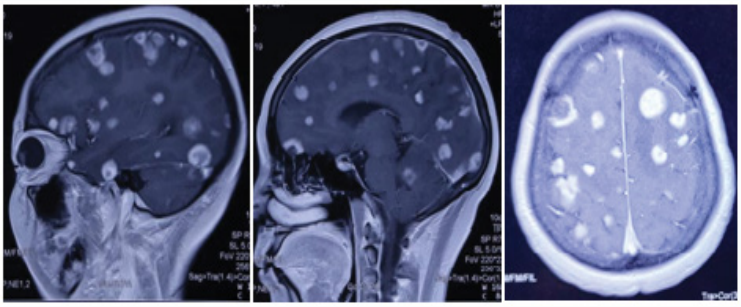

Figure 3: Re-examination of MRI after WBRT showed that the number and size of metastases in the brain increased explosively, covering the entire brain.

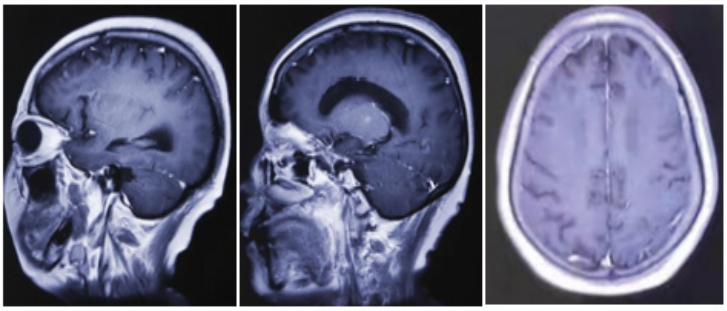

Figure 4: MRI was rechecked at 2 months after the start of hydrogen inhalation, and more than 90% of the patient's brain metastases had disappeared.

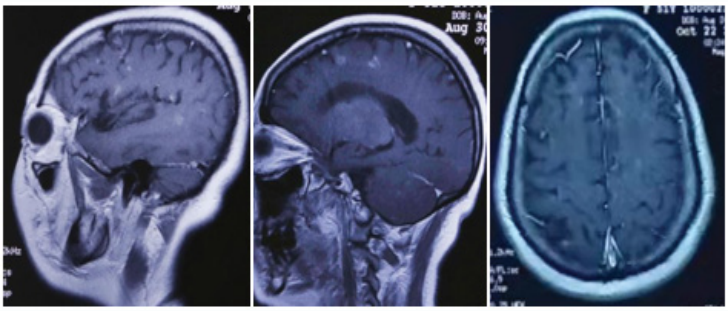

Figure 5: Follow-up 15 months after the start of hydrogen inhalation, the patient's brain metastases are still stable.

instability [8,9]. The original EGFR mutation of this patient turned negative during the reexamination, indicating that the genotype of the tumor has changed, which may be the cause of the failure of the above-mentioned TKI treatment.

The patient's systemic state and brain metastasis progression showed a direct correlation in time with WBRT. As mentioned earlier, for cancer treatment, radiation therapy is a double-edged sword. On the one hand, radiotherapy is an important local control method for many cancers. On the other hand, radiation can promote the growth and invasion of cancer cells, especially metastasis [10]. A large amount of evidence from in vivo and *in vitro* experiments indicates that ionizing radiation applied to cancer cells or host cells, tumors, the entire host, or putative tumor development sites may stimulate the metastasis process.

More than 60 years ago, Kaplan and Murphy [11] showed the local roentgen irradiation increased frequency of pulmonary metastasis in a transplantable mouse carcinoma. In 1988, Milas et al. [12] reported that most tumors growing in irradiated tissues have an increased propensity to metastasize, which is linked to their manifestation of Tumor Bed Effect (TBE). Some randomized and non-randomized clinical studies have reported that radiotherapy promotes metastasis in hepatocellular carcinoma or head and neck cancer [13-17]. Martin et al. [18] identified increased Circulating Tumor Cells (CTC) numbers singly and in clumps in large numbers in patients treated with palliative or curative-intent radiotherapy.

The mechanisms of pro-metastatic effect of radiation are not fully understood, Cui et al. [19] showed that radiation up-regulate the expression of Granulocyte-Colony-Stimulating Factor (G-CSF) and transducing its intracellular signal transduction JAK/STAT3 (Janus kinase/signal transduction), trigger the Epithelial-Mesenchymal Cell Transformation (EMT) of NSCLC. Cancer cells that undergo EMT have been shown to acquire stemness and undergo metabolic changes, promoting metastasis and invasion [20-22]. Further research shows that radiation can increase the production of Reactive Oxygen Specie (ROS), which can mediate most of the biological effects of radiation itself, and is closely related to tumorigenesis and tumor progression [23-25]. There is evidence that ROS have been implicated in radiation-induced EMT, via activation of several EMT transcription factors [26].

Based on the role of ROS in promoting metastasis by radiation, it is not difficult to understand that hydrogen inhalation can reverse

the progression of brain metastasis in this case. In fact, the ability of hydrogen to control cancer should be traced back to 1975, when Dole et al. [27] reported the successful treatment of transplanted skin squamous epithelial carcinoma in mice by inhalation of a mixture of hydrogen and oxygen (97.5% H_2 and 2.5% O_2) at 8 atmospheres. But this major discovery seemed to have been forgotten until 2007, when Oshawa et al. [28] reported that hydrogen could ameliorate cerebral ischemia-reperfusion injury by selectively reducing cytotoxic ROS, including hydroxyl radical (•OH) and peroxynitrite (ONOO-), provoking a worldwide attention. Now it has known that hydrogen gas has a great value as a therapeutic agent for a variety of illnesses, including cancer [29-31].

In 2019, our team [32], took the lead in reporting a retrospective and prospective follow-up study of 82 patients with stage III and IV cancers undergoing hydrogen inhalation therapy, including 22 cases of NSCLC with or without brain metastases. The results showed that inhaled hydrogen (66% H_2 And 34% O_2) can improve the quality of life of patients and control cancer progression. According to our research results, hydrogen inhalation seems to have a unique effect on NSCLC with brain metastases. There is a 44-year-old female patient with NSCLC who has multiple intracranial metastases, and has hydrocephalus in the third and lateral ventricles, as well as bone, adrenal glands, and liver metastases. In the case of failure of conventional treatment, the patient only receives hydrogen and oxygen inhalation therapy. Four months later, the brain tumors significantly shrunk, and the amount of hydrocephalus in the third and lateral ventricles was significantly reduced. One year later, all brain tumors disappeared, liver, lung and other organs metastasis were stable. Tumor markers that were increased before treatment returned to normal range [33].

The mechanism of hydrogen inhibiting cancer has been studied in a series of experiments, and it has been found that hydrogen molecules can inhibit the viability, migration and invasion of cancer cells, and catalyzed cell apoptosis and induced cancer cells G2/M arrest [34-36]. Liu et al. [34] suggested that H_2 can promote lung cancer cell apoptosis via inhibiting the activation of STAT3/Bcl2 signaling. Meng et al. [37] found that H_2 treatment resulted in a decrease in the expression levels of CD47 and cell division control protein 42 (CDC42) in a dose-dependent manner. CD47 is a transmembrane glycoprotein that mediates "self/don't eat me" signal by inhibiting macrophage phagocytosis, and is frequently up-regulated in a variety of cancers, including NSCLC. Wang et al. [38] showed that H_2 down-regulates the expression of a regulator for chromosome condensation, that is, structural maintenance of chromosomes $(SMC)_3$, SMC_5 and SMC_6, and reduces the expression of cyclin D1, CDK4 and CDK6, thereby inhibiting lung cancer progression.

In addition, the better effect of hydrogen on brain metastasis may also be related to its physical properties. Hydrogen molecules are the smallest and highly dispersed, which makes it easy to penetrate the blood-brain barrier into the brain [31].

The inhibitory effect of hydrogen on NSCLC may also be related to its immune regulation. Akagi and baba [39] have confirmed that hydrogen gas inhalation in NSCLC patients can decrease the abundance of exhausted terminal PD1+CD8+ T cells, increased that of active terminal PD1+CD8+T cells, maintain the balance between terminal PD1+ and PD1+CD8+ T cells. Our research [40], showed that two weeks of hydrogen inhalation in 20 NSCLC patients induced decrease of number of exhausted and aging cytotoxic T cells, and the abnormally decreased lymphocyte subsets, including functional helper and cytotoxic T cells, natural killer T cells, and γδ T2cells, tended to be normal. It is particularly important that we [41], observed a case of metastatic gallbladder cancer patient who only received hydrogen inhalation therapy. Before significant improvement was achieved, the tumor and tumor markers not only did not improve, but "worsened", and showed "false progress". Pseudo progression is considered to be a special remission mode that occurs after PD-1 antibody treatment [42], and it may be that cytotoxic T cells infiltrate the tumor and cause edema and necrosis, suggesting immune activation. The similar reaction of hydrogen shows that it has the effect of activating anti-tumor immunity. Unfortunately, we did not follow up the immune status of the NSCLC patient reported now.

In the treatment of cancer with hydrogen, there is no controlled study as to whether it is advisable to inhale pure hydrogen or a mixture of hydrogen and oxygen. There is no evidence that oxygen itself inhibits cancer, but hypoxia will definitely promote the invasion and metastasis of cancer cells. The smallest hydrogen molecules can carry larger molecules of oxygen into the deep tissues [43]. It has been reported that hydrogen can improve the flexibility of red blood cells and enable them to transport oxygen into the capillaries in the final organs, thereby improving the tumor hypoxia and reducing the cancer promotion effect caused by hypoxia [44].

Conclusion

We report here a case of NSCLC with multiple metastases with a very special clinical course. After whole-brain irradiation, brain metastasis increased explosively, and miraculously improved after inhalation of hydrogen (hydrogen and oxygen) only. Although it is difficult to be sure that hydrogen can completely control the disease, at least when the patient is in a critical state, it reverses the condition and provides an opportunity for further treatment.

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Author Contribution

Project administration: Kecheng Xu; Clincal Supervision: Wei Qian, Juan Zhen; Data collection: Tianyu Lu; Writing - original draft: Kecheng Xu; Co-author: Juanjuan Shi; Review & editing: Xiaofeng Kong

References

1. Ulahannan D, Khalifa J, Faivre-Finn C, Lee SM. Emerging treatment paradigms for brain metastasis in non-small-cell lung cancer: an overview of the current landscape and challenges ahead. Ann Oncol. 2017;28(12):2923-31.
2. Ernani V, Stinchcombe TE. Management of brain metastases in non-small-cell lung cancer. J Oncol Pract. 2019;15(11):563-70.
3. Errico A. Radiotherapy: A double-edged sword for NSCLC? Nat Rev Clin Oncol. 2014;11(2):66.
4. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC•3): A multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 2017;18(8):1049-60.
5. Ernani V, Stinchcombe TE. Management of brain metastases in non-small-cell lung cancer. J Oncol Pract. 2019;15(11):563-70.
6. Ballard P, Yates JW, Yang Z, Kim DW, Yang JCH, Cantarini M, et al. Preclinical comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity. Clin Cancer Res. 2016;22(20):5130-40.

7. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med. 2018;378(2):113-25.

8. Errico A. Lung cancer: Heterogeneity in space and time. Nat Rev Clin Oncol. 2014;11(12):684.

9. de Bruin EC, McGranahan N, Mitter R, Salm M, Wedge D, Yates L, et al. Spatial and temporal diversity in genomic instability processes defines lung cancer evolution. Science. 2014;346(6206):251-6.

10. Sundahl N, Duprez F, Ost P, De Neve W, Mareel M. Effects of radiation on the metastatic process. Mol Med. 2018;24(1):16.

11. Kaplan HS, Murphy ED. The effect of local roentgen irradiation on the biological behavior of a transplantable mouse carcinoma; increased frequency of pulmonary metastasis. J Natl Cancer Inst. 1949;9(5-6):407-13.

12. Milas L, Hirata H, Hunter N, Peters LJ. Effect of radiation-induced injury of tumor bed stroma on metastatic spread of murine sarcomas and carcinomas. Cancer Res. 1988;48(8):2116-20.

13. Chung YL, Jian JJ, Cheng SH, Tsai SYC, Chuang VP, Soong T, et al. Sublethal irradiation induces vascular endothelial growth factor and promotes growth of hepatoma cells: implications for radiotherapy of hepatocellular carcinoma. Clin Cancer Res. 2006;12(9):2706-15.

14. Chia-Hsien Cheng J, Chuang VP, Cheng SH, Lin YM, Cheng TI, et al. Unresectable hepatocellular carcinoma treated with radiotherapy and/or chemoembolization. Int J Cancer. 2001;96(4):243-52.

15. Nozue M, Isaka N, Fukao K. Over-expression of vascular endothelial growth factor after preoperative radiation therapy for rectal cancer. Oncol Rep. 2001;8(6):1247-9.

16. Schantz SP, Peters LJ. Patterns of recurrence from head and neck cancer. An immunologic perspective. Am J Clin Oncol.1987;10(6):469-74.

17. Strong MS, Vaughan CW, Kayne HL, Aral IM, Ucmakli A, Feldman M, et al. A randomized trial of preoperative radiotherapy in cancer of the oropharynx and hypopharynx. Am J Surg. 1978;136(4):494-500.

18. Martin OA, Anderson RL, Russell PA, Cox RA, Ivashkevich A, Swierczak A, et al. Mobilization of viable tumor cells into the circulation during radiation therapy. Int J Radiat Oncol Biol Phys. 2014;88(2):395-403.

19. Cui YH, Suh Y, Lee HJ, Yoo KC, Eddin N, Jeong YJ, et al. Radiation promotes invasiveness of non-small-cell lung cancer cells through granulocyte-colony-stimulating factor. Oncogene. 2015;34(42):5372-82.

20. Dave B, Mittal V, Tan NM, Chang JC. Epithelial-mesenchymal transition, cancer stem cells and treatment resistance. Breast Cancer Res. 2012;14(1):202.

21. Marie-Egyptienne DT, Lohse I, Hill RP. Cancer stem cells, the epithelial to mesenchymal transition (EMT) and radioresistance: potential role of hypoxia. Cancer Lett. 2013;341(1):63-72.

22. Chang L, Graham PH, Hao J, Bucci J, Cozzi PJ, Kearsley JH, et al. Emerging roles of radioresistance in prostate cancer metastasis and radiation therapy. Cancer Metastasis Rev. 2014;33(2-3):469-96.

23. Kam WW, Banati RB. Effects of ionizing radiation on mitochondria. Free Radic Biol Med. 2013;65:607-19.

24. Leach JK, Van Tuyle G, Lin PS, Schmidt-Ullrich R, Mikkelsen RB. Ionizing radiation-induced, mitochondria-dependent generation of reactive oxygen/nitrogen. Cancer Res. 2001;61(10):3894-901.

25. Tulard A, Hoffschir F, de Boisferon FH, Luccioni C, Bravard A. Persistent oxidative stress after ionizing radiation is involved in inherited radiosensitivity. Free Radic Biol Med. 2003;35(1):68-77.

26. Lee SY, Jeong EK, Ju MK, Jeon HM, Kim MY, Kim CH, et al. Induction of metastasis, cancer stem cell phenotype, and oncogenic metabolism in cancer cells by ionizing radiation. Mol Cancer. 2017;16(1):10.

27. Dole M, Wilson FR, Fife WP. Hyperbaric hydrogen therapy: a possible treatment for cancer. Science. 1975;190(4210):152-4.

28. Ohsawa I, Ishikawa M, Takahashi K, Watanabe M, Nishimaki K, Yamagata K, et al. Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. Nat Med. 2007:13(6):688-94.

29. Ohno K, Ito M, Ichihara M, Ito M. Molecular hydrogen as an emerging therapeutic medical gas for neurodegenerative and other diseases. Oxid Med Cell Longev. 2012;2012:353152.

30. Iida A, Nosaka N, Yumoto T, Knaup E, Naito H, Nishiyama C, et al. The clinical application of hydrogen as a medical treatment. Acta Med Okayama. 2016;70(5):331-7.

31. Liu MY, Xie F, Zhang Y, Wang TT, Ma SN, Zhao PX, et al. Molecular hydrogen suppresses glioblastoma growth via inducing the glioma stem-like cell differentiation. Stem Cell Res Ther. 2019;10(1):145.

32. Chen JB, Kong XF, Lv YY, Qin SC, Sun XJ, Mu F, et al. Real world survey" of hydrogen-controlled cancer: a follow-up report of 82 advanced cancer patients. Med Gas Res. 2019;9(3):115-21.

33. Chen J, Mu F, Lu T, Du D, Xu K. Brain metastases completely disappear in non-small cell lung cancer using hydrogen gas inhalation: A case report. Onco Targets Ther. 2019;12:11145-51.

34. Liu L, Yan Z, Wang Y, Meng J, Chen G. Suppression of autophagy facilitates hydrogen gas-mediated lung cancer cell apoptosis. Oncol Lett. 2020;20(4):112.

35. Wu Y, Yuan M, Song J, Chen X, Yang H. Hydrogen Gas from Inflammation Treatment to Cancer Therapy. ACS Nano. 2019;13(8):8505-11.

36. Yang Y, Liu PY, Bao W, Chen SJ, Wu FS, Zhu PY. Hydrogen inhibits endometrial cancer growth via a ROS/NLRP3/caspase-1/GSDMD-mediated pyroptotic pathway. BMC Cancer. 2020;20(1):28.

37. Meng J, Liu L, Wang D, Yan Z, Chen G. Hydrogen gas represses the progression of lung cancer via down-regulating CD47. Biosci Rep. 2020;40(4):BSR20192761.

38. Wang D, Wang L, Zhang Y, Zhao Y, Chen G. Hydrogen gas inhibits lung cancer progression through targeting SMC3. Biomed Pharmacother. 2018;104:788-97.

39. Akagi J, Baba H. Hydrogen gas activates coenzyme Q10 to restore exhausted CD8+ T cells, especially PD-1+Tim3+terminal CD8+ T cells, leading to better nivolumab outcomes in patients with lung cancer. Oncol Lett. 2020;20(5):258.

40. Chen JB, Kong XF, Qian W, Mu F, Lu TY, Lu YY, et al. Two weeks of hydrogen inhalation can significantly reverse adaptive and innate immune system senescence patients with advanced non-small cell lung cancer: a self-controlled study. Med Gas Res. 2020;10(4):149-154.

41. Chen J, Mu F, Lu T, Ma Y, Du D, Xu K. A gallbladder carcinoma patient with pseudo-progressive remission after hydrogen inhalation. Onco Targets Ther. 2019;12:8645-51.

42. Cohen JV, Alomari AK, Vortmeyer AO, Jilaveanu LB, Goldberg SB, Mahajan A, et al. Melanoma brain metastasis pseudoprogression after pembrolizumab treatment. Cancer Immunol Res. 2016;4(3):179-82.

43. Zhou ZQ, Zhong CH, Su ZQ, Li XY, Chen Y, Chen XB, et al. Breathing hydrogen-oxygen mixture decreases inspiratory effort in patients with tracheal stenosis. Respiration. 2019;97(1):42-51.

44. Özer A, Arslan M, Çomu FM, Küçük A, Mardin B, Koçak B, et al. The effect of hydrogen-rich saline solution on erythrocyte deformability in power limb ischemia reperfusion injury in rats. GMJ. 2021;32(2A):270-2.