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Case Report

Utilizing Advanced Molecular Analysis to Tailor Treatment for Cancer of Unknown Primary Site: A Case Report and Lecture Review

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Abstract

Cancer of unknown primary site (CUP) presents as metastatic lesions without an identified primary tumor despite extensive evaluation. Because the primary cancer type cannot be determined, there are no standard treatments, leading to challenges in the treatment and suboptimal clinical outcomes. Herein, we report a 59-year-old woman who presented with an enlarged right inguinal lymph node, and the biopsy revealed metastatic adenocarcinoma. Despite a series of treatments including surgery, radiotherapy, and chemotherapy, the disease progressed. After further treatment with combined chemotherapy and immunotherapy, a treatment response was observed. Genomic profiling was done, which identified KRAS G13D and PIK3CA H1047R mutations. She received treatment with the mTOR inhibitor everolimus, and after 2 months, the right inguinal mass continued to regress. This case highlights that CUP remains a diagnostic and therapeutic challenge, representing an urgent and unmet clinical need. However, in the era of precision medicine, the combination of advanced molecular profiling and sophisticated bioinformatic analysis may have the potential to identify druggable targets for tailored and personalized treatment approaches.

Keywords: Cancer of unknown primary site, molecular-guided treatment, next-generation gene sequencing, precision medicine

Introduction

Cancer of unknown primary (CUP) is defined as the presentation of multiple confirmed metastatic lesions without identification of the primary tumor, even after an extensive survey. The pathogenesis is still unclear; however, it may be due to the regression or small size of the primary tumor, making it undetectable with present imaging techniques.[1] It is a rare oncological disease, accounting for only about 2%–4% of all invasive cancers. Due to the difficulty in diagnosis and the lack of precise treatment,

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the prognosis is usually poor, with a 2-year survival rate of <20%.[2]

With the development of molecular testing, genomic-guided treatment has become increasingly promising. It enables more precise medicine and appears to have clinical benefits for patients with CUP. Herein, we present a case of CUP who received genomic-guided treatment and showed a favorable response.

Case Report

A 59-year-old female with a history of resolved hepatitis B and chronic spontaneous urticaria noticed a palpable tender tumor over the right inguinal region in 2019. Pelvic computed tomography (CT) revealed a nodule measuring 3.3 cm in the right inguinal region. Tumor excision was performed, and the pathological report revealed metastatic carcinoma, with neoplastic cells positive for calretinin, focally positive for p16, and negative for estrogen receptor (ER) and progesterone receptor in immunostaining. Due to difficulty in determining the primary site, whole-body positron emission tomography (PET) was performed. However, it did not identify a specific primary focus, except for increased fluorodeoxyglucose accumulation around the perineum [Figure 1a]. Tumor markers, including cancer antigen 19-9 (CA), CA125, tissue polypeptide antigen, carcinoembryonic antigen, and squamous cell carcinoma (SCC) were within normal limits. The patient underwent laparoscopic bilateral salpingo-oophorectomy, but no malignancy was identified. Under the impression of CUP, she received radiotherapy over the pelvis for a total dosage of 5000 cGy.

However, a PET/CT scan 3 years later revealed a highly suspected local recurrent lesion [Figure 1b]. She received wide excision of the tumor and lymph node dissection of the inguinal area, but no malignant component was identified in the pathological report.

One year later, she experienced local recurrence over the right inguinal region, accompanied by bilateral inguinal metastatic lymphadenopathies [Figure 2a and b]. The surgical pathological report showed metastatic adenocarcinoma. Immunohistochemical staining revealed diffuse immunoreactivity for BerEP4, PAX8, and CK7, focally positive for calretinin and GATA3, and negative for WT-1, CK20, ER, and TTF-1, suggesting high-grade serous carcinoma with some components of low-grade serous carcinoma. The clinical impression suggested that the origin could be from the ovary, breast, or peritoneum. Mesothelioma was also considered a differential diagnosis. However, electron microscopy showed the absence of long and slender microvilli in the apical surface of the tumor cells [Figure 3a and b]. Because long thin apical microvilli are the characteristic ultrastructural feature of mesothelioma, the lack of this feature suggested that the tumor was more likely to be carcinoma rather than mesothelioma.

The patient underwent breast echo and mammography, but both examinations failed to detect any abnormalities. After discussion with the pathologist, the most probable origins were either the ovary or peritoneum. She received chemotherapy with bevacizumab, combined with docetaxel and carboplatin. After six cycles of treatment, follow-up PET/CT disclosed the disappearance or shrinkage of the lymphadenopathies, with only a small residual lesion over the right pubic tubercle. Unfortunately, she noticed a swelling mass in the right thigh 9 months later, and PET/CT suggested a recurrent right inguinal tumor with intra-abdominal metastatic lymph nodes. The tumor had a tumor proportion score of 40% and a combined positive score of 50, although a low probability

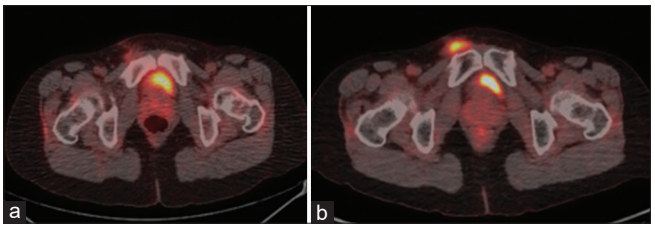

Figure 1: Positron emission tomography/computed tomography (PET/CT) scan at the initial diagnosis and disease recurrence. (a) After wide excision of the tumor, the PET/CT scan only showed mildly increased fluorodeoxyglucose uptake over the right inguinal area, suspected to be due to postoperative inflammation. (b) 3 years after the initial diagnosis, the PET/CT scan showed recurrent tumor lesion

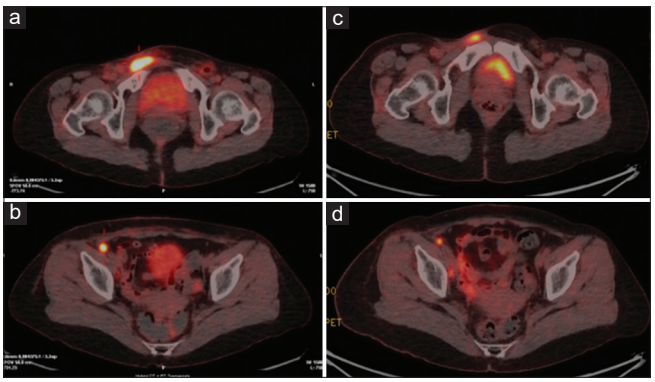

Figure 2: Positron emission tomography/computed tomography (PET/CT) scan of second recurrence. Fluorodeoxyglucose-avid tumors in the right inguinal region (a), right common iliac regions, and external iliac regions (b). After 4 cycles of immunochemotherapy, the PET/CT scan showed a partial response (c and d)

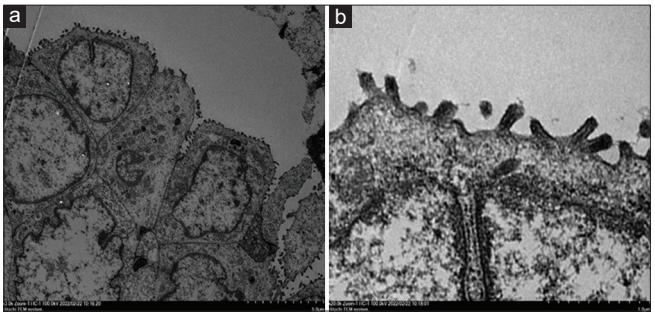

Figure 3: (a and b) Electron microscopy showed short, rather than long and slender microvilli in the apical surface of the tumor cells

of MSI-H. Immunochemotherapy with pembrolizumab along with carboplatin and paclitaxel was initiated. Taxotere was substituted for paclitaxel after the second cycle due to suspected adverse skin effects. Subsequent PET/CT revealed a significant response after four cycles of treatment [Figure 2c and d].

Because of the side effects of chemotherapy, the patient requested to discontinue treatment. For further disease control, the resected inguinal mass was sent for a molecular study, which revealed the presence of KRAS G13D and PIK3CA H1047R mutations. Based on these results, everolimus was prescribed. CT 4 weeks later revealed that the right inguinal mass had stabilized. A physical examination showed regression of the lesion after 8 weeks, and PET/CT 16 weeks later revealed stable disease.

Discussion

CUP is a rare oncological disease, accounting for only about 2%–4% of all invasive cancers. Pathologic immunohistochemical staining studies have revealed that adenocarcinoma is the most common histologic type, with well to moderately differentiated adenocarcinomas accounting for 50%, followed by poorly or undifferentiated adenocarcinomas (~30%). SCCs (~15%) and undifferentiated neoplasms (~5%) are less frequent.[2] CUP can be categorized into favorable and unfavorable subtypes. The former indicates that the tumor is closely related to a currently defined disease entity after evaluation, and that it can be treated with site-specific treatment. However, around 80% of CUP cases are categorized as being unfavorable. Because the primary site cannot be identified, patients with CUP can only receive "empiric chemotherapy." The most commonly suggested regimens are platinum-based chemotherapy, such as paclitaxel with cisplatin or gemcitabine with cisplatin. However, empiric chemotherapy has shown no evidence of survival benefit compared to best supportive care.[2,3] With the rapid evolution of molecular techniques and bioinformatic analysis, more efficient therapeutic strategies are expected for patients with CUP.

The concept and utilization of molecular-guided treatments (MGTs) have evolved over the past decades and become more emphasized in recent years. New technologies such as next-generation gene sequencing (NGS) along with improving biostatistics and even artificial intelligence (AI) can help detect individual genetic mutations, making precise medicine more achievable. These novel treatment approaches have been widely examined in clinical studies. For example, a prospective trial (PERMED-01) evaluated 550 patients with heavily pretreated advanced cancers. Among them, 393 (71%) patients were identified to have at least one actionable genetic alteration, and 17% of the screened patients received a "matched therapy." Of these patients, 36% were shown to have clinical benefits.[4] Another prospective trial (MOSCATO 01) also found that high-throughput genomic analysis could improve outcomes in patients with advanced cancers, and the progression-free survival (PFS) on matched therapy (PFS2) was 1.3 times longer than the PFS on prior therapy (PFS1).[5] In a retrospective study, a molecular analysis platform identified 72 patients with different types of gynecologic malignancies, with 209 total genetic aberrations. Seventeen patients received recommended target therapy, and seven of nine evaluable patients had clinical benefits, including two with a partial response and five with stable disease.[6]

In terms of CUP, the use of NGS in the diagnosis is increasing. Although not fully supported by high-level evidence for routine practice (level IVB), comprehensive gene expression profiling can help provide more personalized and effective therapeutic options.[2] A recent study that utilized a whole-genome sequencing-based tumor type prediction algorithm (CUPPA) correctly predicted the primary tumor type in 78% of samples in an independent validation cohort and in 68% (49/72) of patients with CUP.[7] In addition, AI-based methods are another diagnostic tool that have shown potential for primary site identification. Tumor Origin Assessment via Deep Learning, a deep learning algorithm, provides the differential diagnosis of the primary site by comparing acquired histology slides to whole-slide images of tumors with known origins, and it showed a high concordance rate (61%) in 317 CUP cases.[8]

In addition to the abovementioned techniques, the analysis of circulating tumor DNA also provides valuable diagnostic information. A study analyzing 442 CUP patients found that the TP53 mutation was the most common mutation (37.1%), followed by KRAS (18.6%), PIK3CA (15.4%), BRAF (7.5%), and MYC (7.5%).[9] Although no therapy targeting the TP53 mutation is currently available, other mutation-targeted drugs, especially BRAF inhibitors, have been shown to achieve a favorable treatment response. In addition, therapeutic agents targeting specific genetic mutations such as EGFR, MET, or RET fusion[10] have also demonstrated durable disease control. The CUPISCO trial, an ongoing phase II study, enrolled CUP patients with unfavorable disease status. The participants received three cycles of platinum chemotherapy and were then randomized to receive either MGT or further cycles of chemotherapy. The MGT group showed a better median PFS than the chemotherapy group (6.1 months vs. 4.4 months, $P = 0.0079$), and the safety profiles were similar. The results of this trial highlight the potential of genomic profiling to guide cancer treatment.[11,12]

MGT is increasingly being used in patients with advanced cancers, including CUP. Through genomic profiling, patients can receive individualized treatment. This approach may become a more common therapeutic method; however, more studies are required to provide a stronger evidence base.

Conclusion

The diagnosis and treatment of CUP remain quite challenging, especially for unfavorable subtypes or relapsed/refractory disease. With the rapid advances in technology in the molecular era, genetic profiling followed by genomic-guided treatment may help patients achieve better clinical outcomes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Data availability statement

All data generated or analyzed during this study are included in this published article.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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