VIA MEDICA

REVIEW ARTICLE

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Cancer of an unknown primary with *PDZRN3-RAF1* fusion and *ATR* splice site mutation, with atypical chemosensitivity pattern

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Oncology in Clinical Practice
DOI: 10.5603/ocp.101458

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

A cancer of an unknown primary (CUP) is diagnosed when the primary tumor cannot be identified using standard diagnostic methods. Worldwide, CUP constitutes 1.8% of all cancers, with annual mortality reaching 80%. This study describes a 54-year-old man who presented with fever and epigastric pain. Computed tomography detected multiple liver, peritoneal, and mediastinal metastases. Histopathology confirmed the presence of G3 adenocarcinoma, but its origin remained unclear. The patient was diagnosed with CUP and was treated with cisplatin and paclitaxel therapy with moderate effect. The second-line regimen with gemcitabine and capecitabine resulted in remarkable disease stabilization lasting over 2 years. A next-generation sequencing test was performed, revealing the presence of two pathogenic variants (*PDZRN3-RAF1* fusion and *ATR* splice site), but no targeted therapy could be selected based on the findings. The subsequent treatment regimen with irinotecan and cyclophosphamide brought stabilization that lasted 6 months. FOLFOX7 therapy did not provide a response. Sorafenib resulted in 5-month disease control. Simultaneously, expanded histopathology indicated that the cancer could be hepatocellular carcinoma with an atypical immunophenotype. After starting cabozantinib, the patient developed a severe nephrotic syndrome and died after 4 years of oncological treatment.

The complex and unique nature of each CUP makes both diagnosis and optimal management a great challenge. There is an ongoing need to improve workups to identify the primary. As a heterogeneous and poorly investigated entity, CUP may require treatment beyond established guidelines. More research is needed to establish new therapeutic options for CUP patients.

Keywords: cancer of unknown primary (CUP), *focus primarius ignotus* (FPI), *PDZRN3-RAF1* fusion gene, *ATR* splice site mutation, hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (iCCA), *irinotecan*, gemcitabine and capecitabine (GemCap), next-generation sequencing (NGS), *platinum-resistant.*

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Introduction

Cancer of unknown primary site (CUP), also known as *focus primarius ignotus* (FPI), describes a clinical situation when metastases are present, but the primary tumor cannot be detected using standard diagnostic methods [1]. Worldwide, CUP constitutes 1.8% of all cancers belonging to the top 20 most common ones [2]. In 2021, its incidence in Poland was 1.1% [3]. The prognosis is unfavorable, with annual mortality reaching

Received: 19.07.2024 Accepted: 11.11.2024 Early publication: 24.01.2025

approximately 80%, half of which occurs within the first 3 months after diagnosis [4, 5]. The most common histology of CUP is adenocarcinoma [5, 6]. Metastases occur most often in the liver [5, 7].

A workup for CUP recommended by the European Society of Clinical Oncology (ESMO) includes anamnesis, physical examination, complete blood count, blood chemistry, imaging of the chest, abdomen, and pelvis [at least contrast-enhanced computed tomography (CT)], and an endoscopic examination of the upper and lower gastrointestinal tract. Head and neck, breast, and ovarian cancers, as well as germ cell tumors, should be excluded as well [5].

Good quality histopathology with broad immunohistochemistry (IHC) is crucial. It includes cytokeratins (panCK, CK7, CK20), hematolymphoid, melanoma, and mammary and prostate cancer markers [5]. In patients with a small number of metastases or CUP of the head and neck, positron emission tomography (PET) using [18F]2-fluoro-2-deoxy-D-glucose (FDG-PET-CT) is recommended for planning radical radiotherapy. In other cases, FDG-PET is optional [5].

Cancer of unknown primary site is diagnosed when the aforementioned workup fails to detect the cancer's origin.

There is a subgroup of CUP with a favorable prognosis. They have similar features to cancers with a known primary (e.g., breast-like CUP; ovary-like CUP). The analogies concern IHC, prognosis, and response to therapy. Such cases comprising ~20% of CUPS allow for specific treatments to be used [8]. The rest of the CUPs belong to the subgroup with an unfavorable prognosis that is treated empirically.

Negative prognostic factors for unfavorable CUP include poor performance status, high level of lactate dehydrogenase, male sex, a greater number of metastatically involved organs, especially the liver or other visceral organs, and the adenocarcinoma histology [5, 9]. For patients with unfavorable CUP, chemotherapy is based on platinum with taxane or gemcitabine [5].

The molecular profile obtained by next-generation sequencing (NGS) methods can be used to select targeted therapy or provide clues about the primary site. Analysis of microsatellite instability status, tumor mutational burden (TMB), and programmed death-ligand-1 (PD-L1) expression should also be included [1, 5]. However, genetic profiling alone may not be sufficient to establish a proper personalized treatment because agnostic therapies may work differently in different types of cancer [10, 11].

Hepatocellular carcinoma (HCC) contributes to ~80% of the world's total liver cancer burden [2]. Liver cancer is the eighth most common cancer worldwide and the fourth most common cause of cancer-related deaths [2]. The most important risk factor for HCC is liver cirrhosis. Environmental factors that increase the risk of developing HCC include smoking and non-alcoholic steatohepatitis (NAFLD) [12, 13].

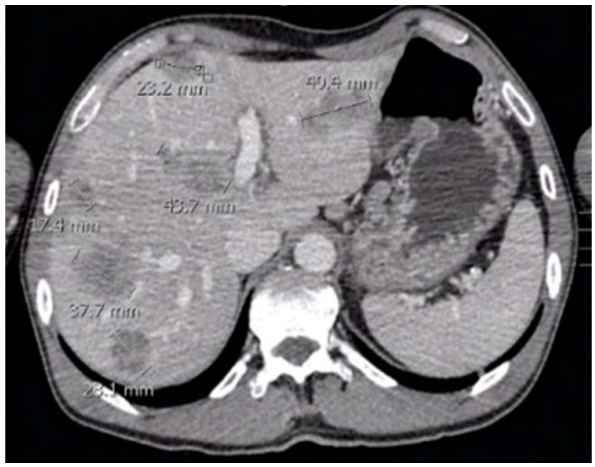

Figure 1. Contrast-enhanced computed tomography (CT). Disseminated lesions in the liver (a total of over 20 lesions involving all segments; largest dimension ~ 43.7 mm)

The first-line treatment for advanced HCC includes immunotherapy (atezolizumab + bevacizumab or tremelimumab + druvalumab) [14]. In the case of any contraindications to the aforementioned regimens, sorafenib or lenvatinib are viable alternatives. Second-line treatments include sorafenib, lenvatinib, regorafenib, ramucirumab, or cabozantinib [14].

Herein, we present the case of a patient who had been diagnosed with CUP and was treated empirically.

Case report

In July 2018, a 54-year-old man without comorbidities, a former smoker (20 pack-years), presented with epigastric pain and fever of uncertain etiology. Computed tomography revealed the presence of disseminated lesions in the steatotic liver (32 mm in the largest dimension, a total of over 20 lesions involving all segments) and lymphadenopathy on both sides of the diaphragm and peritoneal implants (Fig. 1).

Gastroscopy showed only a single inflamed fold. In collected mucosal samples, three small (< 0.2 mm), well-defined clusters of cells were found in blood vessels at the border of the muscle mucosa and the lamina propria. Their morphology and immunophenotype indicated adenocarcinoma (Ki67, expression in approximately 20% of the cells; positive markers: panCK and CK7; negative: CK20; chromogranin, synaptophysin) (Fig. 2). Due to the very sparse tissue, it was not possible to determine the primary site of the tumor, but the picture suggested secondary involvement of the stomach through blood vessels. The colonoscopy did not reveal any pathology.

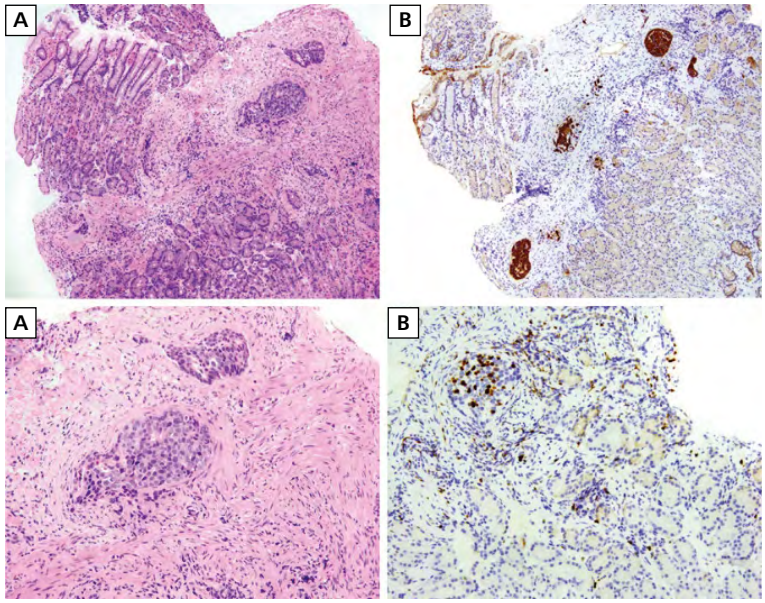

Figure 2. Histopathological picture of the gastric metastases. Neoplastic cells in the blood vessels at the border of the lamina propria and the muscle mucosa; A. Hematoxylin and eosin staining (H&E) ×10; **B.** H&E ×20; **C.** CK7 test: tumor cell emboli are strongly positive and gastric glands are slightly positive; **D.** Ki67 test shows proliferative activity in cancer cells

Subsequently, a core liver biopsy showed the presence of G3 adenocarcinoma expressing Ki67 20% and CK7 (while CK20, chromogranin, synaptophysin, and TTF1 were negative). Of all tumor markers, only the level of alpha-fetoprotein (AFP) was significantly elevated (20 x upper normal limit) (Fig. 3).

Active and latent infection with hepatotropic viruses and environmental risk factors for liver diseases were excluded

An FDG-PET scan indicated the presence of an additional tumor lesion in the thoracic spine (Th3).

The patient was diagnosed with CUP. In August 2018, he began chemotherapy with cisplatin 25 mg/m^2 and paclitaxel 60 mg/m^2 weekly. Four months later, a CT scan showed stabilization of the disease.

In February 2019, the treatment was discontinued due to clinical progression, including increased AFP level (330 IU/mL) and recurrence of pain and fever. Second-line chemotherapy with gemcitabine 1000 mg/m2 and capecitabine 1660 mg/m^2 (d1-21; total q4w; GemCap) was started. After 2 months, a CT revealed a partial response that lasted 25 months (Fig. 4). Due to the severity of hand-foot syndrome, capecitabine was excluded from the treatment regimen in September 2019.

In May 2019, a histopathological examination of another liver lesion showed adenocarcinoma cells with local mucus production in the portal spaces. Immunohistochemistry confirmed the previous immunophenotype without GATA3. The liver samples underwent the Foundation One test which revealed

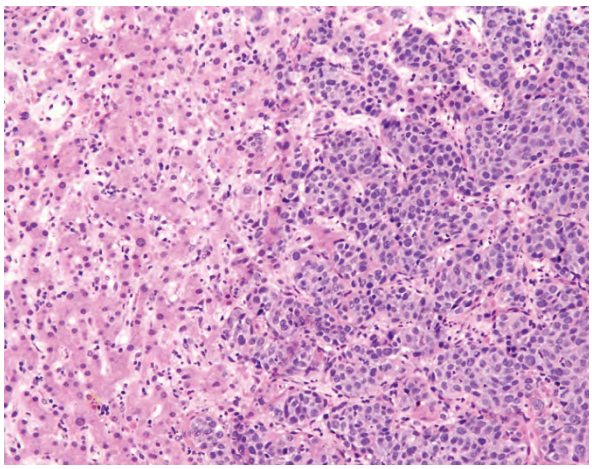

Figure 3. Liver biopsy with tumor infiltration (right side of the picture); H&E ×20

the presence of two pathogenic variants: *PDZRN3-RAF1* fusion and *ATR* splice site (4504-1G>C) and several variants of unknown significance *(ATM* G2508R*; GNAS* R649C*; HIST1H1D* K185_A186>T*; HIST1H1E* A47V; IRS2 A701_V702insA; *KMT2C [MLL3]* P3523L; *MALT1* L67F*, NSD1* S1241T; *SOCS3* T208S). Due to the paucity of samples, it was not possible to determine the mismatch repair and TMB status. A targeted therapy could not be selected based on the results.

In March 2021, a follow-up CT scan showed the presence of new periaortic and supraclavicular lymphadenopathy. Supraclavicular metastasis was confirmed, with similar morphology (adenocarcinoma,

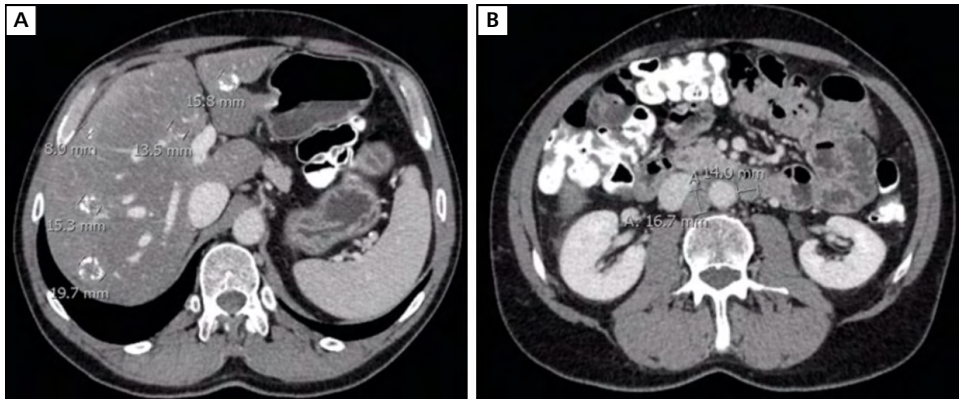

Figure 4. Remission in liver lesions (**A**) and the simultaneous presence of new retroperitoneal malignant lymphadenopathy (**B**) after 25 months of gemcitabine and capecitabine (GemCap) therapy

negative expression of estrogen and androgen receptors, and human epidermal growth factor receptor 2 [Her2]; Ki67 54%, mitotic index: 31/10 HPF). Fusion Plex NGS of the samples showed no mutations in the following genes: *EGFR, ALK, ROS, BRAF, Her2; FGFR1-3, MET, NRG1, NTRK1-3, RET* (insufficient coverage for *PI3K* assessment).

In April 2021, the therapy was changed to irinotecan and oral cyclophosphamide (250 mg/m^2 q3w and 50 mg/d continuously). After 3 months, an objective response was confirmed, lasting another 3 months (Fig. 5).

In November 2021, bone scintigraphy showed new lesions involving the axial and peripheral skeleton. A CT scan confirmed the cancer progression. The AFP level also increased (2700 IU/mL).

In December 2021, FOLFOX7 was initiated [oxaliplatin 85 mg/m^2; 5-fluorouracil (5-FU) 400 mg/m^2 + 5-FU 1200 mg/m^2 + L-folinic acid 100 mg/m^2; intravenously], but it did not induce a response. In March 2022, a CT scan showed new pulmonary lesions and mediastinal lymphadenopathy.

In April 2022, the treatment was changed to sorafenib at a dose of 800 mg daily. The dosing was modified to 2 weeks on and 1 week off due to hand-foot syndrome. A CT performed in July 2022 showed stabilization.

Simultaneously, all previous biopsy specimens were re-verified. Although Heppar and Glycypican were negative, the tumor growth pattern suggested a possible HCC with an unusual immunophenotype.

In September 2022, due to supraclavicular lymphadenopathy, an increased AFP level (9950 IU/mL), and pain, treatment was changed to cabozantinib at a continuous dose of 60 mg/day. After a month, new-onset proteinuria (2.4 g/L) and hypoalbuminemia (28.5 g/L) occurred. Cabozantinib and all nephrotoxic drugs were withdrawn, and supportive therapy was instituted.

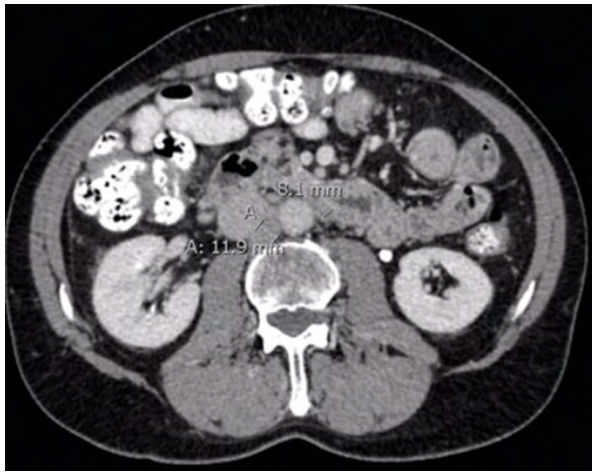

Figure 5. Response to irinotecan + cyclophosphamide regimen after 3 months of treatment

A few days later, the patient's general condition deteriorated. Normocytic anemia, hypoalbuminemia, hypercalcemia, and coagulopathy indicated complicated nephrotic syndrome. Given the lack of response to supportive treatment, the patient died in November 2022 (Fig. 6).

Discussion

Liver metastases are common findings in CUP patients [9]. Primary liver cancers, especially HCC and intrahepatic cholangiocarcinoma (iCCA), must be excluded. Arginase1, HepPar1, and Glypican are specific HCC markers. In the presented case, none of them was positive. The ESMO guidelines recommend excluding HCC when the tumor expresses CK7 [5]. Its expression has been found in up to 22% of HCC (of which 12%

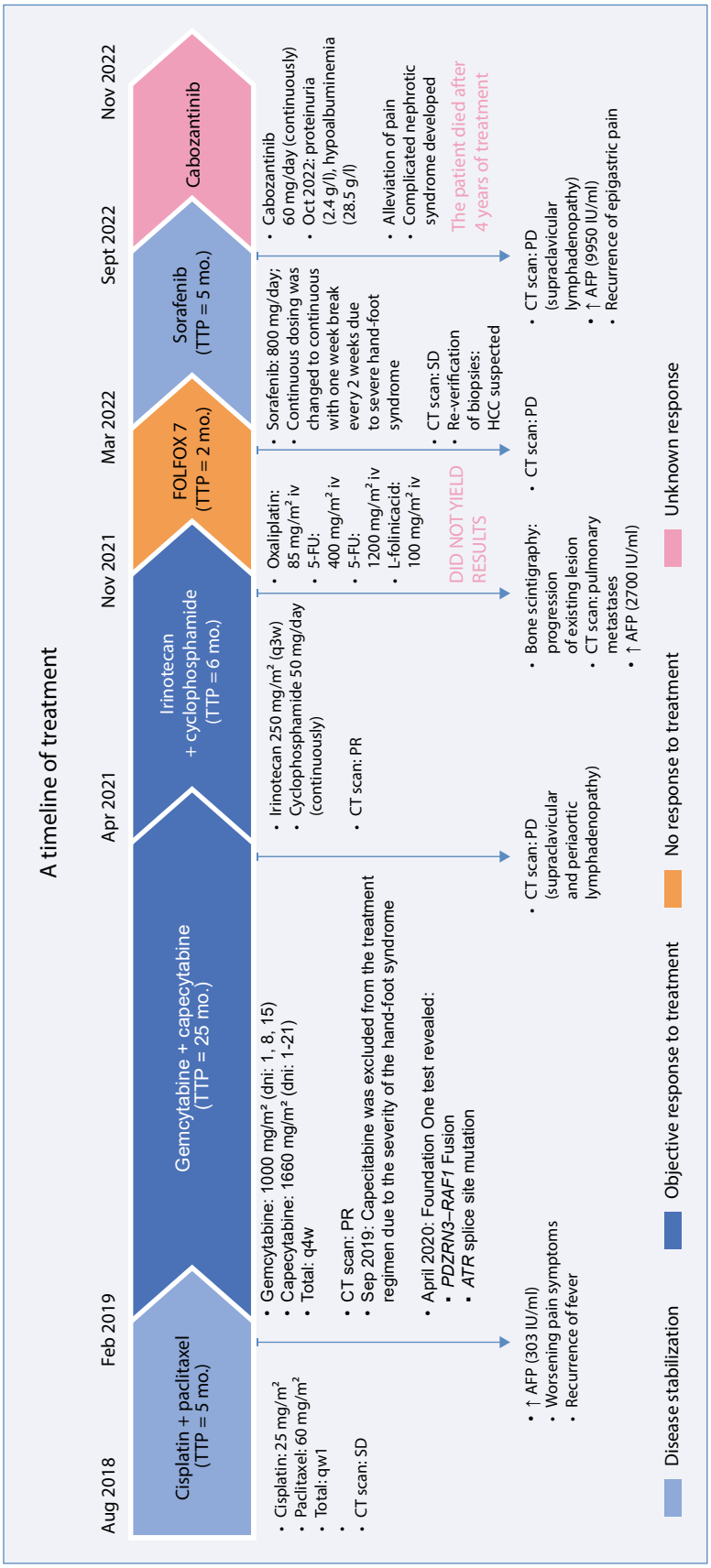

Figure 6. Timeline of treatment; 5-FU — 5-fluorouracil; AFP — α- fetoprotein; CT — computed tomography; mo. — months; PD — progression of the disease; PR — partial response; SD — stable disease; TTP — time to progression; iv — intravenously

expressed only CK7) [15]. Other studies have shown a correlation between CK7 or CK19 and an aggressive course of HCC [16]. As the tumor partially met the criteria for both iCCA and HCC and the molecular makeup pointed to other primaries, the point of origin was uncertain. Moreover, the ESMO recommends excluding CCA in the presence of multiple organ metastases or more than two liver lesions [5].

An exceptionally good response to GemCap is of particular interest. This therapy is used to treat pancreatic and biliary cancer [17, 18]. It has been used in some patients with CUP, but so far, little research on its effectiveness has been conducted. In a 2007 phase II clinical trial, a combination of carboplatin, capecitabine, and gemcitabine was tested in patients with liver metastases, especially when the suspected primary was below the diaphragm [19]. In the case of advanced and metastatic HCC, both gemcitabine and capecitabine alone have shown low effectiveness [20, 21], but their combination remains unstudied.

In this patient, irinotecan + cyclophosphamide was also effective. There are no studies on the effectiveness of irinotecan alone in CUP treatment, although its combination with platinum salts has shown activity in early studies [22–24]. Irinotecan is not active in HCC [25, 26] but is a standard subsequent line option in iCCA [27].

Sorafenib had been the first-line treatment for advanced HCC until the superiority of atezolizumab + bevacizumab was confirmed (IMbrave150 trial) [28]. Sorafenib, lenvatinib, regorafenib, cabozantinib, and ramucirumab are now options in second-line treatment [29]. To date, only a few studies have evaluated the effectiveness of sorafenib in pretreated HCC. They showed modest activity and supported regorafenib and cabozantynib as standard second-line options [30, 31]. The effectiveness of sorafenib in the described patient was comparable to the literature data from its first-line use in patients with advanced HCC. The effectiveness of cabozantinib therapy could not be assessed due to its short duration (one month).

Sorafenib and cabozantinib are antiangiogenic agents. Despite high effectiveness in the treatment of some cancer types, they significantly increase the risk of nephrotoxicity by inducing loss of podocytes, glomeruli fenestrations, and key barrier proteins [32, 33]. They contribute to the development of hypertension and damage to the filtration membrane, leading to proteinuria and renal failure [32, 33]. However, nephrotic syndrome as a result of this therapy is not common, and there are no established standards of care in such cases. Individual studies suggest immediate discontinuation of harmful drugs and initiation of supportive treatment. Kidney biopsy may help plan future management. It is crucial to monitor kidney function before and during antiangiogenic therapy to prevent the development of nephrotic syndrome. Proteinuria and swelling are reduced with glucocorticosteroids and angiotensin convertase (ACE) inhibitors [34, 35].

Approximately 85% of CUP patients have one or more leading genetic variants. Almost 50% of them may benefit from the insertion of licensed or investigational agnostic therapies [36].

Our patient was diagnosed with *PDZRN3-RAF1* fusion. It is a rearrangement of the *RAF-1* gene that encodes proteins activating the mitogen-activated extracellular kinase (MEK) pathway. Its mutations are common in lobular pancreatic cancer [37–39]. Another revealed pathogenetic mutation was the *ATR* splice site variant. *ATR* is a suppressor gene encoding a serine-threonine kinase that detects DNA damage and inhibits cell division. It is the main sensor of cell replication stress [40]. *ATR* mutations have been described in colon and breast cancers [41, 42].

In the presence of *RAF1* rearrangement, there is a reported response to MEK inhibitors (e.g., trametinib and cobimetinib). There are also *ATR* inhibitors that are currently being evaluated in clinical trials (ceralasertib and bersosertib) [43].

In our patient, 16 gene variants with unknown impact on carcinogenesis were found. According to recommendations, clinical trials in which the patient could be included before the initiation of each treatment line were searched.

The agnostic approach appears to be particularly advantageous for CUP patients, in whom treatment based on the primary tumor site cannot be used. However, not all drugs with a molecular predictive factor can be approved as agnostic therapies due to the differences in their effectiveness observed in different types of cancers [11, 10]. Further studies are needed on the efficacy of new agnostic therapies in cancer treatment.

Article Information and Declarations

Ethics statement

Article have been conducted according to the principles stated in the Declaration of Helsinki.All authors have read and agreed to the published version of the manuscript.

Author contributions

W.Z.Z.: formal analysis, investigation, resources, data curation, writing — original draft preparation; M.U.-B., A.G.: formal analysis, investigation, resources, writing — original draft preparation; P.M.P.: conceptualization and patient selection, methodology, investigation, resources, data curation, writing — original draft preparation.This work was created in the Oncology Department, Student Research Group of the Jagiellonian University Medical College, Kraków, Poland (tutor — Paweł M. Potocki).

Funding
None.

Acknowledgments
We would like to thank the patient and his family for their trust and resilience; students from the Student Research Group, Oncology Department, Jagiellonian University Medical College, for their unfading enthusiasm.

Conflict of interest
W.Z.Z., A.G., M.U.-B.: declare no conflicts of interest. P.M.P.: received travel grants, speaker fees, and clinical trial participation from AstraZeneca, Bayer, Ipsen and Roche.

Supplementary material
None.

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