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Challenging Diagnosis of Occult Nasopharyngeal Carcinoma by EBER-ISH Test on Cervical Lymph Node Biopsy without Primary Tumor Biopsy: Successful Concurrent Chemoradiotherapy

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ABSTRACT

Background: Nasopharyngeal carcinoma (NPC) is usually confirmed by primary tumor biopsy which can be challenging if the lesion is occult or inaccessible.

Objectives: This report aims to present a clinical diagnosis of occult NPC without primary tumor biopsy.

Case presentation: A 38-year-old male with a 2-month history of painless left neck swelling revealed a 4.5 cm left cervical lymph node on physical examination with normal nasopharyngeal endoscopy. Fine-needle aspiration (FNA) of the node demonstrated undifferentiated metastatic squamous cell carcinoma and the Epstein-Barr virus-encoded RNA in situ hybridization (EBER-ISH) test was positive. Fluorine-18 fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) imaging revealed a hypermetabolic lesion in the left nasopharynx with maximum standardized uptake value (SUVmax: 11.43). The patient refused to undergo nasopharyngeal biopsy. Based on the American Joint Committee on Cancer (AJCC) 8th edition, a T1N1M0 stage of NPC was established. He completed concurrent chemoradiotherapy and achieved a complete metabolic response at the 6-month follow-up.

Conclusion: A positive EBER-ISH test from a cervical node biopsy combined with a hypermetabolic nasopharyngeal lesion on PET-CT imaging provides definitive clinical evidence of occult NPC. This approach gives a reliable diagnostic alternative when a primary tumor biopsy is not possible and ensures timely definitive treatment.

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a type of cancer associated with the Epstein-Barr virus (EBV). It has specific patterns of occurrence, distinct tissue features, and treatment methods that differ from other head and neck squamous cell carcinomas.[1,2] The standard method for a definitive diagnosis requires a biopsy of nasopharyngeal tissue. However, sometimes the primary tumor is occult, inaccessible, or a biopsy cannot be

done due to issues related to the patient. In these conditions, diagnosis relies on identifying metastatic disease that has characteristics of NPC.

Epstein-Barr virus-encoded RNA in situ hybridization (EBER-ISH) test has better sensitivity and specificity for diagnosing NPC.[3] A positive nuclear result in metastatic undifferentiated carcinoma cells, along with a hypermetabolic nasopharyngeal lesion seen on PET-CT imaging, is widely recognized for confirming occult NPC.[4,5] Despite this recognition, managing a case where the primary tumor location was occult and the patient clearly refused invasive procedures, remains a clinical challenge. Delaying definitive chemoradiotherapy to perform a biopsy of the primary tumor can significantly worsen the patient's prognosis because of the prolonged diagnostic procedure.

Here, a case report of a 38-year-old male diagnosed with T1N1M0 NPC by the EBER-ISH test on a cervical lymph node biopsy without primary tumor histology. The novelty of this report is to show that combining non-invasive procedures, the EBER-ISH test and PET-CT imaging, can be a good alternative to the necessity of a primary tumor biopsy in a patient who does not cooperate. This case highlights an important clinical lesson: when a primary tumor biopsy is not possible, this combined diagnostic method provides sufficient diagnostic certainty to start timely, definitive treatment without losing accuracy.

CASE PRESENTATION

Patient information

A 38-year-old man with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 presented with a two-month history of painless swelling in the left side of his neck. He worked as an administrative staff. He was a non-smoker and had no significant medical or family history of malignancies; however, he reported a long-standing dietary habit of frequent consumption of preserved foods since childhood. The patient did not report any nasal blockage, nosebleeds, ear symptoms, or nerve problems. A physical examination found a 4.5 cm left cervical lymph node.

Clinical findings

Then, the patient underwent PET-CT imaging that demonstrated a hypermetabolic lesion in the left nasopharynx (fossa of Rosenmüller) with SUVmax of 11.43 (**Figure 1A**), an intensely avid metastatic left cervical lymph node 4.5x4.3x3.7 cm in size (**Figure 1B**), and multiple hypermetabolic regional lymph nodes along the left cervical chain (**Figure 1C**); distant metastasis was not identified. A nasopharyngeal endoscopy was also performed and showed no clear mucosal lesions, although visualization of the left fossa of Rosenmüller was limited.

An FNA cytological evaluation of the left cervical lymph node was performed to correlate with the metabolic activity found on the PET-CT imaging. The microscopic examination confirmed pleomorphic malignant epithelial cells with a high nuclear-to-cytoplasmic ratio, consistent with undifferentiated metastatic squamous cell carcinoma. The EBER-ISH test showed intense and diffuse dark nuclear staining in these malignant cell clusters, confirming EBV-encoded RNA positivity. (**Figure 2**).

Several differential diagnoses were considered despite the progressive swelling of the left cervical lymph node, including tuberculous lymphadenitis, primary lymphoma, and metastatic cervical lymph node from an occult NPC.

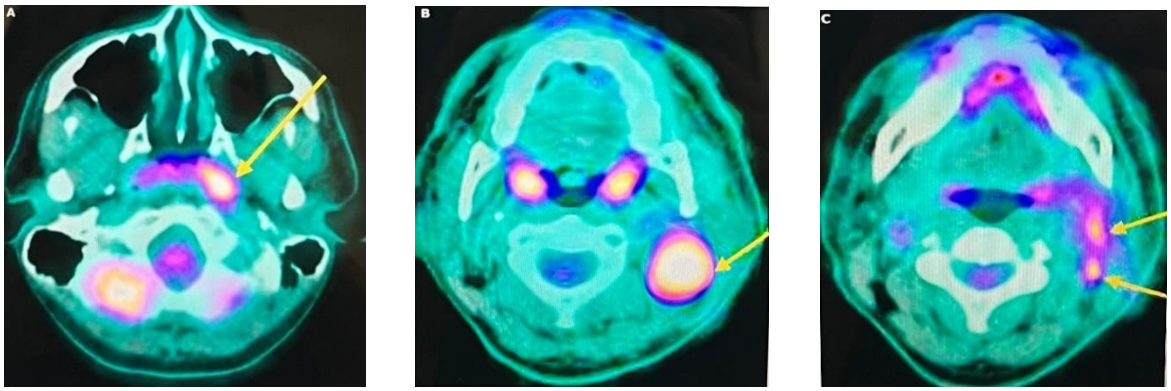


Figure 1. Positron emission tomography-computed tomography (PET-CT) showed (A). A hypermetabolic left nasopharyngeal lesion with maximum standardized uptake value (SUVmax: 11.43), arrow. (B) A hypermetabolic 4.5 cm left cervical lymph node that underwent fine needle aspiration (FNA), arrows. (C) Multiple hypermetabolic regional lymph nodes along the left cervical chain, arrow.

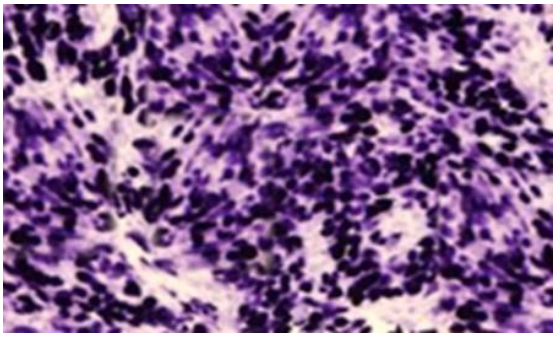


Figure 2. Microscopic examination of the left cervical lymph node biopsy with Epstein-Barr virus-encoded RNA in situ hybridization (EBER-ISH) test demonstrated intense and diffuse dark nuclear staining in malignant cell clusters that confirmed EBV-encoded RNA positivity. (400x)

Diagnostic assessment

A primary tumor biopsy through nasopharyngeal endoscopy was not performed because the patient refused it due to severe anxiety about the procedure. This refusal came from both intense anxiety about the procedure and the patient's concern that an invasive transnasal procedure would produce unclear results which his initial nasopharyngeal endoscopy showed completely normal mucosa with no visible mass. The patient worried about undergoing a painful and invasive intervention that had a high risk of sampling error and false-negative results. Clinically, this concern was well-founded. Performing a blind primary tumor biopsy on normal-looking mucosa often requires repeated samplings which can lead to mucosal damage and significantly delay the start of treatment.

In this situation, our clinical decision-making focused on the urgent need to prevent serious treatment delays. A prolonged examination for primary histology through repeated invasive procedures may lead to local tumor growth or distant metastasis. Quantitative plasma EBV DNA load was also considered as an alternative in this case. However, plasma EBV DNA does not provide tissue-specific localization, which increases the risk of false negatives in early-stage disease. Therefore, we chose a diagnostic approach that combines an EBER-ISH test on a cervical lymph node biopsy with PET-CT imaging.

Therapeutic intervention

Consequently, the clinical staging was determined as T1N1M0 based on the AJCC 8th edition.[6] Following a multidisciplinary tumor board decision, the patient received definitive external beam radiotherapy (EBRT) with with intensity-modulated radiotherapy (IMRT) technique directed to the nasopharynx and bilateral regional lymph nodes (total dose of 70 Gy in 33 fractions) combined with concurrent weekly cisplatin (40 mg/m^2).2.007 [7,8]

Follow-up and outcomes

At the 6-month post-treatment follow-up, surveillance PET-CT imaging demonstrated a complete metabolic response of the primary nasopharyngeal lesion and cervical lymph nodes. The patient remained asymptomatic with no clinical or radiological evidence of locoregional recurrence.

Patient perspective

This successful outcome shows an important clinical lesson: in a specific situation where a primary tumor biopsy is not possible or is refused due to valid clinical concerns about inconclusive results, this combined non-invasive method provides sufficient diagnostic certainty to safely deliver an effective concurrent chemoradiotherapy.

Timeline

- **Month 0:** The patient underwent fine-needle aspiration (FNA) of the left cervical lymph node. Histopathology revealed undifferentiated metastatic squamous cell carcinoma, and the EBER-ISH test was positive. Baseline PET-CT imaging demonstrated a hypermetabolic lesion in the left nasopharynx (fossa of Rosenmüller) with SUVmax of 11.43 and multiple hypermetabolic regional lymph nodes of the left cervical chain (the largest measuring 4.5 cm) with no distant metastasis identified.
- **Month 1:** A clinical diagnosis of T1N1M0 NPC was established based on a comprehensive evaluation by a multidisciplinary team. Definitive concurrent chemoradiotherapy (CCRT) was initiated based on the guidelines.
- **Month 7:** The treatment was completed with mild to moderate side effects (mucositis, dysphagia, and hyperpigmentation) which were relieved 2-3 weeks post-treatment.
- **Month 13 (6-month post-treatment):** The patient remained completely asymptomatic during follow-up, which included endoscopic evaluation and surveillance PET-CT imaging.

DISCUSSION

Nasopharyngeal carcinoma in a patient who presents with an occult primary tumor will significantly complicate the initial diagnostic workflow. The differential diagnosis for adult cervical lymphadenopathy is broad, including metastatic carcinoma, lymphoma, tuberculosis, and infectious lymphadenitis. A delay in determining the primary nasopharyngeal site can lead to misdirected therapies or unnecessary invasive surgical procedures.[7,9]

In cases of metastatic undifferentiated carcinoma with cervical lymph node involvement, a positive EBER-ISH test is considered pathognomonic for NPC.[10,11] While circulating plasma EBV DNA is highly sensitive for screening and monitoring, a positive liquid biopsy alone cannot substitute for tissue-based diagnosis and probably has false-negative results in early-stage disease.[10] Plasma EBV DNA is a useful tool for screening, but its clinical value can be limited because of its reliance on tumor volume and cell shedding patterns, which can sometimes result in false-negative outcomes in early T-stage tumors. On the other hand, EBER-ISH targets the abundant EBV-encoded RNAs found only in the nuclei of cancer cells which means that EBER-ISH is largely unaffected by systemic viral clearance rates and, as a result, it provides a better diagnostic yield for identifying the viral cause of undifferentiated cervical lymph node metastases.[12-15]

The EBER-ISH test has high sensitivity and specificity for identifying occult NPC, establishing it as a highly reliable diagnostic tool when a primary biopsy cannot be performed.[3,11] In this patient, positive nuclear staining from the cervical lymph node FNA (**Figure 2**) provided definitive evidence of an EBV-associated carcinoma despite the inconclusive nasopharyngeal endoscopy. These findings show that undifferentiated metastatic squamous cell carcinoma with strong nuclear staining confirms a positive EBER-ISH test which is pathognomonic for nasopharyngeal carcinoma metastasis. When a standard primary tumor biopsy is compared with EBER-ISH, especially if obtained from normal-appearing nasopharyngeal mucosa, EBER-ISH shows a clear diagnostic benefit. Standard primary tumor biopsy often has a high false-negative rate because of sampling error in occult or submucosal lesions. In contrast, EBER-ISH performed on a cervical lymph node biopsy has very high sensitivity and specificity for EBV-related cancers.[11] This makes it a safer and more dependable option than invasive primary tumor biopsy.

The clinical use of PET-CT imaging is recommended for managing carcinoma of unknown primary in the head and neck, as primary NPC lesions typically show increased FDG uptake even when not visible on endoscopy.[4,5] Meta-analyses indicate that PET-CT has a high sensitivity of more than 90% for identifying occult nasopharyngeal primaries in patients presenting with cervical lymph node metastasis.[16] In certain situations where tissue from the primary tumor is difficult or not possible to obtain, PET-CT imaging can serve as an alternative to replace histopathological confirmation. It offers a clear 'metabolic signature' of the primary tumor reflecting increased glucose metabolism.[17] In this case, the presence of a hypermetabolic lesion in the left nasopharyngeal (SUVmax 11.43, **Figure 1A**) paired with EBER-ISH positivity from the cervical lymph node biopsy (**Figure 1B**) fulfilled the diagnostic criteria for clinical NPC, circumventing the need for a primary tissue biopsy.[18] This combined diagnostic modality effectively avoids treatment delays and is supported by international guidelines.[7]

However, relying only on the EBER-ISH test and PET-CT imaging without a primary tumor biopsy carries potential diagnostic pitfalls that clinicians must be mindful of. High FDG uptake from PET-CT imaging in the nasopharynx can resemble normal lymphoid tissue growth or chronic nasopharyngitis and additionally, some rare EBV-related cancers, such as lymphoma, can also have positive results for the EBER-ISH test.[19] Therefore, it is essential to compare the tumor morphology from the cervical lymph node biopsy to confirm metastatic carcinoma rather than other malignancies to avoid misdiagnosis.

Nasopharyngeal brushing cytology with EBV testing is another option, but it requires visible nasopharyngeal mucosa. For this patient, the EBER-ISH test was the least invasive procedure that provided a definitive diagnosis when he refused a primary tumor biopsy.

Management without primary histology followed multidisciplinary discussions and aligns with National Comprehensive Cancer Network guidelines for EBV-positive cervical lymph node metastases with an unknown primary.[7] A multicentre study supported definitive radiotherapy to the nasopharynx and bilateral neck for EBER-positive cases of unknown primaries, reporting 3-year locoregional control and overall survival rate of 90%, matching the outcomes of histologically confirmed primary tumors.[20] The patient underwent EBRT with IMRT technique, receiving 70 Gy in 33 fractions with weekly concurrent cisplatin at 40 mg/m². He achieved a complete metabolic response at the 6-month follow-up which is consistent with these reported outcomes.

This case report has several limitations that need to be acknowledged. First, the absence of primary tumor histology prevents a histopathological confirmation of the nasopharyngeal lesion which can give a diagnostic bias and cannot completely rule out other lesions in the head and neck area. Second, since this is a single case report, the findings have limited relevance to a larger group which cannot automatically apply the clinical outcomes to all patients with occult NPC. Third, although the patient had a complete metabolic response, the follow-up period after treatment is only 6 months. A much longer period for clinical and imaging monitoring is recommended to evaluate the potential of late locoregional recurrence or distant metastasis. Despite these issues, the high concordance between EBER-ISH test positivity and PET-CT imaging provides a practical diagnostic alternative in this difficult clinical situation.

CONCLUSION

The EBER-ISH test on a cervical lymph node biopsy, along with PET-CT imaging findings, can reliably confirm the diagnosis of T1N1M0 occult NPC when a primary tumor biopsy is refused or not possible. This combined diagnostic procedure allows for timely treatment initiation and prevents delays that can occur with therapy failure. Clinicians should consider the EBER-ISH test for all undifferentiated cervical lymph node metastases, as it offers a clear, tissue-based diagnosis when a standard primary biopsy cannot be performed. However, definitive treatment decisions should always be based on comprehensive evaluation by a multidisciplinary team. This approach helps to ensure the best and most personalized clinical outcomes. It is important to note that this combined approach is not a universal substitute for a standard primary tumor biopsy in every clinical situation. Instead, it is a practical alternative used only in specific cases where a primary tumor biopsy is not possible, the primary lesion is occult, or when the patient refuses invasive procedures.

INFORMED CONSENT FOR PUBLICATION

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

ETHICAL APPROVAL
Not applicable.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY
Data supporting this case report are available from the corresponding author upon reasonable request, subject to patient confidentiality.

AUTHOR CONTRIBUTIONS
The author confirms being the sole contributor of this manuscript and has approved it for publication.

DECLARATION OF USING AI IN THE WRITING PROCESS
The author has nothing to declare regarding the use of generative AI or AI-assisted technologies in the writing process of this manuscript.

LIST OF ABBREVIATIONS
Nasopharyngeal carcinoma (NPC), Epstein-Barr virus-encoded RNA in situ hybridization (EBER-ISH), Positron Emission Tomography-Computed Tomography (PET-CT), Epstein-Barr Virus (EBV).

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