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Paraneoplastic syndromes in cancers of unknown primary: an unknown field for oncologists

Les syndromes paranéoplasiques dans les cancers d'origine inconnue : une mise au point pour les oncologues praticiens

Short title: Paraneoplastic syndromes in CUP

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Abstract

Paraneoplastic syndromes are signs or symptoms that result from tissue damage at locations remote from tumour sites. Paraneoplastic syndromes associated with cancer of unknown primary (CUP) are not well recognized as they are rarely reported. These syndromes can impair various organ functions and include endocrine, neurologic, dermatologic, rheumatologic, hematologic and several other system alterations. To our knowledge, the association between the histological CUP type and the paraneoplastic syndrome has never been assessed. In some instances, paraneoplastic syndromes can become the major clinical problems determining survival. However, they can also herald earlier the occurrence of CUP in patients with asymptomatic tumors. In this article, we review the available literature of CUP patients presenting paraneoplastic syndromes by trying to collect all available published cases during the last three decades. One additional goal of this article is to make practicing oncologists aware of the coexistence of paraneoplastic syndromes in patients with CUP.

Keywords: cancer of unknown primary; CUP; paraneoplastic syndromes

Résumé

Les syndromes paranéoplasiques sont des manifestations cliniques et biologiques qui résultent de dégâts tissulaires survenant à distance de la tumeur primitive. Les syndromes paranéoplasiques associés au cancer de primitif inconnu (CPU) sont peu connus en raison de leur rareté. Il n'y a notamment pas d'association connue entre syndrome paranéoplasique et type histologique du CPU. Ces syndromes peuvent entraîner des dysfonctions de tous les organes et systèmes vitaux chez les patients. Nous avons réalisé une revue systématique de la littérature des syndromes paranéoplasiques publiés durant les trois dernières décennies, ayant été décrits chez les patients dont l'origine de la tumeur primitive n'a pas été retrouvée. Cette revue de la littérature a pour but de mieux informer les praticiens oncologues de l'existence et des spécificités de ces syndromes rares.

Mots clés: cancer d'origine inconnue; syndrome paranéoplasique

Introduction

Cancers of unknown primary (CUP) constitute a heterogeneous group of metastatic tumours without an identifiable primary tumour after a standardized diagnostic work-up [1]. They are characterized by lack of detectable tissue of origin, early dissemination and aggressive behaviour [2]. Limited diagnostic evaluation toward the detection of the primary tumour site as extensive work-up yields a primary site in 20% antemortem and autopsy in 30% [3]. The

minimal basic diagnostic approach requires a thorough physical examination, basic blood and biochemical analysis including certain serum tumour markers and computed tomography (CT) scans of thorax, abdomen and pelvis [1]. Endoscopic investigations are clinically guided according to the signs, symptoms and laboratory abnormalities whereas positron emission tomography (PET)/CT is reserved for patients with cervical adenopathies and single CUP metastasis [1]. Accordingly, CUP patients are classified into two prognostic groups. The majority of patients (80-85%) have chemoresistant tumours (unfavorable subsets), whilst the minority of patients (15-20%) harbor chemosensitive tumours classified into clinicopathologic favorable subsets [4].

Asthenia, cachexia and weight loss are the most common symptoms of CUP patients. However, the principal clinical presentation of CUP depends on the predominant site of metastatic involvement such as digestive and respiratory symptoms, skin nodules and bone pains [2]. Paraneoplastic syndromes, defined as signs and symptoms not attributable to direct tumour invasion or compression, may also occur [5,6]. The pathogenesis of paraneoplastic syndromes remains unclear but they usually manifest before a cancer diagnosis. Their timely recognition may lead to an earlier cancer diagnosis which might substantially affect the prognosis of CUP patients [7]. However, the association of CUP with paraneoplastic syndromes has never been reported outside of individual case reports. This review collects all the published case reports of paraneoplastic syndromes in CUP to provide an overview of this association.

Material and Methods

The Medline database (via PubMed) was searched by using the relevant keywords for a combined search using the following phrases (paraneoplastic syndrome) AND (cancer of unknown primary), (dermatomyositis) AND (cancer of unknown primary), (acanthosis nigricans) AND (cancer of unknown primary), (Leser-Trelat sign) AND (cancer of unknown primary), (Necrolytic migratory erythema) AND (cancer of unknown primary), (Sweet's syndrome) AND (cancer of unknown primary), (Florid cutaneous papillomatosis) AND (cancer of unknown primary), (pyoderma gangrenosum) AND (cancer of unknown primary), (acquired generalized hypertrichosis) AND (cancer of unknown primary), (itching) AND (cancer of unknown primary), (melanosis) AND (cancer of unknown primary), (Cushing's syndrome) AND (cancer of unknown primary), (ACTH) AND (cancer of unknown primary), (syndrome of inappropriate antidiuretic hormone) AND (cancer of unknown primary), (hypercalcemia) AND (cancer of unknown primary), (hypoglycaemia) AND (cancer of unknown primary), (carcinoid syndrome) AND (cancer of unknown primary), (hyperaldosteronism) AND (cancer of unknown primary), (Lambert-Eaton myasthenic syndrome) AND (cancer of unknown primary), (paraneoplastic cerebellar degeneration) AND (cancer of unknown primary), (encephalomyelitis) AND (cancer of unknown primary), (limbic encephalitis) AND (cancer of unknown primary), (brainstem encephalitis) AND (cancer of unknown primary), (opsoclonus myoclonus ataxia syndrome) AND (cancer of unknown primary), (anti-NMA receptor encephalitis) AND (cancer of unknown primary), (polymyositis) AND (cancer of unknown primary), (granulocytosis) AND (cancer of unknown primary), (polycythemia) AND (cancer of unknown primary), (Trousseau syndrome) AND (cancer of unknown primary), (thrombosis) AND (cancer of unknown primary), (nonbacterial thrombotic endocarditis) AND (cancer of unknown primary), (hypertrophic osteoarthropathy) AND (cancer of unknown primary), (amyloidosis) AND (cancer of unknown

primary), (Stauffer syndrome) AND (cancer of unknown primary), (Membranous glomerulonephritis) AND (cancer of unknown primary), (tumour-induced osteomalacia) AND (cancer of unknown primary), (vasculitis) AND (cancer of unknown primary).

The 939 resulting publications identified with this search strategy on October 6th, 2018 were examined by two reviewers (EER and TA) for their title and abstract. No language or time limitations were applied. The relevant papers were 110 articles among which 35 were duplicated. Thus the total number of articles eligible for revision was 75. In addition, the reference sections of the publications identified using the search strategies described above were examined to identify other potentially relevant publications.

Each qualifying publication was reviewed and relevant data was recorded in the following fields of a Microsoft Excel spreadsheet for each CUP patient presenting a paraneoplastic syndrome: publication citation; paraneoplastic syndrome; age and sex; metastatic sites; histopathologies; clinicopathologic subsets; treatment; follow-up. The clinicopathologic subsets are defined by organ involvement as follows: visceral CUP, nodal CUP, neuroendocrine CUP, bone-bone marrow CUP. Cases presenting with more than one paraneoplastic syndromes were mentioned separately in each paraneoplastic syndrome.

Results

A flowchart describing the selection process of reports is presented in Figure 1. Overall, the eligible articles reported on 81 patients with CUP presenting paraneoplastic syndromes. The majority of patients (79%) had one paraneoplastic syndrome whereas the remaining (11%) had two paraneoplastic syndromes. The most commonly reported paraneoplastic syndromes cases

were hematologic followed by rheumatologic, dermatologic, endocrine and neurologic syndromes.

[Paraneoplastic hematologic syndromes](#)

Paraneoplastic hematologic syndromes are commonly asymptomatic, discovered during routine work ups and rarely necessitate specific therapy. The published literature reports multiple paraneoplastic hematologic syndromes in CUP patients: Trousseau's syndrome (10 cases), thrombotic thrombocytopenic purpura (five cases), microangiopathic hemolytic anemia (five cases), leukoerythroblastosis (four cases) and several other manifestations. The patient characteristics, associated malignancies, clinicopathologic subsets, treatments and follow-up are listed in Table 1. The majority of patients had adenocarcinoma pathologies with poor prognostic clinicopathologic CUP subsets. All patients died early after diagnosis despite aggressive treatments (Table 1).

[Paraneoplastic rheumatologic syndromes](#)

Paraneoplastic rheumatologic syndromes constitute a heterogeneous group of clinical manifestations that may have a benign appearance. In view of the high prevalence of rheumatologic disorders, it is not always easy to determine the correlation between a rheumatologic abnormality and an internal neoplasm especially in the absence of a primary tumor [27]. The pathogenesis of paraneoplastic rheumatologic syndromes is complex and not fully understood [27]. The published literature in CUP reports few possible paraneoplastic rheumatologic syndromes: dermatomyositis and polymyositis (18 cases), hypertrophic osteoarthropathy (one case), rheumatoid-like polyarthritis (one case) and polyarteritis nodosa (one case). The patient characteristics, associated malignancies, diagnostic studies, clinicopathologic subsets, treatments and follow-up are listed in Table 2. Similar to

paraneoplastic dermatologic syndromes, the paraneoplastic rheumatologic syndromes are associated with all the CUP clinicopathologic subsets except for bone-bone marrow CUP (Table 2).

[Paraneoplastic dermatologic syndromes](#)

The association between malignancy and skin disorders is complex and intriguing. Paraneoplastic dermatologic syndromes are the expression of an underlying cancer, frequently occult, and can be caused by various mechanisms that have not been fully elucidated [48]. The published literature in CUP reports several possible paraneoplastic dermatologic syndromes: acanthosis nigricans (four cases), Leser-Trelat sign (two cases), pytriasis rubra pylaris (two cases), cutaneous paraneoplastic syndrome (one case), necrolytic migratory erythema (one case), Basex syndrome (one case), paraneoplastic acral vascular syndrome (one case) and chronic itch syndrome (one case). The patient characteristics, associated malignancies, clinicopathologic subsets, treatments and follow-up are listed in Table 3. Except for bone-bone marrow CUP, all the CUP clinicopathologic subsets were associated with paraneoplastic dermatologic syndromes and diagnosed during or following the diagnosis of the paraneoplastic syndromes (Table 3).

[Paraneoplastic endocrine syndromes](#)

CUP seems to secrete functional peptide or ectopic hormones which are not physiologically produced by this type of cells thus leading to paraneoplastic endocrine syndrome. Consequently, the regulatory mechanisms that regulate the release of hormone are lost thus result in the development of endocrine syndromes induced by the ectopic hormonal substances [7]. The published literature reports four possible paraneoplastic endocrine syndromes: Carcinoid syndrome (two cases), Cushing's syndrome (four cases), hypercalcemia (four cases)

and hypoglycaemia (one case). The patient characteristics, associated malignancies, clinicopathologic subsets, treatments and follow-up are listed in Table 4. The paraneoplastic endocrine syndromes are often detected before CUP diagnosis and seem associated mostly with neuroendocrine CUP (Table 4).

[Paraneoplastic neurologic syndromes](#)

Paraneoplastic neurological syndromes are nervous system dysfunctions that are caused by tumour-directed antibodies that are cross reactive with components of the nervous system [71]. These antibodies are secreted by the immune system thus the adequate treatment of the paraneoplastic neurologic syndromes relies on immune suppression in addition to cancer treatment [7]. The available literature reports four paraneoplastic neurologic syndromes associated with CUP: paraneoplastic cerebellar degeneration (three cases), Stiff-Person-Syndrome (one case), limbic encephalitis (three cases), NMDA receptor encephalitis (two cases) and paraneoplastic neurological syndrome (one case). The patient characteristics, associated malignancies, associated antibodies, clinicopathologic subsets, treatments and follow-up are listed in Table 5. The paraneoplastic neurologic syndromes are often detected before CUP diagnosis (range 2-6 months) and improve with immune suppression (Table 5).

[Paraneoplastic miscellaneous syndromes](#)

A wide range of other paraneoplastic syndromes affecting other systems and organs seems to occur in the setting of CUP but the pathogenesis has not been elucidated in most instances (Table 6). Of particular interest are the paraneoplastic nephrologic syndromes which have witnessed great advances in the understanding of their pathogenesis, however they seem rare in CUP patients [79]. The patient characteristics, associated malignancies, clinicopathologic subsets, treatments and follow-up are listed in Table 6.

Discussion

Physicians primarily prescribe diagnostic procedures aiming at confirming or excluding the occurrence of primary diseases. However, these manifestations may be secondary to occult tumours and careful clinical investigation becomes life saving. In the absence of a defined pathogenic link between CUP and the possible paraneoplastic syndromes, establishing a causal relationship is not straight forward and currently relies on Hill's criteria for causation [86]. These criteria include strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy [86]. However, the scientific advances over the last century in regards to molecular genetics and genomics allowed deeper understanding of diseases [87]. Unfortunately, these advances were not contributory to the understanding of CUP as the available evidence is weak and the application of gene expression profiling failed to identify a CUP molecular signature [88]. CUP remains of unknown biology for integration within Hill's criteria for causation [88,89]. This paper does not aim to establish a causal relationship between CUP and paraneoplastic syndromes. Instead, it aims to increase the awareness of medical oncologists to paraneoplastic syndromes that may be associated with CUP. Recognition of the major paraneoplastic syndromes associated with CUP allows the doctor to establish an early diagnosis and treatment, which could lead to a better prognosis for the patient.

Paraneoplastic syndromes in CUP patients may allow a timely diagnosis but may also increase the morbidity and mortality of patients. Our review of the literature showed that the majority of patients with CUP present one paraneoplastic syndrome and the occurrence of two

syndromes is uncommon [23,24,29,35,51,54,61]. Another interesting finding in this review is the lack of reports describing the more commonly encountered paraneoplastic syndromes such as syndrome of inappropriate antidiuretic hormone, polymyalgia rheumatica and Lambert-Eaton syndrome in patients with CUP. As such, physicians should indulge in a thorough work up to identify a primary tumour in patients with these paraneoplastic syndromes. This paper could not conclude on the prognostic role of paraneoplastic syndromes in CUP patient. Given that the literature review included cases reported over three decades, caution is required in interpreting the data as the identification of CUP varies with the availability of adequate immunohistochemical work-up and diagnostic tools. As such, we could not classify the CUP cases according to the standard clinicopathologic CUP subsets which is of prognostic value [1]. Therefore, the reported cases were classified according to organ involvement into four subsets including visceral CUP, nodal CUP, neuroendocrine CUP and bone-bone marrow CUP. We only concluded to some predilection of certain subsets in regard to particular paraneoplastic syndromes. Given the wide variations between the reported case reports regarding the age, performance status, burden of disease and treatment administration, it is not possible to estimate or to compare the survival or prognosis of each CUP subset. To date, the available data does not answer the question of the prognostic role of paraneoplastic syndromes in CUP. As such, the prognosis of CUP patients with paraneoplastic syndromes can be estimated similarly to those without paraneoplastic syndromes [90].

Conclusion

In this review, we have tried to summarize all the published literature of paraneoplastic syndromes in CUP. Despite the fact that paraneoplastic syndromes in CUP being rare, they are of major clinical importance because they often herald other clinical manifestations of CUP which allows a timely diagnosis and better prognosis. Paraneoplastic syndromes can also impact the quality of life and morbidity of CUP patients. Subsequently, the recognition of paraneoplastic syndromes by primary physicians and practicing specialists is highly useful in daily clinical practice as it allows to correctly pre-diagnose malignant tumors and adequately administer cancer treatments.

Conflict of interest

The authors declare that they have no conflict of interest.

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None

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FIGURE 1: Flowchart describing the article selection process.

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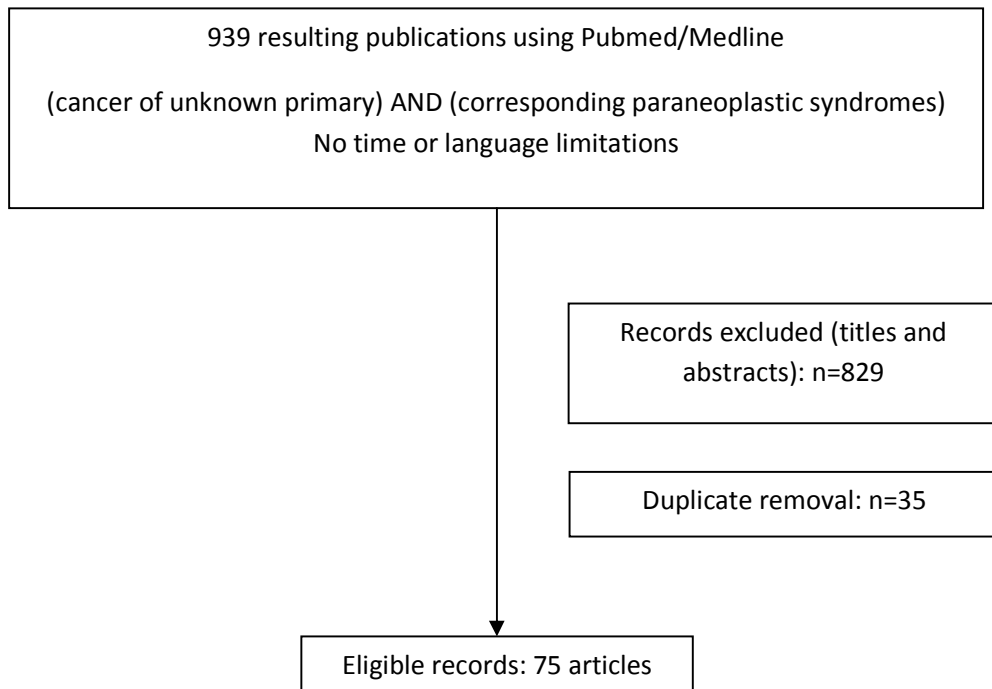


Table 1: Case reports of CUP patients with paraneoplastic hematologic syndromes

Publication	Patient (sex/age)	Metastatic sites	Histopathology	Clinicopathologic subset	Treatment	Follow-up
Trousseau's syndrome						
Levi et al. (1994) [8]	F/38	Intravascular metastases in lungs, liver, ovaries, LN	Carcinoma - poorly differentiated	Visceral CUP	No treatment	Patient died (no details)
Tisdale et al. (1995) [9]	M/54	LN - mediastinal	Carcinoma -poorly differentiated	Nodal CUP	Chemotherapy, radiation therapy	Patient alive
Tisdale et al. (1995) [9]	M/50	LN - mediastinal	Carcinoma -poorly differentiated	Nodal CUP	Chemotherapy, radiation therapy	Died 18 months after diagnosis
Farley et al. (2001) [10]	F/36	LN - iliac and obturator	Adenocarcinoma - poorly differentiated	Nodal CUP	Debulking chemotherapy	Died 18 months after diagnosis
Berghella et al. (2003) [11]	F/35	LN - mediastinal, hilar, supraclavicular	Adenocarcinoma - poorly differentiated	Nodal CUP	Chemotherapy, radiation therapy, steroids	Died 5 months after diagnosis
Apras et al. (2004) [12]	M/29	Pleural effusion, LN - cervical, supraclavicular, mediastinal, axillary	Squamous cell carcinoma	Visceral CUP	Chemotherapy	Died (no details)
Batsis et al. (2005) [13]	M/51	LN - hilar, mediastinal	Adenocarcinoma	Nodal CUP	Radiation therapy, chemotherapy	NA
Seppala et al. (2009) [14]	F/82	Small pulmonary arteries and arterioles	Adenocarcinoma	Visceral CUP	No treatment	Died 3 weeks after diagnosis
Beyer-Westendorf et al. (2011) [15]	F/53	LN - cervical	Adenocarcinoma - poorly differentiated	Nodal CUP	Chemotherapy	Died 19 months after diagnosis
Woo et al. (2014) [16]	F/37	Pleural effusion	Adenocarcinoma	Visceral CUP	No treatment	Died (no details)
Thrombotic thrombocytopenic purpura						
Marcoullis et al. (2002) [17]	F/56	Bone marrow	Adenocarcinoma	Bone marrow CUP	Plasmapheresis, chemotherapy	Patient improved and remains alive after 12 cycles of treatment
Pirrotta et al. (2005) [18]	F/62	Bone, LN -mediastinal, liver, spleen	Adenocarcinoma - mucin producing	Visceral CUP	Plasmapheresis	Died few days after diagnosis
Ng et al. (2006) [19]	F/52	LN - cervical	Adenocarcinoma - signet ring cells	Nodal CUP	Plasmapheresis	NA
Kadikoylu et al. (2008) [20]	F/28	Ovaries, bone marrow	Adenocarcinoma - signet ring cells	Visceral CUP	Plasmapheresis, salpingo-oophorectomy, chemotherapy	Died (no details)
Oberic et al. (2009) [21]	M/79	Bone, bone marrow, lymph nodes	Adenocarcinoma	Bone marrow/Nodal CUP	Plasmapheresis, chemotherapy	NA (no details)

Microangiopathic hemolytic anemia						
Susano et al. (1994) [22]	NA	Bone marrow	Adenocarcinoma	Bone marrow CUP	NA	Died (no details)
Susano et al. (1994) [22]	NA	Bone marrow	Adenocarcinoma	Bone marrow CUP	NA	Died (no details)
Lin et al. (1995) [23]	F/36	Bone marrow	Carcinoma	Bone/bone marrow CUP	Chemotherapy	Patient improved dramatically
Ozkalemkas et al. (2005) [24]	F/57	Bone marrow, LN - axillary, brain, bone	Carcinoma - signet ring cells	Visceral CUP	No treatment	Alive after 38 days (no further follow up)
Abdel Samie et al. (2005) [25]	NA/51	Bone, bone marrow	Carcinoma - signet ring cells	Bone/bone marrow CUP	Chemotherapy, steroids	Patient improved then died after 2 lines of treatment
Leukoerythroblastosis						
Lin et al. (1995) [23]	F/36	Bone marrow	Carcinoma	Bone/bone marrow CUP	Chemotherapy	Patient improved dramatically
Ozkalemkas et al. (2005) [24]	F/57	Bone marrow, LN - axillary, brain, bone	Carcinoma - signet ring cells	Visceral CUP	No treatment	Alive after 38 days (no further follow up)
Ozkalemkas et al. (2005) [24]	F/48	Bone marrow	Carcinoma - undifferentiated	Bone marrow CUP	No treatment	Died 12 days after diagnosis
Ozkalemkas et al. (2005) [24]	F/75	Bone marrow, pleural effusion	Adenocarcinoma	Bone marrow Visceral CUP	No treatment	Died one days after diagnosis
Minimal shift to left						
Ozkalemkas et al. (2005) [24]	M/75	Bone marrow	Adenocarcinoma	Bone marrow CUP	No treatment	Died 14 days after diagnosis
Ozkalemkas et al. (2005) [24]	M/73	Bone marrow	Adenocarcinoma	Bone marrow CUP	No treatment	Died 4 days after diagnosis
Leukemoid reaction						
Chakraborty et al. (2015) [26]	M/64	Lung mass, omentum	Carcinoma – poorly differentiated	Visceral CUP	No treatment	NA

CUP: cancer of unknown primary; F: female; LN: lymph node; M: male; NA: not available

Table 2: Case reports of CUP patients with paraneoplastic rheumatologic syndromes

Publication	Patient (sex/age)	Metastatic sites	Histopathology	Clinicopathologic subset	Treatment	Follow-up
Dermatomyositis and polymyositis						
Hisamura et al. (1981) [28]	M/54	Stomach, pancreas, LN, omentum	Squamous cell carcinoma	Visceral CUP	Surgery	Died 5 months after diagnosis
Garcia Roman et al. (1995) [29]	NA	Brain	NA	Visceral CUP	NA	NA
Nakamura et al. (1997) [30]	M/55	Mass - cervical	Squamous cell carcinoma	Nodal CUP	Surgery	Improvement of paraneoplastic syndrome
Maoz et al. (1998) [31]	M/36	NA	Adenocarcinoma	NA	NA	NA
Maoz et al. (1998) [31]	M/81	NA	Carcinoma	NA	NA	Died 6 months after diagnosis
Fung et al. (1998) [32]	M/40	LN - cervical	NA	Nodal CUP	NA	NA
Galesic et al. (2001) [33]	NA	Peritoneum (Ascitis)	Carcinoma - undifferentiated	Visceral CUP	NA	NA
El-Azhary et al. (2002) [34]	F/54	NA	Adenocarcinoma	NA	NA	NA
Watkins et al. (2004) [35]	M/58	LN - mediastinal, abdominal	Adenocarcinoma - poorly differentiated	Visceral CUP	Steroids, chemotherapy	Excellent response
Perez-Perez (2005) [36]	F/54	Liver, spleen	NA	Visceral CUP	Steroids, hydroxychloroquine, chemotherapy	Alive after 2 years
Kim et al. (2007) [37]	F/62	Mass - iliopsoas muscle, LN paraortic and inguinal	Squamous cell carcinoma	Nodal CUP	Steroids, radiation therapy	Complete remission
Ritchie et al. (2008) [38]	F/59	LN - hilar, axillary, retroperitoneal	Neuroendocrine - poorly differentiated carcinoma	Neuroendocrine CUP	Steroids	Died 2 months after diagnosis
Ghannoum et al. (2009) [39]	F/57	LN - cervical	Squamous cell carcinoma	Nodal CUP	Radiation therapy	Improvement of paraneoplastic syndrome and patient alive after three years
Cao et al. (2009) [40]	M/51	NA	Adenocarcinoma	NA	NA	NA
Ohashi et al. (2010) [41]	M/57	LN - supraclavicular and mediastinal, bone	Adenocarcinoma - poorly differentiated	Nodal/Bone CUP	Steroids	Died (no details)
Resende et al. (2013) [42]	F/70	Nodule - abdomen	Cuteaneous lymphangitis carcinomatosa	Visceral CUP	Steroids, chemotherapy	Died 6 months after diagnosis
Sonnenblick et al. (2015) [43]	F/50	LN - inguinal, cervical and paraaortic	Carcinoma - poorly differentiated	Nodal CUP	Chemotherapy, steroids	Complete remission and improvement of paraneoplastic

						syndrome
Suzuki et al. (2018) [44]	F/50	LN – abdominal and inguinal	Adenocarcinoma - poorly differentiated	Nodal CUP	Steroids, lymphadenectomy, chemotherapy, radiation therapy	Died 31 months after diagnosis
Hypertrophic osteoarthropathy						
Smit et al. (2003) [45]	NA	Mass - Mediastinal	NA	Visceral CUP	NA	NA
Rhumatoid-like polyarthritis						
Mok et al. (2003) [46]	F/69	Masses – Abdominal	Adenocarcinoma	Visceral CUP	Steroids	Died 2 months after diagnosis
Polyarteritis nodosa						
Veitch et al. (2014) [47]	M/65	Pulmonary nodules, mass - abdominal and paravertebral, brain, LN cervical, mediasinal, abdominal	Squamous cell carcinoma	Visceral CUP	Steroids, chemoradiotherapy	NA

CUP: cancer of unknown primary; F: female; LN: lymph node; M: male; NA: not available

Table 3: Case reports of CUP patients with paraneoplastic dermatologic syndromes

Publication	Patient (Sex/age)	Metastatic sites	Histopathology	Clinicopathologic subset	Treatment	Follow-up
Acanthosis nigricans						
Kozlowski et al. (1992) [49]	M/60	Bone, extradural, liver	Adenocarcinoma - well differentiated	Visceral CUP	No treatment	Died after 7 months of diagnosis
Ravnborg et al. (1993) [50]	NA	NA	NA	NA	NA	NA
Yoshino et al. (2008) [51]	M/66	LN - mediastinal	Carcinoma (CK7+,TTF1+)	Nodal CUP	Palliative radiation therapy	Improvement of paraneoplastic syndrome
Brantsch et al. (2010) [52]	M/66	LN - axillary, liver, spleen	Sarcoma - unspecified	Visceral CUP (sarcoma- like)	Radiation therapy	Patient alive 7 months after diagnosis
Leser-Trelat sign						
Schwartz et al. (1991) [53]	F/NA	Liver	Adenocarcinoma - mucinous	Visceral CUP	NA	NA
Tournigand et al. (1994) [54]	F/61	Liver	Adenocarcinoma - poorly differentiated	Visceral CUP	Chemotherapy	Died 3 weeks after first cycle of treatment
Pityriasis rubra pilaris						
Kloos et al. (2002) [55]	F/75	Pleural effusion, LN - axillary, mediastinal, abdominal, inguinal	Adenocarcinoma – moderately differentiated	Visceral CUP	Steroids, hormone therapy	Died (no details)
Remedios et al. (2014) [56]	M/83	Mass - mediasinal, lung nodules	Squamous cell carcinoma - undifferentiated	Visceral CUP	Chemotherapy, radiotherapy	Improvement of paraneoplastic syndrome
Cutaneous paraneoplastic syndrome						
Yoo et al. (2009) [57]	M/26	Liver, spleen, pancreas, lungs, adrenals, LN - inguinal, mediastinal abdominal	Adenocarcinoma	Visceral CUP	No treatment	NA
Necrolytic migratory erythema						
Lolis et al. (2011) [58]	F/52	NA	Carcinoid	Neuroendocrine CUP	Steroids, antibiotics, antifungals, atiprimod	Died 6 years after diagnosis
Basex syndrome						
Matsui et al.	M/63	Mass - cervical	Squamous cell carcinoma	Nodal CUP	Surgery	Improvement of paraneoplastic

(2016) [59]						syndrome and alive 5 years after diagnosis
Paraneoplastic acral vascular syndrome						
Mittal et al. (2017) [60]	M/38	Pericardial effusion, LN - cervical, axillary, mediastinal and inguinal	Adenocarcinoma - poorly differentiated	Visceral CUP	Chemotherapy	Lost to follow up after 2 cycles of chemotherapy
Chronic itch syndrome						
Beigi et al. (2018) [61]	M/68	LN - mediastinal	Large cell neuroendocrine carcinoma	Neuroendocrine CUP	Steroids, chemotherapy, radiation therapy	Improvement of paraneoplastic syndrome but the patient died 6 months after diagnosis

CUP: cancer of unknown primary; F: female; LN: lymph node; M: male; NA: not available

Table 4: Case reports of CUP patients with paraneoplastic endocrine syndromes

Publication	Patient (sex/age)	Metastatic sites	Histopathology	Clinicopathologic subset	Treatment	Follow-up
Carcinoid syndrome						
Takami et al. (1998) [62]	M/30	Abdominal cavity	Carcinoid tumor	Neuroendocrine CUP	Surgery, Chemotherapy	Died 10 months after diagnosis
Mahmood et al. (1999) [63]	M/56	LN	Carcinoid tumor	Neuroendocrine CUP	No treatment	Died 4 months after diagnosis
Cushing's syndrome						
Tournigand et al. (1994) [54]	F/61	Liver	Adenocarcinoma - poorly differentiated	Visceral CUP	Chemotherapy	Died 3 weeks after first cycle of treatment
Molina Garrido et al. (2006) [64]	M/56	Mass - lung, Liver, Bone	Adenocarcinoma	Visceral CUP	Chemotherapy	Progression after first line
Yoshino et al. (2008) [51]	M/66	LN - mediastinal	Carcinoma (CK7+, TTF-1+)	Nodal CUP	Palliative radiation therapy	Improvement of paraneoplastic syndrome
Shahani et al. (2010) [65]	F/56	LN - mediastinal and abdominal, liver	Small cell carcinoma poorly-differentiated. NE features	Neuroendocrine CUP	Metirapone, Chemotherapy	Died after first cycle of treatment
Hypercalcemia						
Gallacher et al. (1993) [66]	M/47	Bone	Carcinoma	Bone CUP	No treatment	Died few days after diagnosis
Yim et al. (1999) [67]	M/21	Bone marrow	Spindle cell tumor	Bone marrow CUP	Chemotherapy	Died 12 months after diagnosis
Dhar et al. (2008) [68]	F/63	Bone	Neuroendocrine - poorly differentiated	Neuroendocrine CUP	No treatment	Died few days after diagnosis
Agaimy et al. (2017) [69]	M/39	LN - mediastinal, hilar and paraaortic, liver	Carcinoma - undifferentiated	Visceral CUP	No treatment	Died few days after diagnosis
Hypoglycemia						
Rusu et al. (2015) [70]	F/58	Liver, bone	Moderately-differentiated neuroendocrine	Neuroendocrine CUP	Interferon + sandostatine	Died 4 months after diagnosis

CUP: cancer of unknown primary; F: female; LN: lymph node; M: male

Table 5: Case reports of CUP patients with paraneoplastic neurologic syndromes

Publication	Patient (sex/age)	Metastatic sites	Histopathology	Antibody	Clinicopathologic subset	Treatment	Follow-up
Paraneoplastic cerebellar degeneration							
Krakauer et al. (1996) [72]	M/68	LN - mediastinal	Adenocarcinoma undifferentiated	Anti-Yo positive in CSF	Nodal CUP	Resection of lymph node, plasmapheresis	Persistence of paraneoplastic syndrome
Bolla et al. (1997) [73]	F/79	Mass -abdominal, LN - abdominal and retroperitoneal	Adenocarcinoma - poorly differentiated	Anti-Yo positive in serum	Nodal CUP	No treatment	Persistence of paraneoplastic syndrome but alive after 22 months
Abdulaziz et al. (2018) [74]	F/68	Cerebellum, LN - axillary, bone	Carcinoma - poorly differentiated	Anti-Yo positive in serum and CSF	Visceral CUP	Steroids	Improvement of paraneoplastic syndrome
Stiff-Person-Syndrome							
Byrne et al. (2012) [75]	F/60	LN - axillary	Adenocarcinoma	Anti-amphiphysin positive in serum	Nodal CUP	Radical mastectomy, intravenous immunoglobulin, steroids, chemotherapy, radiation therapy, hormone therapy	Improvement of paraneoplastic syndrome and alive after 24 months
Limbic encephalitis							
Pagenstecher et al. (1994) [76]	M/71	LN - thoracic	Small cell carcinoma	NA	Neuroendocrine CUP	NA	Died (no details)
Graus et al. (2018) [77]	M/69	LN - cervical	Squamous cell carcinoma	Antibody negative	Nodal CUP	Steroids, chemotherapy	Improvement of paraneoplastic syndrome
Graus et al. (2018) [77]	M/59	LN - cervical	Squamous cell carcinoma	Antibody negative	Nodal CUP	Intravenous immunoglobulin	Partial improvement
NMDA receptor encephalitis							
Coban et al. (2016) [78]	M/62	Parotid	Small cell carcinoma	NMDAR antibody positive in serum and CSF	Neuroendocrine CUP	Steroids, intravenous immunoglobulin, surgery	Disappearance of paraneoplastic syndrome after 4 months
Coban et al. (2016) [78]	M/64	Mass- inguinal	Squamous cell carcinoma/poorly differentiated	NMDAR antibody positive in serum and CSF	Neuroendocrine CUP	Steroids, intravenous immunoglobulin, plasmapheresis, chemotherapy, radiotherapy	Disappearance of paraneoplastic syndrome after 2 months, complete remission after 5 years
Paraneoplastic neurological syndrome							
Beigi et al.	M/68	LN - mediastinal	Large cell	anti-Hu antibodies in	Neuroendocrine	Steroids, chemotherapy, radiation	Improvement of

(2018) [61]			neuroendocrine carcinoma	the CSF	CUP	therapy	paraneoplastic syndrome but the patient died 6 months after diagnosis
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CSF: cerebrospinal fluid; CUP: cancer of unknown primary; F: female; LN: lymph node; M: male; NA: not available

Table 6: Case reports of CUP patients with miscellaneous paraneoplastic syndromes

Publication	Paraneoplastic syndrome	Patient (sex/age)	Metastatic sites	Histopathology	Clinicopathologic subset	Treatment	Follow-up
Wolf et al. (1998) [80]	Membranous glomerulonephritis	M/64	LN - cervical and supraclavicular	Adenocarcinoma – undifferentiated	Nodal CUP	Steroids, Cyclophosphamide (No follow up cancer guided treatment)	NA
Gupta et al. (2008) [81]	Membranoproliferative glomerulonephritis	M/37	Spleen, LN	Adenocarcinoma - moderately differentiated	Visceral CUP	No treatment	Patient died (no details)
Ishikawa et al. (2014) [82]	Nephrotic syndrome	F/57	LN - cervical and mediastinal, pleural effusion	Small cell carcinoma	Neuroendocrine CUP	Chemotherapy, radiation therapy	Improvement of paraneoplastic syndrome and alive after 3 years
Schlittler et al. (2011) [83]	Nonbacterial thrombotic endocarditis	M/63	Liver, aortic vegetation	Adenocarcinoma - signet ring cells	Visceral CUP	No treatment	Died (no details)
Norisada et al. (2011) [84]	Nonbacterial thrombotic endocarditis	M/63	Colon, pancreas, bladder, mediastinum, peritoneum, epicardium, mitral vegetation	Carcinoma - poorly differentiated	Visceral CUP	No treatment	Died 13 days after diagnosis
Aron et al. (2013) [85]	Bilateral Roth spots	M/59	Liver	Adenocarcinoma	Visceral CUP	No treatment	NA

CUP: cancer of unknown primary; F: female; LN: lymph node; M: male; NA: not available