

Case Report

Nasopharyngeal carcinoma with metastasis to the central nervous system: a report of two patients and review of the literature

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Abstract: Nasopharyngeal carcinoma (NPC) is a particularly prevalent carcinoma in southern China. Central nervous system (CNS) metastasis is an infrequent lesion of NPC, although direct intracranial invasion is not uncommon with locally advanced stage. The pathway of CNS metastasis is postulated to be either through hematogenous route or cerebral spinal fluid (CSF) spread. Even though application of surgical management and radiotherapy may contribute to improved survival and neurologic function of some patients, the overall survival in these patients remains poor.

Keywords: Nasopharyngeal carcinoma, central nervous system metastasis, brain metastasis, intramedullary spinal cord metastasis

Introduction

Nasopharyngeal carcinoma (NPC) is distinctive in epidemiology, therapy method, and natural behavior. With a unique pattern of geographical distribution, NPC has a significantly higher incidence in South-Eastern Asia, where the incidence is at least twice as high as elsewhere [1]. Despite being of a similar cell or lineage, the treatment strategies of nasopharyngeal carcinoma are different from the other head and neck carcinomas due to the complicated anatomy and the good response to chemotherapy and radiotherapy. Radiotherapy is recognized as the first choice for NPC treatment, and it can achieve a satisfactory effect in patients with early NPC [2], while systemic treatment has an important role in the treatment of NPC, both in the non-metastatic as well as recurrent or metastatic nasopharyngeal carcinoma [3]. The common clinical symptoms of nasopharyngeal carcinoma, including neck mass (41%), ear complaints (27%), cranial nerve deficits (8%) and other nonspecific symptoms, may be obscure [4]. Therefore, many patients with NPC are at a locally advanced stage at the beginning of diagnosis. With the use of intensity-modulated radiotherapy (IMRT), which has better local

control and less toxicity than older techniques, locoregional control has been improved greatly, and distant metastasis has become the main cause of morbidity of NPC [5-7]. The rate of distant metastases occurrence is higher in locally advanced nasopharyngeal carcinoma [8, 9], and the most common sites are the bone, lung, and liver [10, 11]. Central nervous system (CNS) metastasis of NPC is an extremely rare occurrence, although direct invasion to the skull base is not infrequent in patients at a locally advanced stage. Therefore, only a few studies in the form of case reports had been reported, and no studies have been able to explore its treatment and prognosis systematically. In this report, we present two unique cases of NPC who were found with metastasis to the right temporal lobe and intramedullary spinal cord, respectively. At the same time, we also review the relevant literature to have a deeper understanding of CNS metastasis of NPC.

Case presentation

Brain metastasis

A 44-year-old male was presented to West China Hospital with the left nasal cavity bleed-

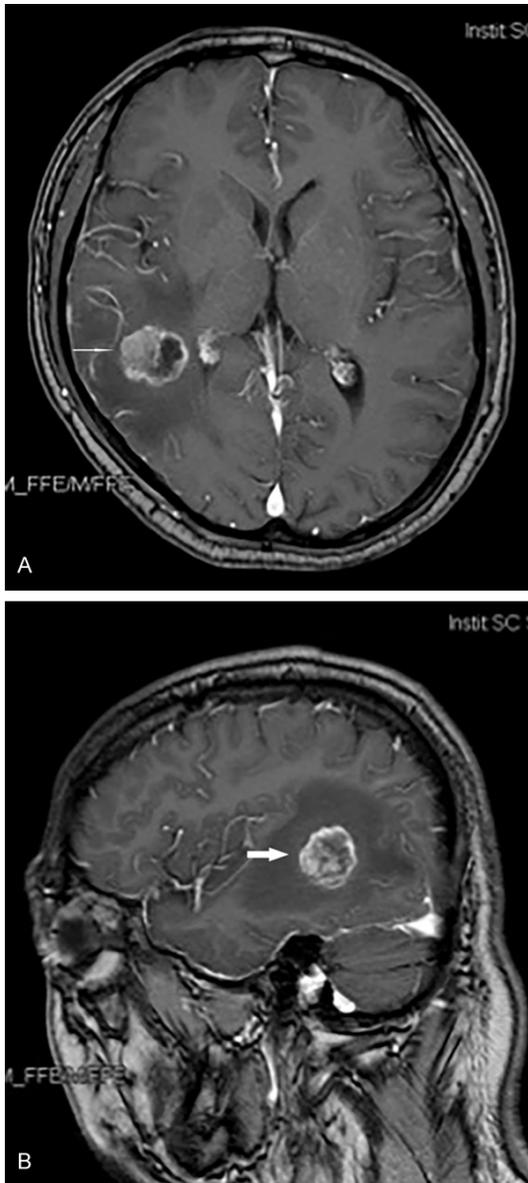


Figure 1. Magnetic resonance imaging (MRI) of the patient with brain metastasis from NPC. A. T1-weighted axial MRI images with contrast. B. T1-weighted sagittal MRI images with contrast.

ing constantly in 2013. Nasopharyngeal fiber optic endoscopy and histopathologic biopsy revealed a poorly differentiated nonkeratinizing NPC (World Health Organization (WHO) type II). Further magnetic resonance imaging (MRI) of nasopharynx and neck demonstrated the invasion of the cavernous sinus from nasopharynx lesion and enlarged and strengthened bilateral cervical lymph nodes, concluded the clinical staging T4N2M0, stage IVA, restaged according to the 8th Union for International Cancer

Control and American Joint Committee on Cancer (AJCC/UICC) staging system. He underwent three cycles of induction chemotherapy using paclitaxel and carboplatin (TC) regimens and then received concurrent chemoradiotherapy. Intensity-modulated radiotherapy (IMRT) was used to deliver the prescribed doses of 70 Gy to the gross tumor volume (GTV) of the nasopharynx and metastatic cervical lymph nodes, concomitant with the three cycles chemotherapy of cisplatin. One month after IMRT, a nearly complete response (CR) was achieved at both the primary site and the metastatic lymph node based on MRI scan.

With regular follow-up, no locoregional or distant relapse was found until 18 months after the completion of concurrent chemoradiotherapy, when multiple mass lesions in bilateral lungs were found through chest computed tomography (CT). Subsequently, palliative chemotherapy of gemcitabine and cisplatin (GP) regimens was administered for five cycles, and this resulted in almost complete disappearance of the lung lesions with only some patchy shadows remained. Three years later, he fainted away suddenly, and the MRI scan of the brain found a brain lesion on the right side of the temporal lobe (**Figure 1**). Surgery was immediately performed to relieve tumor compression and clarify the histologic diagnosis. The pathologic diagnosis was poorly differentiated nonkeratinizing carcinoma (WHO type II) (**Figure 2**), consistent with the initial pathologic findings of nasopharyngeal carcinoma. Epstein-Barr virus- encoded RNA (EBER) staining using in situ hybridization (ISH) was positive in the brain lesion, which further confirmed a brain metastasis from NPC. After that, the patient received three cycles of pemetrexed combined with platinum, aiming to control the dissemination of the disease. Unfortunately, eleven months after the end of surgery to brain metastasis, a recurrent brain lesion in right temporal lobe was found again on an MRI scan (**Figure 3A**), and relevant imaging examinations did not reveal any metastases or recurrences in other sites. Since the patient refused to undergo craniotomy again, IMRT consisting of 50Gy was delivered to the recurrent brain lesion. Nearly six months after IMRT to the recurrent brain metastasis, the complete response (CR) of brain lesion was achieved (**Figure 3B**). The patient was still alive at the last follow-up (June 2019).

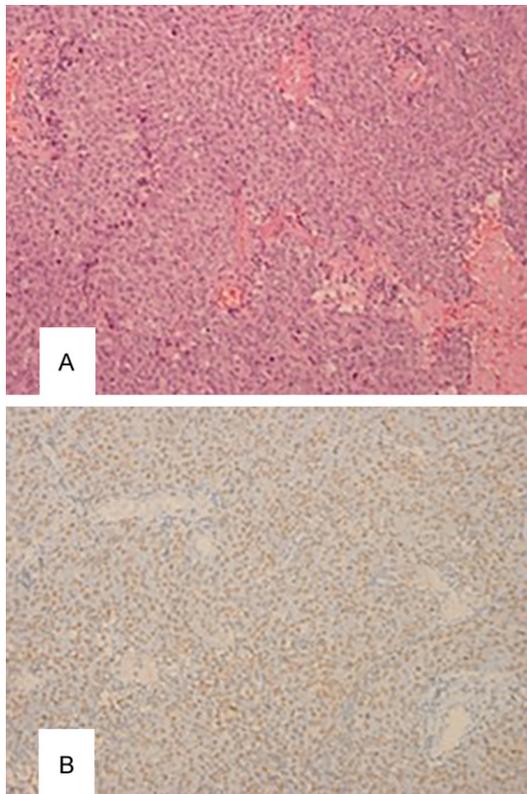


Figure 2. The pathologic results of brain metastasis. A. Hematoxylin and eosin (H&E) stain; original magnification 200×. B. Immunohistochemical analysis and in situ hybridization (ISH) of Epstein-Barr virus- encoded RNAs (EBER).

Intramedullary spinal cord metastasis

A 40-year-old man was admitted to the West China Hospital in 2017, with the complaint of nasal bleeding and obstruction, accompanying vision loss and restricted abduction of the left eye for five months. Gadolinium-enhanced MRI, nasopharyngeal fiber optic endoscopy and other general examinations were undertaken, which detected no lesions were found except in the nasopharynx and bilateral neck. Histopathology of the nasopharyngeal revealed a non-keratinizing carcinoma (**Figure 4**). The immunohistochemistry (IHC) showed the neoplastic cells were positive for EBER-ISH and CK5/6, and the ki-67 index of 70%. He was eventually diagnosed with nonkeratinizing NPC with stage IVA (T4N2MO) according to AJCC/UICC^{8th}. He subsequently received three cycles of induction chemotherapy, consisting of docetaxel, cisplatin, and fluorouracil (TPF). Moreover, concurrent chemoradiotherapy was followed. IMRT was administered with a total radiation dose of 70

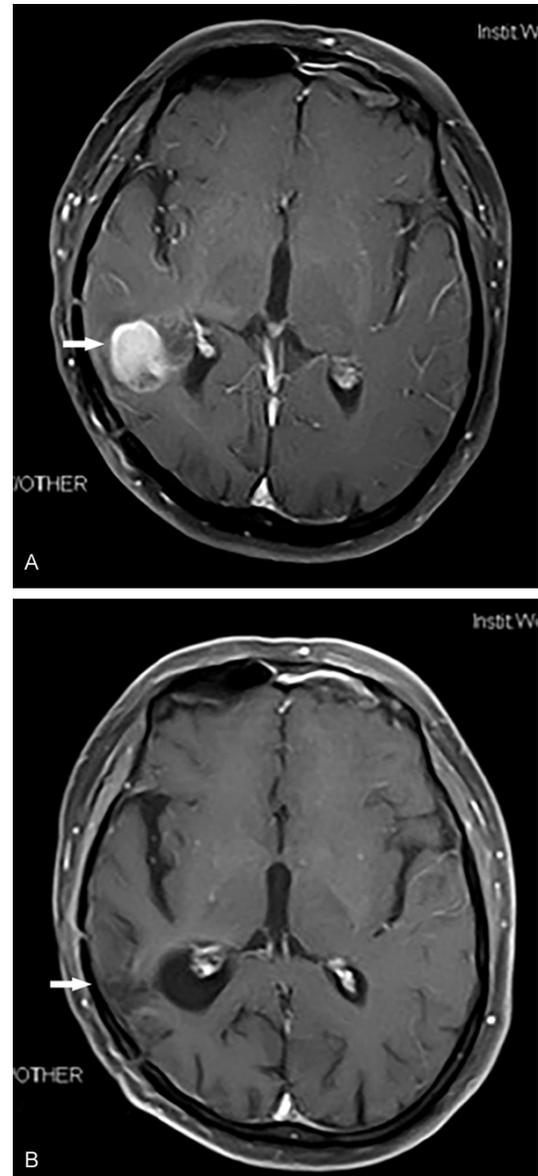


Figure 3. MRI of first patient with recurrent brain lesion in right temporal lobe. A. T1-weighted axial MRI images with contrast before IMRT. B. T1-weighted axial MRI images with contrast after IMRT.

Gy to primary nasopharynx tumor and involved lymph node, 60 Gy to potential tumor invasion of fields, and 54 Gy to bilateral cervical fields. Given the patient's intolerance to chemotherapy side effects, he refused platinum-based concurrent chemotherapy and received concurrent nimotuzumab weekly.

One month after the completion of initial chemoradiotherapy, the patient complained of the deterioration of lower limb power and incontinence of bladder and bowel. The MRI scan of

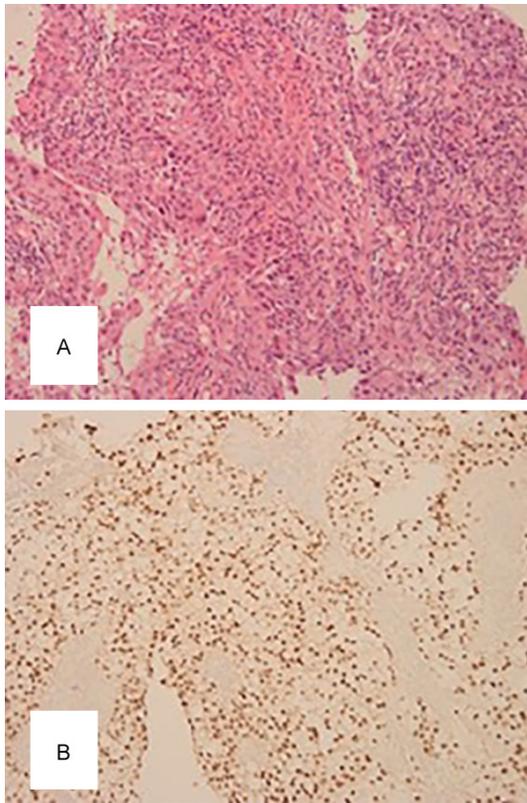


Figure 4. The pathology results of primary nasopharyngeal lesion of the second patient with ISCM. A. Hematoxylin and eosin (H&E) stain; original magnification 200 \times . B. Immunohistochemical analysis and in situ hybridization (ISH) of Epstein-Barr virus-encoded RNAs (EBER).

the spine was performed given physical findings, and the results showed the multiple intramedullary lesions in cervical and thoracic segments (at the C1, C2, T2, T4, T8 and T9 levels), along with the central canal expansion (**Figure 5B, 5C**). MRI scan of the nasopharynx showed the lesion in the nasopharynx was more extensive than before treatment and invaded into the brainstem (**Figure 5A**). Due to the rapid progression of the disease, the patient's condition deteriorated within a short period after the detection of intramedullary spinal cord metastasis (ISCM). He finally received only supportive treatment and died of complications of ISCM one month after the metastases were diagnosed.

Discussion

Even though increasing widespread use of IMRT has dramatically improved the local recurrence rate and survival of NPC patients, distant

metastasis is still the leading cause of treatment failure [6]. The metastatic patterns observed in 629 NPC patients reported by Huang et al. showed that most of the distant metastases (95%) occurred within three years after the end of therapy [10]. Moreover, confirmed by other studies, Huang et al. further revealed that bone was the most common distant metastatic sites for NPC, followed by lung and liver [8-10, 12, 13]. It is generally believed that lymphatic and hematogenous spreads are the main routes of NPC metastasis. Although intracranial invasion through the skull base is not infrequent in advanced NPC, it is rare to disseminate to the CNS by blood circulation or CSF circulation before or after treatment, which may be attributed to the self-protective function of the CNS. Currently, only a few relevant cases of CNS metastasis of NPC from a PubMed search had been well-described, and the reports are summarized in **Tables 1, 2** [14-19].

From the previous reports, we noted that most cases of brain metastases from NPC were accompanied by other common metastatic sites such as skeleton and lung. Ngan et al. and Kaidar-Person et al. described two patients who presented with lung metastasis preceding brain metastasis [12, 13]. Another case reported by Liaw et al. was diagnosed as NPC, simultaneous with the brain and skeletal metastases [14]. Tumor cells are usually transferred to common metastatic sites through the hematogenous route [9, 10]. Most scholars consider that brain metastases from NPC with other visceral metastases may disseminate by a hematogenous route [12, 14]. Besides hematogenous spread, spread through the CSF is also considered to be one of the possible pathways for CNS metastasis of NPC, because tumor cells may enter the CSF by invading the skull base and disrupting the dural barriers [12]. For our first patient with brain metastasis, even though he presented with lung metastases preceding brain metastasis after the completion of primary treatment, we found that the initial primary tumor of the patient had invaded the skull base and cavernous sinus at the initial diagnosis. Therefore, it is not certain which pathway is responsible for this patient's dissemination. Considering the literature stated above, the sites of brain metastases were mainly in the frontal and occipital lobe, with fewer temporal lobe, and no case had been reported in the

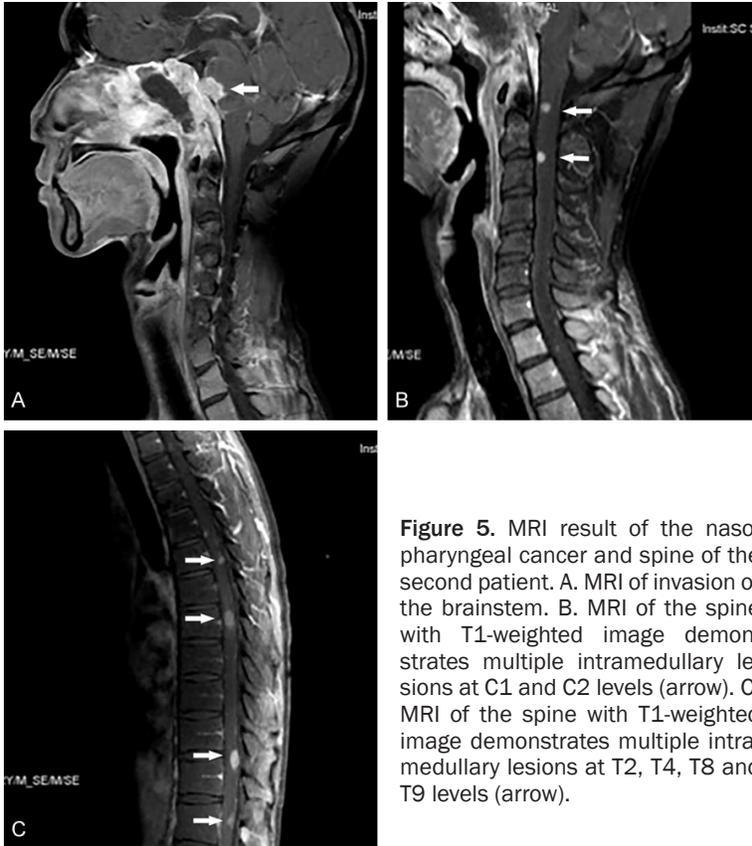


Figure 5. MRI result of the nasopharyngeal cancer and spine of the second patient. A. MRI of invasion of the brainstem. B. MRI of the spine with T1-weighted image demonstrates multiple intramedullary lesions at C1 and C2 levels (arrow). C. MRI of the spine with T1-weighted image demonstrates multiple intramedullary lesions at T2, T4, T8 and T9 levels (arrow).

parietal lobe. Ngan et al. suggested that there may be specific micro-environment that facilitates the colonization of circulating cells of NPC in the occipital lobe of the brain [12]. Nevertheless, as far as the limited reports show, it has not been clear whether there is a certain regularity by which tumor cells prefer to occur in a particular site in the brain, which needs further exploration.

Chemotherapy with/without targeted therapy is the main treatment for NPC with distant metastasis, according to expert opinion [12]. However, the treatment strategy for brain metastasis remains controversial. Effective therapies are limited due to poor understanding of the brain micro-environment. Furthermore, the blood-brain barrier (BBB) prevents systemic therapy drugs from entering the brain; therefore, many drugs fail to accumulate at therapeutic doses [13]. From previous studies above, we can find that brain metastasis of NPC is often a single occurrence. Local treatments, such as resection of the metastatic tumor or/and radiotherapy as the patients listed above had undertaken, may become the appropriate choice to improve

the prognosis of patients and reduce nerve compression. For our first patient, immediate craniotomy resecting the brain metastasis was taken after the first discovery of brain metastasis, which successfully alleviated the symptoms and provided pathological evidence. One year later, a new brain metastasis on the edge of the surgical bed was found again in our first patient. We administered 50 Gy in 25 fractions using IMRT with the recurrent brain metastasis. Nearly six months after IMRT to the brain lesion, complete response (CR) of the brain lesion was achieved.

Compared with brain metastasis, ISCM is even more scarce, presenting in 4.2~8.5% of all CNS metastases and seen in 0.1-0.4% of all cancers [14]. Generally, ISCM is often associated with rapid deterioration of neurological deficits, and

bears an extremely grim outcome with a median OS of 3-4 months by previous research [15-17]. Lung and breast cancer remain the most common primary sources of ISCM [15, 16]. Meanwhile, tumor cells from NPC can also disseminate to the intramedullary spinal cord. ISCM from NPC was first reported by Morariu et al. in 1974 [18]. The patient who suffered ISCM at the second cervical segment just received supportive treatment and died 11 weeks later. Similar to brain metastasis of NPC, dissemination through blood or CSF are possible routes for the occurrence of ISCM. We deemed that spread through the CSF was the most likely route for our patient with ISCM. Nearly one month after the end of primary chemotherapy and radiotherapy, he experienced direct invasion from the lesion of nasopharynx into the brainstem, simultaneous with multiple involvements of the spinal cord. Attack on the brainstem indicates destruction of the dural barriers, which gives the opportunity for tumor cells to enter the CSF. Moreover, common sites of distant metastasis such as lung, bone, and liver, which usually undergo spread by a hema-

Central nervous system metastasis from nasopharyngeal carcinoma

Table 1. Brain metastasis from nasopharyngeal carcinoma

Author/year	Gender/age	Other organ involvement	Site in the CNS	Histology from CNS metastasis	Timing of metastasis	Treatment	Outcome at the time of report
Ngan et al./2001 [20]	Male/33	Lung	Left occipital lobe of brain	Undifferentiated carcinoma; positive EBER by ISH	Fifty-eight months from end of primary radiotherapy	Surgery and chemotherapy	Died 6 months later
Liaw et al./1996 [22]	Male/69	Bone	Bilateral occipital lobes of brain	NA	At presentation of NPC	Systemic chemotherapy	Alive on treatment
Kaidar-Person et al./2011 [23]	Male/56	Lung	Occipital lobe of brain	Undifferentiated carcinoma	More than three months from end of primary therapy	Radiotherapy	Alive but performance status continued to deteriorate
Su et al./2017 [24]	Male/43	Frontal-bone	Frontal lobe of brain	Undifferentiated nonkeratinizing carcinoma	Nine months after the end of primary therapy	Chemotherapy and radiotherapy	Alive at the last follow-up
Shen et al./2017 [21]	Male/47	Bone and liver	Right frontal lobe of brain	squamous cell carcinoma (The primary lesion: nonkeratinizing, undifferentiated carcinoma; positive EBER by ISH)	Twenty months after the completion of radiotherapy	Surgery and radiotherapy	Died 31 months after his brain metastasis had been diagnosed
Current report	Male/44	lung	Right temporal lobe	Poorly differentiated nonkeratinizing carcinoma; positive EBER by ISH	Eighteen months after the completion of concurrent chemoradiotherapy	Surgery; radiotherapy for brain recurrence 11 months later	Alive at the last follow-up

CNS: Central nervous system; EBER: Epstein-Barr virus-encoded RNA; ISH: in situ hybridization; NA: no information available.

Table 2. Intramedullary spinal cord metastasis from nasopharyngeal carcinoma

Author/year	Gender/age	Other organ involvement	Site in the CNS	Histology from CNS metastasis	Timing of metastasis	Treatment	Outcome at the time of report
Morariu et al./1974 [18]	Male/50	NA	Cervical spinal cord	NA	Three year after the primary treatment	Supportive treatment	died 11 weeks later
Ngan et al./2001 [20]	Male/52	Lung	Lumbar and sacral spinal cord	Undifferentiated carcinoma; positive EBER by ISH	Eighteen months after the end of radiotherapy	Surgery and radiotherapy; second course radiotherapy for spine recurrence 29 months later	40 months from the first diagnosis of his intradural metastasis
Shen et al./2017 [21]	Female/47	Right frontal lobe	Thoracic spinal cord preceding cervical and lumbus spinal cord	Squamous cell carcinoma (The primary lesion: nonkeratinizing, undifferentiated carcinoma)	Sixteen months after the completion of radiotherapy	Surgery and radiotherapy	succumbed approximately 20 months from her diagnosis of CNS metastases
Current report	Male/40	-	cervical and thoracic spinal cord	No histology	One month after the completion of initial chemoradiotherapy	Supportive treatment	one month after the ISCM metastases were diagnosed

CNS: Central nervous system; EBER: Epstein-Barr virus-encoded RNA; ISH: in situ hybridization; NA: no information available; ISCM: intramedullary spinal cord metastasis.

Central nervous system metastasis from nasopharyngeal carcinoma

togenous manner, had not been found at the time of his death.

At present, there is no standard treatment for ISCM of NPC. Due to the existence of the blood-spinal barrier, which stops the entry of some chemotherapy, chemotherapy fails to improve the survival for ISCM [19]. From some retrospective researches, radiotherapy and surgery may contribute to improved neurologic outcomes and confer a significant survival in selected ISCM patients [14, 15]. Ngan et al. described a case of lumbosacral spinal nerve root involvement from NPC [20]. Surgery and palliative radiotherapy were given to relieve the neurologic symptoms. Twenty-nine months after the surgery and radiotherapy, second-course radiotherapy was taken for the recurrent spine lesions. At the last follow-up, the patient almost survived 40 months from the first diagnosis of ISCM. Another NPC patient reported by Shen et al. had multiple involvements of spinal cord [21]. After completing surgery and radiotherapy for initial spine lesions, the patient succumbed approximately 20 months from her diagnosis of CNS metastases. However, surgery and radiotherapy are not feasible for all patients with ISCM of NPC. For those patients with multiple involvements of spinal cord segments, or inferior physical status, local resection and radiotherapy were not options. Our second NPC patient had rapidly progressing neurological deficits after the diagnosis of multiple involvements of spinal cord segments, which made him intolerant to surgery or radiotherapy, but only best supportive care was offered, and the patient succumbed one month after the ISCM was diagnosed.

Conclusion

CNS metastasis from NPC is a devastating problem with limited research. The diagnosis mainly depends on pathologic results of the lesion after excision or biopsy, but for most ISCM patients with NPC whose histopathology were not available, they were mainly diagnosed by imaging combined with the clinical history. Spread through CSF or a hematogenous route is the most likely route for the occurrence of CNS metastasis. The gold standard treatment for these patients is yet to be determined. Although surgery or radiotherapy may improve survival and neurological outcome in a selected group of patients, survival for these patients

remains poor, for they often have rapidly progressive neurologic deficits, and most of the tumors will progress ultimately.

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Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Disclosure of conflict of interest

None.

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References

- [1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65: 87-108.
- [2] Peng H, Chen L, Zhang J, Li WF, Mao YP, Zhang Y, Liu LZ, Tian L, Lin AH, Sun Y and Ma J. Induction chemotherapy improved long-term outcomes of patients with locoregionally advanced nasopharyngeal carcinoma: a propensity matched analysis of 5-year survival outcomes in the era of intensity-modulated radiotherapy. *J Cancer* 2017; 8: 371-377.
- [3] Lee AW, Tung SY, Ngan RK, Chappell R, Chua DT, Lu TX, Siu L, Tan T, Chan LK, Ng WT, Leung TW, Fu YT, Au GK, Zhao C, O'Sullivan B, Tan EH and Lau WH. Factors contributing to the efficacy of concurrent-adjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma: combined analyses of NPC-9901 and NPC-9902 trials. *Eur J Cancer* 2011; 47: 656-666.
- [4] Kamran SC, Riaz N and Lee N. Nasopharyngeal carcinoma. *Surg Oncol Clin N Am* 2015; 24: 547-561.
- [5] Wu VW, Kwong DL and Sham JS. Target dose conformity in 3-dimensional conformal radiotherapy and intensity modulated radiotherapy. *Radiother Oncol* 2004; 71: 201-206.
- [6] Kam MK, Chau RM, Suen J, Choi PH and Teo PM. Intensity-modulated radiotherapy in nasopharyngeal carcinoma: dosimetric advantage over conventional plans and feasibility of dose escalation. *Int J Radiat Oncol Biol Phys* 2003; 56: 145-157.
- [7] Lee N, Xia P, Quivey JM, Sultanem K, Poon I, Akazawa C, Akazawa P, Weinberg V and Fu KK. Intensity-modulated radiotherapy in the treat-

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- ment of nasopharyngeal carcinoma: an update of the UCSF experience. *Int J Radiat Oncol Biol Phys* 2002; 53: 12-22.
- [8] Ho JH. An epidemiologic and clinical study of nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 1978; 4: 182-198.
- [9] Khor TH, Tan BC, Chua EJ and Chia KB. Distant metastases in nasopharyngeal carcinoma. *Clin Radiol* 1978; 29: 27-30.
- [10] Huang CJ, Leung SW, Lian SL, Wang CJ, Fang FM and Ho YH. Patterns of distant metastases in nasopharyngeal carcinoma. *Kaohsiung J Med Sci* 1996; 12: 229-234.
- [11] Shen LJ, Wang SY, Xie GF, Zeng Q, Chen C, Dong AN, Huang ZM, Pan CC, Xia YF and Wu PH. Subdivision of M category for nasopharyngeal carcinoma with synchronous metastasis: time to expand the M categorization system. *Chin J Cancer* 2015; 34: 450-458.
- [12] Chen YP, Wang YQ, Li WF, Chen L, Xu C, Lu TX, Lin AH, Yao JJ, Li YC, Sun Y, Mao YP and Ma J. Critical evaluation of the quality and recommendations of clinical practice guidelines for nasopharyngeal carcinoma. *J Natl Compr Canc Netw* 2017; 15: 336-344.
- [13] Fecci PE, Champion CD, Hoj J, McKernan CM, Goodwin CR, Kirkpatrick JP, Anders CK, Pendergast AM and Sampson JH. The evolving modern management of brain metastasis. *Clin Cancer Res* 2019; [Epub ahead of print].
- [14] Goyal A, Yolcu Y, Kerezoudis P, Alvi MA, Krauss WE and Bydon M. Intramedullary spinal cord metastases: an institutional review of survival and outcomes. *J Neurooncol* 2019; 142: 347-354.
- [15] Lv J, Liu B, Quan X, Li C, Dong L and Liu M. Intramedullary spinal cord metastasis in malignancies: an institutional analysis and review. *Onco Targets Ther* 2019; 12: 4741-4753.
- [16] Lee SS, Kim MK, Sym SJ, Kim SW, Kim WK, Kim SB and Ahn JH. Intramedullary spinal cord metastases: a single-institution experience. *J Neurooncol* 2007; 84: 85-89.
- [17] Schiff D and O'sNeill BP. Intramedullary spinal cord metastases: clinical features and treatment outcome. *Neurology* 1996; 47: 906-912.
- [18] Morariu MA and Serban M. Intramedullary cervical cord metastasis from a nasopharynx carcinoma. *Eur Neurol* 1974; 11: 317-322.
- [19] Kalita O. Current insights into surgery for intramedullary spinal cord metastases: a literature review. *Int J Surg Oncol* 2011; 2011: 989506.
- [20] Ngan RK, Yiu HH, Cheng HK, Chan JK, Sin VC and 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.
- [21] Shen C, Ying H, Lu X and Hu C. Nasopharyngeal carcinoma with central nervous system metastases: two case reports and a review of the literature. *Medicine (Baltimore)* 2017; 96: e9175.
- [22] Liaw CC, Ho YS, Koon-Kwan NG, Chen TL and Tzann WC. Nasopharyngeal carcinoma with brain metastasis: a case report. *J Neurooncol* 1994; 22: 227-230.
- [23] Kaidar-Person O, Kuten J, Atrash F, Billan S and Kuten A. Brain metastasis of nasopharyngeal carcinoma: a case report and literature review. *Case Rep Med* 2012; 2012: 405917.
- [24] Su Z, Cao X and Zou G. Brain and frontal-bone metastasis from nasopharyngeal carcinoma: Case report and literature review. *Head Neck* 2019; 41: E153-E158.