

Differential diagnosis of cervical malignant lymphadenopathy among Iranian patients

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ABSTRACT

الأهداف: دراسة التشخيصات المختلفة في الحالات المحولة التي تعاني من وجود كتل في العنق يشتهى في كونها عقد لمفاوية خبيثة، وعلاقتها بالمتغيرات الجغرافية السكانية.

الطريقة: تم إعادة تقييم الأفراد الذين أدرجوا في هذه الدراسة ذات الشريحة المقطعية بواسطة التاريخ المرضي، الفحص السريري والدراسات التصويرية. تم الحصول على عينة من الإبرة الدقيقة (FNA). تبين وجود 232 حالة تعاني من المرض الخبيث، والتي تم تأكيد إصابتها عن طريق تقارير قسم الأمراض. خضعت الحالات التي تعاني من ورم أولي غير معروف للمزيد من الفحوصات والتي اشتملت على الفحص بالمنظار والمزيد من الدراسات التصويرية لتحديد موضع الورم الأولي. تم أخذ البيانات الجغرافية، نوع الجنس، العمر، مكان الورم، حجم الورم، والحالة المرضية للورم بعين الاعتبار. أجريت هذه الدراسة خلال الفترة ما بين مايو 1995م وحتى أبريل 2005م، في جامعة مشهد للعلوم الطبية - مشهد - إيران.

النتائج: أظهرت النتائج أن 50% من المرضى الذين تم تحويلهم وهم يعانون من وجود كتل في العنق وورم نسيجي جديد خبيث. كان الورم اللمفاوي هو الأكثر شيوعاً لدى المرضى الذين تقل أعمارهم عن 40 عاماً (55%)، وسرطان الدرقية (26%). بينما كان السرطان الغدي الحارشي الأكثر شيوعاً لدى المرضى الذين تزيد أعمارهم عن 40 عاماً (67%) (SCC). كانت العقد اللمفاوية الأكثر إصابة هي سلسلة العضلة ذات البطنين. كانت الخنجر والبلعوم التحتاني أكثر المصادر الرئيسية الشائعة للانتشار من مسلك العضلة ذات البطنين.

خاتمة: وفقاً لارتفاع الإصابة بالمرض الخبيث (50%) بين آفات العنق، يجب الأخذ بعين الاعتبار الكتل العنقية الغير متماثلة لدى البالغين كمرض خبيث حتى يتم إثبات العكس. يبدو أن العمر مهم جداً في التنبؤ بالنوع المرضي للورم وسوف يكون من المساعد في التحديد لإجراء المزيد من الفحوصات التشخيصية.

Objectives: To investigate the differential diagnosis in cases referred with neck lumps suspicious to malignant nodal masses and its relation to demographic variants.

Methods: Individuals who entered in this cross-sectional study conducted at the Department of Otolaryngology, Ghaem Medical Center, Mashhad, Iran from May 1995 to April 2005 were re-evaluated by history taking, physical examination and imaging studies. Fine needle aspiration was applied to obtain tissue sampling. Among the patients, 232 cases had malignant disease confirmed by pathology reports. Cases with unknown primary tumor underwent investigations including pan-endoscopy, and further imaging studies were carried out to determine the primary tumor site. Demographic data as gender, age, location, size, and pathology of tumor were considered.

Results: The results of this study showed that 50% of patients which were referred with neck masses had malignant neoplasm. The most common pathology in patients younger than 40 years were lymphoma (55%) and thyroid cancer (26%), whereas, in patients older than 40 years squamous cell carcinoma (67%) was more common. The most involved lymph nodes were jugulodigastric chain. Larynx and hypopharynx are the most common sources of aerodigestive tract metastatic.

Conclusion: According to high incidence malignancy (50%) among neck lesions, an asymmetrical neck mass in adults should be considered malignant until proven otherwise. It seems that age is an important predictor of tumor pathology, and determination of further diagnostic investigations would be helpful.

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Anatomical and surgical importance of the neck makes it a unique region despite its limited extension. More than one third of all lymph nodes in the body lie in the neck, therefore neck masses due to their inflammation are exceedingly common. As a primary barrier, cervical nodes are also an early predictive of malignant growth. However, beside lymphadenopathy, various causes can present as neck masses, which are categorized to 3 main groups of congenital disorders, inflammatory and neoplastic lesions. The initial management of a neck mass differs based on many factors among them age and location are more considerable. According to age patients are divided into 3 groups: pediatric (0-15 years of age), young adults (16-40 years of age) and older adults (older than 40 years of age).¹ Inflammation, congenital, and developmental disorders are the most common causes of neck masses in pediatric group, while in older patients malignancies are the main etiology. Location of neck lumps may have both diagnostic and prognostic value as similar to inflammatory diseases; distribution of head and neck carcinomas follows by specific lymphatic chain. Although the most important diagnostic step to identify the underlying pathology of a neck mass is physical examination, even the most precise examination should be followed by routine laboratory and imaging procedures. Many methods including radionuclide scanning, computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, arteriography, and sialography were applied, however, finding the origin and appropriate management of a neck mass is still a challenging problem as diagnostic measurements and work up processes are still under debate.² If the history, physical examination, and routine diagnostic tests could not define the diagnosis, any unknown neck mass must be considered as neoplastic lesion, and should undergo further investigation using fine-needle aspiration (FNA), open biopsy, endoscopy and guided biopsy and excisional biopsy.¹ As a general rule, any neck mass in adults should be approached as being neoplastic lesion.³ The incidence of malignant disease in a neck mass reported to be approximately 50% in adults.⁴ The neoplastic lesions of head and neck are grouped into unknown primary lesions and known primary lesions by presence of known primary neoplasm; each concerns special management.¹

This study evaluates the Iranian patients referred with unknown neck masses and defines the differential diagnosis of malignant cases with relation to demographic data including gender, age, and tumor location and size.

Methods. From May 1995 to April 2005, more than 500 adults with unknown neck masses suspicious to malignancy referred at the Department Otolaryngology of Ghaem Medical Center, Mashhad, Iran. Patients were

re-evaluated by history taking and physical examination followed by laboratory investigations and imaging studies. Patients in whom above primary survey was negative underwent FNA, excisional biopsy, endoscopy, and guided biopsy. All the collected samples were sent to the Department of Pathology for histological diagnosis. The pathology report for 232 cases confirmed malignant disease, which entered the study. Informed consent was obtained from all subjects prior to any investigations and this study was approved by the ethic committee of Mashhad University of Medical Sciences, Mashhad, Iran. Other reported pathologies were inflammatory lymphadenopathy, cysts and benign process, which were excluded from study. According to pathology reports, further investigations performed to determine the exact site of primary tumor in metastatic cases. Demographic data including gender, age, location, and size of adenopathy and tumor pathology were considered. Patients were divided into 2 groups of young adults (15-40 years) and old adults (older than 40 years).

We used the Statistical Package for the Social Science version 11.5 to analyze the data and to determine the relationship between tumor pathology and demographic data.

Results. During the study course, more than 500 adults with unknown neck masses, suspicious to malignant nodal masses were referred to our department, among them, we detected malignancy in 232 cases (50%). The patient with metastatic reports underwent further diagnostic investigations. The primary site of the tumor was detected in these patients except in 21 cases, which primary site was not recognized in spite of extensive evaluations. These individuals had squamous cell carcinoma (SCC) in their pathology report. These cases were omitted in further statistical analysis and determined as carcinoma of unknown origins or unknown primary site. Among the remained patients (n=211), there were 130 men (67%) and 81 women (33%) with an age ranged of 18-81 years (mean 47.02

Table 1 - Anatomical distribution of dissected nodes.

Region	Percentage
Jugulodigastric	30.5
Posterior chain	20.8
Sub-mandibular	15.8
Median jugular	15.8
Super clavicular	11.6
Submental	3.0
Inferior jugular	2.5

years). From these patients, 278 lymph nodes were isolated and studied (Table 1).

The histological distribution as shown in Table 2, revealed that SCC was the most common pathology of regardless to the age (45.9% of cases). Other common pathologies were lymphoma (26%), thyroid cancer (15%), and salivatory gland cancer (5%). When the samples were age adjusted it showed in patients older than 40 years old, SCC (67%), lymphoma (15%), and thyroid cancer (8%) were the most common pathologies, whereas in younger patients, lymphoma (55%), thyroid cancer (26%), and SCC (8%) were the most common. Further evaluations for determination of the primary tumor sites revealed that in 97% of cases the primary tumor site was in the head and neck area and only in 3%, a malignancy outside this region was responsible of adenopathy. Investigations revealed that larynx and hypopharynx were the most common site of metastatic SCC with the most detection in supraglott region. The SCC was more than 3 times common in men. The mean age of these patients was 57.3 years old (range 24-81 years). Most of the metastatic lymph nodes' size was <3 cm, whereas metastatic lymphadenopathies from nasopharynx SCC were 3-6 cm in size. The SCC of esophagus was more common than its adenocarcinoma.

The mean age for esophagus SCC was 59.5 years comparing to 55 years for esophagus adenocarcinoma. Jugulodigastric lymph nodes were the common site of metastasis from larynx and hypopharynx, whereas posterior chain was the common site for nasopharynx SCC. The major affected group of lymphadenopathy in esophageal SCC was supraclavicular nodes.

Lymphoma was the second pathology of malignant lymphadenopathies and the common cause in patient <40. Among the patients affected with lymphoma 61% (38 cases) were men and 39% (24 cases) were female. Two thirds of patients had Hodgkin lymphoma and one third had none-Hodgkin lymphoma. The mean age of patients with Hodgkin lymphoma was 6 years lower comparing to none-Hodgkin. The greatest number of affected lymphadenopathies sized <3 cm. Again, jugulodigastric lymph nodes had the most involvement. Thyroid cancer was the next malignancy in patients. The most common form was papillary thyroid cancer (81%). The mean age of patients with thyroid cancer was 34.5 years. Thyroid cancer was much frequent in females (68%). The jugulodigastric nodes, such as others, were the common affected groups. Among salivatory glands tumors, parotid gland tumors were more common. The mean age of affected patients was 38 years. Posterior

Table 2 - The pathologies of isolated neck masses and their corresponding primary sites.

Tumor pathology	Distribution			Tumor size (cm)			Age		
	Male	Female	Total	<3	3-6	>6	Minimum	Maximum	Mean
<i>Squamous cell carcinoma</i>	74	23	97 (45.9)	63	56	23	24	81	57.3
Larynx and hypopharynx	30	6	36	12	22	12	45	78	61.31
Nasopharynx	24	2	26	8	16	6	36	81	57.4
Esophagous	8	5	13	15	8	3	43	69	59.5
Tounge	2	10	12	18	8	-	24	70	52.6
Lip	4	-	4	4	-	2	54	68	60.5
Boucal	4	-	4	2	2	-	62	74	67.75
Oral base	2	-	2	2	-	-	40	44	42
<i>Lymphoma</i>	38	24	62 (29.4)	38	26	10	14	77	34.58
Hodgkin	24	18	42	24	16	6	14	44	32
Non-Hodgkin	14	6	20	14	10	4	8	77	37.7
<i>Thyroid cancer</i>	10	22	32 (15.1)	22	6	8	11	75	34.5
Papillary	6	20	26	18	4	6	11	75	43.53
Medulary	4	-	4	2	2	2	20	39	30
Follicular	-	2	2	2	-	-	24	36	30
<i>Salivatory gland carcinoma</i>	6	4	10 (4.7)	10	4	-	18	54	38
Parotid	4	2	6	7	2	-	21	50	35.5
Submandibular	-	2	2	1	2	-	18	48	38
Sublingual	2	-	2	2	-	-	24	54	39
Adenocarcinoma (esophagus)	2	2	4	1	4	4	20	74	55.5
Neuroblastoma	-	2	2	1	3	-	26	36	31
Melanoma	-	2	2	2	-	-	58	69	63.5
Breast cancer	-	2	2	2	-	-	30	54	42
Total	130	81	211	134	99	45	11	81	47

chain was the most common sites of metastasis for this pathology.

Discussion. Several researchers have studied the origin of metastatic cancer in patients with enlarged cervical lymph nodes.⁵⁻¹⁰ However, this study is a large study of cervicallymphadenopathy in a patient population with no previous reports. Like similar studies, this study revealed that occult head and neck cancer usually presents as a middle aged man complaining painless neck mass mainly in jugulodigastric or posterior chain region.^{8,10} An asymmetric neck mass in adults should be considered malignant until proven otherwise.¹¹ Previous studies also reported 50% incidence of neoplasia in adult neck masses, which was similar to data achieved in Iranian population.¹² Although we could detect the primary tumor in most of the patients, beside all the investigations it is impossible to determine the primary site of tumor in some metastatic head and neck cancers. This group is categorized as carcinoma of unknown origin. It presents with histological features of malignancy while the primary tumor is not usually seen.¹⁰ These metastases with unknown primary sites to cervical lymph nodes are rare and include 2-5% of all head and neck malignancies.¹¹ In our study, we could not detect the primary site of tumor in 21 cases (9%) in spite of numerous investigations categorized as unknown primary site carcinomas.

The important role of age in determination of probable neck mass pathology among malignant and none malignant causes malignant tumors also vary according to age. Therefore, the age seems to be an important predictor of underlying pathology and suggests further investigations. In patients <40 years, lymphoma (55%), and thyroid cancers (26%) should be considered as the most likely causes (81%). In this group, FNA would differentiate these pathologies and imaging studies including CT-scan, MRI, and ultrasonography would determine the original tumor site. Previous studies have demonstrated a sensitivity of 85% and specificity of 90%, would achieve using FNA for diagnosis cervical adenopathy.¹³ On the other hand, SCC is the most probable diagnosis (70%) in patients more than 40 years old. Unknown masses in patients in this group should be considered as an aerodigestive tract metastatic SCC unless proven otherwise. Larynx and hypopharynx are the common primary sites. In these cases, endoscopy and guided biopsy would determine the origin of malignancy. Previous studies are also considering the upper aerodigestive tract endoscopy if FNA was not diagnostic or if metastatic SCC is suggested.¹⁴ It is suggested that endoscopic biopsies should be taken of any suspicious

site detected by CT scan and also from base of tongue and nasopharynx. The location of lymphadenopathy itself does not lead to exact diagnosis, however as it is shown in previous studies¹⁵ it would help to categorize differential diagnosis. In posterior chain metastatic lymphadenopathy, carcinoma of nasopharynx should be suspected. Whereas metastatic lymphadenopathy with SCC pathology in jugulodigastric and middle jugular regions suggests other part of aerodigestive tract including larynx as origin of malignancies. Previous studies, showed that 85% of malignant nodes in the anterior triangle have their primary tumor in the head and neck.¹⁶ This knowledge would simplify further approach. Although most of the dissected nodes were less than 3 cm in diameter, the size of node is reported as an important predictor of malignancy and nodes larger than 3 cm should be considered as malignant.¹⁶

There were some limitations in our study: firstly, we missed some patients because of incomplete demographic profiles. Secondly, endoscopic investigations are operator dependent procedures and it may be responsible for reporting of varying percentage of unknown primary tumors detection in deferent studies. Finally, we could not follow up the cases with unknown primary site to find the underlying tumor as most of them referred for further investigations to other centers.

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Related topics

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