〈Case Report〉

Successful Drug Therapy Initiation Via Cancer Genome Profiling in Primary Cancer with Bone Metastasis of Unknown Origin

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ABSTRACT Cancer of unknown primary (CUP) with bone metastasis poses significant diagnostic and therapeutic challenges. This case report focuses on the successful application of cancer comprehensive genomic profiling (CGP) in guiding treatment. This study included an 81-year-old female who presented with severe lumbago and functional impairment due to bone metastases. The biopsy findings confirmed the malignancy, but the primary tumor site remained unidentified. The CGP findings revealed a high tumor mutational burden (TMB) of 17 Muts/Mb, leading to the indication of pembrolizumab therapy. After 18 cycles, a significant improvement in bone metastases with no adverse events was observed. Furthermore, this case emphasizes the utility of CGP in identifying actionable targets as well as the transformative potential of immunotherapy in CUP management. doi：10.11482/KMJ-E202551001 *(Accepted on December 18, 2024)*

Key words：Cancer of unknown primary, Comprehensive genomic profiling, Tumor mutational burden, pembrolizumab

INTRODUCTION

CUP with bone metastasis poses a diagnostic and therapeutic challenge due to its elusive origin and aggressive nature. Advances in cancer genome profiling have provided a pathway to identify potential therapeutic targets and improve patient outcomes. Genome sequencing allows the detection of clinically actionable mutations and biomarkers, facilitating precision medicine even in cases where the primary cancer site remains undetermined. This approach provides potential therapeutic benefits and emphasizes the importance of integrating genomic insights with clinical care.

Several studies have proven the effectiveness of genomic profiling in CUP management. For instance, genomic profiling has identified actionable mutations in 40.9% of CUP patients, leading to targeted therapy recommendations[1]. DNA methylation profiling also effectively identified the primary tumor site in 87% of cases and improved the survival outcomes for patients receiving site-specific therapy[2]. Moreover, proteomic and transcriptomic analyses have expanded diagnostic capabilities, improving tumor classification and therapeutic stratification[3].

This case report emphasizes the effectiveness of

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cancer genome profiling in guiding drug therapy in a patient with CUP and bone metastasis, suggesting the transformative role of personalized medicine in overcoming the diagnostic and therapeutic challenges associated with this condition.

CASE REPORT

This study included an 81-year-old female who complained of lumbago and pain in the buttocks. Her medical history included gastric cancer surgery at the age of 31, rectal LST (carcinoma in situ) at the age of 75, and basal cell carcinoma resection at the age of 81. She had no notable family medical history. Her physical measurements were as follows: 142 cm in height and 38 kg in weight, with an ECOG performance status of 4 (PS4).

The patient initially sought care because of worsening lower back pain and difficulty moving. An abdominal surgical scar was noted upon physical examination, but no significant findings in the chest or other areas were identified. The findings of the lumbar X-ray performed at a nearby clinic revealed a suspected compression fracture at the 12th thoracic vertebra (T12). She was hospitalized for further evaluation. Subsequent MRI scans have revealed extensive metastatic involvement, including C3, Th5, Th8, Th12, and L5 vertebrae and the 3rd and 8th ribs. Positron Emission Tomography/CT revealed no Fluorodeoxyglucose uptake, including in the bone lesions. Additionally, upper and lower gastrointestinal endoscopy showed no abnormalities. Blood tests were conducted for CEA, AFP, CA19-9, NSE, and proGRP, with NSE showing only a mild elevation at 19.2 ng/mL (normal range: 0-16.3 ng/mL).

The patient was transferred to our hospital for further evaluation and management. A CT-guided biopsy was performed on a sternal lesion, while the presence of a malignant tumor was confirmed via a pathological examination. A detailed pathological examination, including immunohistochemical testing (as outlined in Table 2), suggested a possible plasma cell origin, such as myeloma or solitary plasmacytoma. However, a definitive diagnosis could not be established, and the case was ultimately classified as CUP.

Table 1. Result of FoundationOne CDx.

Biomarkers or Gene Name	Genomic Findings
Microsatellite status	Stable
Tumor mutational burden	17Muts/Mb
CIC	E83*
DNMT3A	G590fs*61
KRAS	D119N
MUTYH	splice site 892-2A > G
NOTCH2	M1V

Table 2. Result of immunohistochemical testing.

Markers	Results
CD138	positive
MUM1	positive
CD20	negative
Cyclin D1	negative
ALK-1	negative
CD30	negative
EBER-1	negative
Cytokeratin AE1/AE3	negative
Ki-67 labeling Index	97%

Radiation therapy (30 Gy in 10 fractions) was administered to the L5 lesion, which was identified as the primary cause of her severe functional impairment (PS4). Moreover, bone-modifying agents were also provided to manage skeletal-related events.

The procedure was explained, and consent for a FoundationOne CDx (CGP) examination was obtained, which revealed a TMB of 17 Muts/Mb. Based on these findings, pembrolizumab therapy (200 mg/body, administered on Day 1 of a 21-day cycle) was initiated. A total of 18 cycles of pembrolizumab were completed. The bone scintigraphy findings confirmed the efficacy of pembrolizumab for bone metastases without any observed adverse events (Fig. 1).

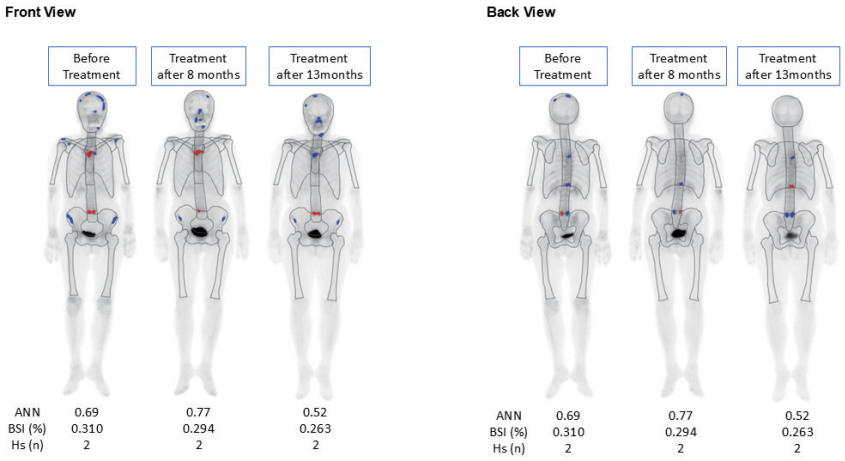

Fig. 1. Bone scintigraphy images show front and back views before and after pembrolizumab treatment. ANN represents Artificial Neural Network, BSI denotes Bone Scan Index, and Hs indicates the number of Hot spots.

DISCUSSION

CUP presents a significant clinical challenge because of its elusive origin and limited standard treatment options. The advent of immunotherapy, particularly the use of pembrolizumab, has shown promising outcomes in CUP patients with actionable molecular profiles, such as high TMB or PD-L1 expression. In this case, a TMB of 17 Muts/Mb indicated suitability for pembrolizumab therapy, which resulted in a significant clinical response and the resolution of bone metastases without adverse events. These findings are consistent with those of recent studies emphasizing pembrolizumab's potential in CUP management, especially for patients with favorable biomarkers.

A phase 2 clinical trial revealed that pembrolizumab achieved an overall response rate (ORR) of 20%, with durable responses lasting a median of 14.7 months among CUP patients[4]. Another study reported a 23% ORR and a clinical benefit rate of 54%, emphasizing the use of pembrolizumab as a potential first-line therapy for CUP patients[5]. Moreover, the efficacy of pembrolizumab is amplified in patients with molecular markers of immune responsiveness. For instance, in cases where the tumor proportion score of PD-L1 ≥ 50%, an ORR of 29.6 % was achieved[6].

The immunohistochemical findings suggested a possible plasma cell origin, such as multiple myeloma or plasmablastic lymphoma. However, given the high TMB and the notable efficacy of pembrolizumab[7], which is atypical for plasma cell-related tumors, the malignancy in this case may not be plasma cell-derived. This raises the likelihood that the tumor belongs within the spectrum of CUP. These findings highlight the complexity of CUP diagnosis and underscore the importance of integrating genomic profiling with clinical and pathological assessments.

In Japan, CGP is covered by insurance and can be performed during or after standard treatment. However, the impact of CGP testing that is performed post- or pre-standard treatment on patient prognosis needs to be determined[8, 9]. The findings of this study revealed that CGP testing prior to treatment initiation, particularly for cancers without established standard-of-care options, can provide significant therapeutic benefits. Early genomic profiling may allow the identification of effective treatments like pembrolizumab, enhancing the

outcomes of challenging cases of CUP.

Furthermore, this case emphasizes pembrolizumab's favorable safety profile and its transformative potential in CUP management. The combination of pembrolizumab with other therapeutic modalities, such as radiotherapy, has shown synergistic effects in some cancers. For example, radiotherapy to the primary tumor has been shown to enhance pembrolizumab efficacy, improving progression-free survival and overall survival in some cases[10]. These findings emphasize the potential for innovative treatment strategies that combine immunotherapy with other modalities.

CONCLUSION

This study confirmed the effectiveness of pembrolizumab in CUP patients with high TMB, providing durable responses and minimal toxicity, and also emphasizes the critical role of genomic profiling in identifying actionable molecular targets and integrating precision medicine into CUP management. Incorporating CGP into routine diagnostic workflows prior to treatment initiation may improve the outcomes of patients with limited therapeutic options. Future research should focus on optimizing immunotherapy regimens and developing combination strategies to enhance efficacy, ultimately improving the outcomes of CUP patients.

DECLARATIONS

Competing interests

The authors declare that they have no competing interests.

Author Contributions

MO drafted the manuscript and managed patient care. HN and HS provided the patient data and summarized the clinicopathological data. TN assisted with interpreting all data and drafted the manuscript. All authors have read and approved the final manuscript.

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