Aggressive Surgical Resection of Enormous Cervical Metastasis from Nasopharyngeal Carcinoma

Introduction

NPC is one of the most common epithelial malignancies of the head and neck in southern China and it also has a high morbidity rate in some Southeast Asia countries, where the incidence of this disease is 20-30 per 100 000 (1,2). Nasopharyngeal region is rich in lymphatic plexus and the epithelium is commonly infiltrated by many small lymphoid cells. Lymphoid metastases are found in almost 90% of patients at...
diagnosis (3,4). Radiotherapy has proved to be the most effective therapeutic approach, nevertheless, chemotherapy is also needed in advanced disease (5,6). This article deals with a patient with dysphagia and limitation of neck movement resulting from a huge cervical metastasis of NPC. We describe this case in details regarding clinical presentation, histology, medical imaging and therapeutic regimen.

Case report

In March 2011, a 23-year-old Chinese man with severe malnutrition was admitted to the Department of Oral and Maxillofacial Surgery Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China. He had a 19-month and 16-month history of progressively enlarging mass in the left neck and right neck, respectively. The cervical mass had undergone a rapid increase in size and firmness over the previous 1.5 months and was accompanied by presence of dysphagia and limitation of neck movement but no symptoms of headache, dyspnea, nasal occlusion or blood-stained nasal discharge.

On physical examination, a firm, fixed, non-tender, and lobulated tumor was palpable in left cervical levels II, III, which was measured 15×10×7 cm with non-defined boundary. Meanwhile, physical examination revealed the other hard tumor on the right cervical level II which was measured 7×6×6 cm (Figures 1A and B). There was a slight flushing of the skin in the cervical region but no papules were found and there were no phanerous lesions in the oral cavity, parotid glands and submaxillary glands.

The usual pre-operative work-up was implemented. Computed tomography (CT) of the head and neck showed thickening of the soft tissue in posterior nasopharynx and enlarging nodes in the left parapharyngeal space. In two sides of the neck, multiple cystic lesions were found; most of them were 14×10 cm in size (Figures 2A and B). The CT scans of the chest, abdomen, and pelvis found no evidence of primary malignancy or metastatic disease. Therefore, NPC as the initial diagnosis was considered. Then, pharyngorinoscopy was applied and showed neoplasm in the nasopharynx, while biopsys revealed undifferentiated non-keratinizing carcinoma (Figure 4A). For blood test, moderate anemia was found and no infectious disease was detected, such as HIV.

To relieve symptoms, a selective neck dissection was performed on the neck bilaterally. In the left neck, dissection included levels I, II, III and IV, while the sternocleidomastoid (SCM) muscle and internal jugular vein was sacrificed because of tumor infiltration (Figure 3). Meanwhile, lympho adipose tissue and cervical mass of levels I, II and III were dissected away in the right neck. Subsequently, histopathological examination of bilateral cervical mass revealed undifferentiated non-keratinizing carcinoma (Figure 4B), which was later proven CKs, CK5/6, P63, Epstein-Barr virus-encod ed RNA in situ hybridization (EBER ISH) positive (Figures 4C, D, E and F), thus supporting NPC cervical lymph node metastasis. The final diagnosis of this case was nasopharyngeal non-keratinizing carcinoma pT3N2M0 according to the 2002 American Joint Committee on Cancer (AJCC) staging dioterapija se pokazala kao najučinkovitiji terapijski pristup, no potrebna je i u slučaju napređovale bolesti (5,6). U ovom članku opisuje se bolesnik s disfagijom i ograničenim kretanjima vrata kao posljedicama goleme metastaze NPK-a u vratu. Taj slučaj detaljno opisujemo s obzirom na kliničku sliku, histologiju, medicinsku sliku i terapijske postupke.

Prikaz slučaja

U ožujku 2011. godine u bolnicu je primljen 23-godišnji Kinez s teškom pothranjenošću i to na Odjel za oralnu i maksilo-facialnu kirurgiju Memorijalne bolnice Sun Yat-Sen Sveučilišta Sun Yat-Sen u Guangzhou u Kini. U njegovoj povijesti bolesti bilo je zabilježeno progresivno povećanje mase u lijevom dijelu vrata prije 19 mjeseci i u desnom dijelu prije 16 mjeseci. Masa u vratu brzo je rasla i postojala čvršća unutrašnjeg centimetara (slike 1. a i b). Pojavilo se blago crvenilo kože u vratoj regiji, ali nisu nađene papule i nije bilo vidljivih lezija u usnoj šupljini te na parotidnim i submakusarnim zlijezdam. Provedena je uobičajena prijediopejskrajska obrada. Komputertomografska analiza (CT) glave i vrata pokazala je zadebljanje mekog tkiva u stražnjem nazofarinkusu i povećanje čvorova u lijevom parafaringealnom prostoru. Na obje strane vrata pronadene su višestruke cistične ležije – većina je bila 14 × 10 centimetara (slike 2. a i b). Na CT otkriveno je psrnog koša, trbuha te ujedno i zbijelice nisu pronađeni dokazi o primarnoj malignosti ili metastatskoj bolesti. Zato je razmatran NPK kao početna dijagnoza. Nakon toga je obavljena faringorinoskopija i nalazi su pokazali novotvorinu u nazofarinkusu, a biopsija nediferencirani karcinom koji nije keratinizirao (slika 4. a). Analizom krvi ustanovljena je umjerena anemija, ali nisu otkriveni infektivni bolesti, kao što je HIV.

Na vratu je obostrano obavljena selektivna disekcija radi ublažavanja simptoma. Na lijevoj strani disekcija je uključivala razine I, II, III i IV, a sternokleidomastoidni (SCM) miješić i unutarnja jugularna vena bili su žrtvovan zbog infiltracije tumor. Na obje strane vrata disecirano limfno-adipozno tkivo i cervicalna masa razine I, II i III. Nakon toga je histopatološkim pregledom bilaterne masu vrata otkriven nediferencirani rak koji nije keratinizirao (slika 4. b), a poslije je i dokazan [CKs, CK5/6, P63, Epstein-Barr virusno kodiran RNK, in situ pozitivna hibridizacija (EBER ISH) (slike 4. c, d, e i f)], čime je poduprta hipoteza o metastazi vrata kao metatatskoj bolesti. Konačna dijagnoza u ovom slučaju glasi nazofarinski ne-keratinizujući karcinom pT3N2M0 prema američkom Za jedničkom odboru za rak (AJCC) iz 2002. godine. Pacijent je tada bio podvrgnut istodobnoj dvomjesečnoj kemoterapiji. Trodimenzionalna radioterapija temeljena na CT-u primijen-
Enormous Cervical Metastasis from NPC

Figure 1  Preoperative front view (A) and profile (B) showing bilateral cervical enlarging mass.

Figure 2  Preoperative axial CT (A) at the level of the oropharynx showing parapharyngeal extension (arrow). Coronal CT (B) showing multiple cystic lesions in bilateral neck.

Figure 3  Surgical resection of left cervical mass with a length 14.5 cm.

Figure 4  Histopathological examination of NPC with bilateral enormous cervical lymph nodes metastasis. (A), (B) Hematoxylin and eosin-staining of primary nasopharyngeal carcinoma and left cervical lymph nodes metastasis, respectively. (C), (D), (E), (F) revealing CKs, CK5/6, P63, EBER expression was positive in left cervical lymph nodes metastasis (magnification 200 X).

Slika 1. Prijeoperacijski frontalni pogled (a) i profil (b) – vidi se obostrana povećana masa u vratu

Slika 2. Prijeoperacijski aksijalni CT (a) na razini orofaringsa na kojemu se vidi parafaringealno proširenje (strelica); koronarni CT (b) prikazuje višestruku obostranu cističnu leziju u vratu

Slika 3. Kirurška resekcija lijeve mase u vratu u dužini od 14,5 centimetara

Slika 4. Histopatološka analiza NPK-a s obostranim golemim metastazama vratnih limfnih čvorova; hematoksinjsko i eozinsko bojenje primarnog nazofaringealnog karcinoma (a) i lijeve metastaze u vratnom limfnom čvoru (b); (c), (d), (e), (f) prikazuju CKs, CK5/6, P63, EBER pozitivni izričaj u lijevoj metastazi vratnoga limfnog čvora (povećanje 200 X)
system. The patient then underwent concurrent chemo radiotherapy during a two-month period. The CT-based three-dimensional radiotherapy was given with a total dose of 66 Gy delivered to the primary tumor and 60 Gy to bilateral neck metastatic areas, while concurrently a 40 mg/m2 dose of cisplatinum was administered weekly.

There was no evidence of persistent malignancy in primary tumor or any recurrence in cervical areas, one month after completion of the definitive treatment. The patient was in good condition at the time of the last follow up in December 2016 and was living a normal life.

**Discussion**

The majority (75–90%) of newly diagnosed NPC patients have loco-regionally advanced disease, commonly with nodal metastases (1). Retropharyngeal nodes are the first echelons of nodal metastases for NPC while internal jugular nodes are the most frequently involved non-retropharyngeal nodes (72%), (3,7). Superior deep cervical lymph nodes are the most common area of involvement, with directed spread reaching or occasionally jumping to the supraclavicular region. In a study of 101 patients, Ng et al. reported that the incidence of level II, III and IV cervical lymph node metastases was 95.5%, 60.7% and 34.8%, respectively (8). In a study of 104 cases, Chow et al. reported that the largest size of metastatic cervical lymph nodes of NPC was 10cm. Therefore, the case of the patient with bilateral enormous cervical lymph nodes metastasis described in this report is extremely rare and the patient was only complaining about dysphagia and limitation of neck movement.

Histologically, NPC is subdivided into three types: keratinizing squamous cell carcinoma differentiated non-keratinizing carcinoma and basal-like squamous cell carcinoma. Undifferentiated non-keratinizing carcinoma is the most common in Southern China (95% of patients, which has been shown to have high correlation with EBERISH positivity (8, 10). EBER ISH has been well-described and used to confirm systemic metastases of NPC (10, 12). Ngan et al. propose one could argue about another unknown primary cancer as a potential source of metastasis if there is no EBER ISH confirmation (11). In the present case, the final histopathological examination showed that the bilateral enormous cervical lymph nodes metastasis was EBER positive and supported the NPC metastasis. Generally, non-keratinizing carcinomas have better primary tumor control rates and nodal control rates than keratinizing squamous cell carcinoma, while the latter group has a poorer survival rate than former group because of higher incidence of deaths from uncontrolled primary tumors and nodal metastases (13). The present case was identified undifferentiated non-keratinizing carcinoma in primary tumor and cervical mass. The patient received concurrent chemo radiotherapy after bilateral neck dissection and no tumor recurrence or metastasis was found in a 67 months follow-up. Nevertheless, metastatic cervical nodes from NPC are more readily controlled than cervical nodes of similar size arising from other head and neck squamous cell carcinomas.

**Rasprava**

Većina novodijagnosticiranih bolesnika s NPC-om (75 – 90 %) ima lokalno-regionalno napredovalo bolest, obično s metastazama limfnih čvorova (1). Retrofaringealni čvorovi su veštački nodalnih metastaza kod kojih je riječ o NPC-u, a najčešće uključeni retrofaringealni čvorovi su unutarnji jugularni čvorovi (72%) (3, 7). Gornji duboki limfni čvorovi najčešće su dio zahvata, u usmjerenim širenjem koje doseže ili povremeno prelazi u supraklavikularnu regiju. U istraživanju 101 pacijentka, Ng i suradnici istaknuli su da je učestalost metastaz cervikska na razini II, III i IV bila 95.5 %, 60.7 %, odnosno 34.8 % (8). U studiji o 104 slučajima, Chow i suradnici izvijestili su da je najveća veličina metastatskih limfnih čvorova NPK-a 10 centimetroa (9). Zato je slučaj bolesnika s obostrano golemim metastazama limfnih čvorova opisan u ovom izvješću iznimno rijedak, a pacijent se žalio samo na disfiguraciju i ograničene kretanje srca.

Histološki se NPC dijeli na tri oblika – karcinom pločastih stanica keratiniziranih diferenciranih karcinoma koji nisu keratinizirani, nediferencirani karcinom koji nije keratiniziran i karcinom bazalnog tipa pločastih stanica. Nediferencirani karcinom koji nije keratiniziran najčešće je u južnoj Kini. Kod 95 % bolesnika, za koje se pokazalo da imaju visoku korelaciju s pozitivnošću EBER ISH-a (8, 10). EBER ISH je dobro opisan i korišten kod riječi o potvrdi sustavnih metastaza NPC-a (10, 12). Ngan i suradnici predložili su da se raspravlja o još jednom nepoznamatom primarnom raku kao potencijalnom izvoru metastaza, ako ne postoji potvrda EBER ISH-a (11). U ovom slučaju, konačni histopatološki pregled pokazao je da su bilateralno goleme metastaze limfnih čvorova bile EBER pozitivne i podupirale su stajalište o metastazama NPC-a. Općenito, nekeratinizirajući karcinomi imaju bolju stopu kontrole primarnoga tumora i stopu nodalne kontrole negoli keratinizirajući karcinom pločastih stanica, a druga skupina ima lošiju stopu preživljavanja od prve zbog veće smrtnosti od nekontroliranih primarnih tumora i metastaza čvorova (13). U ovom slučaju identificiran je ne-diferencirani karcinom koji nije keratiniziran u primarnom tumoru i masi srca. Pacijent je primio istodobnu kometorapiju nakon obostrane disekcije srca i nije bilo recidiva ili metastaza tumora tijekom 67-mjesecne kontrole. Ipak, metastatski vratni čvorovi iz NPC-a lakše se kontroliraju negli cervikalni slične veličine koji nastaju od drugih karcinoma pločastih stanica glave i srca (9). Većina nedavnih istraživanja jasno je pokazala da NPK više nije problematična bolest...
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Conflict of interest

The authors report no conflict of interest.

Sukobi interesa

Autori nisu bili u sukobu interesa.

Zaključci

Naš je pacijent imao obostrano golemu metastazu vrata koja je rezultirala značajnim kliničkim simptomima pri postavljanju dijagnoze. Najprije smo obavili agresivnu kiruršku resekciju mase u vratu, nakon čega je slijedila istodobna kemoterapija. Sveobuhvatnim liječenjem NPK-a postignut je razuman ishod u tom slučaju napredovale bolesti.

Conflict

Although surgical resection has a limited role in metastasis of NPC, there are some cases of advanced disease with a reasonable outcome after resection (11,18,19). The patient in our report presented with dysphagia and a limitation of neck movement at diagnosis. We performed a selective neck resection of metastatic cervical mass as primary treatment. He received a good symptomatic relief which was helpful for improving defective nutrition condition and for building confidence for further treatment.

Conclusions

In conclusion, our patient had a bilateral enormous cervical metastasis from NPC which was resulting in significant clinical symptoms at the time of diagnosis. First, we performed an aggressive surgical resection for cervical mass, followed by concurrent chemo-radiotherapy; the comprehensive treatment regimen reached a reasonable outcome in such a case of advanced disease.

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