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Metastasis of Unknown Origin with Mets to Right Inguinal Lymph Node

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Introduction

Metastatic cancer of unknown primary site (MUO) accounts for 3-5% of all malignant neoplasms, and it is defined as metastatic cancer from an unknown primary site, for which no original site can be detected even after performing all possible tests. The definition of MUO includes patients who present with histologically confirmed metastatic cancer in whom a detailed medical history, complete physical examination, full blood count and biochemistry, urinalysis and stool occult blood testing, histopathological review of biopsy material with the use of immunohistochemistry, chest radiography, computed tomo- graphy (CT) of the abdomen and pelvis and, in certain cases, mammography fail to identify the primary site. **[**1**]**

As the primary site, the lungs, the pancreas and the bile duct system, and the gastro- intestinal system were most prevalent. It was more difficult to find the primary lesion in poorly differentiated carcinoma cases.

The reporting of positron emission tomography (PET) scan in various fields- the diagnostic technique to find the unknown primary site has become became advanced. Nevertheless, until now, cases of which the origin could not be found are more abundant, and results cannot be obtained even by empirical therapeutic methods. Thus the diagnosis and therapy of MUO remains a real dilemma for practising oncologists.**[**2**]**

We experienced a case of squamous cell carcinoma of the inguinal lymph node from an unknown primary site, with no other accompanying tumours and thus this case is reported here together with a brief review of the literature.

Case Report

A 52-year-old gentleman consulted the Department of General Surgery at a Private Hospital, in the December 2022, with complaints of the presence of a wound over the anterio- medial aspect of right thigh at the inguinal region. n the right inguinal area. On the time of the initial visit, the general condition of patient appeared to be good, blood pressure was 120/70 mmHg, pulse was 70 beats/min and temperature was 36.2 C. There were no enlarged lymph nodes of the cervical and supraclavicular regions.

On systemic examination, chest auscultation revealed normal breathing sounds and heart beat, and no abnormal findings were detected in the abdomen, all limbs, the perineum, and the perianal area. The right inguinal lymph node was enlarged to 5 x 4 cm in size, was hard in consistency, non tender, non mobile, with overlying skin pinchable. No enlargement of lymph nodes in other areas was observed.

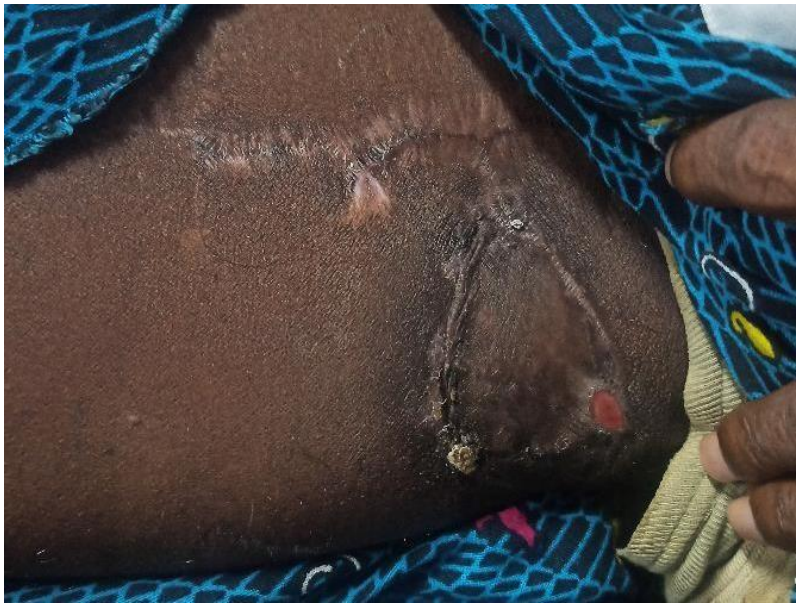
Histopathology of the lesion, was as follows :

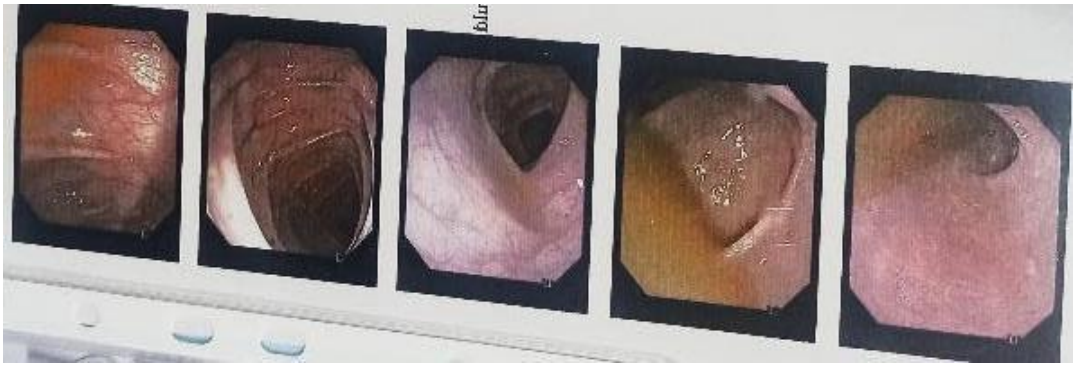
Gross - Elliptical bit of skin with grey white to yellowish soft tissue altogether measuring 5.5 x 2.5 x 3.5 cm, skin measuring 4.5 x 2 x 0.5 cm, cross section white nodule measuring 5 x 2 cm.

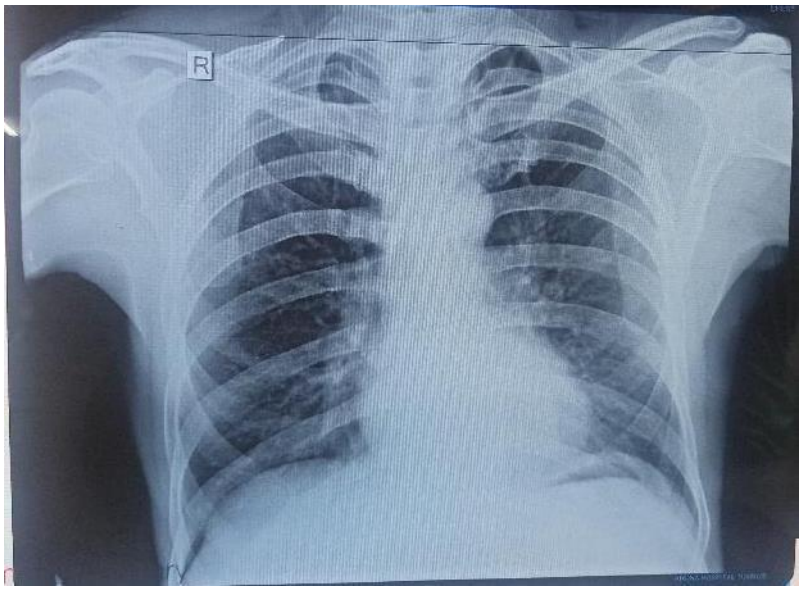
Microscopy - Skin with lesions tissue in the dorms showing capsule, residual lymphocytes and tumour deposits. Tumour is also seen outside the capsule. The tumour is composed of sheets and lobules of pleomorphic squamous cells with anisonucleosis, prominent eosinophilic nucleus and moderate amount of cytoplasm. Keratin pearl formation is also seen.

Impression - shows features suggestive of Moderately Differentiated Squamous cell carcinoma deposits.

Colonoscopy showed Normal Colonic mucosa.



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In complete blood cell count, hemoglobin was 10.1 g/dl, hematocrit was 29.9%, white blood cell count was 7,300/mm, and platelet count was 150,000/mm. The results of other examinations, including urinalysis, liver function tests and renal function tests, revealed no abnormalities.

Sigmoidoscopy, thyroid function test, chest x-ray, cardiac ultrasound, and pulmonary function test showed normal results.

CT Neck with contrast study - k/c/o metastatic squamous cell carcinoma of right inguinal node, showing no abnormally enhancing lesions in the neck, no enlarged cervical nodes. Thyroid, nasopharynx and larynx are normal.

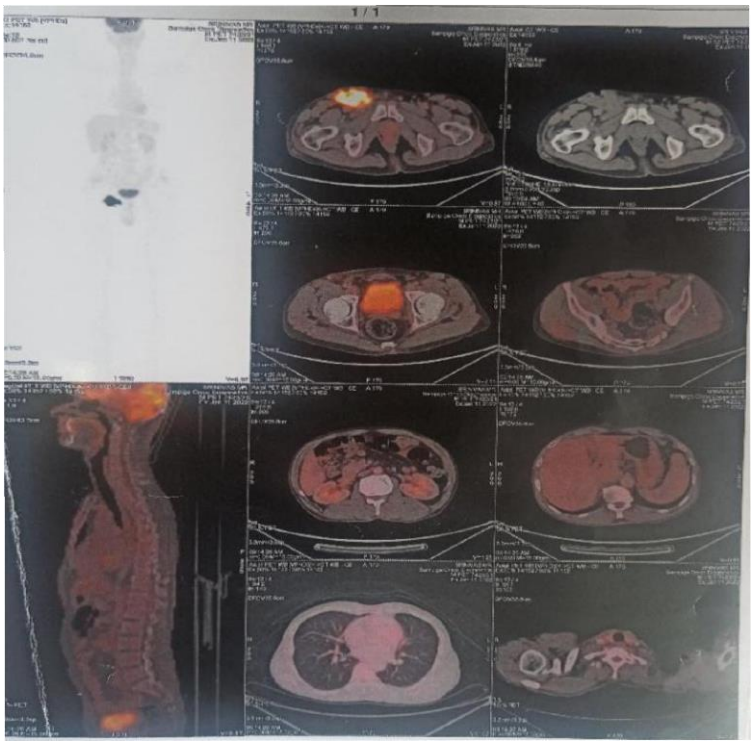
Under general anesthesia, Right Upper Thigh Medial Aspect Wide Local Excision with Split Skin Graft was done on 22/06/2022, by Surgical Oncology team of doctors, where Wide local excision of lesion with 1cm margin and excision of cuff of underlying muscle, and homeostasis was achieved. Split skin graft was taken from Left thigh and the defect was covered.

Findings were -3x3 cm lesion in Right Upper Thigh Medial Aspect, hard consistency , non mobile, with overlying skin pinchable.

Histopathology as reported on 29/06/22 shows all round skin and soft tissue margins are free from tumour, 4 Lymph nodes positive. All extensive squamous cell carcinoma metastasis with extra nodal extension. Base is free of tumour.

During the surgery, the condition of patient was tolerable. The postoperative course was uneventful.

To find the primary lesion of the metastatic squamous cancer that was found in the inguinal lymph node, a PET scan was performed.



PET CT showed FDG uptake in heterogeneously enhancing mass lesion in right inguinal region with cutaneous ulceration 4x 5.2 x 4.8cm, AP x TR x CC, SUV max 2.8. Mild FDG uptake is seen in right external iliac lymph node, size 2 x 1.3 cm, SUV max 2.8.

Impression - Hypermetabolic lymph node mass in right inguinal region - biopsy suggestive of Squamous Cell Carcinoma.

Mildly FDG avid tiny hypo density in segment VII of liver - like benign.

No significant hyper metabolic lesions anywhere else in the body.

Nonetheless, no suspicious primary site that could be detected.

Three months after chemoradiation therapy, chest X-ray, cervical cytologic test, and tumor markers were performed as follow up tests. Recurrent malignant tumor or lymph node enlargement was noted, for which patient came to Vydehi Oncology Centre.

For the treatment of squamous cell cancer detected in the inguinal lymph node, chemoradiation therapy was planned. The inguinal area was irradiated with 4,500 cGY and 60 mg/m2 cisplatin was administered at one week interval, total 6 times.

During the chemoradiation therapy, weekly blood investigations and serum electrolytes were done, with acceptable values. Patient tolerated the treatment well.

Discussion

The lymphatic circulation is a system responsible for immunity, and it produces antibody and plays a role of removing foreign materials or cancer cells. On the other hand, cancer cells migrate through the lymphatic duct and thus lymphatic system becomes a pathway to transfer cancer cell to distant organs. Therefore, depending on abnormal lymph node location, associated diseases could be predicted, and disease stage and prognosis are determined based on the location or number of metastatic lymph nodes. **[**3**]**

The patient that we treated was a 52-year-old man, and he was admitted with recurrence of enlargement of the inguinal lymph node. Generally, inguinal lymph nodes receive as afferent lymphatic vessels from the vulva, the vagina, the perineum, the buttocks, the low abdominal wall, and the perianal lymphatics, and lymph node enlargement is associated with infection and malignancy in such areas. Cases other than that are very rare, and metastatic cancer with unknown primary site also belongs to this category.

In 1978, Zaren and colleagues examined 2,232 patients with metastatic cancer cells in the inguinal lymph node. Among them, 99% were cases with metastasis from a primary lesion, and most patients were found to have malignant tumors in the skin of lower limbs, the cervix, the uterine body, the ovary, the perineum, the rectum, the anus, and the remaining 1% was metastatic cancer with unknown primary site. In 1987, Guarischi and colleagues examined 56 patients diagnosed as metastatic cancer in the inguinal lymph node without a primary lesion. The 29 were male patients and 27 were female. Regarding the distribution according to histological types, anaplastic carcinoma was 42% (24 patients), squamous cell carcinoma was 19% (11 patients), adenocarcinoma was 16% (9 patients), melanoma was 16% (9 patients), and others were shown to be 5% (3 patients). According to a previous report, malignant tumor with unknown origin comprises 3-5% of all malignant neoplasms, and it is defined as a metastatic cancer of unknown primary site, for which no original site can be detected even after performing all possible tests.**[**4**]**

The diagnostic evaluation of patients with MUO consists of laboratory or clinical investigations including the past history, complete physical examination, blood test, urinalysis, stool examination, pathology, immunohistochemistry, chest X- ray, CT, mammography, endoscopy.

As tumor markers, serum β-hCG and AFP may be performed to rule out extragonadal germ cell tumors, and CA15-3 for axillary adenocarcinoma and CA125 for peritoneal papillary adenocarcinoma could be of some help. In all other cases, routine evaluation of commonly used epithelial serum tumour markers (CEA, CA19-9, CA15-3, CA125) has no proven prognostic or diagnostic value, and non-specific elevations of multiple markers occurs in the majority of CUP patients.

MUO are categorized into four major subtypes by routine light microscopy criteria: (a) adenocarcinomas well-moderately differentiated, (b) undifferentiated or poorly differentiated adenocarcinomas, (c) squamous cell carcinomas and (d) undifferentiated neoplasms. Approximately half the patients will be diagnosed with metastatic adenocarcinoma, 30% will have undifferentiated or poorly differentiated carcinomas, 15% squamous cell carcinomas and the remaining 5% will have undifferentiated neoplasms.**[**5**]**

More than 50% of MUO patients present with multiple sites of involvement, while the rest have a single site most commonly in the liver, lymph nodes, the peritoneum, the lung, the bone, and the brain.

The progression of such cancer with unknown origin is rapid in most cases, and it shows atypical metastatic patterns. In general, it appears that patients with MUO have a limited life expectancy with a median survival approximately of 6-9 months.

The therapeutic strategy for MUO patients should always be individualized according to the clinical subset. The therapeutic approaches include chemotherapy, surgery, with or without postoperative radiotherapy, radiotherapy alone and radiotherapy followed by surgery.

In this patient with squamous cell carcinoma in the inguinal lymph node, the PET scan could not identify any occult primary site or other metastatic lesions. The solitary development in the inguinal lymph node occurs in 1-3.5% cases of metastatic cancer with unknown origin. Examination of the anorectal region, and cystoscopy are necessary investigations for this patient. Lymphomas and metastatic or amelanotic melanomas of unknown primary site should also be ruled out.

Since there is no metastasis in adjacent tissues or lymph node, it is adequate to treatment with simple Wide Local Excision alone. As in such a case of a solitary lesion of cancer with unknown origin, local treatment such as surgery or radiation therapy could be performed, and favorable outcomes can be expected.

However, in cases in which progression of the primary lesion is very slow, cancer cells may not be detected by conventional diagnostic methods. Therefore we performed adjuvant chemoradiation therapy.

Despite the development of various diagnostic methods, the optimal diagnostic algorithm in metastatic cancer with unknown origin has not yet been established. Also, it shows a progression pattern different from other malignant tumors, and thus their progress is difficult to predict. Since the benefit of current therapy remains is limited in most patients, the evaluation of novel treatment approaches is essential. Promising classes of agents currently in development, including epidermal growth factor receptor inhibitors and anti- angiogenesis agents, should be explored in patients with MUO. Ongoing basic research and focused translational studies are also critical in advancing the understanding and management of patients with MUO.

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