Case Report

Carcinoma of unknown primary detected by whole-body diffusion-weighted imaging: A case report and review of the literature

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A B S T R A C T
Carcinoma of unknown primary accounts for 2%-5% of all head and neck tumors. Identification of the primary site is challenging. We present a case report of a 43-year-old man with metastatic cervical lymphadenopathy for 3 years, and the primary tumor was unknown after routine examinations, including positron emission tomography/computed tomography. Whole-body diffusion-weighted imaging was performed to detect small lesions in the nasopharynx, and a biopsy confirmed the lesions as squamous cell carcinoma. Therefore, the primary tumor site was found in a patient with carcinoma of unknown primary, suggesting that whole-body diffusion-weighted imaging can be very helpful in detecting small occult cancer.

Introduction
Carcinoma of unknown primary (CUP) is a metastatic malignancy with an unknown origin of the primary tumor. Approximately 2%-5% of head and neck tumors are CUPS [1], among which the most common type is squamous cell carcinoma (SCC) [2]. It is difficult to determine the therapeutic strategies for CUPs in clinical practice, which usually results in a poor outcome [3]. Therefore, an effective approach for determine the primary tumor is importantly and urgently needed. Various new imaging and endoscopy technologies, such as positron emission tomography/computed tomography (PET/CT), narrow band imaging combined with magnifying endoscopy [4], and transoral robotic surgery [5], may identify the primary tumor site in 44%-71% of cases when

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Fig. 1 – Nasopharyngeal CT scan, nasopharyngoscopy and microscopic views of biopsy (HE × 200) of the patient. CT scan (A) and nasopharyngoscopy (B) show that the nasopharyngeal morphology is normal. A biopsy of a suspected thickening of the mucosa in the posterior parietal wall of the nasopharynx suggests chronic inflammation (C).

traditional methods are unsuccessful, but the primary lesions of a small number patients still cannot be detected. In this case report, we present an occult nasopharyngeal carcinoma (NPC) detected by whole-body diffusion-weighted imaging (WB-DWI) but missed by all other examinations. WB-DWI, a modern diffusion-weighted imaging (DWI) technique introduced by Takahara et al. in 2004, can illustrate tumors clearly, similar to 18F-fluorodeoxyglucose PET/CT (18F-FDG PET/CT) [6], is free of ionizing radiation and is noninvasive. WB-DWI has been shown to be effective for tumor detection, but has not yet been applied for occult NPC.

Case presentation

A 43-year-old man presented to our hospital with a 3-year history of painless nodules on the left side of neck. He observed a peanut-sized mass on the left side of his neck in 2015, and 3 years later, another walnut-sized mass was found beneath the first mass, with no epistaxis. His personal history included twenty years of smoking (an average of 30 cigarettes a day) and occasional drinking.

Physical examination showed that many enlarged lymph nodes could be touched in the posterior border and root of the sternocleidomastoid muscle in the left side of neck, with a hard texture, clear boundaries, a smooth surface, and partially good activity. The lymph nodes were not adhered to the surrounding tissue, and the largest lymph node was approximately 2 cm × 2.5 cm.

After admission to our hospital, the patient underwent left cervical lymphadenectomy, and postoperative pathology indicated metastatic SCC. Then, we attempted to find the primary tumor, but all examination results were negative, including: (1) laboratory examinations: tumor markers and circulating cell-free Epstein-Barr virus DNA; (2) esophagoscopy: esophageal and gastric mucosa heterotopia but no abnormality in the pharynx; (3) laryngoscopy: lymphoid follicle hyperplasia in the posterior pharyngeal wall and the root of the tongue but no abnormalities in the hypopharynx and throat; (4) neck and nasopharynx CT: multiple enlarged lymph nodes at the left cervical root and normally shaped nasopharynx without thickening (Fig. 1A); (5) nasopharyngoscopy: no abnormality in the nasopharynx except for suspected thickened mucous membrane in the posterior parietal wall of the nasopharynx and chronic mucosal inflammation on biopsy (Fig. 1B and C); (6) MRI scan (including T1WI, T2WI, DWI and contrast enhanced T1WI) of the neck and nasopharynx (Fig. 2A-F): multiple enlarged lymph nodes in the bilateral deep neck and left supraclavicular fossa, with the larger one located in the left cervical V area (about 1.7 × 1.2 cm) (Fig. 2A and B), as well as normal nasopharyngeal morphology without abnormal signal, and clear pharynx recess (Fig. 2C-F); (7) chest and abdomen CT: no obvious mass or nodule; (8) 18F-FDG PET/CT covering the areas from the skull to the mid-thigh (Fig. 2G-I): multiple enlarged lymph nodes on the left side of neck with mild increased uptake of FDG, which we suspected was an inflammatory lesion, and no increased uptake of FDG in the rest. Following the above examinations, to determine the origin of the metastatic disease, a random endoscopic biopsy of the suspected mucous membrane within the oropharynx and hypopharynx and even tonsilllectomy were further considered. However, after consultation in our hospital, we proposed to perform a WB-DWI scan instead because random biopsy is invasive and may still miss the lesion. Encouragingly, WB-DWI in the craniocaudal direction covering the areas from the vertex to the upper thigh revealed multiple lesions in the bilateral pharyngeal recesses and the adjacent bilateral retropharyngeal space, as well as the bilateral submandibular region, deep neck and left supraclavicular fossa (Fig. 3A-E). Then, an endoscopic biopsy targeting the site of the abnormality identified on WB-DWI (the right nasopharyngeal submucosal tissue) confirmed the lesion as a nonkeratinizing SCC (Fig. 3F and G). The primary site was located to avoid random biopsy for the patient.

The patient underwent chemotherapy (docetaxel and nedaplatin) combined with radiotherapy, and his lymph nodes in the neck were reduced at the subsequent follow-ups, although at a slower rate than that of other patients.

Discussion

We present an occult NPC detected by WB-DWI but missed by all other routine examinations, and we are the first to report a case of WB-DWI detecting an occult NPC in a patient with CUP. Small NPCs may have slow initial growth and are challenging to screen [7]. The clinical presentations of NPCs include epistaxis, conductive hearing loss, unilateral nasal obstruction,
Fig. 2 – MRI scan of the neck and nasopharynx and \(^{18}\text{F}\)-FDG PET/CT of the patient. Transaxial axial T2-weighted images (A) and coronal Gd-enhanced T1-weighted images (B) with fat suppression reveal multiple large cervical lymphadenopathies, and the lesions are hyperintense on T2WI with remarkable homogenous enhancement, the largest lesion is located in the left cervical V area (arrow), with no primary tumor detectable in the neck. Transaxial axial T2-weighted images with fat suppression (C) and Gd-enhanced T1-weighted images (D) show that the nasopharyngeal morphology is normal. DWI b600 (E) and the corresponding ADC map (F) show no abnormal signal. \(^{18}\text{F}\)-FDG PET/CT in axial views (G, H) show mild-to- high uptake of FDG in the left side of the neck, and this nodule was diagnosed as an inflammatory lesion, \(^{18}\text{F}\)-FDG PET/CT (I) shows negative detection for tumors in the rest of the body. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; \(^{18}\text{F}\)-FDG, \(^{18}\text{F}\)-fluorodeoxyglucose.

Fig. 3 – Inverted WB-DWI scan and nasopharyngeal endoscopy and microscopic views of an endoscopic biopsy (HE × 200) of the patient. WB-DWI maximum intensity projection image (A, B) shows nasopharyngeal lesions (long arrows) and multiple cervical lymph nodes (short arrows); WB-DWI b800 axial image (C, D, E) show nasopharyngeal lesions in the bilateral pharyngeal recesses (thick arrows), retropharyngeal lymph node (thin arrows) and multiple enlarged neck lymph nodes (short arrows). Nasopharyngeal endoscopy (F) shows that the left nasopharyngeal mucosa is normal. Endoscopic biopsy of the submucosal tissue targeting the site of the abnormality identified from WB-DWI reveals nonkeratinizing squamous cell carcinoma (G). WB-DWI, whole-body diffusion-weighted imaging.
and cranial nerve palsies [8]. Additionally, NPCs commonly spread to superior deep cervical lymphatic nodes, and a few patients may show only cervical masses [9]. Consistent with this, the patient in this case presented with a painless mass on the left side of the neck without any other symptoms. Although presenting with an atypical symptom, the patient was suspected of having NPC and underwent a random sampling biopsy after admission to our hospital, but endoscopic biopsy showed chronic mucosal inflammation.

The diagnosis and treatment of early-stage NPCs can improve the outcome, and the 5-year survival rate can reach approximately 80%, but for advanced-stage NPC, it decreases to less than 50% [10]. Endoscopic biopsy is one of the most common examinations for identifying the vast majority of NPCs [11], but it may miss the diagnosis of some small primary tumors that are hidden in the nasopharynx side recess and the submucosa. However, MRI (T2/T1-weighted conventional MRI) as another common examination method can find some NPCs missed by endoscopy. In general, the accuracy of MRI in detecting NPCs is approximately 95%, among which 10% cannot be observed by nasopharyngoscopy [12,13]. If the combination of nasopharyngoscopy with conventional MRI is used to detect NPCs, most of them can be diagnosed, but a small percentage of T1 NPCs still cannot be observed, because these tumors are diffuse and symmetrical and do not result in a focal mass [12]. Recent evidence indicates that 18F-FDG PET/CT may be a more sensitive response for this tumor than conventional MRI or nasopharyngoscopy [14], but unfortunately in this case, it did not work, possibly due to the poor FDG uptake of this tumor [15]. Another examination for early-stage NPC screening is the plasma Epstein-Barr virus DNA test, with 97.1% sensitivity and 98.6% specificity [8], but it had a false-negative result in this case.

This case was considered a CUP after all above mentioned examinations had been performed. To find the primary lesion, blind biopsy of the suspected mucous membrane, tonsillectomy or even removal of the tongue tonsil would be conducted in turn according to clinical practice [16–18], which may be a last resort for seeking out the primary lesion, although they may still miss the diagnosis [16]. Before blind biopsy, we attempted to use WB-DWI to detect the primary site of CUP. Fortunately, the primary lesion was found by WB-DWI, so the patient avoided unnecessary damage.

DWI, a form of functional MRI, has been employed in the assessment of various malignancies. DWI can reflect the alteration of cell-water homeostasis, cell density and cytoarchitecture, so it may identify the tumor prior to its undergoing a morphological change [11,19]. DWI has also been applied in the assessment of NPCs. For example, DWI can differentiate cervical lymph node metastases of NPC from non-metastatic NPC [11], as well as NPCs from benign hyperplasia (lesions larger than 5 mm) [20]. However, in this case, DWI could not find the primary lesion. We think there are, at least, 2 possible reasons for this: (1) the spatial resolution of DWI is not very high; and (2) image distortion and artifacts at the air-bone interface affected the observation. In contrast, WB-DWI may overcome the shortcomings of DWI.

WB-DWI, a modern diffusion-weighted imaging technique introduced by Takahara et al., can indicate tumors more clearly than DWI by suppressing the background body signal and provides high spatial resolution images, similar to 18F-FDG PET/CT [6]. Unlike DWI, WB-DWI uses the short tau inversion recovery sequence in place of the conventional spectral presaturation inversion recovery sequence for suppressing fat interference, allowing it to stably and reliably inhibit the background; the sensitivity encoding technique can effectively shorten the time of the backward wave chain needed for single-shot echo planar imaging to reduce artifacts and image aberrations and ensure a high spatial-resolution image [21]. Moreover, WB-DWI has excellent reproducibility and good interobserver agreement for reading the images [22]. In addition, WB-DWI can be used to assess primary malignancies and distant metastases via large-scale scanning in a short period of time. However, WB-DWI has not been reported in the detection of occult NPCs. In this case report, WB-DWI demonstrated obvious advantages in detecting the primary lesions of occult NPC, thus providing guidance for accurate biopsy. To better observe the location of lesions, we suggest combining the 3-dimensional maximum intensity projection reconstruction images of WB-DWI with the sectional images because 3-dimensional maximum intensity projection reconstruction images have a certain amount of overlap and artifacts.

Conclusion

Our case report and previous reports have demonstrated that NPC cannot be ruled out when the nasopharynx is of normal shape and there are no hypermetabolic lesions detected by 18F-FDG PET/CT. WB-DWI should be a complementary strategy to detect occult NPCs and may be a highly useful approach for finding the primary site of cervical metastatic carcinoma that cannot detected using the usual methods of investigation.

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