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ETIOPATHOLOGICAL REVIEW OF CHOLANGIOCARCINOMA IN AYURVEDA

Dr SWATHY KRISHNA, Dr MINI P
FINAL YEAR PG SCHOLAR, Associate Professor
DEPT. OF ROGANIDANA, GOVERNMENT AYURVEDA COLLEGE, KANNUR, KERALA

Introduction

Ayurveda offers a cohesive perspective on health with distinctive paradigms, theories and concepts regarding life, health and illness which includes a person's body type, digestive capacity, immunity and mental well-being. Every patient is unique in his / her clinical condition with a definite presentation. In Ayurveda, the diagnosis is made based on the identity of disease phenomenon rather than the 'name' of the illness. Even though the classics do not directly reference all present ailments, those diseases can still be addressed by careful evaluation of every fundamental component of the disease process. This phenomenon can be explained in terms of *Samprapti* (pathogenesis) of the disease, which covers factors such as *Dosha, Dhatu, Upadhatu, Agni, Srotas* and *Adhisthana* (i.e., the humors, body tissues, the disease etc.) So, understanding the *samprapti* of each disease is necessary in planning a proper treatment protocol. Despite yielding promising results, the modern treatment protocols, viz., chemotherapy poses certain side effects. [1] Cholangiocarcinoma (CCA) is a highly lethal, epithelial cell malignancy that occurs anywhere along the biliary tree and/or within the hepatic parenchyma. [2] It represents the second most frequent type of primary liver cancer and ~3% of all gastro-intestinal neoplasia. [3]

In general, CCA is a rare malignancy (incidence <6 cases per 100,000 people. The epidemiological profile of CCA and its subtypes display enormous geographical variation, perhaps related to exposure to different risk factors [4] CCA exhibits characteristics of cholangiocyte differentiation, the epithelial cells that line the bile ducts; however, depending on the location and underlying liver disease, the cancers may also develop from hepatocytes and parietal glands. CCA tends to be asymptomatic in its early stages and most patients have advanced unresectable disease at the time of diagnosis accounting for its dismal prognosis. The exact incidence of CCA is unknown in India. [5] However, there are certain factors such as Genetic predisposition, Primary sclerosing cholangitis (PSC) especially with concomitant IBD, parasitic infections induced chronic biliary inflammation, cystic biliary lesions, environmental and lifestyle diseases such as Type-2 diabetes, obesity, determinants like cigarette smoking, alcohol etc. confers increased risk. [6] Genetic involvement is mediated by mutations in a variety of protooncogenes and tumor suppressor genes. The most frequent mutations are K-*ras* and *TP53*. CCA can be best classified according to the primary, anatomic subtype as extrahepatic / perihilar CCA (eCCA / pCCA), intrahepatic CCA (iCCA), or distal CCA (dCCA). [7] Each anatomic subtype has distinct genetic aberrations, clinical presentations and therapeutic approaches. In the case of iCCA, Jaundice is the initial symptom only in around 10%-15% of the cases, when biliary obstruction confined to the liver hilum by lymph nodes or migration of detritus and subsequent failure of the correct drainage of the biliary ducts. [8] Extrahepatic cholangiocarcinoma is symptomatic earlier presented with jaundice, pruritus, clay-colored stools, and dark-colored urine. There may be a palpable mass and ascites in later stage. In advanced cases, malaise, night sweats, asthenia, nausea, and weight loss are the symptoms that patients usually report. Patients diagnosed with CCA typically come with many intrahepatic or extrahepatic metastases or peritoneal carcinomatosis, which indicate a high probability of

recurrence. These patients have the worst prognosis since the tumors might have grown beyond surgical limit. Considering all the established mechanisms that modern medicine has demonstrated underlie the pathophysiology, diagnosis and prognosis of CCA, it is imperative to understand it from an Ayurvedic perspective.

CCA – Ayurvedic view

Even though Ayurveda has its epistemological understanding of various *Nidanas, Rogamargas, Samprapthi ghatakas* and for the clear understanding of a disease, many of the diseases are not mentioned as primary diseases which lacks those elaborations. *Acharya Charaka* comprehends the concept of *Trividha bodhya sangraha* [9] which is a unique approach to understand the pathogenesis of these diseases which can be sensibly used for explaining *Anukta vyadhi*. *'Kupito Dosha Samuthanavisheshat Sthanaantaragatah'* describes that *Vikara Prakruti, Adhisthanantarani,* and *Samuthana Vishesha* [10] can be taken into account for understanding the pathology of diseases such as Cholangiocarcinoma as it can be considered as an *Anukta Vyadhi*. In addition to determining the prognosis, this aids in early detection of illness, which is crucial for timely prevention and palliative management of CCA.

ETIOLOGY (SAMUTHANA VISHESA)

Cholangiocarcinoma can be considered multifactorial. Sometimes it presents as an acquired solitary disease without any antecedent disorders, or it can present as a complication either. When analyzing the various *nidanas*, we can classify it as;

a. *Beejadushti nidana*
b. *Aharaja nidana*
c. *Dooshivisha as Nidana*

Beejadushti

Cholangiocarcinoma is a complication of IBD. The primary mechanism of IBD appears to be genetic, in which the Ulcerative colitis disease involves the inflammatory changes in the mucosa and submucosa layers of intestine whereas in Crohn's, the whole intestine is affected. Various studies reveals that prolonged IBD duration is associated with an increased risk of CCA accompanied with Primary sclerosing Cholangitis.[11] Thus genetic abnormality that is *Beejadushti* can act as *nidana* for Cholangiocarcinoma

Aharaja nidana

In Samhitas, we understand that *Arbuda* is *Kapha-Pradhana Tridosha Vyadhi*. Consumption of *Guru, Snigdha, Medya, Abhishyandi aharas* and *viharas* like *diwaswapna are* identified as important causative factors for *Kapha dushti, mamsa dhatu* and *medo-dhatu* along with its *srotas*. The intake of foods that contain high fructose, low fiber, high fat, and high carbohydrates causes high exposure of liver to insulin because of the portal circulation of insulin. Consequently, disruption of insulin-related pathways may encourage the development of liver or biliary tract cancer. Simultaneously the long-term use of *Pittakopaka nidanas* like *ati ushna, lavana,* and *madyapana* causes *raktadhatu dushti* and *raktavaha srotodushti,* It causes *paka* in the form of inflammation inside the gut and inflammatory cytokines undergo enterohepatic circulation with the possibility to trigger portal inflammation as in PSC. Similarly consuming too much salt causes the liver damage including distorted cells, increased rates of cell death, and decreased rates of cell proliferation, all of which can result in liver fibrosis. Long-term alcohol use has been linked to an increased risk as regular alcohol in heavy doses can lead to inflammation and scarring and eventually results in intrahepatic or extrahepatic Cholangiocarcinoma. [12]

Garavisha as *nidana*

Most of the *garavisha adhishtana* mentioned in the ayurveda classics such as *anna, pana, anulepana, vastra, abhyanga*, etc. can be related to the resources that we are using daily. Foods, drinkables, cosmetics, toothpaste etc. are assorted with any form of incompatible combinations or less potent toxins. As liver plays a central role in detoxification, it is probably the most affecting organ to these exposures. Adulterants, artificial colors, additives such as BHA in foods, preservatives, heavy metals and artificial sugar like aspartame in drinkables, Talcum powder in cosmetics, imidazolidinyl in hair dyes, sodium lauryl sulphate in moisturizers and face creams, various modern drugs like paracetamol, erythromycin etc. proved as having significant carcinogenic effect on body if runs in a long-term manner which can be corelated as *Dushi Visha* having the *Kalantaravipaki swabhava.*

ADHISHTANA AND VIKARA PRAKRTHI (SITE OF MANIFESTATION AND PATHOGENESIS)

Adhisthana describes the place where *Dosha Dushya Sammurchana* occurs. The vitiated and unsettled *doshas* combined with *dhatus* to form *dosha-dushya sammurchana* in a specific locus where there is a *khavaigunya* happened due to long term *nidanaseva,* causing disease to develop at the same place. Here *adhishtana* can be taken as *Yakrt* and related appendages which is the *moolastana* of *Raktavaha srotas* where the *samprapti* can be extended

PURVARUPA

The *lakshanas* in early stages in a mild form can be considered as the Purvarupa here. *Sopha,* the localized inflammation and formation of *Granthi* which is smaller as compared to *Arbuda,* should be regarded as the *Visesha Purvarupa* [13] although *samanya puravrupas* are overlapeped with the *lakshanas* of other diseases.

SAMPRAPTI

While deeply analyzing the *nidanas,* it is clearly understood that Kapha and Pitta doshas have predominance in the pathogenesis of Cholangiocarcinoma, as both are simultaneously vitiated in different stages of samprapti. Previous studies [14] proved that inflammatory signaling pathways appear to induce development of CCA indicates the significance of pitta in the early stages. Compared to the extrahepatic area, intrahepatic biliary tree is large and therefore the *srotovaigunya* is more likely to occur there. This causes a higher incidence of intrahepatic CCA than extrahepatic variant. Due to *pittakopakara nidanas,* the vitiated *pitta* gets accumulated in the *pittavahi sira* situated inside *yakrt* and the area undergoes *paka.* This induces various inflammatory cytokines, growth factors and the transporting bile causing alteration in proliferations, DNA damage and blocks the compensatory mechanism such as apoptosis. Concurrently the patients also having *kaphadushtikara nidanas* from *guru, abhishyandi, madhura bhojana* and *diwaswapna* causes *kapha prakopa* and excert influence on developing a mass which is dense, highly proliferating, deep rooted and circular in nature. This causes the mechanical obstruction of *pittavahi sira* and the *pitta* will be obstructed there. Regarding the *dhatu dushti, Acharya charaka* mentioned *Arbuda* under *Mamsapradoshaja vikaras,* while *Susutha* included it under *Rakta, Mamsa* and *Medo-pradoshaja vikaras.* [15,16]

When scrutinizing the role of *Rakta, Mamsa* and *Medas* in the *samprapthi of Arbuda,* we must assess the tumor environment. *Rakta* is in similar *yoni* to the *pitta*. The pitta dushti will be equally attributable to the *raktadushti.* The alterations in the stroma, recruitment of fibroblasts, changing patterns of immune cell migration, and promotion of angiogenesis suggested that *raktadhatu* and *raktavaha srotas* are having a crucial role in carcinogenesis. It makes sense that tumors in CCA are characterized by a dense and reactive desmoplastic stroma that contains many α-smooth muscle actin (αSMA)–positive myofibroblasts, also known as cancer associated fibroblasts (CAFs) are a part of *mamsadhatu* and *mamsavaha srotas* whereas the reprogramming of lipid metabolism (typical feature of malignant tumors) and its up-regulation, inhibition of apoptosis, rapid progression, invasion and migration of tumor proved that lipid metabolism or *Medodhatu* and its *srotas* is also having a critical part in carcinogenesis. [17]

ROLE OF AGNI

Most ailments, including *Arbuda,* are caused by a deranged *Agni.* It can malfunction at different levels in different stages of *samprapthi* due to different *doshasammurchana* Cholangiocarcinoma starts with an inflammatory condition revealed that *agni* will be *teekshna* in *koshta* level. Here the patient presents *paitikka grahani lakshanas* like *amla udgara, hrit-kanta daha* etc. Afterwards, *kapha* will be predominant that causes *srotorodha,* simultaneously *agni* will be *manda* results in the development of *Ama* accumulated in the form of toxins and waste materials in liver. Later due to the *srotorodha, dhatus* will be vitiated and eventually *dhatwagni mandya* occurs, resulting in *dhatusoshana* and *vata dushti* and v*ishamagni.* In a long-term process, the increased *aama* in the form of tissue inflammation and deterioration of dhatus weakened by an improper lifestyle leads to *tridosha dushti* and a compromised immune system make the patient prone to the advancement of disease

LAKSHANA

Since CCA tumors are clinically silent in their early stages, individuals usually consult a physician in the later stages of the disease. Since our classics don't specifically address the symptomatology of *arbuda* of *pittavahi sira,* it can be understood in relation to *lakshanas of Kaphaja gulma, paittika grahani, Ruddhapatha kamila* and *Lakshanas* of *Udara,* specifically *Sannipataja Udara* and *Yakritodara.* Symptoms only manifest whenever the growth can obstruct a bile duct partially or fully. Initially there will be non-specific symptoms like abdominal discomfort in the right quadrant, localized dense feeling over the area, vague abdominal pain which can be taken

as *admana, atopa* as explained in *kaphaja gulma lakshana* [18] it can be accompanied with *paittika grahani lakshana* like *amla udgara, kantadaha,* etc [19] Later the presentation becomes clear as the patients presents *lakshanas* of *Ruddhapatha kamala* [20] which can be in cooperated with obstructive jaundice. The patient presents icterus, whitish stools and dark urine as main symptoms. Pruritis may be an associated complaint. In addition to that, nausea, vomiting, fever, and abdominal pain are seen as non-specific symptoms. Later the pain confines to the right upper quadrant similar in *Yakrtodara* [21] As the disease progresses, it will affect multiple systems and can exhibit symptoms of *Udara.*

Table -1

Samanya lakshana of *Udara* and *lakshanas* of *Sannipataja Udara*	Symptoms in Advanced stages of CCA [22]
• *Dourbalya* • *Karshya* • *Vairasya* • *Karapada sopha* • *Slakshna gandata* • *Nakha vivarnata* • *Nanavarna raji* • *Pipasa* • *Tamapravesa* • *Murcha*	• Fatigue • Unexplained weight loss • Metallic taste in mouth • Unilateral or bilateral oedema • Cutaneous changes like Paper-money skin • Nail abnormalities like Terry's nails, Leukonychia etc. • Excess thirst • Cognitive disturbances • Dizziness

DIAGNOSIS

Thorough examination of the patient (*pariksha*) is the first step in clinical practice for planning an appropriate treatment as quoted by *Acharya Charaka* [23] *Trividha, Dasavidha, Ashtavidha* and *Nadi Pariksha* can be employed suitably.

LFT is the first choice of laboratory investigation to diagnose hepatobiliary disorders. It is useful in assessing the diseases' progression or regression in different stages. During the early stages of CCA, Unconjugated Bilirubin value will be slightly raised, ranges from 4-6 mg/dL along with normal liver enzyme values (AST, ALT, ALP). The presence of pallor and absence of icterus will be evident in *darshana pariksha.* During progression, features like *Tilapishtanibha varchas* (clay-colored stools) can be observed directly through *mala pariksha.* Other constitutional symptoms like *hikka, swasa, aruchi,* and *jwara* can be perceived during *pratyaksha pramana* and *prasna pariksha.* The elevation of AST, ALT can be seen along with Icterus and pruritis. A/G ratio will be low. ALP will be markedly raised in cholestatic conditions, malignancies with significant increase in AST and ALT (ALT>AST). In post-hepatic / obstructive jaundice, greenish yellow icterus and pruritis will be present. Here conjugated bilirubin value will be high with marked increase in AST, ALT, ALP. The hepatocellular damage caused by persistent obstruction leads to an increase in transaminases and prolonged prothrombin time causes the peak pattern of liver enzymes throughout the progression of disease. Based on values, *nidana* and *samprapti* can be better understood thereby *samprapti vighatana* can be executed properly

Conclusion

Cholangiocarcinoma can be considered as a *kaphapradhana tridoshaja arbuda* caused due to *sahaja, aharaja, vishajanyaja* factors making the patient debilitated as immune compromised as the disease progresses. The Derangement of Agni also plays an important role in the *jataragni* and *dhatwagni* level whereas the accumulation of ama in the form of toxins as well as a byproduct of *dosha-dushya sammurchana* in the *srotas*

(pittavahi sira) lead the way to the development of *arbuda.* This article reviewed many variables, such as *Vikaraprakriti, Samuthana visesha*, and *Adhishtana nirupana* of CCA which covers genetic mutations, lifestyle, exposure to the environment, and infectious agents, that can lead to its development. The *lakshanas* will be vague in the early stages and become clear as the disease progresses. As the disease is multifactorial and involving many systems, the symptomatology can be completely understood from in-context of diseases like *gulma, kamala, udara* etc. Since many cancers are asymptomatic in its initial stages, understanding the clear etiopathology along with mindful examination is essential for early detection and proper planning of preventative strategy before going to unmanageable phase.

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