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Case Report

Multiple brain metastases from nasopharyngeal carcinoma: a case report and literatures review

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Abstract: Although direct intracranial invasion is common in patients with nasopharyngeal carcinoma (NPC), multiple brain metastases from NPC is extremely rare. In this case, the clinical features, imaging, pathological findings, treatment outcomes, prognosis of an NPC patient with brain metastasis are described. Combining the clinical symptoms with auxiliary examination, the disease more likely to be originated from lung at first. Multiple biopsies confirmed that the primary lesions was nasopharynx finally. This is the first case of a patient with brain and lung metastasis from NPC that mimicked as a lung cancer. We also retrospectively reviewed the medical records of about 3200 patients with NPC treated in our hospital during 30 years and review relevant literatures from PUB-MED database. In summary, multiple brain metastases from NPC is extremely rare, and radiotherapy of brain lesions is an important auxiliary treatment besides the systematic therapy. The ultimate survival time depends on the effects from the chemotherapy and the control of extra-cranial disease.

Keywords: Nasopharyngeal carcinoma, multiple brain metastasis, lung metastasis, immunohistochemistry, treatment, prognosis

Introduction

Nasopharyngeal carcinoma (NPC) is endemic in Southeast Asia compared with Western countries. During the past decade, the incidence of NPC is gradually declining, even in some endemic regions, and mortality from the disease has fallen substantially [1]. Race, genetics, environment and Epstein-Barr virus (EBV) all play a role in the pathogenesis of NPC [2]. NPC has a propensity to cause distant metastasis; the most common sites of distant metastasis are the bone, lung and liver [3]. Maximizing the local control and minimizing the risk of distant metastasis and late complications should be the main objectives in clinical work [4]. The presence of hepatic metastases, short metastasis free interval, and older age at presentation significantly predicted short survival after the diagnosis of distant metastasis from NPC [5]. Because of nasopharyngeal anatomical location, NPC with direct extension to the brain is not rare, but true brain metastasis of NPC is exceedingly uncommon [6-9]. The prognosis of NPC patients with brain metastasis is poor, which was depended on age, surgical excision and synchronous metastases, the survival generally does not exceed 6 months [10]. Here, we reported a case of brain and lung metastasis from NPC which only appeared with the symptoms of thoracic diseases.

Case report

A 49-year-old Chinese man was admitted to West China Hospital of Sichuan University, complaining of cough and expectoration for more than 1 months, and got deteriorated with accompanying bloody aputum and emptysis which was not alleviated with anti-inflammation treatment. The patient did not have epistaxis, rhinostegnosis, facial numbness, diplopia, headache and vomit. None of positive signs were found upon physical examinations. Decreased breathing sound was found in his left lung.

Chest computed tomography (CT) showed soft tissues at the right hilum and left lower lobe

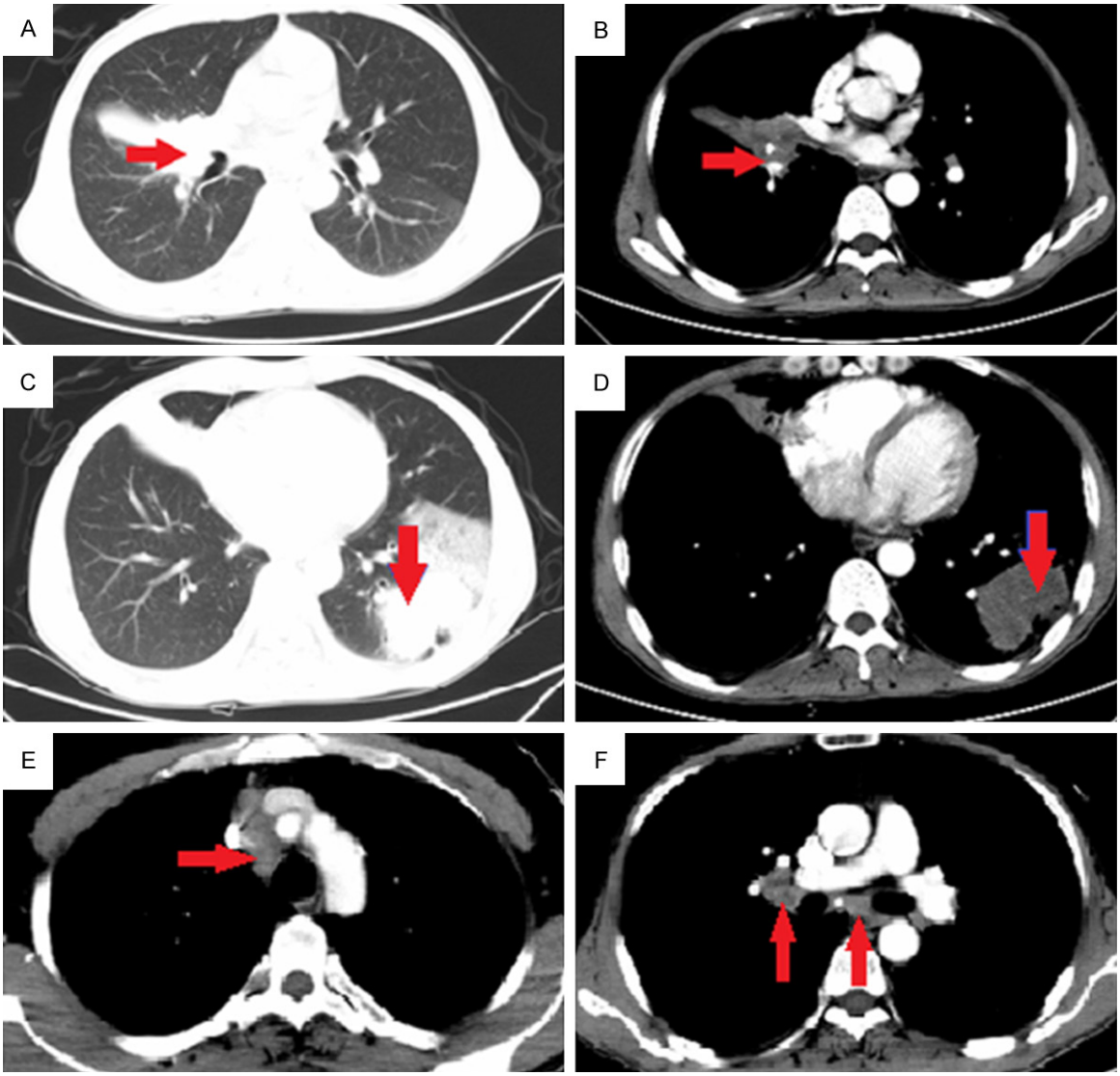

Figure 1. Chest computed tomography (CT) showed soft tissues at the right hilum (aboat 3.8 × 3.6 cm, A: Lung window, B: Mediastinum window) and left lower lobe (aboat 6.3 × 4.2 cm, C: Lung window, D: Mediastinum window) with enlarged hilum and mediastinum lymph nodes (E, F).

with enlarged hilum and mediastinum lymph nodes (**Figure 1**). The head magnetic resonance imaging (MRI) was performed, which showed multiple ring-enhancement lesions at left occipital lobe and bilateral parietal and frontal lobe (**Figure 2**). However, partial views of head MRI revealed incrassate tissue of right pharyngeal recess. In order to define the position and scope of lesion, the nasopharyngeal MRI was perfomed. It showed right pharyngeal recess disappeared and was coveraged with soft tissue. Enlarged retropharyngeal space and cervical lymph nodes also can be detected (**Figure 3**).

Bronchoscopy detected a strip of neoplasm at the orifice of the right middle bronchus. Immunohistochemical staining of tumor cells demonstrated: CD5/6(+), P63(+), P40(+), CK7(-), TTF-1(-), ALK-V(-), ROS-1(-). The pharyngorhinoscopy and needle biopsy comfirmed its neoplasmtic nature. The Immunohistochemical staining of tumor cells showed CK(-), P63(+), S-100(-), Ki67(+, 40%) in situ hybridization EBER1/2(+), indicating it was the non-keratinizing carcinoma (**Figure 4**). Then the pathologist comfirmed EBER (partial +) in the tissue from the bronchoscopy. From these results, it can be concluded that the primary lesion was nasophar-

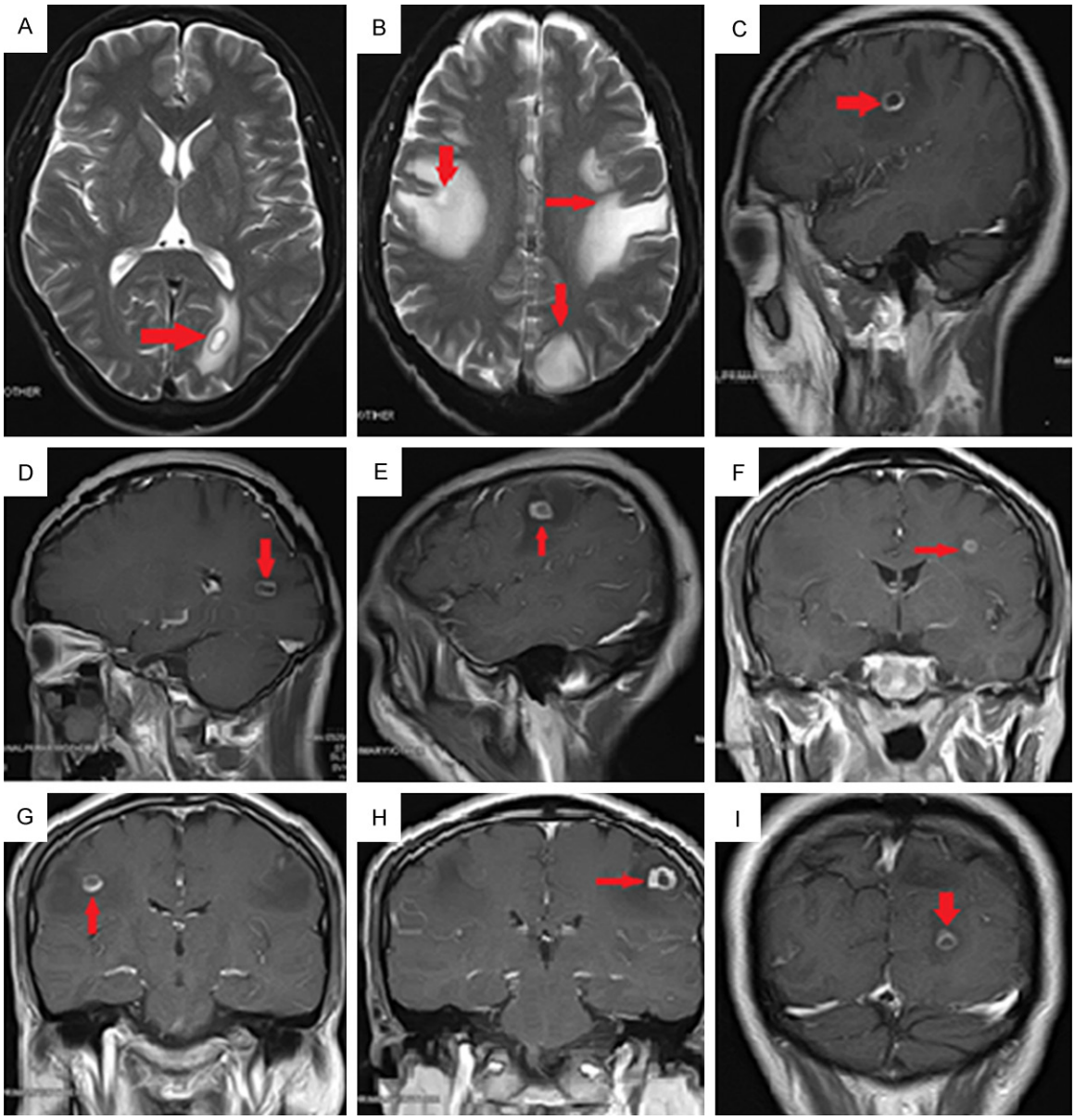

Figure 2. Head magnetic resonance imaging (MRI) showed multiple ring-enhancement lesions at left occipital lobe and bilateral parietal and frontal lobe (arrows, A, B: Axial views; C-E: Sagittal views; F-I: Coronal views).

ynx. Finally, The patient was diagnosed with nasopharyngeal non-keratinising squamous carcinoma accompanying with pharyngeal and mediastinum lymph nodes, bilateral lung, multiple brain metastases, T1N1M1b, stage IV [11].

Because that none of symtoms caused by brain metastasis was observed and the performance status of the patient was 2, the chemotherapy with Paclitaxel plus Cisplatin was performed after diagnosis, and the whole brain radiation therapy (WBRT) was acheduled. During chemotherapy process, the patient deteriorated with the thoracic symptoms rapidly and refused further anti-tumor treatment, only received best suppotive care, especially hemostatics. The patient finally died 4 months later from the diagnosis of NPC. He died of terminal massive hemoptysis and respiratory failure. Slight neurologic symptoms were observed, but no progressive nasopharyngeal symptoms were observed before his demise.

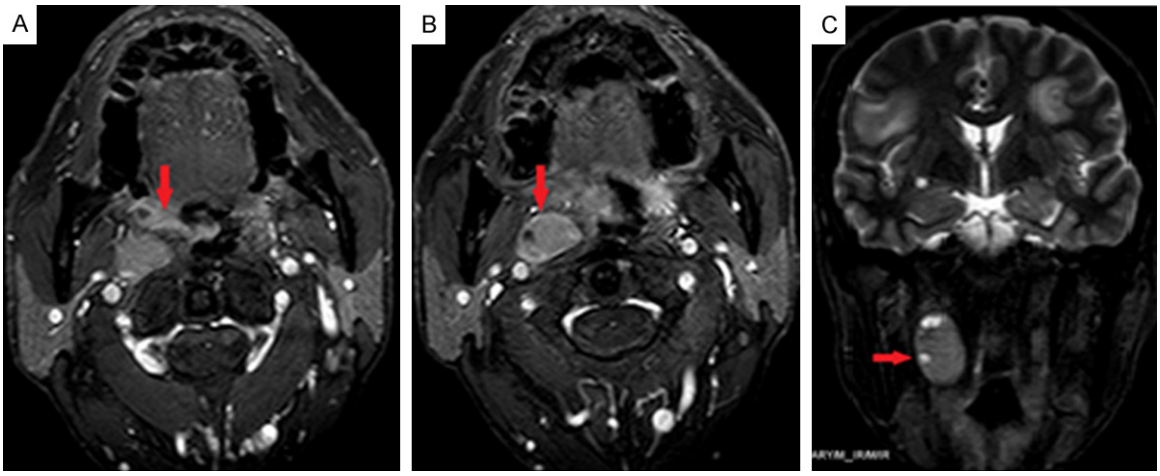

Figure 3. Nasopharyngeal magnetic resonance imaging (MRI) in (A, B) axial and (C) coronal views showed right pharyngeal recess disappeared and was coveraged with soft tissue. Enlarged retropharyngeal space and cervical lymph nodes also can be detected (arrows).

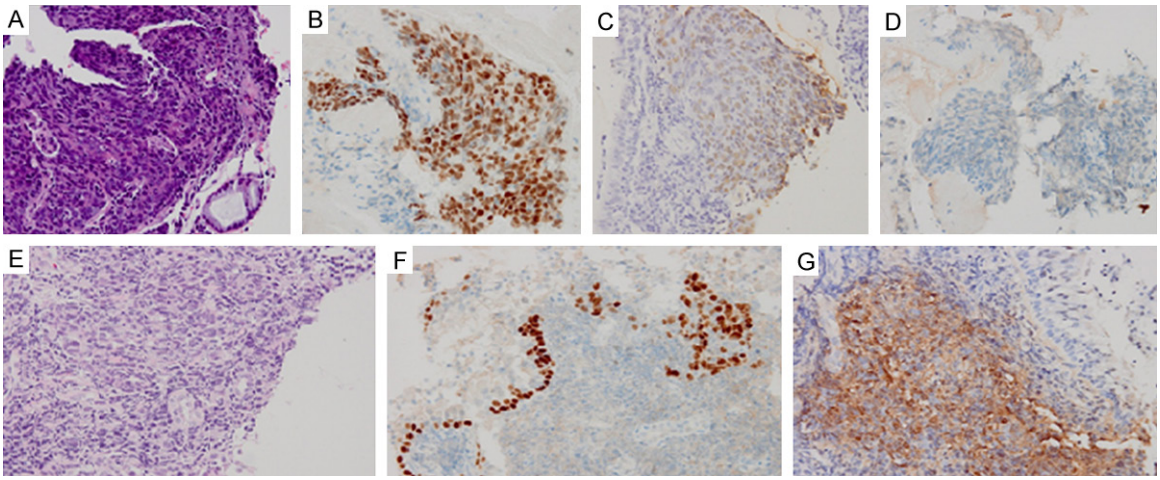

Figure 4. Photomicrographs of lung tumour cells (A-D) show (A) non-keratinising carcinoma (Haematoxylin & eosin, original magnification × 400), (B) Positive P63 staining in tumour cells (original magnification × 400), (C) positive Epstein-Barr virus-encoded RNA staining in tumour cells on in situ hybridisation (original magnification × 400) and (D) negative TTF-1 staining in tumour cells (original magnification × 400). Photomicrographs of nasopharyngeal tumour cells (E, F) show (E) non-keratinising carcinoma (Haematoxylin & eosin, original magnification × 400), (F) positive P63 staining in tumour cells (original magnification × 400) and (G) positive Epstein-Barr virus-encoded RNA staining in tumour cells on in situ hybridisation (original magnification × 400).

Discussion

This is the first case reported a patient with brain and lung metastasis from NPC that mimicked as the lung cancer at first, and multiple biopsies confirmed primary lesions was nasopharynx finally. Sometimes, it is easy to misdiagnose in practice. Missed diagnosis might cause the diseases deteriorated quickly or lead to other serious consequences. In clinical practice, we should keep in mind the possibility of NPC brain and lung metastasis patient only appeared with the symptoms of thoracic diseases.

In order to obtain more insight on incidence, clinical features, natural course, and treatment results of NPC with brain metastasis. We retrospectively reviewed the medical records of about 3200 patients with nasopharyngeal carcinoma treated in our hospital during 30 years (between 1985 and 2015). Patients with direct extension to the brain are excluded. Among them, 6 patients had been identified with brain

Table 1. Brain metastasis from nasopharyngeal carcinoma in our hospital

Case	Gender/age	IT*	Brain metastasis	Metastasis†	Treatment after brain metastasis	Chemotherapy regime	Treatment response‡	ST§
1	Male/62	96	Multiple	None	WBRT, chemotherapy	Cisplatin+5-Fu*4	SD	2
2	Male/48	24	Oligo	Lung, bone	BSC¶	None	NA#	1
3	Male/59	84	Multiple	None	Surgery, WBRT, chemotherapy	Paclitaxel+Cisplatin*6	SD	9
4	female/42	17	Multiple	Lung, thyroid	BSC	None	NA	1
5	Male/43	72	Single	Lung, bone	Gamma knife, chemotherapy	Irinotecan+S-1*8	PR	46
Present	Male/49	0	Multiple	Lung, Mediastinum Lymph nodes	Chemotherapy+BSC	Paclitaxel+Cisplatin*2	SD	4

*Interval time between diagnosis of NPC and brain metastases in months; †Systemic metastasis at the time of brain metastasis diagnosis; ‡According to the RESIST criteria [12]; §Survival time after the diagnosis of brain metastases; #Not available; ¶Best supportive care.

Table 2. Brain metastasis from nasopharyngeal carcinoma from PUB-MED database

Case	Gender/age	IT*	Brain metastasis	Metastasis†	Treatment after brain metastasis	Chemotherapy regime	Treatment response‡	ST§
Liaw [6]	Male/69	0	Multiple	Bone	WBRT+chemotherapy	NA#	NA#	NA
Ngan [7]	Male/33	56	Single	Cervical lymph nodes	Surgery+chemotherapy	Vincristine+5-Fu+Cyclophosphamide+Mthotrexate*2	PD	6
Ozyar [9]	Male/41	45	Single	Lung	Surgery+WBRT	None	SD	NA
Orit [8]	Male/54	7	Single	Petrous bone	WBRT	None	PD	NA
Rafee [14]	NA	7	Multiple	Lung	WBRT+chemotherapy	Carboplatin+5-FU*4	PR	NA

*Interval time between diagnosis of NPC and brain metastases in months; †Systemic metastasis at the time of brain metastasis diagnosis; ‡According to the RESIST criteria [12]; §Survival time after the diagnosis of brain metastases; #Not available.

metastasis. Their information is shown in **Table 1**. We evaluate the treatment response according to the RESIST criteria [12]. SPSS statistical software (version 19.0) was used to calculate median time and corresponding 95% confidence intervals (CIs).

The interval time between the diagnosis of NPC and brain metastases is among 0-96.0 months, and the median interval time of all patients is 48 months (95% CI 20.5-76.0 months). The patients' survival time after brain metastasis is among 1.0-46.0 months, the median survival time is about 3.0 months (95% CI 1.7 -25.2 months). Among them, two patients' performance status worsened rapidly after they had brain metastases. Both of them were accompanied by disease recurrences in multiple sites and lost in our follow-up.

It's worth mentioning that one patient's survival time after brain metastasis is 46 months. This patient had lung metastasis and progressive nasopharyngeal lesion 64 mouths after the diagnosis of NPC. We treated him with chemotherapy of Docetaxel and Oxaliplatin. However, a new cerebellum metastasis (about 1.1*1.7 cm) was observed after 8 months from the diagnosis of lung metastasis. It has been concluded that in patients with a single or less than three, small sized brain metastasis, Gamma knife treatment was less invasive, and it could control local tumor as effectively as surgery plus postoperative whole brain irradiation (WBRT) in a randomized controlled multicentre phase III trial [13]. So, the patient had received Gamma-knife therapy. In order to control the systematic metastasis of NPC, we treated the patient with multi-line chemotherapy, including Taxol plus Oxaliplatin, Vinorelbine plus Cisplatine, Etoposide alone after his disease progression each time. Finally, the thoracic disease became refractory, and the patient died after 46 months from the diagnosis of brain metastasis. The symptoms of brain and nasopharyngeal didn't worsen before he died.

Furthermore, we conducted a systematic search in the PUB-MED databases to identify all reports that contained nasopharyngeal carcinoma with brain metastases. Only 5 reports are identified, as shown in **Table 2**. The interval time between the diagnosis of NPC and brain metastases is among 0.0-56.0 months, and the median interval time of these patients is 7 months (95% CI 4.2-44.0 months).

Only Ngan et al [7] recorded the patient's survival time after the diagnosis of brain metastasis, it was 6.0 months. This patient had left occipital lobe metastasis after 2 cycles chemotherapy consisting of vincristine, 5-fluorouracil, cyclophosphamide, and methotrexate which was used to control the lung metastases. Then a neuro-surgery was performed to remove the brain tumor. However, the thoracic disease progressed gradually after the craniotomy. The patient died 6 months later from the diagnosis of brain metastasis. The authors believed that no matter radiotherapy or not, patients with CNS metastasis can achieve good symptom and disease control after surgery, and the ultimate survival depends on the control of extracranial disease after aggressive therapy.

Rafee et al [14] presented a patient achieving good response to the treatment. This patient had leptomeningeal disease and multiple brain metastasis eight months after treatment of primary NPC. Palliative radiotherapy was administered to the spine and brain, and palliative chemotherapy with Carboplatin and 5-FU infusion every three weeks, with Cetuximab weekly and intrathecal Cytarabine infusion every two weeks. After six cycles of treatment, MRI revealed a significant improvement with near resolution of intracranial metastases.

For the first time, we reported a patient with multiple brain and lung metastases from NPC who was admitted with pulmonary symptoms. The lung metatases of this patient were not multiple small nodular lesions in peripheral pulmonary. There were massive lesions in bilateral hilus, so the symptoms of bloody aputum and emptysis were observed at first. As we know, platinum-based chemotherapy is the recommended as the first-line treatment for metastatic NPC, but no standard treatment regimens have been established. Chen et al [15] reported a triplet combination chemotherapy with paclitaxel, cisplatin and 5-FU was an effective and safe option to improve the response rate and prolong OS among these pateints. However, Jin et al [16] considered that the three-drug combined regimens brought more toxicity without survival benefits, cisplatin-based doublets may be the more appropriate choice as the first-line treatment for patients

with metastatic NPC. The platinum-based doublet regimens also could achieve the response rates of 70-80% [1]. Because the performance score of this patient was 2 and accompanied with obvious emptysis, we considered the patient might not tolerate a triplet combination chemotherapy and choosed TP regimen (Paclitaxel and Cisplatin). During chemotherapy process, the patient deteriorated with the thoracic symptoms rapidly and died of terminal massive hemoptysis and respiratory failure finally.

Conclusion

Based on literatures review, it could be concluded that multiple brain metastases from NPC is extremely rare. Systematic therapy is the main treatment method, and radiotherapy of brain lesions is an important auxiliary treatment method. The prognosis of NPC patients with brain metastasis is poor. The ultimate survival time depends on the reaction to chemotherapy and the control of extra-cranial disease.

Disclosure of conflict of interest

None.

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References

[1] Chua ML, Wee JT, Hui EP, Chan AT. Nasopharyngeal carcinoma. Lancet 2016; 387: 1012-1024.

[2] Thompson LD. Update on nasopharyngeal carcinoma. Head Neck Pathol 2007; 1: 81-86.

[3] Huang CJ, Leung SW, Lian SL, Wang CJ, Fang FM, Ho YH. Patterns of distant metastases in nasopharyngeal carcinoma. Kaohsiung J Med Sci 1996; 12: 229-234.

[4] Leung TW, Tung SY, Sze WK, Wong FC, Yuen KK, Lui CM, Lo SH, Ng TY, O SK. Treatment results of 1070 patients with nasopharyngeal carcinoma: an analysis of survival and failure patterns. Head Neck 2005; 27: 555-565.

[5] Teo PM, Kwan WH, Lee WY, Leung SF, Johnson PJ. Prognosticators determining survival subsequent to distant metastasis from nasopharyngeal carcinoma. Cancer 1996; 77: 2423-2431.

[6] Liaw CC, Ho YS, Koon-Kwan NG, Chen TL, Tzann WC. Nasopharyngeal carcinoma with brain metastasis: a case report. J Neurooncol 1994; 22: 227-230.

[7] Ngan RK, Yiu HH, Cheng HK, Chan JK, Sin VC, Lau WH. Central nervous system metastasis from nasopharyngeal carcinoma: a report of two patients and a review of the literature. Cancer 2002; 94: 398-405.

[8] Kaidar-Person O, Kuten J, Atrash F, Billan S, Kuten A. Brain metastasis of nasopharyngeal carcinoma: a case report and literature review. Case Rep Med 2012; 2012: 405917.

[9] Enis O, Gozde Y, Gaye T, Aysenur C. Undifferentiated nasopharyngeal carcinoma with isolated central nervous system metastasis. Arch Oncol 2004; 12: 121-123.

[10] Elloumi F, Ben AM, Ghorbel L, Mnif H, Boudawara T, Ghorbel AM, Frikha M, Daoud J. [Clinical aspects of brain metastases from nasopharyngeal carcinoma]. Cancer Radiother 2013; 17: 768-770.

[11] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010; 17: 1471-1474.

[12] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92: 205-216.

[13] Muacevic A, Wowra B, Siefert A, Tonn JC, Steiger HJ, Kreth FW. Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial. J Neurooncol 2008; 87: 299-307.

[14] Rafee S, Elamin YY, Cronin K, Brennan S, Osman N. A rare case of nasopharyngeal carcinoma with widespread CNS metastases. Ir Med J 2014; 107: 180-181.

[15] Chen C, Wang FH, An X, Luo HY, Wang ZQ, Liang Y, Zhang L, Li YH. Triplet combination with paclitaxel, cisplatin and 5-FU is effective in metastatic and/or recurrent nasopharyngeal carcinoma. Cancer Chemother Pharmacol 2013; 71: 371-378.

[16] Jin Y, Shi YX, Cai XY, Xia XY, Cai YC, Cao Y, Zhang WD, Hu WH, Jiang WQ. Comparison of five cisplatin-based regimens frequently used as the first-line protocols in metastatic nasopharyngeal carcinoma. J Cancer Res Clin Oncol 2012; 138: 1717-1725.