

## Paraneoplastic syndromes in cholangiocarcinoma

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### Abstract

Paraneoplastic syndromes are the symptoms or signs which result from damage to tissues that are distant from the site of malignancy, due to complex interactions between the body's immune system and malignant neoplasm. Cholangiocarcinoma (CCA) is an aggressive epithelial malignancy of hepatobiliary tree and it is found to be associated with various paraneoplastic syndromes. These syndromes can present as dermatological, neurological, renal, hematological, or multi-systemic manifestations. Clinical suspicion and timely recognition of these syndromes can lead to early diagnosis of covert malignancies like CCA. The management plan remains the removal of the underlying cause which in this case is CCA.

**Key Words:** Cholangiocarcinoma; Paraneoplastic syndrome; Malignancy; Immune system; Biliary tree; Multi-organ

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**Core Tip:** Various case reports have been published focusing on single paraneoplastic syndromes associated with cholangiocarcinoma (CCA) but none of the studies has reported these manifestations collectively. This review summarizes different paraneoplastic syndromes which are associated with CCA to give a better idea about how it affects various organ systems.

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## INTRODUCTION

Cholangiocarcinoma (CCA) is an aggressive epithelial malignancy of hepatobiliary tree, accounting for 10%-20% of primary liver cancers<sup>[1,2]</sup>. It is strongly linked to chronic liver disease and is classified according to an anatomical location in the biliary tree as intrahepatic (iCCA), perihilar (pCCA) and distal (dCCA) subtypes<sup>[3]</sup>. The incidence of CCA, particularly iCCA has increased worldwide between 1993 and 2002. Highest rates were found among Asian countries with South Korea on the top having an age-standardized incidence rate (ASR) of 2.80, followed by Thailand (2.19) and Japan (0.95)<sup>[4]</sup>. In the USA, the incidence of iCCA has increased in the last 40 years between 1973 and 2012 from 0.44 to 1.18 cases per 100000 person-years<sup>[5]</sup>. iCCA accounts for about 20% of the deaths from hepatobiliary cancers, which cause 13% of the total cancer mortality worldwide<sup>[6]</sup>. Recent diagnostic techniques and early management have led to an improvement in 1-year mortality over time but the 5-year survival is still as low as 10% due to the appearance of clinical symptoms in the later course of the disease<sup>[7]</sup>.

Paraneoplastic syndromes are the symptoms or signs which result from damage to tissues that are remote from the site of malignancy, due to complex interactions between the body's immune system and malignant neoplasm<sup>[8]</sup>. CCA has been reportedly found to be the source of various paraneoplastic manifestations including alopecia<sup>[9]</sup>, sensory neuropathies<sup>[10]</sup>, hypercalcemia, polycythemia, leukocytosis<sup>[11]</sup> and increased parathyroid hormone-related protein (PTHrP)<sup>[12-14]</sup>.

Several individual cases of paraneoplastic syndrome with CCA have been reported in the literature. This mini-review summarizes all these cases with their clinical presentation and pathophysiology associated with CCA.

## PARANEOPLASTIC SYNDROMES

### *Dermatological manifestations*

**Acanthosis nigricans:** Acanthosis nigricans (AN) presents as a brown to black hyperpigmented velvety patch found on neck, groin, and axilla<sup>[15]</sup>. However, AN associated with internal organ malignancy mostly appears as a diffuse patch over palms and soles, and can also involve the oral cavity and/or esophagus<sup>[16]</sup>. Of all the reported cases, internal organ malignancies are found to be associated with AN of palms in 90% of the cases<sup>[17]</sup>. Paraneoplastic syndrome that occurs as a result of CCA is associated with the production of biologically active particles in the malignant tissue. These include growth factors like epidermal growth factor (EGF) or alpha-transforming growth factor (αTGF) which are associated with the malignant proliferation of skin resulting in AN<sup>[18]</sup>. AN resolves after effective treatment of the underlying malignancy and might progress if there is any recurrence or metastasis of the tumor as stated in the study of Ravnborg.

**Alopecia:** Alopecia is the most common hair disease reported in oncology patients<sup>[19]</sup>. It usually presents as a round patch of hair loss on the top of the skull with well-demarcated edges. The type of alopecia associated with cholangiocarcinoma is usually alopecia areata<sup>[20]</sup>. Alopecia in CCA is triggered by several neurological, hormonal, and emotional factors but in most cases, the actual cause remains undetermined. Alopecia caused by CCA has an increasing trend of incidence in the people of the United States as compared to those in Europe hinting towards the role of environmental factors as well<sup>[21]</sup>. Although it can occur as an independent condition, but remission of cancer resulting in the resolution of alopecia, and relapse leading to recurrence favors the paraneoplastic nature as mentioned in the study of Antoniou<sup>[20]</sup>.

**Dermatomyositis:** It is relatively a rare paraneoplastic manifestation of CCA<sup>[22]</sup>. It presents as weakness of the proximal group of muscles with a bluish-purple skin lesion on upper eyelids (heliotrope rash) and erythematous papules on knuckles are noticed (Gottron papules) as evident from the study of Suh<sup>[23]</sup>. Muscle weakness in

dermatomyositis caused by CCA is attributed to increasing energy consumption of carcinoma cells than normal cells, resulting in excessive glucose breakdown<sup>[24]</sup>. Dermatomyositis also results from an autoimmune response against highly active cancer cells that cross-react and attack the affected muscles<sup>[25]</sup>. Myositis specific auto-antigens are also expressed in tumor cells that cross-react and cause this disease. Successful treatment of CCA results in the improvement of dermatomyositis<sup>[26]</sup>.

**Disseminated superficial porokeratosis:** Disseminated superficial porokeratosis (DSP) is a benign proliferation of keratinocytes resulting in a hyperkeratotic skin tumor<sup>[27]</sup>. DSP is linked to internal organ malignancies such as hepatocellular carcinoma and CCA suggesting a paraneoplastic nature<sup>[28]</sup>. DSP presents as well-demarcated reddish-brown papules, ranging from 0.5 cm to 1.5 cm, and become noticeable a few months before the onset of cancer-related symptoms. These are visible on the extensor surface of all limbs and trunk, consisting of multiple annular and itchy lesions with elevated borders sparing mucosa, palms, and soles as explained by Cannavo in his study<sup>[29]</sup>. Overexpression of the *p53* gene product is associated with the appearance of widespread DSP as a manifestation of internal organ malignancy like CCA<sup>[30]</sup>. All of these abnormalities in the *p53* pathway result in a lack of keratinocyte differentiation and dysregulation of loricrin expression. Loricrin is a precursor protein formed in the last stage of keratinization and its dysregulation results in the formation of a cornified envelope<sup>[31]</sup>.

**Necrolytic Migratory Erythema:** Necrolytic migratory erythema (NME) is an erythematous erosive patch with an advancing scaly border<sup>[32]</sup>. NME in the setting of CCA, presents as annular erythematous lesions of almost 1-2 cm in size with a central glassy surface, surrounded by scaling that occurs on the face, trunk, and extremities as mentioned by Chiyomaru in his case report. NME mostly presents before CCA is clinically diagnosed<sup>[33]</sup>. Several conditions like primary sclerosing cholangitis, liver fluke infection, and biliary malformation are associated with increased risk of CCA which results in paraneoplastic NME<sup>[34]</sup>. Moreover, low nutritious conditions are also aiding the development of NME. Thus patients with NME, without a known cause, should always be checked and screened for malignancies periodically<sup>[33]</sup>.

**Persistent erythema multiforme:** Erythema multiforme (EM) is one of the cutaneous disorders that occur in the setting of a pre-existing internal organ malignancy and are collectively known as paraneoplastic dermatoses. EM is typically self-limited and benign. It usually occurs early in the disease course of CCA. Persistent erythema multiforme (PEM) is a rare form of erythema multiforme that comprises of both typical and atypical cutaneous/mucosal lesions and doesn't resolve on its own<sup>[35]</sup>. On examination, EM appears as a painful erythematous rash with scaling that occurs in patches over the chest, upper back, and both thighs. After a few days, it changes to hemorrhagic bullae with violaceous edges. Vital signs are normal and there is no mucosal involvement as shown by the study of Tzovaras<sup>[36]</sup>. EM is sudden in onset and usually resolves in 1- 6 d. Skin paraneoplastic syndromes are commonly associated with internal organ malignancies but EM is a rare skin manifestation in these cases. It is believed that PEM occurs in the setting of CCA as a result of continuous stimulation by antigenic tumor material<sup>[37]</sup>. There is no direct involvement of tumor cells and no other acquired factors are present marking REM as a paraneoplastic manifestation of CCA. Moreover, the treatment of CCA results in regression of PEM, and relapse of the tumor results in its reappearance<sup>[36]</sup>.

**Sweet syndrome:** Sweet syndrome (SS) is an acute febrile neutrophilic dermatosis. Malignancy associated Sweet syndrome occurs in approximately 15% of the population suffering from solid tumors<sup>[38]</sup>. It presents as rapidly growing painful erythematous plaques over the face, neck, and legs and is associated with fever, generalized malaise, cough, and arthralgia according to the case report presented by Shinojima<sup>[39]</sup>. According to recent studies, it is observed that granulocyte-colony stimulating factor (G-CSF) has a major role in the pathogenesis of SS<sup>[40]</sup>. Increased G-CSF results in production, activation, and chemotaxis of the neutrophils<sup>[41]</sup>. Malignant tumors like CCA result in excessive production of G-CSF that further stimulates neutrophils resulting in paraneoplastic SS<sup>[42]</sup>.

**Bazex syndrome:** Bazex syndrome is characterized by the appearance of hyperkeratotic lesions on various parts of the body in association with an underlying malignancy. It clinically presents as pruritic scaly dusky red eruptions covered with adherent scales on face, ear, buttocks, palms, and soles. They are commonly associated with fatigue, recurrent abdominal pain, nausea, vomiting, constipation, weight loss,

and liver enlargement as mentioned by Karabulut in his study<sup>[43]</sup>. Pathophysiology of bazex syndromes is cross-reaction of antigens from tumor to skin. This cellular immune system alteration results in increase release of various growth factors like epidermal growth factor- $\alpha$ <sup>[44]</sup>. Treatment of bazex syndrome shows how strongly this manifestation is paraneoplastic. Regular dermatological treatment doesn't show any response but the removal of the underlying tumor results in complete resolution of the disease<sup>[45]</sup>.

**Erythema gyratum:** Erythema gyratum is rapidly moving erythema and is a marker of underlying malignancy. It is most commonly associated with lung, esophageal, and breast carcinoma<sup>[46]</sup>. Clinically it presents as a 3-wk history of rash on the lower limbs. The eruption of the rash began as small erythematous macules which gradually enlarge resulting in concentric raised scales on the lateral aspect of the right thigh as Liau mentioned in his study<sup>[47]</sup>.

**Pityriasis rubra pilaris:** Pityriasis rubra pylaris (PRP) is a papulosquamous dermatosis of skin. It clinically presents as a 10-d history of widespread pruritic rash that begins appearing on thighs and progresses gradually over shins, lower back, trunk, face, and forearms as mentioned in the case report presented by Bar-Ilan. It is associated with mild fever as well<sup>[48]</sup>. Pathophysiology involved in the appearance of PRP is increased secretion of peptides and hormones from the tumor due to cross-reactivity of the antigens<sup>[49]</sup>.

**Sign of Leser-trelat:** Leser-trelat sign is the appearance of multiple pigmented seborrheic keratosis mostly associated with underlying malignancy. It is mostly associated with GI adenocarcinoma and rarely with CCA<sup>[50]</sup>. It clinically presents as a 1-week history of worsening jaundice, pale stools, and recent onset abdominal pain as evident by the study of Morgenthau<sup>[51]</sup>. The pathophysiology behind this sign is a sudden increase in cytokines and various growth factors like epidermal growth factor- $\alpha$  resulting in hyperpigmentation of the skin<sup>[52]</sup>.

**Subacute cutaneous lupus erythematosus:** Subacute cutaneous lupus erythematosus (SCLE) is an inflammatory skin disorder mimicking skin manifestations of systemic lupus erythematosus. It is one of the rare paraneoplastic manifestations linked to CCA. It clinically presents as explosive onset of new pruritic rash along with arthralgia and lower extremity edema in a patient with previous history of CCA as explained by Opneja in his study<sup>[53]</sup>. The pathophysiology behind SCLE lies in self-activation of the body's immune system resulting in photosensitive rash as it is in the usual SLE<sup>[54]</sup>.

A summary of all the dermatological paraneoplastic syndromes is explained in [Table 1](#) at the bottom of the review

### Neurological manifestations

**Limbic encephalopathy:** Limbic encephalopathy (LE) is the sub-acute onset of memory impairment and confusion<sup>[55]</sup>. LE is reported in CCA but is a rare finding. In the starting phase, it presents as a polyneuropathy quite similar to diabetic polyneuropathy, with gradual progression to focal seizures. As the disease progresses, temporal lobe association is noted resulting in pilomotor erection (autonomic seizures) and eventually symptoms of rapidly progressive dementia appear<sup>[56]</sup>. Thus, autonomic seizures, delusion, and rapidly progressive dementia are the hallmarks of LE<sup>[57]</sup>. Different mechanisms are linked to LE in the setting of CCA. The formation of new anti-neuronal antibodies is associated with limbic encephalitis. In some cases, autoantibodies are formed against intracellular antigens in the mesiotemporal region while others suggest that they are formed against surface antigens<sup>[58]</sup>. Both hypermetabolism and hypometabolism of mesiotemporal lobe has also been reported after the onset of LE symptoms<sup>[59]</sup>.

**Paraneoplastic cerebellar degeneration:** Paraneoplastic cerebellar degeneration (PCD) typically presents in women with a sudden onset of ataxia progressively involving limbs and trunks, dysarthria, diplopia, and dysphagia that occurs in the background of a malignancy. It is rarely reported with CCA. In a case report by Bruhnding *et al.* it began with lower limbs, but gradually involved upper limbs as well. Sensation in legs was affected as well. Eventually, the patient was unable to stand anymore. Dysmetria ensued and interfered with self-sufficiency in feeding leading to a weight loss of 60 pounds over six months. Imaging revealed a 2 cm liver mass. Biopsy proved intrahepatic cholangiocarcinoma. Anti-Yo antibodies were also found positive in association with PCD<sup>[60]</sup>. The underlying mechanism is not clearly understood. The

**Table 1 Summary of literature on dermatological paraneoplastic syndromes in cholangiocarcinoma**

Ref.	Year	Paraneoplastic syndrome	Mediator
Dermatologic			
Ravnborg <i>et al</i> <sup>[15]</sup>	1993	Acanthosis nigricans	TGF-alpha
Suchonwanit <i>et al</i> <sup>[19]</sup>	2018	Alopecia	T-lymphocytes
Antoniou <i>et al</i> <sup>[20]</sup>	2012	Alopecia	T-lymphocytes
Suh <i>et al</i> <sup>[23]</sup>	2016	Dermatomyositis	
Yasuda <i>et al</i> <sup>[26]</sup>	2018	Dermatomyositis	
Sotoodian <i>et al</i> <sup>[27]</sup>	2018	Disseminated superficial porokeratosis	p53
Cannavó <i>et al</i> <sup>[29]</sup>	2008	Disseminated superficial porokeratosis	p53
Chiyomaru <i>et al</i> <sup>[33]</sup>	2010	Necrolytic migratory erythema	
Tzovaras <i>et al</i> <sup>[36]</sup>	2007	Persistent erythema multiforme	
Shinojima <i>et al</i> <sup>[39]</sup>	2006	Sweet syndrome	G-CSF, IL-1, IL-6
Karabulut <i>et al</i> <sup>[43]</sup>	2006	Bazex syndrome	
Liau <i>et al</i> <sup>[47]</sup>	2016	Erythema gyratum	
Bar-Ilan <i>et al</i> <sup>[48]</sup>	2017	Pityriasis rubra pilaris	
Morgenthau <i>et al</i> <sup>[51]</sup>	2019	Sign of Leser- Trelat	EGF-alpha
Opneja <i>et al</i> <sup>[53]</sup>	2015	Subacute cutaneous lupus erythematosus	

TGF-alpha: Tissue growth factor-alpha; G-CSF: Granulocyte-colony stimulating factor; IL: Interleukin; EGF-alpha: Epidermal growth factor-alpha.

autoimmune nature of PCD is thought to be due to malignant cells expressing onconeural antigens that are otherwise found on neurons<sup>[61]</sup>. Thus cross-reactivity leads to the development of PCD. However, no direct link between these antibodies and PCD has been developed yet.

### Renal manifestations

**Glomerulonephritis:** Glomerulonephritis is defined as inflammation of small blood vessels inside the kidneys. Fibrillary glomerulonephritis (FGN) is a rare type of glomerulonephritis. A rare case of FGN is recently reported showing its association with iCCA. It presents as edema of lower limbs and face with uncontrolled hypertension. Nephrotic range proteinuria is evident (3 g/d) with 24 h-proteinuria of 0.74g/d mentioned by Normand in his study. Microscopic hematuria is also present. Complete remission of glomerulonephritis indicates the paraneoplastic nature of this disease<sup>[62]</sup>.

### Hematological manifestations

**Paraneoplastic vasculitis:** Vasculitis is an inflammation of the wall of a blood vessel. Malignant diseases are both associated with vasculitis of arteries and veins. Paraneoplastic vasculitis constitutes less than 5% of all the forms of vasculitis<sup>[63]</sup>. Vasculitis is more commonly associated with hematological malignancies than solid tumors<sup>[64]</sup>. Small vessels are frequently linked to the paraneoplastic nature of vasculitis. The type of vasculitis associated with CCA is giant cell arteritis. It presents with one-month history of headache, scalp tenderness, pain, and stiffness in the neck, shoulder, and pelvic girdles. The resolution of symptoms right after removal of the tumor indicated the paraneoplastic nature of this vasculitis<sup>[65]</sup>.

**Trousseau syndrome:** Trousseau syndrome, also known as migratory thrombophlebitis, is an acquired abnormality of blood clotting. According to several reports, it is concluded that several clotting disorders are closely linked to internal organ malignancy<sup>[66]</sup>. There have been 2 cases of trousseau syndrome with underlying isolated CCA, while others had either a hepatocellular CA or a lung adenocarcinoma along with CCA<sup>[67]</sup>. Trousseau syndrome, in the setting of CCA, presents as weight loss, mild shortness of breath, right upper quadrant tenderness, and abnormal liver

function tests with raised alkaline phosphatase as evident from the studies of Jang and Blum<sup>[68]</sup>. It is believed that tissue hypoxia leads to activation of the coagulation pathway and endothelial adhesion molecules<sup>[69]</sup>. Low molecular weight heparin (LMWH) along with removal of the primary tumor has been found effective in its treatment<sup>[70]</sup>.

**Anti-phospholipid antibody syndrome:** Antiphospholipid antibody syndrome (APAS) is an autoimmune disorder that results in the formation of antibodies against phospholipids on platelets resulting in hypercoagulability. APAS has been linked to various solid organ malignancies but a few cases are found in association with CCA<sup>[71]</sup>. APAS, in the setting of CCA, presents as unilateral leg pain, swelling, and tenderness. Moreover, lupus anticoagulant is raised with normal antinuclear antibodies as mentioned by Samadian in his case report<sup>[72]</sup>.

**Paraneoplastic leukemoid reaction:** Leukemoid reaction means an increase in the number of leukocytes (WBC's > 50000) particularly neutrophils, in reaction to any infection or carcinoma. Leukemoid reaction in the setting of CCA mimics a pyogenic liver abscess and clinically presents as pyrexia and leukocytosis<sup>[73]</sup>. The fever is intermittent and remains there for at least a month along with weight loss, progressive generalized weakness, and a leukocyte count above 20000 (> 78% neutrophils) mentioned by Ham in his study related to leukemoid reaction<sup>[74]</sup>. Only 2 cases of paraneoplastic leukemoid reaction have been reported with the primary cause of CCA<sup>[75]</sup>. Treating CCA resulted in the resolution of leukemoid reaction.

### **Multisystemic manifestations**

**Polyarteritis nodosa:** Polyarteritis nodosa (PAN) is a rare form of systemic necrotizing vasculitis that has heterogeneous forms of presentations<sup>[76]</sup>. PAN that occurs due to underlying neoplasia is termed as paraneoplastic vasculitis. It may precede or follow the onset of neoplasia or it may also be evident on the recurrence of many malignant diseases, showing a strong link with carcinomas<sup>[77]</sup>. PAN occurring in the setting of CCA is a rare finding but a study reports an association of CCA with PAN<sup>[78]</sup>. Paraneoplastic vasculitis is mostly cutaneous but it can also affect internal organs<sup>[79]</sup>. The earliest sign experienced in PAN is bilateral numbness in lower limbs followed by gradually increasing fever. After approximately 2 wk, an arthritis-like pathology is noticed with severe pain in bilateral lower limbs, ankles, metatarsal, and phalangeal joints. After a few months, skin manifestations appear which are necrosis and gangrene evident on distal phalanges. Lastly, gastrointestinal symptoms appear comprising of severe abdominal pain, nausea, and vomiting. The gradual sequence of these clinical symptoms has been mentioned by Hatzis in his case report. Digital ischemia is also a complication of paraneoplastic vasculitis<sup>[80]</sup>. Paraneoplastic vasculitis such as PAN is highly associated with raise in titers of anti-neutrophilic cytoplasmic antibodies (ANCA)<sup>[81]</sup>. Moreover, patients with raised ANCA and PAN also have raised CA 19-9, a tumor marker that rises in CCA and pancreatic carcinomas<sup>[82]</sup>. Recent studies suggest immune dysregulation as the primary cause of paraneoplastic vasculitis. Another study states that it might be due to cross-reaction of tumor antigens, directly causing vascular damage or indirectly by releasing humoral agents like chemotactic factors. PAN is poorly responsive to steroids or other treatment modalities but the removal of the tumor or chemotherapy results in its resolution<sup>[83]</sup>.

**Adult-onset still disease:** Adult-onset Still disease (AOSD) is an adult version of juvenile idiopathic arthritis. It is caused by an altered immune response of the body against any foreign body or carcinoma. Previously, AOSD has been linked to various carcinomas like breast, esophageal, thyroid, and lung<sup>[84]</sup>. This is the first case, reporting link of AOSD with CCA. Symptoms of AOSD occur before malignancy is diagnosed<sup>[85]</sup>. AOSD linked to CCA clinically presents as high-grade fever and chills for 1 week along with other symptoms like sore throat, myalgia, pleuritic chest pain, cough, and pain in various joints as mentioned by the study of Raza<sup>[85]</sup>.

### **Humoral manifestations**

**Humoral hypercalcemia of malignancy:** Parathyroid hormone-like hormone (PTHrH) is formed by proliferating bile duct epithelial cells in CCA that further interacts with various growth factors resulting in loops of uncontrolled proliferation<sup>[86]</sup>. PTHrH derived from CCA cells is involved in causing humoral hypercalcemia of malignancy (HHM). HHM is evident in approximately 10%-20% of the patients with underlying malignancies<sup>[87]</sup>. Almost 80%-90% of them are due to PTHrH. Clinical signs evident in a patient with HHM are changes in mental status, constipation, nausea, abdominal

discomfort, polydipsia, polyuria, and weakness. These are due to the increased concentration of calcium in the body<sup>[88]</sup>. There is good evidence that proves hypercalcemia as a paraneoplastic manifestation of CCA. Patients showing symptoms of hypercalcemia with normal PTH levels and an increased PTHrH in the setting of CCA supports that it is paraneoplastic. PTHrH works with tumor growth factor-alpha and tumor necrosis factor-alpha to cause hypercalcemia that is HHM.

A summary of all the paraneoplastic syndromes associated with other systems is explained in [Table 2](#) at the bottom of the review.

### **Association with other neoplasms**

Recent diagnostic studies have indicated the presence of certain serological markers in CCA which are raised in other malignancies too suggesting that CCA might be having a concomitant neoplasm that shares the same paraneoplastic syndrome. For example, erythematous skin rash, associated with CCA, has raised CA 19-9. This serological marker is also linked to certain malignancies like colorectal and pancreatic carcinomas<sup>[53]</sup>. Another example is hypercalcemia. It is associated with CCA and also found to be raised in 10%-20% of malignancies like squamous cell carcinoma of the lung, head and neck, esophagus, and skin cancers<sup>[89]</sup>. Further detailed studies might reveal the hidden facts of this involvement.

### **Early detection of occult malignancy**

CCA has poor prognosis which has led to equalization of incidence and mortality rates<sup>[90]</sup>. Although CCA has a poor prognosis, it has been reported that early screening and diagnosis can lead to decreased mortality rates. All the manifestations explained above showed how treating CCA resulted in resolution of symptoms. Thus any patient with the above paraneoplastic manifestation and clinical symptoms should always be screened for cholangiocarcinoma as this could lead to a better chance of survival.

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## **CONCLUSION**

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CCA can cause a wide range of paraneoplastic syndromes. The exact mechanism linking them to CCA in most of these syndromes remains undetermined. Hence, no particular treatment modality can be recommended. The best management plan remains the removal of the underlying cause which in this case is CCA. The timely recognition of these syndromes and clinical suspicion can lead to early diagnosis of covert malignancies like CCA. The presence of symptoms can also predict the efficacy of treatment, relapse, or recurrence of the disease. Further studies are pertinent to understand the underlying mechanisms and targeted therapies for these paraneoplastic syndromes.

**Table 2 Summary of literature on paraneoplastic syndromes in cholangiocarcinoma associated with other systems**

Ref.	Year	Paraneoplastic syndrome	Mediator
Neurological			
Schmidt <i>et al</i> <sup>[57]</sup>	2016	Limbic encephalopathy	ANNA-1, Anti-Ma2, Anti-PCA-2/anti-Tr, Anti-VGKC
Bruhnding <i>et al</i> <sup>[60]</sup>	2016	Paraneoplastic cerebellar degeneration	Anti-Yo antibodies
Renal			
Normand <i>et al</i> <sup>[62]</sup>	2017	Glomerulonephritis	
Hematological			
Solans-Laquer <i>et al</i> <sup>[65]</sup>	2008	Vasculitis	
Blum <i>et al</i> <sup>[67]</sup>	2016	Trousseau syndrome	
Jang <i>et al</i> <sup>[68]</sup>	2006	Trousseau syndrome	
Samadian <i>et al</i> <sup>[72]</sup>	1999	Anti-phospholipid Antibody Syndrome	
Ham <i>et al</i> <sup>[74]</sup>	2015	Paraneoplastic leukemoid reaction	
Multisystem			
Hatzis <i>et al</i> <sup>[78]</sup>	1998	Polyarteritis nodosa	p-ANCA
Raza <i>et al</i> <sup>[85]</sup>	2013	Adult-onset still disease	
Humoral			
Erdinc <i>et al</i> <sup>[88]</sup>	2019	Humoral hypercalcemia of malignancy	PTHrP

TGF- $\alpha$ : Tissue growth factor- $\alpha$ ; G-CSF: Granulocyte-colony stimulating factor; IL: Interleukin; EGF- $\alpha$ : Epidermal growth factor- $\alpha$ ; ANNA: Antineuronal nuclear antibody; PCA: Purkinje cell antibody; VGKC: Voltage-gated potassium channel; ANCA: Antineutrophil cytoplasmic antibody; PTHrP: Parathyroid hormone-related protein.

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