Case report

Comprehensive evaluation on cancer of unknown primary site and how we managed it: A case report

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ABSTRACT

Introduction and importance: Cancer of unknown primary site (CUP) is metastatic cancer without primary tumor found from comprehensive medical history, physical examination, and regular laboratory examination. Eighty percent of CUP include unfavorable groups with 3 to 6 months of median survival despite chemotherapy treatment.

Case presentation: A 52-year-old male was presented with a chief complaint of a recurrent lump in the neck and axilla. After comprehensive examinations over three years, the primary site of the metastatic tumor could not be found. Therefore, this patient was diagnosed with cancer of an unknown primary site.

Clinical discussion: In patient with CUP, more precise therapy can only begin when the exact form of cancer is identified. However, the delay in diagnosis would worsen the patient's condition, as treatment measures cannot be implemented.

Conclusion: Trimodal modalities including surgery, chemotherapy, and radiotherapy are suitable for CUP with squamous cell carcinoma proven in immunohistochemistry evaluation.

1. Introduction

Cancer of unknown primary site (CUP) is a type of metastatic cancer in which the underlying tumor is undetected using the conventional diagnostic method (history taking, physical examination, and regular laboratory tests). CUP is not only a singular disease but also is a diverse group of cancers with a wide range of manifestations that tend to metastasize early [1]. CUP accounts for approximately 2 to 5% of new cancer cases every year worldwide. Moreover, it is often identified in individuals who have severe and rapid progressing metastasis-related symptoms. It is the sixth to eighth most prevalent cancer worldwide and the third to the fourth most prevalent cause of cancer-related death [2,3]. Because of the difficulty in finding the organ of origin, CUPs of epithelial origin (the majority of cases) are treated with empiric chemotherapy. The overall survival rate is 12 months and this remains almost constant over the previous years [2].

The evidence for germline CUP susceptibility is weak and familial studies cannot prove it. This is because malignancies in relatives may be coincidental and unrelated to genetic predisposition. Environmental factor such as smoking was found to be correlated to the pathogenesis of CUP. There are two proposed mechanisms on how metastasis occurs preceding the primary tumor growth of CUP. First, the cells spread into the metastatic sites and modify the microenvironment, resulting in metastasis before the cells in the primary site become detectable or transform into malignant type. Second, the tumor microenvironment supports inhibition of the growth of genetically similar cells in the primary site and supports the growth of tumor cells at the metastatic site, resulting in metastasis without parallel progression [4].

CUP is commonly manifested by metastases in the lymph nodes (40–45%), lung (30–40%), liver (30–40%), bone (25–35%), and pleura
(5–15%). The majority of patients (75–85%) have disseminated metastases. Only 15 to 25% of patients have solitary metastases or metastasis confined to lymph nodes. The severity of CUP symptoms is influenced by the organs involved and the degree of metastasis. Furthermore, in mostly asymptomatic individuals, the diagnosis might be achieved as a secondary or accidental finding of radiological imaging [5].

Based on the clinical manifestation and clinicopathological characteristics, the patients are divided into two groups, favorable group (15–20%) and unfavorable group (80–95%). The favorable group has 10 to 16 months median survival and 30 to 60% long-term disease control. On the other side, the unfavorable group has 3 to 6 months median survival despite treatments [4,6]. Several factors have been associated with poor prognosis, including male gender, multiple brain metastases, adenocarcinoma type of histology, and involvements of pleural/lung, aerobic bacteria, and other systemic diseases.

Fig. 1. PET Scan showing uptake on the right tonsil and multiple lymphadenopathies.
liver, and adrenal [7].

The neuroendocrine tumors treatment is protocol-specific, where squamous cell CUP is treated as primary head and neck cancers. Moreover, adenocarcinoma and undifferentiated CUPs are managed with a combination of a platinum-based regimen and a more specialized treatment for rare patients. A novel therapeutic approach based on molecular profiling is suggested, which is linked with treatment benefits in 96% of cases. CUP has at least one clinically relevant genetic mutation that can impact the targeted treatment. Biomarkers such as epigenetic modifications and small non-coding RNAs are being developed for helping patients gain access to more targeted treatments and increase their life expectancy. Liquid biopsy for CUP patients may be able to reveal druggable changes in a non-invasive manner [3,8]. This case report has been reported in line with the SCARE 2020 criteria [9].

2. Presentation of case

A 52-year-old male came to the first hospital (a private hospital) in October 2018 with a chief complaint of a neck lump with a size of a marble on the right side of the neck without changes in color, any pain, or wound. The patient did not have a history of tuberculosis infection, no complaints of night sweats, decreased appetite, fever, cough, difficulty in breathing, or chest pain. There was a complaint of decreased weight (3 kg in the last 3 months). The patient had been smoking for 20 years, 6 cigarettes a day, but stopped 3 years ago. There were no similar complaints or history of malignancy in the family. The patient was given antibiotics and the lump disappeared. Six months later (April 2019), there were multiple lumps reappeared with different sizes on the same site. Fine needle aspiration biopsy (FNAB) revealed a suspect of carcinoma metastasis with unknown origin. Two months later (June 2019), chest X-ray and abdomen ultrasonography was performed and the results came back negative. MSCT scan showed bilateral neck pathologic lymphadenopathy. Neck biopsy showed that there were undifferentiated carcinoma metastasis cells with salivary gland lymphoepithelial carcinoma as the differential diagnosis. Immunohistochemistry examination concluded metastasis of nonkeratinized squamous cell carcinoma in the lymph node. It showed AE1/AE3 positive; CK7, CK 20, TTF-1 negative; and p63 positive in some cells. In July 2019, a positron emission
tomography (PET) scan (Fig. 1) showed that there was a hypermetabolic lesion on the right tonsil and multiple hypermetabolic supraclavicular lymphadenopathies. Right tonsillectomy and biopsy were conducted by an otolaryngologist in August 2019. The result was a chronic hyperplasia right tonsilitis with Actinomyces found.

Then, bilateral radical neck dissection was performed by a surgical oncologist (intraoperative view provided in Fig. 2). The tissues were sent for pathology examination. From bilateral multiple lymph nodes on the level I to V; salivary gland lymphoepithelial cyst and salivary duct carcinoma lymph node metastasis were found (Fig. 3). Nasopharynx Magnetic resonance imaging (MRI) examination two months later (November 2019) showed that there were hypointense lesions with homogenous uptake after contrast and minimal diffusion restriction. The patient thereafter received combination chemotherapy, consisting of cisplatin and radiation therapy. Seven cycles of cisplatin treatment and 33 cycles of radiation therapy were done in two months period. After the treatment, the patient complained of a sore throat and swallowing difficulty. The patient adhered to the follow-up schedule until December 2020 with no complaint of a new lump.

In April 2021 (2.5 years after the first admission), this patient came to the second hospital (a national referral public hospital) with a chief complaint of a lump in the right axilla for 3 months before admission. The lump was originally in size of a marble that grew over 3 months to a size of an egg. On physical examination, scars were found on both sides of the neck (from the previous bilateral neck dissection) and a hard lump in size of 6 cm × 5 cm × 2 cm was found on the right side of the neck with characteristics of smooth surface, defined border, and no pain on pressure. On the right axilla, there were scan and hard, immobile lump with undefined border, no pain on pressure, and bumps on the surface.

Cytology of lymphadenopathy was performed on the current admission; however, the result came back as inconclusive. Ultrasonography examination (as shown in Fig. 4) showed that there were multiple lymphadenopathies with malignant characteristics in the right axilla. The biggest size of the tissue found was 3.9 cm in diameter. The pathology report from the biopsy in May 2021 showed that there were carcinoma metastases in the lymph nodes; however, the type and origin of the tumor were difficult to be determined. As shown in Fig. 5, a Chest CT scan showed right axilla lymphadenopathy without any other pathological lesion, nodule, or opacity in the lungs.

Nasopharynx CT scan with contrast (Fig. 6) showed that there was
not any mass in the bilateral of the nasopharynx, oropharynx, parotids, and sub mandible. However, there was an oval isohyperdense lesion with a defined border and no enhancement with contrast in size of $1.9 \times 2.2$ cm in the right intraocular. This intraocular lesion was the silicon injected to the eye for retinal detachment management in 2016.

The patient was then diagnosed with carcinoma of an unknown primary site (CUP) and was advised to get the axilla lymphadenopathy resected. Axilla dissection was done and the tissue was sent for pathology anatomy examination. Pathology examination revealed metastasis, which tended to be a high-grade mucoepidermoid carcinoma type. Lymphovascular invasion was also found. A follow-up CT scan examination revealed that there were no abnormalities in the nasopharynx, oropharynx, bilateral parotid glands. There was also no bilateral neck lymphadenopathy while the size and density of the right intraocular lesion were relatively the same as the previous scan.

3. Discussion

In patient with CUP, more precise therapy can only begin when the exact form of cancer is identified. Pharmacological treatment in CUP is less successful because of the lack of specific treatments. However, the delay in diagnosis would worsen the patient’s condition, as treatment measures cannot be implemented.

Based on previous studies, the median survival of CUP is less than one year. According to the study of 33,224 patients in Swedish, two essential factors determining CUP prognosis are sites of metastasis and histological type with the highest incidence in patients aged 85–89 years [10].

Several possible risk factors of CUP have been identified, including heavy smoking (26 or more cigarettes per day), larger waist circumference, low level of education (weak association), alcohol consumption,
human papillomavirus infection, and tumor suppressor protein (p16) overexpression [3].

The National Comprehensive Cancer Network (NCCN), The United States National Cancer Institute (NCI), and the European Society of Medical Oncology (ESMO) created a guideline regarding diagnostic workup in patients suspected of CUP. Diagnostic workup begins with comprehensive medical history with previous illnesses and treatments, physical examination including breast, genitourinary, and rectal examination. Laboratory tests and computed tomography (CT) scans of the chest, abdomen, and pelvis can also be done. For diagnosing CUP with neck lymph nodes involvement, PET/CT and multiparametric 3T-MRI (MP-MRI) are both equally accurate. The inquiry of choice for assessing the complete body state in a single examination is whole-body PET/CT. Following positive PET/CT results, MP-MRI is utilized to assess the local soft tissue metastases. For medical and predictive reasons, MP-MRI aids in tumor staging and determining the amount of tissue metastases [11].

On the PET scan, there was a positive result on the tonsil and multiple lymphadenopathies. Tonsillectomy and bilateral neck dissection were done and the tissues were sent to the pathologists. However, the result was chronic hyperplasia right tonsillitis with actinomycosis. Hence, hypermetabolic lesion in the right tonsil could be due to inflammation or focus of infection rather than neoplasm. Based on the MRI result, it was assumed that uptake of contrast could lead to suspicion of the tumoral lesion rather than only as a postoperative lesion.

Based on the immunohistochemistry examination, there are five morphological subtypes of CUP, which are neuroendocrine tumors (1%), poorly differentiated neoplasms (5%), squamous cell carcinoma (5%), poorly differentiated adenocarcinoma or undifferentiated carcinoma (29%), and well or moderately differentiated adenocarcinoma (60%) [12].

On the immunohistochemistry examination, our patient has squamous cell carcinoma. In patient with squamous cell carcinoma with the involvement of cervical lymph nodes, trimodal surgery consisting of surgery, chemotherapy, and radiotherapy are required [11]. These treatment modalities were performed on this patient before he came back with axilla lymphadenopathy on the last admission.

For further information on the possible primary tumor, immunohistochemistry staining can be used. In the beginning, the use of CK 7 and CK 20 staining combination can provide the information needed to determine the more specific IHC staining that needed to be done. In CK7+/CK20+, the samples can be assessed for pancreatic cancer, urothelial cancer with urothelin, and p63 as the next IHC staining examination, gastric cancer with CDX-2, and CDH17 as IHC staining examination, and cholangiocarcinoma [11]. Immunohistochemical staining was not performed in our patient due to the unavailability and high cost of such examination in our country.

Gene expression profiling and molecular mutation profiling are also available to aid the identification of the primary site and actionable molecular alterations. Specific gene expression profiles allow differentiation between solid tumors, providing valuable insight into the tissue of origin. More than 40 cancers and their subtypes can be identified with molecular cancer classifier assays (MCCAs). Several trials have shown that MCCA was more accurate compared to the IHC examination, especially for poorly differentiated neoplasm of unknown origin. On the other side, molecular mutation profiling can rarely determine the cancer types because it was made to detect oncogenes and other molecular alterations. Comprehensive molecular profiling has allowed targeted therapies to be tested in various advanced cancer types. However, the management of CUP through molecular profiling is still premature. In any solid tumor type, only a few targeted medicines are now indicated for first-line single therapy. In the treatment of many malignancies, chemotherapy combination still poses an essential role [13,14]. For individuals whose genetic profile can't identify tumor origin, empirical chemotherapy remains the treatment of choice [11].

4. Conclusion
CUP often presents late and difficult to diagnose, hence prompt diagnosis and treatment are required. Trimodal modalities consisting of surgery, chemotherapy, and radiotherapy are suitable for CUP with squamous cell carcinoma proven in immunohistochemistry evaluation.

Presentation at a meeting
None declared.

Declaration of competing interest
The authors declare that there is no conflict of interest in this case report.

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