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LETTER TO THE EDITOR

Familial cancer of unknown primary

Elie Rassy[1,2] · **Joseph Kattan**[1] · **Nicholas Pavlidis**[3]

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Abstract
Cancer of unknown primary site (CUP) is a deadly disease diagnosed through metastases at various organs without primary tumor identification. Despite the major molecular and technological advances, the carcinogenesis of CUP remains enigmatic which hampers adequate study design of treatments leading to survival improvement. To date, the pathogenesis of CUP is still debatable with one hypothesis considering CUP simply a group of metastatic tumors with unidentified primaries and another considering it a distinct entity with specific genetic and phenotypic aberrations. Familial CUP seems to favor the first hypothesis due to common genetic predisposition factors between known primaries and CUP. Two clinical implications may be withdrawn from the pathogenesis of familial clustering of CUP. The detailed family history and environmental risk factors may orient towards the primary tumor identification. Smoking avoidance and adherence to general population guidelines for cancer screening would be strongly encouraged.

Keywords Cancer of unknown primary · CUP · Familial · Genetics

Dear Editor,

Cancer of unknown primary (CUP) is a well-recognized clinical syndrome that constitutes a clinical challenge for oncologists in the absence of a primary tumor site after extensive laboratory and clinical investigations [1]. It accounts for 3–5% of cancer diagnosis in the historical series but recently a decreased incidence has been recorded as it currently comprises < 2% of cancer diagnosis [2, 3]. Nevertheless, it remains the fourth most common cause of cancer death which constitutes a major clinical challenge [2, 3]. The currently adopted clinical rationale in the management of CUP categorizes patients into favorable and unfavorable subgroups [4]. The first includes predefined clinicopathologic subsets that are commonly chemosensitive whereas the later is a chemoresistant disease with very poor prognosis [4]. The recent technological advances achieved disappointing improvements in patients with CUP. The natural history and carcinogenesis of CUP remain poorly understood despite of the capacity of sensitive diagnosis of tumor metastasis and the ability of pathologists to identify the tissue-of-origin [5]. Liquid biopsy was suggested to present hypothetical benefits but its clinical validation has not been established [6]. Moreover, treatment with disease-oriented therapy and targeted therapies failed to ameliorate the overall survival of patients with CUP [7–9].

The lack of substantial improvement in CUP is attributed to its enigmatic pathogenesis. One hypothesis considers CUP simply a group of metastatic tumors with unidentified primaries whereas another hypothesis considers CUP a distinct entity with specific genetic and phenotypic aberrations [10]. Confirmation of one of the two hypotheses is speculated to improve primary disease-oriented therapy or develop CUP-oriented treatments targeting molecular aberrations that drive neoplastic growth and dissemination [11]. As family studies are informative of shared disease mechanisms which are mainly a result of genetic and environmental factors, familial CUP may potentially lead to better understanding of the CUP pathogenesis [12]. Thus, understanding of familial CUP may have major clinical implications in regards to tissue-of-origin identification and treatment options. This may ultimately guide the screening of the family members

✉ Nicholas Pavlidis
npavlid@uoi.gr

[1] Department of Cancer Medicine, Gustave Roussy Institut, Villejuif, France

[2] Department of Hematology-Oncology, Hotel Dieu de France University Hospital, Faculty of Medicine, Saint Joseph University, Beirut, Lebanon

[3] Emeritus Professor, University of Ioannina, Niarchos Avenue, 45110 Ioannina, Greece

of a patient with CUP for earlier identification of associated cancers.

Evidence of familial cancer of unknown primary

The original evidence supporting the hypothesis that some proportion of CUP might have a genetic basis is drawn from observations of familial CUP clustering (Table 1). The first study evaluating familial CUP included a total of 35,168 patients with CUP from Swedish Family-Cancer Database [12]. Familial clustering was assessed by calculating risks between family members for concordant (CUP–CUP) and discordant (CUP—any other cancer) cancers [12]. Familial cases of concordant CUP account for 2.8% whereas discordant cancers occur in 2.4% [12]. Interestingly, some of the discordant familial pairs were more common than concordant CUP, the highest being the CUP-lung cancer cluster, which accounts for 3.1% of lung cancer in the offspring generation. Other possible primary sites include kidney and colorectal cancers [12]. Similarly, another study of 4160 patients with CUP from the Utah Cancer Registry analysis showed that first-degree relatives of patients with CUP have an increased risk of CUP as well as lung and pancreatic cancers [13].

Genetics of familial cancer of unknown primary

The evidence of germline susceptibility in familial CUP is weak as the concordance of CUP and other tumors may be incidental. Moreover, the absence of any genetic signature and the prominence of chromosomal instability in CUP limit the understanding of the genetics of familial CUP [5, 14]. A genome-wide associated study of 515 patients with CUP has identified germline genes that increase the risk of CUP [15]. LTA4H, a gene coding for an enzyme catalyzing the production of leukotriene B4 and TIAM1 commonly involved in cancer and inflammatory processes were associated with CUP. In patients with liver metastasis from CUP, DHCR7 and NADSYN1 encoding key enzymes in cholesterol and NAD synthesis as well as KRTAP5-7 encoding a keratin-associated protein were associated with CUP [15]. Such analysis in patients with CUP and their family members could establish hereditary relationships between colon, pancreatic, and lung cancer associated with CUP. One hypothetical genetic basis involves aberrant DNA repair which leads to neoantigen-induced immunogenic elimination of the primary tumor [16]. For example, CUP cases clustered with colon cancer may be driven by frameshift mutations which lead to the development of immunogenic neoantigens, or frameshift proteins, that are implicated in the prominent antitumor lymphocytic proliferation [17].

Table 1 Summary of the population-based studies reporting on familial CUP

	Utah Cancer Registry [13]	Swedish Family-Cancer Database [12]
Time period	1980–2010	1858–2008
Number of CUP cases	4160	35,168
Median age at CUP diagnosis	72 years	58 years
Male/female ratio	0.91	Not reported
Histological subtypes	Adenocarcinoma 36.3%	Not reported
	Squamous cell carcinoma 7.8%	
	Neuroendocrine carcinoma 5.0%	
	Carcinoma not otherwise specified 26.4%	
Familial CUP	Not reported	2.80%
	First-degree relative HR = 1.35, 95%CI 1.07–1.70[a]	Parent only SIR = 1.08, 95%CI 0.9–1.27[b]
	Second-degree relative HR = 1.05, 95%CI 0.89–1.24[a]	Sibling only SIR = 1.27, 95%CI 1.27–2.21[b]
	First cousin HR = 1.03, 95%CI 0.92–1.15[a]	

CUP cancer of unknown primary, *HR* hazard ratio, *SIR* standardized incidence ratio

[a]Hazard ratio for CUP compared with controls matched on sex and birth year CUP-free controls

[b]Standardized incidence ratio calculates the familial risk for CUP in offspring according to familial history

Clinical implications of familial cancer of unknown primary

In the Swedish registry, a total of 9171 offsprings with CUP were analyzed among which 60% had a first-degree relative with any cancer [18]. The median age at CUP diagnosis in the offspring generation is 59 years which did not seem to deviate between familial and non-familial cases. Familial clustering is associated with metastatic locations with the affected organ system in the family member. The diagnosis of concordant CUP is increased in siblings (relative risk [RR] = 1.45; 95%CI 1.16–1.79) whereas the diagnosis of discordant cancer sites occurred with two tumors in parents (lung and oesophagus), five tumors in siblings (rectum, liver, lung, and breast connective tissue), and four tumors in parents and siblings (colon, liver, lung, and ovary). Reversely, the risk of cancer in offspring when a relative has CUP is increased in multiple tumors including mainly ovarian (RR = 1.30; 95%CI 1.13–1.48), liver (RR = 1.28; 95%CI 1.08–1.52), and colon cancers (RR = 1.26; 95%CI 1.15–1.38). Interestingly, the location of CUP in offspring has significant associations with that of cancers in first-degree relatives. The risk of abdominal CUP in offspring is increased in those with parents diagnosed with ovarian (RR = 1.63; 95%CI 1.22–2.14) or gastric (RR = 1.29; 95%CI 1.01–1.63) cancers. Similarly, liver CUP is associated with liver (RR = 1.44; 95%CI 1.05–1.92), lung (RR = 1.41; 95%CI 1.17–1.68) and breast (RR = 1.19; 95%CI 1.02–1.43) cancers in relatives as well as head and neck CUP with esophageal (RR = 2.56; 95%CI 1.02–5.31) and kidney (RR = 2.90; 95%CI 1.15–6.02) cancers in relatives [18]. Moreover, CUP patients died often from metastases in the lungs (RR = 1.85; 95%CI 1.49–2.8), liver (RR = 1.84; 95%CI 1.15–2.94), ovaries (RR = 2.35; 95%CI 1.69–3.26) or other organs when their relatives were diagnosed with primary cancers at the same sites [19].

These high levels of concordance may be attributed to the presence of metastatic sites that are unidentified from the familial cancer site because of phenotypic plasticity [18, 20]. Common environmental risk factors such as smoking may be confounding factors that could bias these associations; however, the magnitude of their effect seems very weak [21]. Altogether, these findings favor the presence of common genetic mechanisms between certain primary cancers and CUP [19].

Conclusion

Familial clustering of CUP and other tumors favors the hypothesis that CUP is a metastatic tumor with an unidentified primary rather than an anarchic metastatic tumor. The identification of the tissue-of-origin is not straightforward as phenotypic modifications complicate pathological tissue assignment. The available data suggest that common genetic predisposition factors facilitate the recognition and elimination of the primary tumor. Subsequently, the detailed family history and environmental risk factors may orient towards the primary tumor identification. The pathogenesis of familial CUP underlies the presence of a genetic susceptibility that renders the family members of a patient with CUP at an increased risk of CUP and other tumors. In this scenario, smoking avoidance and adherence to general population guidelines for cancer screening would be strongly encouraged.

Compliance with ethical standards

Conflict of interest No author has any conflict of interest.

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