

# DIFFERENTIATION OF REGIONAL LYMPH NODE METASTASIS OF NASOPHARYNGEAL CANCER OR DISTANT METASTASES OF CERVICAL CANCER

Nguyen Van Dang<sup>1</sup>✉, Nguyen Viet Anh<sup>2</sup>, Nguyen Xuan Hien<sup>2</sup>, Ngo Thanh Tung<sup>3</sup>

<sup>1</sup>Department of Oncology, Hanoi Medical University

<sup>2</sup>Master, Oncology Resident Doctor

<sup>3</sup>Department of Head and Neck Radiation, Vietnam National Cancer Hospital

*Nasopharyngeal cancer (NPC - Nasopharyngeal carcinoma) is a common cancer in the head and neck area in Asian countries such as China, Vietnam, Taiwan. In epidemiological areas, the main histopathology is type III according to WHO classification. Virus epstein-barr (EBV) is considered a risk factor as well as a prognostic factor in this group of diseases. Recently the role of HPV has been mentioned frequently in oropharyngeal cancer and cervical cancer, and there have been studies linking the association between HPV and type I nasopharyngeal cancer. Our clinical case is a patient with a history of cervical cancer previously diagnosed and treated. This patient was diagnosed with nasopharyngeal cancer metastasized to the neck lymph nodes at the time of examination. The use of the HPV marker has helped us identify the origin of the metastatic lymph node. This patient's clinical presentation is consistent with the diagnosis of recurrent cervical cancer metastasis to the neck lymph nodes. The patient died after 5 months from the time of diagnosis.*

**Keywords:** Cervical cancer, nasopharynx cancer, HPV virus, EBV virus, ...

## I. INTRODUCTION

Nowadays, nasopharyngeal cancer is the most common cancer in the head and neck area. In Vietnam, according to GLOBOCAN 2018 data, this disease ranked 6th among common cancers if it is classified in both genders, and ranked 5th in males only. Nasopharyngeal cancer has many different etiologies and varies among geographic regions.<sup>1</sup> Epstein Barr virus (EBV) is the most common etiology.<sup>2</sup> Human papillomavirus (HPV), although rare, is also associated with NPC.<sup>3</sup> HPV is known as the primary etiology of cervical and oropharyngeal cancer (OPC). Positive HPV is considered as a

prognostic factor in oropharyngeal cancer. The virus is sexually transmitted and in that type 16 (p16) is directly related to head and neck cancer. In this article, we present a clinical case of nasopharyngeal cancer that previously had been diagnosed and treated for cervical cancer.<sup>4</sup> This patient has neck lymph node metastasis, and the determination of metastatic of nasopharyngeal cancer or cervical cancer is very important for stage assessment and treatment goals.

## II. CLINICAL CASE

A 54-year-old female patient was diagnosed with cT2bN0M0 cervical cancer (FIGO IIB) with histopathological results of cervical squamous cell carcinoma in October 2016. Patient was treated with definitive chemoradiation according to the standard regimen. There was complete response after treatment; the patient is

---

Corresponding author: Nguyen Van Dang  
Hanoi Medical University

Email: [nguyenvandang@hmu.edu.vn](mailto:nguyenvandang@hmu.edu.vn)

Received day: 29/06/2020

Accepted day: 20/09/2020

discharged from the hospital and followed – up periodically. One year after treatment at the National Cancer Hospital, the patient was in remission and continued to have follow-up in the local hospital. In November 2018, the patient was admitted to the hospital because of the right neck lymph node; clinical examination revealed that the lymph node was about 2cm in

size, firm but still mobile. There was no lesion detected by vaginal examination. It was nothing special except the right supraclavicular lymph node. This patient has normal eating condition. Patient's weight is 50kg, height is 1.55m (BMI 20.8). This patient has not shown signs of weight loss during the past 3 months.

### III. RESULTS

The SCC tumor marker and blood test results are normal. An ultrasound of the neck revealed the supraclavicular lymph node of about 1.5x2.5 cm in size, loss of umbilical node structure. Colposcopy showed cervicitis, vaginitis, and no recurrent lesions. ENT endoscopy revealed a suspicious mass on the right nasopharynx region corresponding to the thick position on the MRI result.

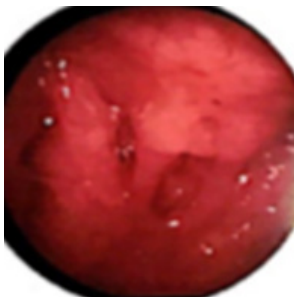


Figure 1A

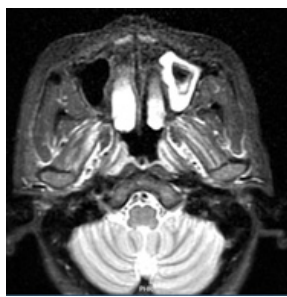


Figure 1B



Figure 1C

Figure 1A. Images of nasopharyngeal tumors on endoscopic ENT

Figure 1B. Images of nasopharyngeal tumors on MRI result

Figure 1C. Images of the supraclavicular lymph node on MRI result

The patient underwent a nasopharyngeal biopsy which showed undifferentiated carcinoma with microscopic images of cells arranged in clusters or bands with rounded nuclei, many of which were unevenly divided with crude chromatin (type III according to WHO - UCNT - Undifferentiated carcinoma of nasopharyngeal type) (Figure 2A).

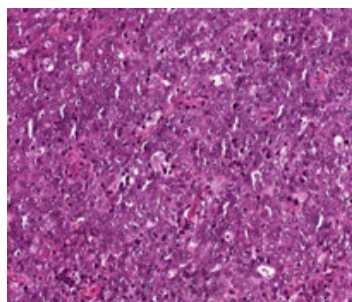
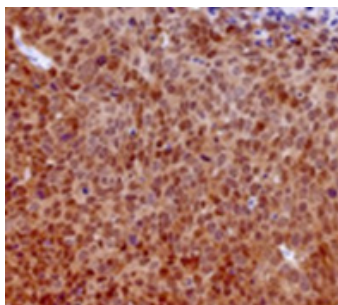


Figure 2A. Undifferentiated carcinoma nasopharynx

Results of cell aspiration and lymph node biopsy concluded lymph node metastasis of squamous carcinoma (Figure 2B).

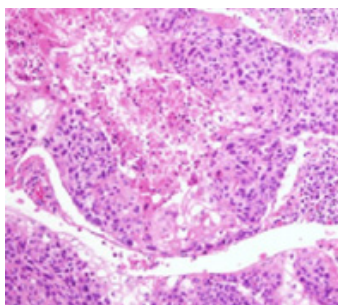


**Figure 2B. Images of HPV (p16) on cytoplasm and nucleus**

Computerized tomography of the chest - abdomen has not detected any abnormality.

Based on the above clinical examination and the subclinical results, there are two possible diagnosis: Nasopharyngeal cancer metastasis to the lymph nodes or nasopharyngeal cancer/recurrent cervical cancer metastasis to the neck lymph nodes. With these two diagnoses, there will be two different directions of treatment and prognosis. If this is a metastatic regional lymph node, the diagnosis is nasopharyngeal cancer/treated cervical cancer. The most appropriate treatment is definitive chemoradiation and patient prognosis is generally good. In contrast, if this is a metastatic lymph node of the cervix cancer, the patient has both nasopharyngeal cancer and distant metastases of the cervical cancer. The patient's prognosis would be very poor.

The Immunohistochemistry result of the right supraclavicular lymph node was positive for HPV and negative for EBV (Figure 2C).



**Figure 2C. Image of the right supraclavicular lymph node on hematoxylin and eosin**

The immunohistochemistry test is performed at the Pathology Center – Vietnam National Cancer Hospital. The assay was performed on a sample of neck lymph nodes, using the HPV and EBV markers, respectively. The definite diagnosis is that nasopharyngeal cancer/ recurrent cervical cancer metastases neck lymph nodes. The patient went for consultation with the subcommittee on breast cancer and gynecologic cancers and the head and neck cancer subcommittee of the Vietnam National Cancer Hospital. The consensus of

the consultation was upfront chemotherapy treatment and re-evaluation after 3 cycles for the treatment of nasopharyngeal cancer.

However, the patient declined treatment at the hospital and continued to have follow-up at the local hospital; after 5 months, the disease progressed seriously and this patient passed on. Given this fact, it seems consistent with the impression that this lymph node is metastatic cervical cancer rather than metastatic lymph node of nasopharyngeal cancer.

#### IV. DISCUSSION

The World Health Organization has classified nasopharyngeal cancer (NPC) into three types of histopathology.<sup>5</sup> Type I is keratinizing squamous cell carcinoma and is related to HPV that is not related to EBV, types II - III are non-keratinizing, undifferentiated and directly related to EBV virus. In this case, if the pathology of the nasopharynx palate is type I, related to HPV, it will be more difficult to identify the neck lymph nodes as metastatic lymph nodes of nasopharynx or cervical cancer.

According to a study in North America, 50% of nasopharyngeal cancer type I according to WHO has HPV positive for immunohistochemistry, for type II / III, this figure is only 5% (p =

0.015).<sup>6</sup> In another study, the positive HPV of type I PCR was also 50% and that of type II, III was 33.8%.<sup>7</sup> HPV is now also considered a prognostic factor in nasopharyngeal cancer with improved survival in the HPV-positive group.<sup>8</sup> There are also studies showing that a positive HPV infection has a equivalent prognosis to positive EBV in nasopharyngeal cancer, and always a better prognosis than that of a negative HPV or EBV group.<sup>9</sup> Other research indicates that overexpression of p16 in the EBV positive nasopharyngeal cancer group improves disease free survival.<sup>10</sup> In contrast, some studies show no association between HPV and prognosis in nasopharyngeal cancer (Table 1).<sup>11</sup>

**Table 1. Some research about linked HPV and nasopharyngeal cancer**

Author	Country	Year	Number of patient	Test HPV	Type HPV	EBV	Treatment	Result
Atighechi	Iran	2014	9	PCR	5 HPV 18, 3 HPV 16, 1 HPV 6	No report	Chemoradiation	4-year OS 100%
Dogan	USA	2014	6	p16 IHC/ HPV ISH	nonspecific type	(-) IHC	3/6 Chemoradiation	Average 85 months
Jiang	USA	2015	40	p16 IHC/ HPV ISH	23/40 p16+	13/40(+)	No report	Average 140 months
Stenmark	USA	2014	18	p16 IHC/ PCR	9 HPV 16, 5 HPV 18, 2 HPV 59, 1 HPV 39, 1 HPV 45	All Negative	Chemoradiation or Radiotherapy	5-year OS 48%
Robinson	UK	2013	11	p16 IHC/ PCR/ HPV ISH	9 HPV 16, 1 HPV 18, 1 unknown	All Negative	No report	Average 54 months

Our patients were diagnosed with nasopharyngeal cancer, the pathology was undifferentiated carcinoma (type III according to WHO classification), patients had a metastatic lymph node that had previously been diagnosed and treated for cervical squamous cell carcinoma (SCC). Lymph node pathology showed metastatic squamous cell carcinoma and lymph node immunohistochemistry results in EBV negative, positive for HPV. This confirms the diagnosis of a supraclavicular lymph node metastatic of cervical cancer and the patient has been treated as a distant metastatic squamous cell carcinoma. In the case of a patient whose pathology in the nasopharynx is a squamous cell carcinoma (type I according to WHO), the diagnosis will be a nasopharyngeal cancer with metastatic lymph nodes and definitive chemoradiation should be conducted.

Accurate diagnosis of primary tumor in the case of cervical metastatic lymph node especially in patients with multiple-site cancer is very important in the stage evaluation. According to the study of Haoran Li and colleagues of 47 patients with advanced cervical cancer, only 2 patients had metastatic cervical lymph nodes metastases.<sup>12</sup> And the prognosis of overall survival for cervical cancer with upper lymph node metastases is relatively poor with a 3-year OS of 16.5% according to research by Qiu JT et al.<sup>13</sup>

## V. CONCLUSION

Cervical cancer with the main risk factor is the HPV virus. However, HPV is also a risk factor for oropharyngeal cancer and nasopharyngeal cancer, although rare but can be seen and the rate is higher in the group NPC type I pathology follows the WHO classification. The rate of supraclavicular lymph node metastasis in cervical cancer is very low and this group of patients has a relatively poor prognosis. The

results of lymph node biopsy combined with immunohistochemistry confirm the diagnosis, especially for patients with a second head and neck cancer. More research is needed to help determine the role of HPV in nasopharyngeal cancer and oral cancer as well as other head and neck cancers.

## REFERENCES

1. Chang ET AH. The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomark Prev.* 2006(15):1765-1777.
2. Raghupathy R HE, Chan AT. *Epstein-Barr virus as a paradigm in nasopharyngeal cancer: From lab to clinic.* Alexandria, VA2014.
3. Isayeva T LY, Maswahu D, et al. Human papillomavirus in non-oropharyngeal head and neck cancers: A systematic literature review. *Head Neck Pathol.* 2012(6):104-120.
4. (CDC) CfDCaP. *Human papillomavirus-associated cancers—United States, 2004–2008.* MMWR Morb Mortal Wkly Rep2012.
5. Chan AT TP, Johnson PJ. Nasopharyngeal carcinoma. *Ann Oncol.* 2002(13):1007-1015.
6. Lo EJ BD, Woo JS, et al. Human papillomavirus and WHO type I nasopharyngeal carcinoma. *Laryngoscope.* 2010(120):1990-1997.
7. Laantri N AM, Kandil M, et al. Human papillomavirus detection in Moroccan patients with nasopharyngeal carcinoma. *Infect Agents Cancer.* 2011(6):1-6.
8. Atighechi S BM, Mirvakili SA, et al. Human papilloma virus and nasopharyngeal carcinoma: Pathology, prognosis, recurrence and mortality of the disease. *Exp Oncol.* 2014(36):215-216.
9. Dogan S HM, Ferris RL, et al. Human papillomavirus and Epstein-Barr virus in naso-

pharyngeal carcinoma in a low-incidence population. *Head Neck*. 2014(36):511-516.

10. Jiang W CP, Garden AS, et al. Prognostic value of p16 expression in Epstein-Barr virus-positive nasopharyngeal carcinomas. *Head Neck*. 2015(38):1459-1466.

11. Robinson M SY, Paleri V, et al. Oncogenic human papillomavirus-associated nasopharyngeal carcinoma: An observational study

of correlation with ethnicity, histological subtype and outcome in a UK population. *Infect Agents Cancer*. 2013(8):1-7.

12. Li H. Advances in diagnosis and treatment of metastatic cervical cancer. *J Gynecol Oncol*. 2016;27(4):40-43.

13. JT Q. Supraclavicular lymph node metastases in cervical cancer. *Eur J Gynaecol Oncol*. 2007;28(1):33-38.