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Case Report

Immunohistochemistry-guided management of colon-like CUP in a 20-year-old female: a case report

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ABSTRACT

Cancer of unknown primary site (CUP) is characterized by metastatic disease without an identifiable primary tumor, even after extensive evaluation. It accounts for approximately 2% of all cancers and is most commonly diagnosed in older adults, with the highest incidence in patients aged 60-75 years. Diagnosis involves clinical, pathological, and imaging evaluations, including PET and immunohistochemical (IHC) staining, to determine tumor lineage and guide treatment. We present a case of a 20-year-old female with a right inguinal mass. Initial evaluation revealed metastatic adenocarcinoma with no primary tumor identified. The patient's history included a prior breast fibroadenoma excision, and comprehensive diagnostic work-up, including PET scan, was unremarkable. Immunohistochemistry results were consistent with colon-like CUP, and the patient underwent excision of the inguinal node followed by adjuvant chemotherapy with the FOLFOX regimen. CUP treatment and prognosis vary by tumor subtype, with colon-like CUP typically managed using colorectal cancer-specific therapies. This case underscores the importance of IHC in guiding treatment for CUP and highlights the role of site-specific therapy in improving patient outcomes. Further studies are needed to validate treatment strategies in younger patients with CUP.

Keywords: Cancer of unknown primary, Adenocarcinomas, Immunohistochemistry, Colon-like cancer of unknown primary site, FOLFOX

INTRODUCTION

Cancer of unknown primary site (CUP) is a significant clinical entity, comprising roughly 2% of all invasive cancers.[1] It is characterized by the presence of metastatic disease without the identification of a primary tumor, even after an extensive diagnostic evaluation. In recent times a decline in the incidence of CUP has been observed across various metastatic sites and histologic subtypes.[2] After a CUP diagnosis, patients are classified into one of four categories based on light microscopy of the biopsy. These categories help guide further diagnosis and treatment. The classifications include adenocarcinoma, squamous cell carcinoma, neuroendocrine carcinoma (which can be well or poorly differentiated), and poorly differentiated tumors. Most poorly differentiated tumors are identified as carcinomas, though some cases may have uncertain lineage, such as lymphoma, sarcoma, melanoma, or germ cell tumors. Treatment and prognosis vary across these groups. Adenocarcinomas of unknown primary site comprise approximately 70 percent of CUPs.[3]

The evaluation typically includes a detailed patient history, physical examination, complete blood count, urinalysis, and basic serum chemistries. Imaging studies, such as computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis, are integral to the assessment. Females with CUP should undergo a pelvic examination and mammography. Positron emission tomography (PET) can be helpful in

certain cases for diagnostic staging, identifying a primary site in about 40% of patients in retrospective studies. However, there is evidence that PET is no better than CT in many situations. Therefore, PET use should be limited to specific cases, such as squamous carcinoma in single site lymph nodal metastases. PET is also useful for monitoring treatment response in patients with bone-dominant metastases.[4]

Once CUP is diagnosed, further pathological evaluation is often necessary, guided by the clinical and pathological findings. Histologic analysis of a biopsy sample usually enables classification of the cancer's lineage, distinguishing between carcinoma, sarcoma, lymphoma, or melanoma. Although histologic examination alone cannot differentiate between types of adenocarcinomas, immunohistochemical (IHC) staining proves valuable in suggesting the primary site in approximately one-third of cases. Here, we present a unique case of CUP in a young girl.

CASE REPORT

A 20-year-old unmarried, nulliparous, not sexually active girl presented with a lump in right groin region (Figure 1). She reported no additional symptoms, such as asthenia, abdominal or pelvic pain, or any other swelling. She had been evaluated at another institute prior to reporting to our centre, wherein she had been subjected to a FNAC of the lump. The FNAC was suggestive of poorly differentiated carcinoma possibility of metastatic. Her surgical history indicated that she had undergone a lump excision in the right breast one year ago, with histopathology confirming a fibroadenoma.

\Her medical and family history was unremarkable. On examination, she appeared in good general condition with vital signs within normal limits: blood pressure 110/70 mmHg, pulse 70 beats/min, and temperature 36.2°C. No lymphadenopathy was noted in the cervical or supraclavicular regions. Breast examination did not reveal any abnormality. Chest auscultation revealed normal breath and heart sounds, and there were no abnormalities detected in the abdomen, limbs, perineum, or perianal areas.

The right inguinal lymph node was 3-4 cm in size, mobile, and non-tender with normal overlying skin. Laboratory tests showed CA125 at 28 IU/ml, CA19-9 <1 IU/ml, CEA 2.43 ng/ml, AFP 1.68 ng/ml, beta-hCG 0.4 ng/ml, and LDH 209 U/l. A complete blood count revealed haemoglobin of 11.1 g/dl, hematocrit of 33.3%, white blood cell count of 7,000/mm^3, and platelet count of 120,000/mm^3. All other tests, including liver and renal function, urinalysis, upper gastrointestinal (GI) endoscopy, colonoscopy, thyroid function tests, and chest X-ray, were normal (Figure 2,3). A PET scan was performed to locate the primary source of metastatic adenocarcinoma found in the inguinal lymph node, but no primary lesion was identified. The patient subsequently underwent excision of the inguinal mass with 2 cm margins under general anaesthesia (Figure 4 ,5). Histopathology confirmed metastatic adenocarcinoma and immunohistochemistry results were positive for CK20, CDX2, MOC31, PAX-8 and Vimentin but negative for CK7. The surgery was well tolerated, and the postoperative course was uneventful. After a thorough review by the multidisciplinary tumor board, the patient was recommended to undergo chemotherapy with the FOLFOX regimen.

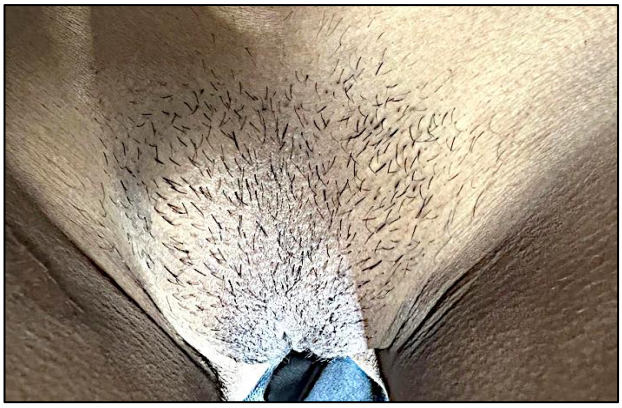

Figure 1: Clinical examination of patient.

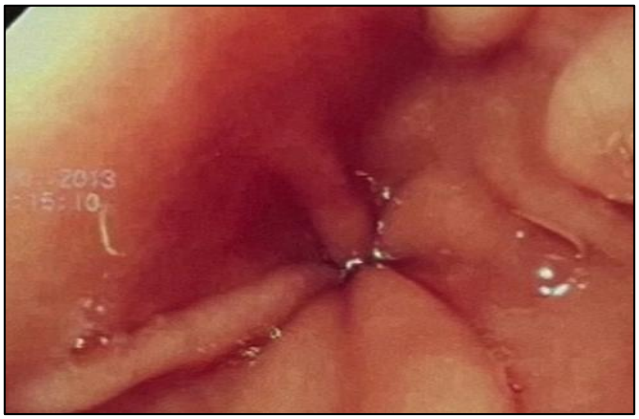

Figure 2: Upper gastrointestinal endoscopy.

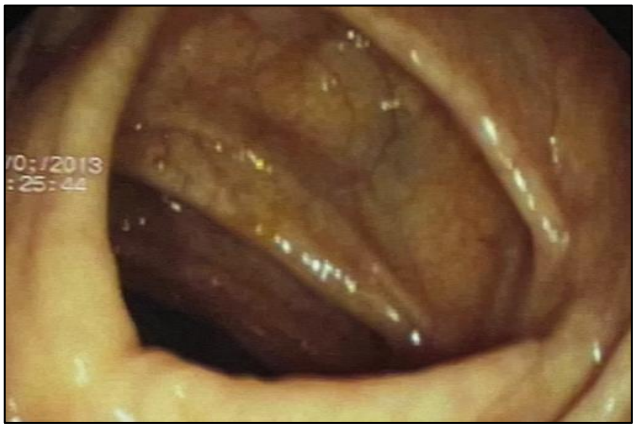

Figure 3: Colonoscopy.

Figure 4: Post-operative specimen -outer surface.

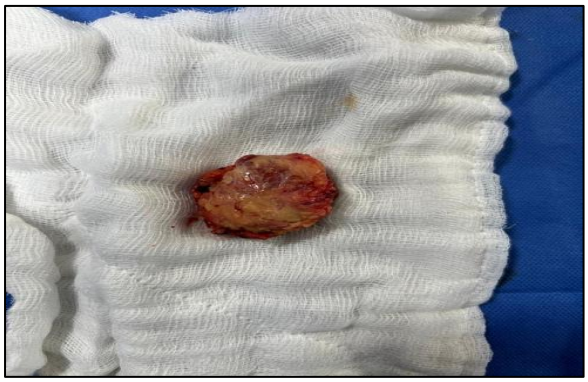

Figure 5: Post-operative specimen inner surface.

DISCUSSION

The diagnosis of CUP is established after an exhaustive clinical evaluation fails to identify the primary tumor site. The clinical presentation of CUP depends on the organs involved by metastasis, leading to tissue samples being collected from different anatomical sites. This can include endoscopic biopsies, small CT or ultrasound-guided biopsies, and cytology samples for diagnostic purposes. Additional evaluations with IHC and Molecular cancer classifier assays (MCCAs) have enhanced the ability to pinpoint the tumor's origin and have improved outcomes for selected patients who receive site-specific treatments.

CUP is most frequently diagnosed in patients aged 60 to 75 years. Another study showed peak incidence in the 85-89 age group, followed by a notable decline in those over 90, with a 7-fold decrease in men and 3-fold in women.[5]

Smokers have an increased risk of developing CUP, with the risk rising from 1.8-fold for those smoking 1-15 cigarettes per day to 4.1-fold for more than 25 cigarettes daily. Additionally, type 2 diabetes, autoimmune disorders such as polymyositis/dermatomyositis (3.5-fold), and familial predisposition are associated with elevated CUP risk. Other potential factors include high body mass index, low socioeconomic status, and black ethnic background.[6] In our case however there was no identifiable risk factor. Survival after a CUP diagnosis remains low, with a median of about three months and 20% surviving beyond one year. Prognosis is worse for adenocarcinoma and undifferentiated carcinoma, while squamous cell carcinoma has a slightly better outcome. Older age and extranodal disease further reduce survival chances.[7]

Colon-like CUP is characterized by adenocarcinoma resembling a gastrointestinal (GI) primary, with intra-abdominal metastases and a specific immunohistochemical (IHC) profile: CK7-negative, CK20-positive, and CDX2-positive. Despite a negative colonoscopy, this IHC signature is typical of colorectal cancer (CRC). While gene expression-based tests are less strict than IHC, retrospective studies show that patients with colon-like CUP who receive CRC-specific chemotherapy, such as FOLFOX or FOLFIRI, have response and survival rates similar to those with metastatic CRC.

Although these findings are based on small studies and need further validation, CRC-based treatments are generally recommended for colon-like CUP. In patients with microsatellite-stable tumors, 5-FU-based chemotherapy regimens, possibly combined with bevacizumab or anti-EGFR antibodies (for those without KRAS/NRAS mutations), are advised. For patients with MSI-high tumors, immune checkpoint inhibitors (ICIs) are preferred.[4] Similarly, in our case the final histopatgilogy was similar to colon like CUP, hence we proceeded with adjuvant 5FU based chemotherapy. Similarly, in our case, the final histopathology was consistent with colon-like CUP, leading us to proceed with adjuvant 5FU-based chemotherapy.

CONCLUSION

Based on the case report, this young patient with colon-like CUP was successfully managed through site-specific treatment with the FOLFOX chemotherapy regimen. This emphasizes the critical role of immunohistochemistry in guiding the management of CUP and improving patient outcomes.

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