Carcinoma of Unknown Primary (CUP) in a patient presenting with lower back pain: An Important Clinical Lesson

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ABSTRACT

Carcinoma of unknown primary (CUP) is associated with high rates of morbidity and mortality. We report a case of a 33-year-old female, diagnosed with CUP, after presenting with gradual onset worsening lower back pain. Immunohistochemistry, blood tests, further investigations, and Multidisciplinary team meetings failed to identify the primary malignancy. This is not an uncommon pathway for patients with CUP. This report highlights how CUP can affect the quality of life of patients and how management for CUP should be focused on enhancing Quality of Life (QOL). It also addresses the difficulty of identifying which group of patients may benefit from further investigations to identify the primary and thus receive target treatment therapy.

Keywords:
Carcinoma, Tumour, Computerised tomography.

Introduction
Malignancy of Unknown Origin (MUO) or Carcinoma of Unknown Primary (CUP), is a rare condition, however, it remains a serious public health concern[1,2]. It represents the fourth most common cause of death from cancer [3]. The malignancies often possess a unique set of biochemical and genetic mechanisms which result in an aggressive phenotype that does not respond well to chemotherapy [1,2,4-6]. The one-year survival for patients with CUP is currently less than 2% [1,2]. Spinal metastasis can be associated with CUP and can result in a particularly poor quality of life with back pain, pathological fractures, vertebral instability, and cord compression [4,7]. Cord compression can be a pre-terminal event [7]. Some of the challenges faced with CUP is the early diagnosis and symptomatic control.

Case Presentation
A 33-year-old female presented to the Emergency Department with a three-month history of worsening back pain and reduced mobility. There was no history of trauma and no reported neurology. She also explained that she had a reduced appetite and had lost 7kg in weight. The patient had a past medical history of spontaneous pneumothorax and breast fibroadenoma which was surgically removed. She had a family history of breast cancer. She was not on any regular medication. A plain thoracolumbar radiograph was performed which demonstrated vertebral collapse at L1 and L2 with pedicle destruction (Figure 1).

A subsequent MRI spine was performed which demonstrated cauda equina compression at L2 with diffuse signal abnormalities in the T12-S1 vertebral bodies suggestive of widespread metastatic disease (Figure 2). A Computerised Tomography (CT) scan of the chest, abdomen, and pelvis was performed which identified a large irregular, lobulated, retroperitoneal mass straddling the midline at the level of the adrenal glands, with no clear origin (Figure 3). Tumour markers (CEA, CA19-9, CA-125, alpha-fetoprotein, hCG) were all negative. The patient underwent urgent surgical spinal decompression, stabilization, and biopsy (Figure 3).

Histology from the L2 vertebral body confirmed metastatic adenocarcinoma. Initial Immunohistochemistry (IHC) indicated thyroid carcinoma (positive for Cytokeratin 7, Cytokeratin 19, and Thyroglobulin) but was inconclusive. Recognizing the limitations of IHC, the Head and Neck Multidisciplinary Team (MDT) recommended further IHC panels in this patient which subsequently excluded thyroid cancer (negative for S100 and Thyroglobulin) and suggested renal cell carcinoma. A whole-body nuclear medicine bone scan showed extensive skeletal spread including vertebral hot spots and asymptomatic metastases in the occipital skull and left hemipelvis. The working diagnosis of renal cell carcinoma in this patient was not confirmed. Deterioration in the patient’s condition made diagnosis of the retroperitoneal mass inappropriate. Mammography was considered but due to normal breast.
examination and CT findings, this was also deemed unnecessary. The presence of strong family history for inherited breast cancer in this patient may have indicated further evaluation for BRCA1 and BRCA2 tumour suppressor gene mutations. Following the spinal decompression, her condition continued to decline, and her mobility remained poor. Physiotherapy and palliative radiotherapy were planned but deferred due to her rapid deterioration. She was discharged home with a full package of care and passed away shortly afterward.

Discussion

Managing patients with CUP is difficult for several different reasons. One reason this condition is so difficult to manage is because the unknown origin and nature of the cancer. For this reason, the patient is often managed by the team that the patient was initially referred to following the presenting symptom which perhaps may not be the optimal team to be managing the condition. The management of these patients is further complicated by the different investigations that are usually requested for such patients to distinguish a primary cause. This involves separate discussions with other specialists, which often is discussed in their subsequent MDT meetings. Unfortunately, as a result, the patient may be subjected to delays in involving the palliative care team and addressing their psychosocial needs and concerns. Other cases of CUP document similar challenges including one case of a gentleman who had a retroperitoneal mass of unknown origin that had invaded three adjacent foramen in the lumbar vertebral bodies. His differential diagnosis included tuberculosis and lymphoma. Gastric and pancreatic primaries were suggested based on preliminary CT guided biopsies and IHC. The patient deteriorated and a primary remained unknown [8]. These cases, and others alike, demonstrate that management of CUP is complex. It is not obvious at the first presentation which patients will eventually be diagnosed with CUP. With a low yield, extensive investigation in patients with CUP is criticized [4]. However, the identification of a primary can improve prognosis by allowing targeted treatment and care by site-specific cancer teams [2]. Therefore, some patients will benefit from the extensive investigation. Identifying these patients however is a challenge. Routine use of CT scans has resulted in the diagnosis of up to 20% of cases that would previously have been classified as CUP [2]. Studies suggest that the early use of Positive Emission Tomography-Computed Tomography (PET-CT) in CUP may improve the diagnosis of primary cancer [4,9,10]. However, due to limited evidence, PET-CT is not yet approved in extra-cervical presentations of MUO [4]. CUP patients will not be diagnosed with a named primary. This is often due to rapid disease progression. Interestingly, 15-25% of post-mortem in patients with CUP also cannot identify a primary [3,5]. With such a prognosis and short timeline between diagnosis and mortality, over investigating this condition can result in longer hospital stays and causes significant psychological and physical distress [4]. The National Health Service (NHS) have recognized these challenges and developed guidelines for managing CUP [4]. The key recommendation of these guidelines is the importance of establishing MUO/CUP teams in hospitals which should streamline the investigation of patients with simultaneous symptom control, treatment, and support [4].
Healthcare professionals need to be aware of these teams to facilitate early referral of MUO/CUP patients. At present, the true incidence of CUP may be underestimated as some deaths are reported as a result of a suspected primary rather than CUP [2,4]. Additionally, increasing the awareness of this condition and enhancing the knowledge of medical professionals that may care for such patients, combined with accurate documentation and prompt communication, can help in developing a more efficient pathway for such patients.

**Conclusion**

Carcinoma of unknown primary is a serious public health concern with high rates of mortality. Managing these patients is highly complex. Diagnosing this condition is difficult and over investigating may lead to delayed diagnosis and, subsequently, reduced quality of life. This report highlights the importance of early identification and early involvement with the specialist team to optimize patient experience and outcomes.

**References**


