—Original Article—

Clinical application of endonasopharyngeal ultrasound-guided transnasopharyngeal needle aspiration in the diagnosis of submucosal nasopharyngeal carcinoma

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ABSTRACT

Background and Objectives: Submucosal nasopharyngeal carcinoma (NPC) is a rare type, which is usually difficult to obtain tissue samples. We aimed to evaluate the diagnostic yield and safety of a new technique of endonasopharyngeal ultrasound-guided transnasopharyngeal needle aspiration (ENUS-TNNA) for submucosal NPC. **Subjects and Methods:** This was a retrospective study. Between March 2018 and September 2019, 11 patients with submucosal nasopharyngeal neoplasms detected with previously computed tomography or magnetic resonance imaging underwent ENUS-TNNA. All patients had cytological evaluation by smears and tissue evaluation of aspiration specimens. Mean and rate. **Results:** There were seven males and four females, with ages ranging from 33 to 77 years. Needle puncture biopsies were successfully performed in all cases, and sufficient tissue sample for histopathological examination was obtained from each of the 11 patients. Of the 11 patients, nine of these patients were diagnosed using ENUS-TNNA without on-site cytology assistance, false negative in two cases. The sensitivity of the ENUS-TNNA technique in diagnosing submucosal NPC was 81.82%. In the absence of any major complications, the procedure was uneventful. **Conclusions:** ENUS-TNNA is a safe and effective method to provide a pathological diagnosis of submucosal growth type of nasopharyngeal neoplasms, which has a great clinical value.

Key words: endonasopharyngeal ultrasound-guided transnasopharyngeal needle aspiration, submucosal nasopharyngeal carcinoma, ultrasonic bronchoscope

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is one of the most common malignant tumors in the head-and-neck region. NPC is more common in southern China, especially in Hong Kong and Guangdong Province.[1] Definitive diagnosis is typically achieved by endoscopy-guided biopsy

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of the primary nasopharyngeal tumor and subsequently confirmed by histopathological examination. However, given difficulties in tissue sampling, the pathological diagnosis of a submucosal growth pattern in NPC is not easy to obtain.

A retrospective review was performed on the 11 patients on whom an endonasopharyngeal ultrasound-guided transnasopharyngeal needle aspiration (ENUS-TNNA) was performed between March 20, 2018, and September 24, 2019. The aim of the study was to evaluate the diagnostic yield and safety of ENUS-TNNA for the diagnosis of submucosal growth type of nasopharyngeal neoplasms.

SUBJECTS AND METHODS

Characteristics of patients

Among the 11 newly diagnosed patients included in the study, seven were male and four were female. The mean age was 52.6 years (range: 33–77 years). To date, indications for ENUS-TNNA examination include: (1) clinical diagnosis of NPC was made by head-and-neck computed tomography (CT) or magnetic resonance imaging (MRI) [Figure 1a-c], (2) no remarkable abnormalities were found by nasopharyngoscopy, or the mucosa of the nasopharynx is locally raised, but the surface is smooth [Figure 1d], (3) no obvious disorder of microvascular in nasopharynx mucosa was detected under the mode of narrow-band imaging,[2] and (4) no serious complications or important organ dysfunctions, and the patient could tolerate the procedure.

Endonasopharyngeal ultrasound-guided transnasopharyngeal needle aspiration

The experimental protocol was approved by the Ethics Committee of Sichuan Cancer Hospital. The same endoscopist (Zhen-Ming Zhang) performed all the ENUS-TNNA procedures. ENUS-TNNAs were performed with the patients under total intravenous anesthesia or local anesthesia (using 2% lidocaine hydrochloride mucilage only) that depends on the patient's choice. A linear array ultrasonic bronchoscope (BF-UC260F-OL8, Olympus Ltd., Tokyo, Japan) was employed for the puncture procedure [Figure 2a]. The operating portion of the endoscope is

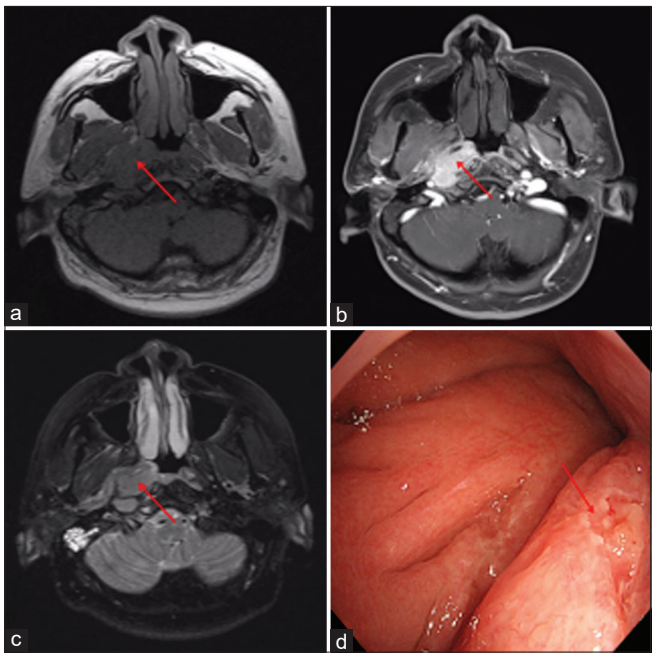

Figure 1. Representative images of the head-and-neck magnetic resonance imaging and nasopharyngoscopy. (a) The submucosal lesion exhibited isointense T1 signals on T1-weighed images (arrow). (b) After contrast scanning on T1-weighed image, the tumor was obviously enhanced (arrow). (c) The signal intensity of the tumor revealed a slightly long T2 on the T2-weighed image (arrow). (d) Nasopharyngoscopy revealed no remarkable abnormalities with the exception of thickening of the right torus, and the previous biopsy site can be seen on it (arrow)

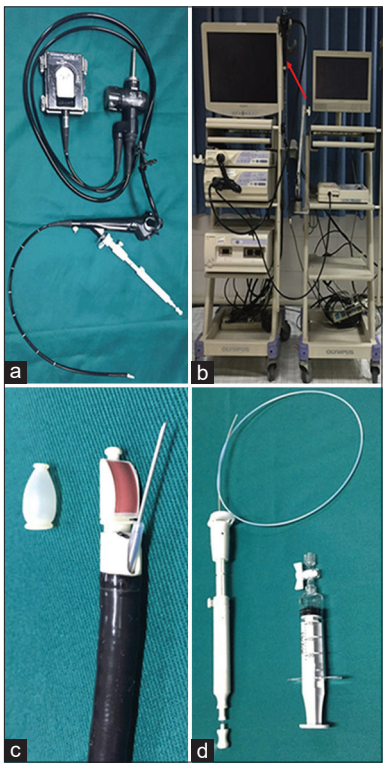

Figure 2. Apparatuses used for the procedure of endonasopharyngeal ultrasound-guided transnasopharyngeal needle aspiration. (a) An ultrasonic bronchoscope with a puncture needle inserted. (b) An ultrasonic bronchoscope (arrow) was linked to the video processor (left) and ultrasound processor (right). (c) A water-inflatable balloon and the distal end of the ultrasonic bronchoscope with an electronic convex array ultrasonic transducer and a 21G needle introduced through the biopsy channel. (d) A dedicated 21G puncture needle and a syringe used during the procedure

similar to a common bronchoscope. The outer diameter of the insertion tube is 6.2 mm. The working length is 600 mm (total length: 890 mm), and the endoscope has a 2.0-mm biopsy channel. The angulation range of the distal end of the bronchoscope is 120° upward and 90° downward. A 30° oblique forward-viewing fiber-optic lens was embedded adjacent to the end of the biopsy channel (angle of view 80°). The instrument has a small curved electronic convex array ultrasound transducer that is 6.9 mm in diameter and mounted at the distal end of the endoscope [Figure 2c]. A scanning frequency of 7.5 MHz was performed with a maximal penetration depth of 50 mm. The scanning direction is parallel to the longitudinal axis of the endoscope with a scanning angle of 50°. The ultrasonic bronchoscope was then linked to an ultrasound processor (EU-C2000, Olympus Ltd., Tokyo, Japan) and video processor (CV-260SL, Olympus Ltd., Tokyo, Japan) [Figure 2b]. A water-inflatable balloon (MAJ-1351, Olympus Ltd., Tokyo, Japan) was mounted around the transducer for better ultrasonic coupling with the nasopharyngeal wall [Figure 2c], and a dedicated 21G needle (NA-201SX-4021, Olympus Ltd., Tokyo, Japan) was used for aspiration of targeted submucosal lesion [Figure 2d].

The ultrasonic bronchoscope was then inserted to the nasopharyngeal cavity through the nasal cavity, and target lesions were then examined by ENUS [Figure 3a]. Transnasopharyngeal needle biopsies were performed with a needle introduced through the biopsy channel of the endoscope. Before puncturing, color power Doppler ultrasound was used to exclude the presence of vessels within the planned puncture area. Under the guidance of real-time ultrasound, the needle was placed into the target lesion [Figure 3b]. Suction was added with a syringe, and the needle was moved back and forth inside the lesion. Two or more needle aspirations were performed to obtain sufficient histology material [Figure 3c]. No on-site cytological evaluation was used. Next, liquid-based cytology was smeared and assessed by an experienced cytopathologist [Figure 3d]. Aspirated histology specimens were then formalin-fixed and examined by a pathologist. Finally, the nasopharyngoscope was placed to the nasopharynx again to verify the absence of bleeding from the biopsy sites.

RESULTS

The ENUS-TNNA biopsy was performed successfully on 11 patients, including 8 cases of the right nasopharynx and 3 cases of the left nasopharynx. The average time of puncture was 20.7 min (range: 11–50). A mean of 3.36 (range: 2–6) puncture attempts were performed at each aspiration site. No major complications, such as major bleeding, persistent bleeding, or infection of the nasopharynx, were reported.

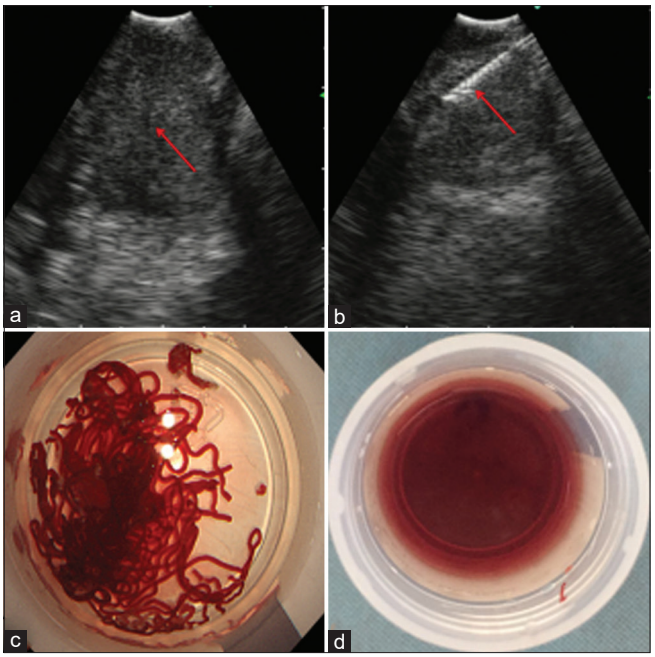

Figure 3. Submucosal nasopharyngeal carcinoma diagnosed by endonasopharyngeal ultrasound-guided transnasopharyngeal needle aspiration in a 33-year-old patient. (a) Endonasopharyngeal ultrasonography showed an abnormally low echo signal next to the right wall of the nasopharynx (arrow). (b) A 21G needle penetrating into the submucosal lesion of the right sidewall of the nasopharynx with heterogeneous low echo (arrow). (c) Aspirated histology specimens obtained during endonasopharyngeal ultrasound-guided transnasopharyngeal needle aspiration. (d) Liquid-based cytology obtained during endonasopharyngeal ultrasound-guided transnasopharyngeal needle aspiration

Among all the 11 patients who accepted ENUS-TNNA, the nine nasopharyngeal nonkeratinizing carcinoma diagnoses were clarified by the procedure [Figure 4a-d] and two negative cases were found, sensitivity was 81.82%.

DISCUSSION

NPC, which has a close relationship with Epstein–Barr virus infection, is a squamous cell carcinoma arising from the nasopharyngeal cavity. Currently, several methods are available for making a clinical diagnosis for patients with a suspected NPC, including nasopharyngoscopy, multislice MRI, and CT of the nasopharynx and base of the skull and neck. In

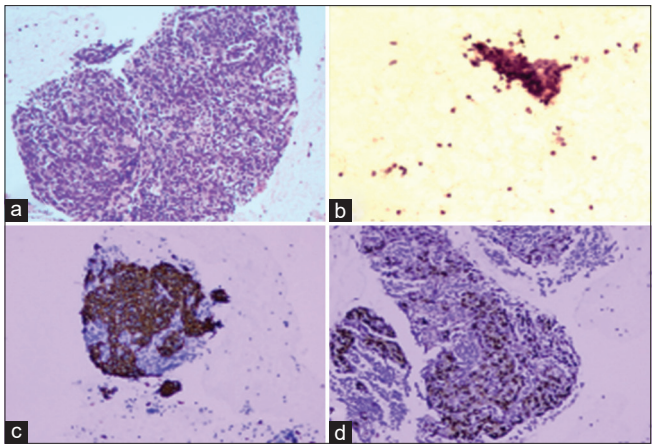

Figure 4. Pathological examination demonstrated nonkeratinizing squamous cell carcinoma. (a) Histological findings indicate clusters of atypical epithelial cells (×100). (b) Cytological results showing atypical epithelial cells with large irregular nuclei (H and E, ×100). (c) Immunohistochemistry showed positive staining for CK19 (×200). (d) Immunocytochemical staining for positive Epstein–Barr virus-encoded RNA demonstrating a network of epithelial cells infected by Epstein–Barr virus (×200)

addition, the use of positron emission tomography-CT is also effective in the detection of an occult primary tumor in the nasopharynx or distant metastatic disease. However, pathological examination is the gold standard for the final diagnosis of an NPC; thus, biopsy of the primary abnormality in the nasopharynx is required for a definitive diagnosis. In clinical practice, the clinically commonly used techniques for pathological diagnosis of an NPC include endoscopy-guided biopsy of primary sites under direct visualization and ultrasound-guided fine-needle aspiration biopsy of enlarged cervical nodes. Conventionally, the current clinical standard of endoscopy and endoscopy-guided biopsy can be used as an effective tool for tissue sampling for most patients. Submucosal nasopharyngeal neoplasms is very uncommon, comprising only 8.8% of all tumors in the nasopharynx.[3] However, given diffiulties in tissue sampling, the pathological diagnosis of a submucosal growth pattern in NPC is not easy to obtain.

In the literature, several techniques are clinically designed to obtain specimens from submucosal nasopharyngeal lesions, such as deep site biopsy with large biopsy forceps, CT-guided needle biopsy, and core-needle biopsy. However, each of these methods has limitations. Conventional deep biopsy with large biopsy forceps has the disadvantages of increased trauma, bleeding, and pain due to mucosal tears in the nasopharynx.[4] Some researchers advocated CT-guided percutaneous puncture biopsy as a useful alternative approach for the diagnosis of NPC in the parapharyngeal space.[5] However, this procedure is relatively complicated and requires advanced skills. Moreover, given the complexity of anatomical features in the head and the increased number of tissues involved during the puncture procedure, a high risk of injury to major blood vessels and nerves may be encountered. Recently, Li *et al*.[6] reported preliminary outcomes of core-needle biopsy through the nasal route. In their study, superiorities of minimal trauma, reduced bleeding, shorter operative time, and less pain were provided. However, given its "blind" nature, the relationship between tumors and surrounding tissues should be carefully assessed through MRI or CT images before puncture, and the biopsy point, needle path, and direction should also be precisely designed. In addition, the injury risk of main blood vessels and nerves during the entire procedure is also problematic, especially for the internal carotid artery.

Convex probe endobronchial ultrasound was initially developed for the evaluation of lymph node staging in 2002. With an embedded ultrasound probe on the tip of the bronchoscope and a special aspiration biopsy needle, this device can perform real-time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). Only a few years after the initial invention in 2002, EBUS-TBNA had been recommended as an important tool for preoperative evaluation by the US National Comprehensive Cancer Network and American College of Chest Physicians in 2007.[7,8] In a recent multicentered randomized controlled trial, Navani *et al*.[9] reported a sensitivity of 92%, a negative predictive value of 90%, and an accuracy of 95% of EBUS-TBNA performed in 66 patients with suspected lung cancer. In addition, EBUS-TBNA reduces the time to treatment decision compared with conventional approaches. In another study, including 11 studies with 1299 patients, EBUS-TBNA had a pooled sensitivity of 0.93 and a pooled specificity of 1.00.[10] As a safe, effective, and less invasive tool for the diagnosis and staging of lung cancer, EBUS-TBNA has been used worldwide.

Inspired by the great success of EBUS-TBNA in lung cancer, we innovatively and successfully performed ENUS-TNNA with a linear array ultrasonic bronchoscope in patients with the clinical diagnosis of NPC under the normal nasopharyngeal mucosa. Through careful literature review, the technique of EUS-FNA through the nasopharynx has been previously reported.[11,12] In their reports, the authors

successfully performed fine-needle aspiration of retropharyngeal lymph nodes guided by EUS in patients with suspected recurrence of NPC. Unlike their reports, we here describe the successful and unique application of ENUS-TNNA for the diagnosis of primary submucosal nasopharyngeal lesions. As far as we know, this is the first study of submucosal nasopharyngeal neoplasms diagnosed by ENUS-TNNA, and we provide a new method of targeted biopsy for the diagnosis of NPC under the normal mucosa.

The sensitivity of ENUS-TNNA in diagnosing submucosal type of NPC, as revealed in the present study, was 81.82%, inferior to results from prior studies involving the diagnosis of lung cancer using the technique of EBUS-TBNA.[13] A possible reason for these false-negative cases might be the endoscopists' lack of experience in performing ENUS-TNNA. In addition, an ultrasonic bronchoscope was originally designed to diagnose lung cancer and lymph node staging on the basis of anatomic features of the lower respiratory tract, not for NPC; thus, this may have an impact on the diagnostic yield. Finally, the unique anatomical structure of the nasopharynx makes it difficult to scan the submucosal lesions of the nasopharynx with a built-in ultrasound probe on the tip of a bronchoscope; thus, this may have an influence on the detection of the submucosal neoplasms.

Compared with traditional biopsy methods, the advantages of the ENUS-TNNA procedure are as follows. First, ENUS-TNNA provides better outcomes in terms of reduced trauma and blood loss due to its tiny biopsy site with the use of a dedicated needle, and the function of integrated color power Doppler ultrasound also avoids unintended punctures of vessels between the wall of the nasopharynx and lesions. In addition, under real-time ultrasound guidance, it is easier to accurately target a biopsy compared with conventional methods, and the operator could choose the best puncture sites and puncture direction at any time if necessary. Furthermore, specimens obtained during the procedure are suitable for histological examination with the use of a 21G needle, and liquid-based cytology also assists in the identification of tumor cells. Finally, the ENUS-TNNA procedure may reduce the time required for a pathological diagnosis, and the subsequent therapy could be immediately administered.

CONCLUSION

ENUS-TNNA is a safe, effective, and minimally invasive approach with a high diagnostic yield for diagnosing submucosal growth type of nasopharyngeal neoplasms. More experience and further studies are needed to evaluate the validity of this technique.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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