Annals of Case Reports
Bentaleb N, et al. Ann Case Report 6: 713.
www.doi.org/10.29011/2574-7754.100713
www.gavinpublishers.com

Case Report

Immune-Mediated Complete Response in a Patient with Carcinoma of Unknown Primary: A Case Report

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Citation: Bentaleb N, Mineur L, Vazquez L, Boustany R. (2021) Immune-Mediated Complete Response in a Patient with Carcinoma of Unknown Primary: A Case Report. Ann Case Report 6: 713. DOI: 10.29011/2574-7754.100713

Received Date: 02 December 2021**; Accepted Date:** 06 December, 2021**; Published Date:** 10 December 2021

Abstract

Background: Cancer of unknown primary site (CUP) is not rare and occurs in a heterogeneous group of patients with a generally poor prognosis. We report an uncommon case of lymph nodes metastatic CUP managed with immunotherapy providing a complete long-term response.

Case presentation: A 74-years old man presented to our center with multiple lymphadenopathy (enlargement of lymph nodes) revealing a moderately to poorly differentiated carcinoma. A large diagnostic workup did not identify a primary tumor. Immunohistochemistry and clinical course pointed to a pulmonary or gastrointestinal origin, without being able to conclude. Despite a good response to empiric chemotherapy associated with anti-HER2 antibody, a relapse occurred in the form of carcinomatous skin lymphangitis. Considering the finding of PDL1 amplification and overexpression, immunotherapy was administered and achieved a long-term remission.

Conclusions: This case report highlights the importance to evaluate targeted therapeutic therapies, including immunotherapy, in the management of CUP.

Keywords: Cancer of unknown primary (CUP); Immunotherapy; Immunohistochemistry; Carcinomatous lymphangitis

Abbreviations: **CUP:** Cancer of Unknown Primary; **ECOG:** Eastern Cooperative Oncology Group; **LDH:** Lactate Dehydrogenase; **CT:** Computerized Tomography; **ESMO:** European Society for Medical Oncology; **FDG-PET:** 2-deoxy-2-[18F]fluoro-D-glucose-positron emission tomography; **PDL-1:** Programmed Death Ligand 1; **ICI:** Immune Checkpoint Inhibitor; **CK:** Cytokeratin; **TTF-1**: Thyroid Transcription Factor; IHC: Immunohistochemistry; **FISH:** Fluorescence in situ hybridization; **HER-2/neu:** Human Epidermal growth factor Receptor 2/proto-oncogene Neu.

Introduction

Carcinoma of unknow primary origin (CUP) constitute a heterogeneous group of cancers for which metastases are clinically and histologically confirmed with no identified primary tumor at the time of the diagnosis, despite standardised diagnostic work-up. In CUP, the primary tumor may remain diminutive and thus escape detection, may disappear after seeding the metastasis or may be eliminated or contained by the body's defences [1]. CUP account for approximately 3-5% of all cancer diagnoses and most commonly extend to the lymph nodes, lungs, liver or bones [2,3]. These patients represent a diverse group of neoplasms, with varying clinical presentation, tumor biology, response to treatment and prognosis [4]. If almost 20% of patients fit into one of the subsets with favourable prognosis, the vast majority of patients have a poor outcome with empiric chemotherapy, with a response rate between 30% and 40% [5].

Patients with poorly differentiated carcinoma comprise approximately 18%-30% of patients with CUP [6-8]. Treatment of these patients who do not have characteristics of extragonadal germ cell tumor remains a subject of controversy [9]. Cisplatin-

based regimens have yielded relatively high response rate but carboplatin-based regimens or taxane/platinum-based combination regimens are also a good choice for this group of patients, with no evidence of superior efficacy of any of these regimens [6,10]. Several retrospective studies identified factors with unfavourable response to chemotherapy including age older than 35 years, history of smoking more than 10 pack-years, more than 2 sites of metastases, metastatic sites other than retroperitoneal or peripheral lymph nodes, and elevated LDH serum levels [11]. Extensive investigations have developed to identify the origin of the tissue and possible primary site by using gene expression arrays and immunohistochemistry from the biopsy site [7]. In comprehensive genomic profiling, almost all CUP harboured at least one clinically relevant genomic alteration that can influence the targeted therapy [12]. The era of empiric therapy has ended in favour of site-specific therapy, based on the precise diagnosis of the tumor type present in each patient [13]. We report a patient with a moderately to poorly differentiated carcinoma of unknown primary site managed with an immune checkpoint inhibitor (ICI) that resulted in a complete and durable response.

Case presentation

A 74-years old Caucasian man (Eastern Cooperative Oncology Group (ECOG) Performance Status of 0) presented to our center with multiple lymph nodes metastases (Figure 1), without comorbidities or significant medical, family or psychosocial history. Two months before presentation, the patient presents palpable and non-painful subcutaneous masses in the cervical and axillary regions. He had been diagnosed with cervical and axillary lymphadenopathies. Histopathological analysis of the biopsied left supraclavicular lymph node revealed a moderately to poorly differentiated adenocarcinoma. Immunostaining for PSA exclude possible prostate cancer. The first immunohistochemistry profile including staining for keratins CK7, CK20, and TTF1 was CK7+/CK20-/TTF1+. Computed tomography (CT) scan of thorax, abdomen and pelvis revealed multiple lymphadenopathies with latero-cervical, supraclavicular, axillar, mediastinal and hilar lymph nodes metastases. No primary tumor was found. Note that basic blood and biochemical analyses, gastric endoscopy and bone scan were normal, except an insignificant increase in LDH levels (238U/I [135-225]). Following these results, a preliminary diagnosis of CUP was considered with a digestive or pulmonary primary origin taking into account the immunohistochemistry profile. The patient was treated with one cycle of Cisplatin and Gemcitabine according to the ESMO Clinical Practice Guidelines followed by three cycles of Carboplatin and Gemcitabine due to Cisplatin's renal toxicity. Patient biopsy was immunostained for HER-2/neu and c-MET, and fluorescence in situ hybridization (FISH) was performed to identify ALK and ROS rearrangements and to confirm HER-2/neu and c-MET amplification. Only HER-2/neu was positive. At this moment, CT-scan revealed partial response with about a halving of the size of the lymph nodes. Given the results of FISH, a new protocol based on FOLFOX (Oxaliplatin and 5-FU) and Trastuzumab was performed for four cycles with an excellent response of around 90% reduction in size of the lymph nodes on the CT-scan. This 14-months-chemotherapy regimen associated with a concomitant radiotherapy for residuals lymph nodes allowed to obtain complete remission. Close monitoring was performed. Nine months after stopping treatment, the patient developed a recurrence with a cutaneous lymphangitic carcinomatosis, confirmed with a positive FDG-PET, only on this cutaneous lesion (Figure 2). The second immunohistochemistry profile on cutaneous biopsy was CK7+/CK20-/TTF1+, pointing towards a pulmonary origin. Immunohistochemical detection of PDL-1 (BENCHMARK ULTRA, PD-L1 clone QR-1 Diagomics) on patient cutaneous biopsy was positive with expression levels of 90% (Figure 3). According to these results and with the consent of the patient and his family, an ICI-based treatment was started with Pembrolizumab, the first therapeutic antibody PD-1 inhibitor. Cutaneous lymphangitis disappeared after six months of treatment. Currently, 28 months after Pembrolizumab initiation, the patient is still in complete remission. Treatment should be stopped 24 months after complete remission, as recommended.

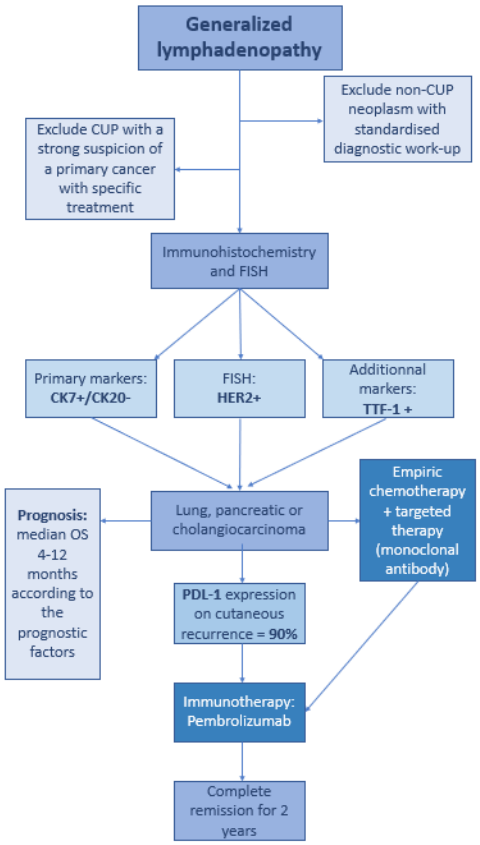

Figure 1: Patient clinical management.

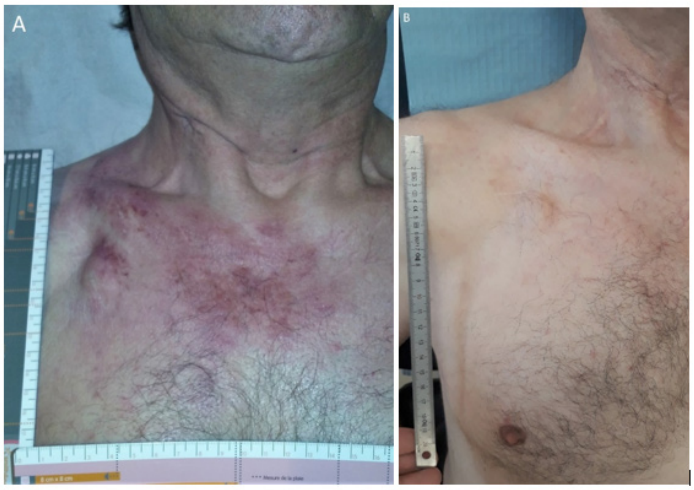

Figure 2: Images of the patient cutaneous recurrence (carcinomatous lymphangitis) before pembrolizumab treatment (A) and 26-months after pembrolizumab treatment initiation (B).

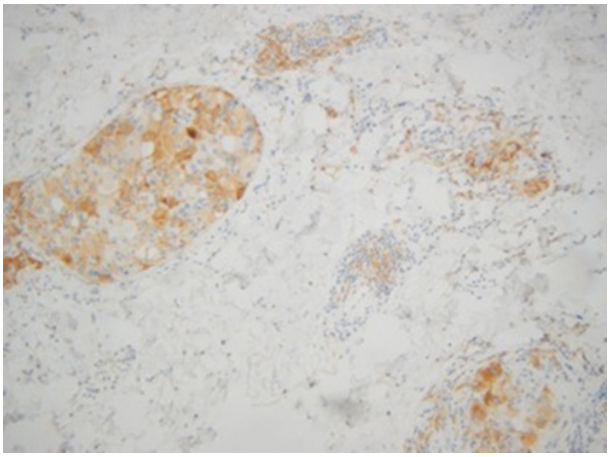

Figure 3: Immunohistochemical detection of PDL-1 expression on patient cutaneous biopsy.

Discussion

Despite the recent decline observed in the diagnosis of CUP, mainly due to improvement in detection of the primary tumours, CUP stays the sixth to the eighth most common malignancy worldwide and the third to fourth most common cause of death due to cancer-related mortality [7]. For CUP patients who do not fit into clinicopathologic subsets with favourable prognosis, as our patient, empiric chemotherapy with taxane-platinum regimens is widely used. Among poorly differentiated carcinomas and although this is a heterogeneous group, some of patients have neoplasms that are highly sensitive to chemotherapy. Nevertheless, in CUP patients with poorly differentiated carcinoma and adenocarcinoma treated with cisplatin-based chemotherapy, the overall response rate was 62%, with 26% complete responders and the median survival was 12 months [14,15].

Cutaneous lymphangitic carcinomatosis is a rare presentation of skin metastasis, accounting for approximately 5% of all cutaneous metastases and characterized by an occlusion of dermic lymphatic vessels by neoplastic cells. It has been reported in the literature in association with several malignancies, including breast carcinoma (most commonly as direct extension of the tumor), lung and ovarian cancer. Cutaneous metastases have also been reported in gastrointestinal cancer but most commonly in large intestine carcinoma [16]. These data from the literature guided us to a pulmonary origin. Nevertheless, among the published cases of cutaneous lymphangitis carcinomatosis with lung cancer, all patients died few months after the diagnosis of the skin involvement [17]. Cutaneous metastases of lung or gastrointestinal malignancies portend a poor prognosis [18]. The thyroid transcription factor (TTF-1) is a nuclear protein traditionally used to identify tumours of lung and thyroid primary. However, in recent years, several studies have reported that some cancer arising in other organs can manifest unexpected TTF-1 positivity, in up to 25% of gastric adenocarcinomas especially [19,20]. These results highlight the potential for diagnostic confusion when dealing with metastatic disease of unknown primary. TTF-1 positivity cannot be used as conclusive evidence of pulmonary origin and gastrointestinal origin must be considered in the differential diagnosis [19].

In this context, and as it happens in 25% or more of CUP patients, diagnostic workups fail to locate the primary tumor site despite the use of multiple imaging modalities, invasive procedures, serum biomarker tests, and IHC staining [12]. Given the poor prognosis of CUP treated by non-targeted therapy, a test that can guide targeted therapy selection for patients with CUP could help avert the expensive search for primary lesion while often it does not improve outcome [12]. Identify targeted therapeutic approaches could improve outcomes for this disease. For this purpose, comprehensive genomic profiling assay based on next-generation sequencing of tumoral DNA seems more effective than IHC, FISH, or mRNA biomarkers [12]. In their large prospective trial, Hainsworth et al. illustrate the improved outcome of patients with responsive tumor types who received site-specific therapy [8].

Among all the targeted therapies under development, immunotherapy has recently been a source of promising new cancer treatments. The objective is to trigger the immune system to attack the cancer cell. Among all the immunotherapeutic treatments, immune checkpoint-directed antibodies have increased overall survival for patients with various cancers, including lung or gastrointestinal cancer, with a better safety profile than chemotherapy [21]. Markers of responsiveness to immunotherapy are under investigation. The efficacy of pembrolizumab have been demonstrated in tumours with mismatch repair deficiency (dMMR)

and high microsatellite instability (MSI), irrespective of tumour cell origin [22,23]. So, pembrolizumab is the first drug to gain pan-cancer FDA approval for use in any MSI-high/dMMR solid tumor, i.e. up to 28% of CUP tumours [24-26]. Determining a potential immunotherapy-responsive subgroup of CUP is hampered by a lack of validated predictive biomarkers and further research is desesperalty needed [27].

Conclusions

This case report highlights the outcome interest to identify targeted therapeutic approaches in the management of CUP patients rather than determining the primary tumor site at all costs. This search for the primary site, often unsuccessful, emerges as being uninformative and often does not improve patient outcome.

Declarations

Ethics Approval and consent to participate: Not applicable

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of supporting data: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Funding: No funding.

Competing interests: The authors have no conflict of interest to declare.

Author's contribution: NB conceived the study and participated in data collection with LM. LV performed a literature search and wrote the manuscript. NB, LM and RB critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript version.

Acknowledgements: We thank all physicians who participated in data collection and the patient for accepting the publication.

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