MALIGNANT AXILLARY LYMPHADENOPATHY - A PROBLEM FOR MANAGEMENT

C T Lim, R Nambiar

ABSTRACT

Axillary lymph node enlargement can be the first and only manifestation of malignancy. Although lymphoma and metastasis from melanoma, breast and lung cancers are known causes, the primary tumour may remain undetected in some cases despite exhaustive investigations. Therefore, once the diagnosis of malignancy is confirmed by clinical examination followed by histology, further investigations should be limited to a search for treatable malignancies only. Extensive investigations with a hope of discovering the primary is useless and not cost effective. Close follow up may occasionally reveal new clinical signs when further investigations can be justified.

This paper reports the clinical approach to diagnosis and management of such cases with examples of illustrative cases.

Keywords : axillary lymph node, metastasis, melanoma, breast carcinoma, lymphoma, lung carcinoma

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INTRODUCTION

Enlarged lymph nodes in the axilla, like cervical lymphadenopathy, may be the first presenting feature of malignancy in patients though this is less commonly encountered in clinical practice. Unlike cervical lymph node metastasis where the primary tumour is predominantly in the head and neck regions, malignancy in the axillary lymph nodes is usually due to lymphoma or metastasis from primary tumour in the breast, lung or skin. Less frequently the primary sites include thyroid gland, gastrointestinal tract and kidney.

The challenge in the management of a patient presenting with enlarged axillary lymph node lies in establishing the diagnosis of malignancy and the site and type of the occult primary tumour, both of which influence the treatment and prognosis of the patient. The four cases below represent a variety of malignancies which presented initially as "a lump in the armpit".

CASE 1

A 76-year-old Chinese man, presented with a right axillary lump and backache for one month. He had no other systemic symptoms whatsoever. On examination, his general condition was satisfactory. A firm mobile lump of 4 cm in diameter was palpated in the right axilla. His liver was palpable at 8 cm below the costal margin. Chest radiograph was normal but lumbar spine radiographs showed retrolisthesis of L3 vertebra over L4. The CT scan of abdomen confirmed hepatomegaly with multiple liver nodules, enlarged para-aortic lymph nodes and tumour in the L3 vertebral body. As the fine needle aspiration cytology of the axillary lymph node showed only lymphocytes, an excision biopsy of the lymph node was performed. Histology revealed follicular large cell non-Hodgkin lymphoma (Fig 1a & b). The patient was treated with chemotherapy and radiotherapy with satisfactory response.

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CASE 2

A 69-year-old Chinese lady, had a 3-cm diameter lump in her right axilla excised in a clinic one month prior to her consultation. The histology of the excised lump revealed adenocarcinoma. On examination, no abnormality was detected in her breasts. However, a mammogram demostrated a lesion suspicious of malignancy in her right breast (Fig 2a & b). A total mastectomy with axillary clearance was done. Histology confirmed a 1-cm diameter infiltrative duct carcinoma in the upper medial quadrant of the breast (Fig 2c). No further lymph node metastasis was detected in the excised axillary tissue. Following sugery, she was given Tamoxifen.

Fig 1a - Follicular lymphoma involving an axillary lymph node. (20X. H&E)

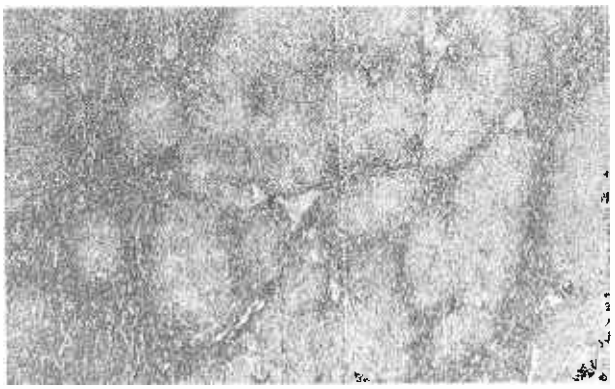
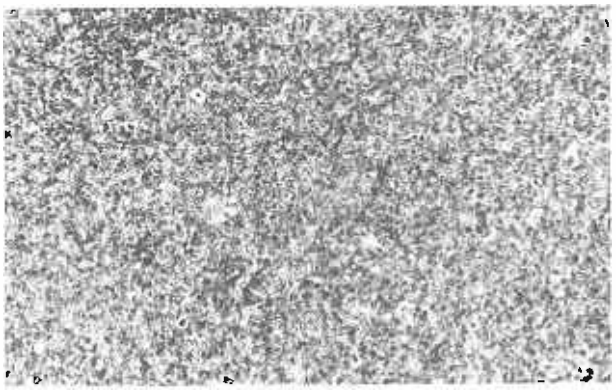


Fig 1b - Higher magnification showing an infiltrate of abnormal large lymphoid cells (200X. H&E)



CASE 3

A 24-year-old Chinese lady, complained of a lump in her right axilla for one month. The lump was gradually getting bigger and painful. Two years ago, she had a 0.5 cm diameter papillomatous lump on her right lateral chest wall excised by a general practitioner and the histology was reported as Spitz

Fig 2a & b - Mammograms of case 2. The clinically impalpable breast cancer lesion is seen as an area of fine microcalcification.

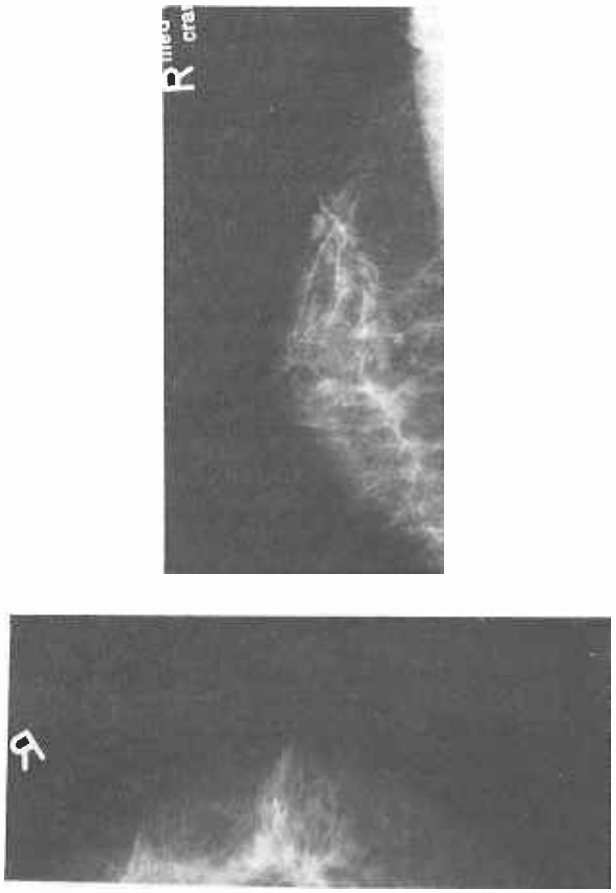
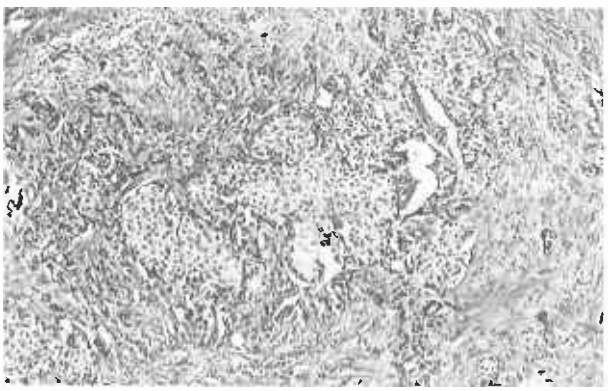


Fig 2c - Infiltrative lobular carcinoma of the breast which was not palpable and presented as a metastasis to the axillary lymph node. (100X. H&E)



naevus. On examination, a 4-cm diameter firm mobile lymph node was palpated in her right axilla. No lesion was detected in her breasts, chest and on the skin. Her liver was not palpable. Chest radiograph and mammogram did not reveal any lesion. Fine needle aspiration cytology of the lump did not indicate any malignancy. The lymph node was excised. Frozen section revealed carcinoma of undetermined origin. Further pathological evaluation including histochemical tests confirmed malignant melanoma (Fig 3a & 3b). A right axillary clearance was done but did not show any metastasis in the remaining lymph nodes. A review of the previously excised lump from the chest wall revealed it to be a melanoma. Four months after the axillary clearance, the patient was noted to be free of further metastasis.

CASE 4

A 63-year-old Chinese man, presented with a lump in his right armpit for two weeks. He had a long history of tobacco consumption. On examination, mild clubbing of his fingers were noted. A 2-cm diameter mobile lymph node was present in his right axilla. Clinical examination of his chest elicited signs of consolidation on the upper zone of his right lung and a chest radiograph showed this to be a large soft tissue mass in the right upper lobe (Fig 4a & b). Fine needle aspiration cytology yielded clumps of malignant cells with little cytoplasm (Fig 4c). Flexible bronchoscopy revealed tumour in the right upper bronchus which on biopsy was reported as oat cell carcinoma. He was given palliative radiotherapy.

Fig 3a - Fine needle aspirate cytology of a metastasis malignant melanoma. Tumour cells show abundant cytoplasm. (200X. H&E)

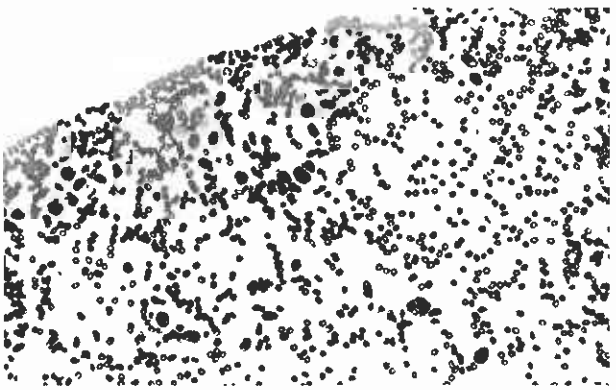
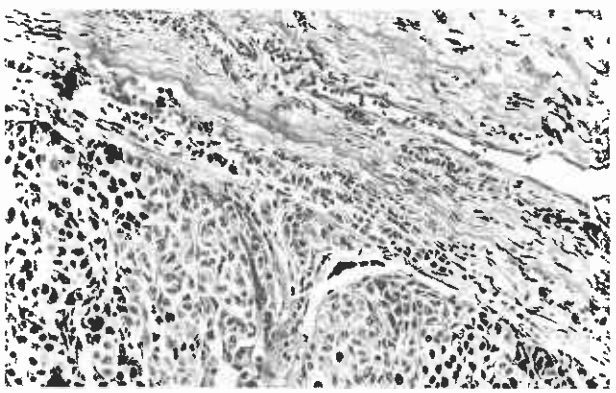


Fig 3b - Metastatic malignant melanoma invading the subcapsular sinus of an axillary lymph node. (200X. H&E)



DISCUSSION

Patients presenting with axillary lymphadenopathy are encountered not infrequently in clinical practice. Although the majority of the cases may be benign, the probability of metastatic lymphadenopathy being the first presenting symptom of malignancy is high. In a study of 72 patients presenting with unilateral axillary lymphadenopathy, 76.4% was due to benign lesions, lymphoma accounted for 13.9%, and metastases were found in the remaining 9.7%[1].

In women, the most likely primary site for metastasis in the axillary lymph nodes is the breast as seen in Case 2[2-7]. Rarely such a presentation can occur in man[6]. Primary tu-

Fig 4a - Chest X-ray of case 4 demonstrating a tumour in the upper zone of the right lung.

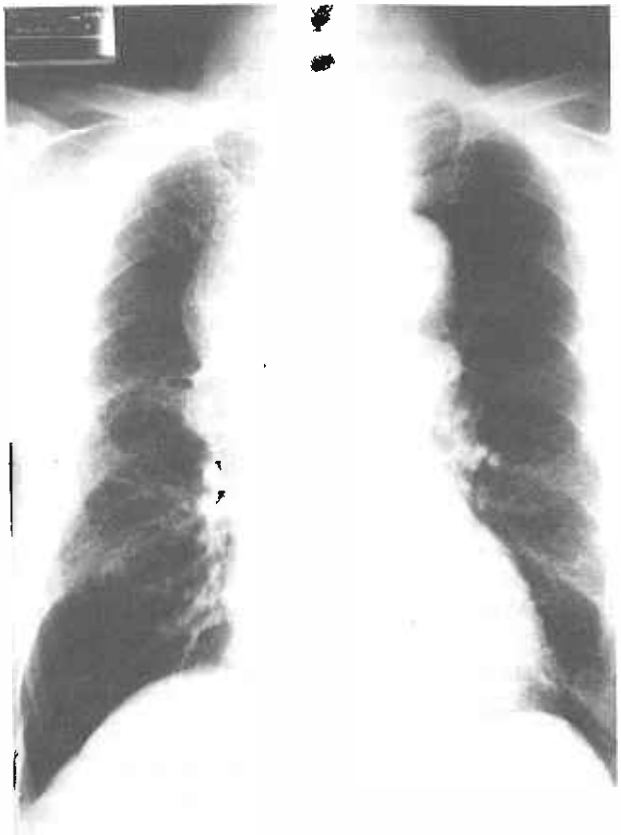


Fig 4b - CT scan of case 4 revealing a large solid lesion in the same reglon.

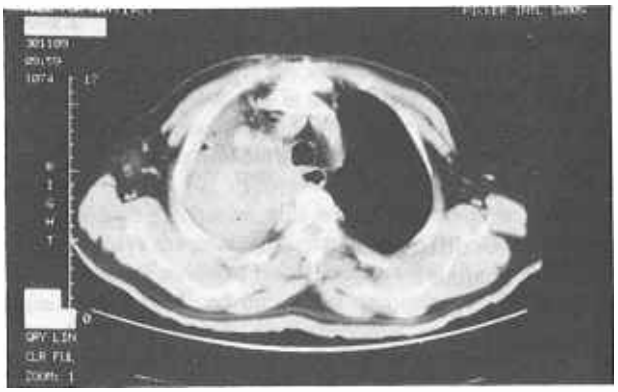
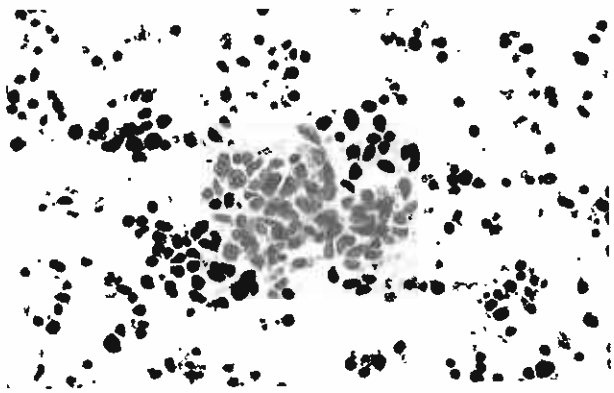


Fig 4c - Flne needle aspirate cytology of a metastlc at cell carcinoma to the axillary lymph node. Cluster of small cells with hyperchromatic nuclei showing nuclear moulding are seen. (200X. Papanicolau)



mours in the lung and skin are also common sources of metastases to the axillary lymph nodes as illustrated by three cases presented here. Less frequently, the axillary metastasis may arise from primary tumours in the thyroid gland, gastrointestinal tract, ovary and kidney[3-5].

In an adult, an enlarged, discrete axillary lymph node should be considered malignant, either metastatic or primary, till proven otherwise[4]. This was the clinical approach in all the four cases here. The management should begin with a detailed history and a thorough clinical examination of all possible primary sites (Fig 1). Initial imaging investigation should include a chest radiography and mammogram in women.

If the patient had undergone surgical removal of any skin lump, birth mark or other lesion, every attempt must be made to obtain the histological report as well as the histological slides of the excised specimen. A second histological opinion must be obtained to evaluate the diagnosis. Such effort was fruitful in Case 3, in whom a benign Spitz nevus was the initial diagnosis but on histological review, the diagnosis was confirmed to be a malignant melanoma. Unnecessary investigations for the occult primary tumour can be avoided in this way.

Histopathological Diagnosis

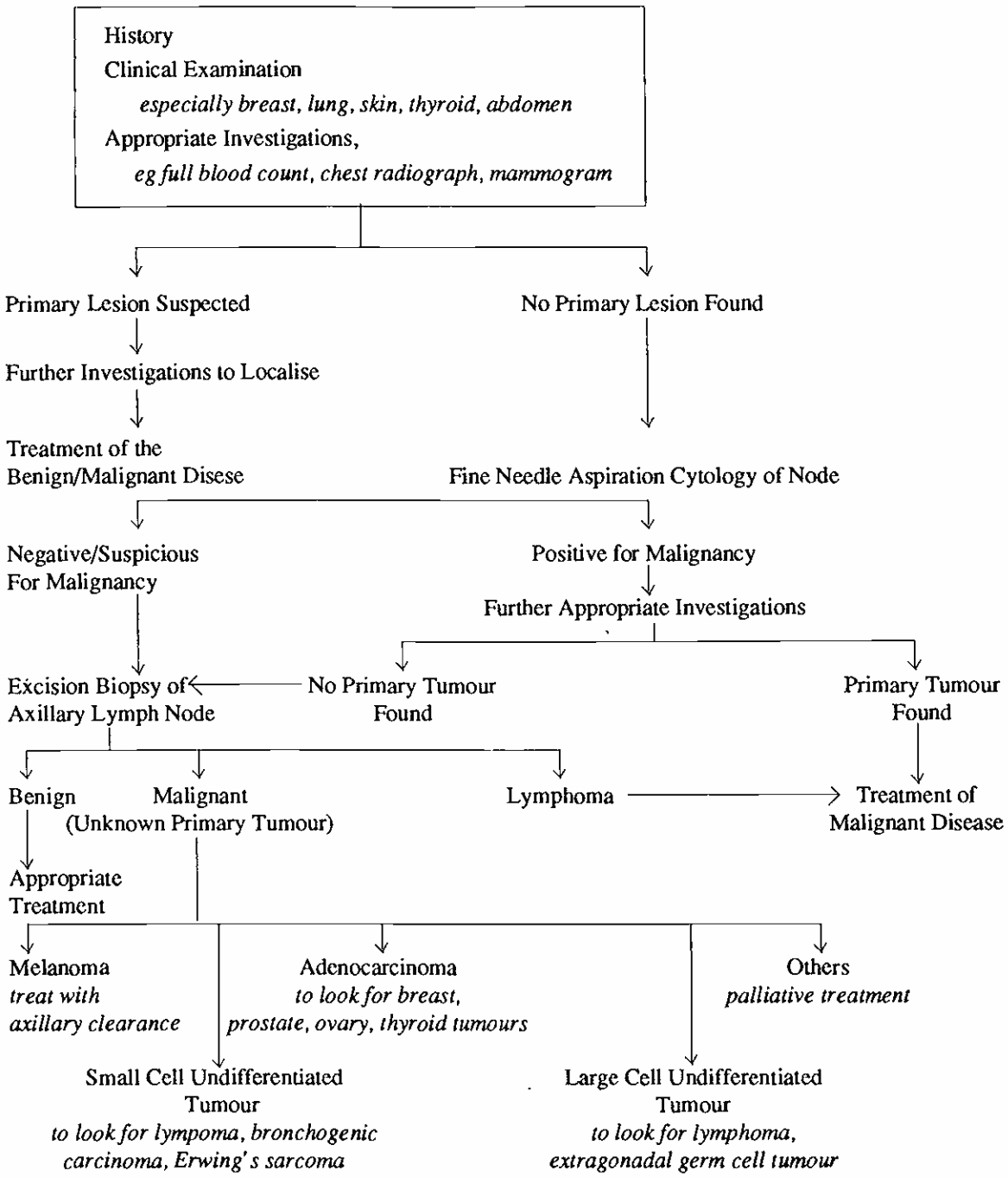
Fine needle aspiration cytology (FNAC) may provide a preliminary diagnosis of malignancy and aid the treatment plan. This procedure, performed in the clinic, is quick, easy and safe. However, an experienced pathologist must be available to examine the smears. The overall sensitivity of FNAC for metastases in superficial lymph nodes was found to be as high as 96.5%[8]. However, FNAC for lymphoma is known to be less accurate, being sensitive in only 67.5%. There were no false positive instances but the false negative rate was 11.3%. However, the diagnosis of benignity should not be confirmed without an open biopsy of the lymph node. If the FNAC is positive for malignancy and the primary lesion is still not identified at this stage, further investigations based on the cytology are done to locate the primary site. FNAC was done in three cases but the histological diagnosis was obtained in only one patient, Case 4. In Case 1, although lympohocytes were seen in the FNAC, the diagnosis of lymphoma could only be made on the excised lymph node. In Case 3, the type of malignancy was difficult to diagnose histologically and the diagnosis of malignant melanoma was concluded only after histochemical studies.

The most important step in patient management is to obtain an accurate histologic diagnosis, particularly in cases in which the FNAC reveals malignant cells and the primary lesion remains obscure. An excision biopsy of the lymph node should be done at this stage when the history, clinical examination and investigations are still inconclusive. However, excision biopsy of the lymph node must be avoided before the patient has been thoroughly evaluated for the occult primary tumour. This happened in Case 2 where the lymph node was excised before a mammogram was done. The clinician has to liaise closely with the pathologist when open biopsy of the lymph node is done. The whole lymph node should be excised and sent fresh to the pathologist who will portion it for frozen section, paraffin section, immunohistological studies, and electron microscopy[4,9]. The value of an experienced pathologist cannot be overemphasised in this exercise.

Occult Primary Tumour

Metastatic cancer from an occult primary tumour is defined as histologically proven metastatic carcinoma in which no primary site been identified despite a thorough history, careful physical examination and screening tests. This is found in 3 to

Plan of Management of Unilateral Axillary Lymph Node Enlargement



4% of all those presenting with malignancy[4]. This group of patients poses a challenging and somewhat controversial problem in diagnosis and treatment. The aim of identifying the primary site is to have a better directed treatment for the patient. Numerous studies have stressed the futility of over investigations; the time and expenses involved, the low detection rate, the lack of effective treatment when the primary is found, and above all, the stress and discomfort brought to an already symptomatic patient[4-10].

In a study of 254 patients with metastases from occult primary tumour, it was reported that median survival period was only nine months with a range of one to 215 months. The two year survival rate was 15%, the three year and five year rates were 11% and 9% respectively. Ninety-three percent died from the tumour while the remainder died from other causes[11].

In another report on 46 patients with metastatic adenocarcinoma or undifferentiated tumour from occult primary, the median survival period was only 20 weeks from the time of histologic diagnosis[12].

Although investigations are required to determine the site of the primary tumour as well as the extent of the disease, the success rate of identifying the primary site is low. In a review of 87 patients with unknown primary adenocarcinoma or undifferentiated carcinoma, the investigators could detect the primary tumour after extensive non surgical investigations in only 8 patients[13].

Greenberg and Lawrence[4] approached this problem by searching for the most treatable malignancies, when the pathologist is able to classify the metastasis into one of the three groups; adenocarcinoma, small cell undifferentiated cancer and large cell undifferentiated cancer. Treatable adenocarcinomas are breast, prostate, ovary and thyroid tumours. Treatable small cell cancers are bronchogenic carcinoma, lymphoma and

Ewing's sarcoma. Treatable large cell undifferentiated cancers include lymphoma and extragonadal germ cell tumour. This classification would determine the need for further investigations to locate the occult primary tumour.

If the primary tumour remains unidentified after extensive work-up, the clinician should stop further investigations and give supportive treatment to the patients with unknown primary adenocarcinoma and undifferentiated carcinoma as the median survival period is only about 20 weeks from the time of diagnosis. In some centres, empirical systemic chemotherapy, eg 5 flurouracil, doxorubicin and mithomycin C, is adminstered to these patients. Advocators of this treatment regime claimed a response rate of 30% and a median survival rate of 14 months for those who responded to the treatment, although the drug-related mortality rate was about 9%. Other investigators have not substantiated such optimistic results[4].

Occult breast carcinoma is defined as histologically proven carcinoma of the breast with axillary nodal involvement in a patient who has manifested no signs or symptoms of any abnormality of the breast[7]. The age distribution was similar to that of breast carcinoma in general. The reasons given for the failure to detect the primary site in the breast include the small size of the primary lesion, the deep location of the lesion within the breast, and surrounding inflammatory reaction[7].

Mammogram should be done and any suspicious lesion is biopsied with mammographic localisation before the axillary lump is excised. However, a negative mammogram does not rule out the presence of an occult breast tumour. Patel et al[5] reported six out of eight patients with axillary metastases and positive or suspicious mammography were found to have breast cancer, as compared to only four out of nine with negative mammography.

If there is no abnormality in the breast or a breast biopsy is normal, then an excision of the axillary mass is done. During excision, whether the lump is in the lymph node or in the tail of the breast should be determined. Estrogen and progesterone receptor assays should be done on the excised specimen as this may identify the primary tumour. Also, this may be the only opportunity to determine the steroid hormone receptor status of the malignancy because in some cases, after sectioning the excised breast tissue, the primary tumour is never found or the quantity of tumour tissue is inadequate for the hormone receptor analysis[9].

The high frequency with which the breast is ultimately found to have the primary tumour site has led many clinicians to recommend modified radical mastectomy. A primary breast tumour will be found on careful sectioning of the breast in over 50% of the cases. Radiotherapy without mastectomy as the primary treatment is usually not recommended. The survival rate of patients with occult breast cancer is similar or somewhat better than that of patients with clinically overt breast cancer[2-8,14,15].

The incidence of unknown primary melanoma is reported to be in the range of 4 to 9%. Typically, there is no history to suggest the primary tumour, and the diagnosis is made after biopsy of an enlarged lymph node or resection of a visceral metastasis[16]. Melanoma is postulated to arise de novo in lymph nodes, resulting in apparent lymph node metastasis with no obvious primary[17]. The most accepted explanation of unknown primary melanoma is the spontaneous regression of a primary cutaneous lesion.

The clinician must always find out if the patient has undergone any previous excision of "benign" mole or skin lump as in Case 3. If excision has been performed, the histologic specimen must be re-evaluated. In the physical examination, the skin is searched carefully for possible primary. Any suspicious lesion is biopsied. An ophthalmoscopy is done as well. The extent of metastases is also assessed in the physical examination and by chest radiography, liver function test, liver scan and brain scan. If these studies do not reveal disseminated disease, a radical lymphadenectomy of the axilla is performed[14,18].

The outcome of patients with unknown primary melanoma is highly variable, ranging from apparent cure to rapid tumour dissemination and death.

CONCLUSION

The four clinical cases presented here represent the common variety of malignancies that may occur in axillary lymph nodes. The clinician must be alert to the possibility of malignancy when an adult patient presents with a single large discrete lymph node in axilla. In the work-up to locate the primary tumour, the clinician must devise a plan of management that is cost-effective. A detailed history is taken, a thorough clinical examination conducted, relevant investigations carried out and FNAC done to determine the presence of malignancy in the axillary lymph node. If the FNAC is negative for malignancy or if the FNAC is positive for malignancy and the primary tumour remains unknown, an excision biopsy of the lymph node is carried out after liaising with the pathologist. The excised lymph node is sent fresh to the pathologist who will then perform the relevant analyses on the specimen to arrive at a diagnosis. The treatment and prognosis will depend entirely on the histological diagnosis.

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REFERENCES

1. Pierce EH, Gray HK, Dockerty MB. Surgical significance of the isolate axillary adenopathy. Ann Surg 1957; 145: 104-7.
2. Feigenberg Z, Zer M, Dintsman M. Axillary metastasis from an unknown primary source. Isr J Med 1976; 12: 1153-8.
3. Copeland EM, McBride CM. Axillary metastases from unknown primary sites. Ann Surg 1973; 178: 25-8.
4. Greenberg BR, Lawrence HJ. Metastatic cancer with unknown primary. Med Clin North Am 1988; 72: 1055-65.
5. Patel J, Nemoto T Rosner D et al. Axillary lymph node metastasis from an occult breast cancer. Cancer 1981; 47; 2923-7.
6. Feuerman L, Attie JN, Rosenberg B. Carcinoma in axillary lymph nodes as an indicator of breast cancer. Surg Gynecol & Obstet 1962; 114: 5-8.
7. Owen HW, Dockerty MB, Gray HK. Occult carcinoma of the breast. Surg Gynecol Obstet 1954; 98: 302-8.
8. Martelli G, Pilotti S Lepera P et al. Fine needle aspiration cytology in superficial lymph nodes: An analysis of 266 cases. Eur J Surg Oncol 1989; 15: 13-6.
9. Garbern AO, Rice P et al. Metastatic malignant disease of unknown origin. Am J Surg 1983; 145: 493-7.
10. Steckel RJ, Kagan AR. Diagnostic persistence in working up metastatic cancer with an unknown primary site. Radiology 1980; 134: 367-9.
11. Didolkar MS, Fanous N, Elias EG, Moore RH. Metastatic carcinomas from occult primary tumours. Ann Surg 1977; 186: 625-30.
12. McMillan JH, Levine E, Stephens RH. Computed tomography in evaluation of metastatic adenocarcinoma from an unknown primary site. Radiology 1982; 143: 143-6.
13. Stewart JF, Tattersall, Woods RL, Fox RM. Unknown primary adenocarcinoma: Incidence of overinvestigation and natural history. Br Med J 1979; 1: 1530-3.
14. Klop CT. Metastatic cancer of axillary lymph node without a demonstrable primary lesion. Ann Surg 1950; 1311: 437-9.
15. Osteen RT, Kopf G, Wilson RE. In pursuit of the unknown primary. Am J Surg 1978; 135: 494-8.

16. Giuliano AE, Moseley HS, Morton DL. Clinical aspects of unknown primary melanoma. Ann Surg 1980; 191: 98-104.
17. Gupta D, Bowden L, Berg J. Malignant melanoma of unknown origin. Surg Obstet Gynecol 1969; 128: 841-6.
18. Panagopoulos E. Metastatic malignant melanoma of unknown primary origin: A study of 30 cases. J Surg 1980; 191: 98-104.