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Human Hepatic Alveolar Echinococcosis Of Liver ;How Rare Is Rare ? Case Series With Review Of Literature

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Abstract: *Echinococcosis also known as Hydatidosis or Hydatid Disease is a major human and veterinary concern. It is endemic in many parts of the world and is caused by infestation with the larval/meta-cestode stage of organisms belonging to genus Echinococcus. It is among the most dangerous zoonoses known. Transmission of AE to humans is by consumption of parasite eggs excreted with faeces of definitive hosts, foxes and dogs.Liver is the most common organ involved but the disease can also disseminate to other organs like lung, long bones and brain. Although AE is geographically confined to the northern hemisphere, but globalization and urbanization resulting in major population shifts has made it necessary for all global health care providers to have knowledge about this disease. This disease is now increasingly being reported from previously unaffected areas. Associated morbidity, treatment related costs and DALY's (Disease Adjusted Life Years) are high.*

The incidence of Cystic Echinococcosis (CE) caused by Echinococcus Granulosus (EG) is very high in our part of the world. We present our experience of four cases of AE over a short period of time. The treatment options offered and the short term follow up is discussed.

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I. Introduction

Echinococcosis is an endemic zoonosis. It is a major human and veterinary health concern. It is caused by infestation with the larval stage of organisms belonging to genus Echinococcus.Four species of the genus Echinococcus are known to be pathogenic to humans. E. Granulosus causing Cystic Hydatid Disease, E. Multilocularis causing Alveolar Hydatid Disease, E. Vogeli and E. Oligarthus cause a disease with a Polycystic pattern which affects various organs[1,2]

Alveolar Echinococcosis(AE) is amongst the most dangerous zoonoses known and has been referred to as'Neglected Malignant Parasitic Disease'.It stands one among the 17 neglected tropical diseases prioritized by the WHO. Transmission of AE to humans is by consumption of parasite eggs excreted withfaeces of definitive hosts. The result of infestation by EM is a disease with a long latentperiod, finally culminating into a chronic debilitating disease with a fatal outcome if not treated timely and aggressively[3]. Liver is the most common organ involved. The disease can disseminate to other organs like lungs and long bones[4,5]. Unlike Cystic Echinococcosis which is present globally throughout all continents, AE is geographically confined to the northern hemisphere, but within that range it has a very wide distribution [6].

Globalization and urbanization resulting in major population shifts has made it mandatory for allhealth care providers to have knowledge and understanding about this disease. The disease is now increasingly being reported from previously unaffected areas. Associated morbidity, treatment related costs and DALY's are quite high.

II. Cases :

CASE 1 :Fig 1,2

A 50 year old femalewas referred to our clinic with complaints of pain upper abdomen and post prandial fullness. AFP, CEA and CA19-9 levels were normal. ELISA for hydatid was positive. USG showed aheterogenous lesion in left lobe of liver. CT correlation revealed a hypo-dense lesion in left lobe of liver with extension into segment 5 of right lobe. The lesion had few foci of calcifications also.Left lobe IHBR were dialated and left branch of portal vein was not visualized.

The patient underwent lefthepatectomy with excision of segment 5 lesions and CBD exploration + T-tube drainage (for a dialated CBD). Intra-operatively a hard mass of 10x12cm was found replacing the whole left lobe. Post-operative course was uneventful. Final histo-pathology report confirmed the diagnosis of AE. The patient was put on Albendazole + Praziquentel, has completed 16 months of follow up and is currently symptom free with no recurrence.

CASE 2 : Fig 3,4

A 21 year old female was referred to our hospital with complaints of a dull ache in upper abdomen since last few weeks. Abdominal examination revealed hepatomegaly. Pre-operative investigations werenormal. USG revealed a 15x15 cm thick walled cystic lesion in right lobe of liver. CT correlation showed a 22x16x15 cm mass in right lobe of liver. Multiple calcific foci were seen within the lesion.

She underwent a right hepatectomy. Intra-operatively whole of right lobe was replaced by the cystic lesion. There was compensatory hypertrophy of left lobe of the liver. The cyst was adherent to IVC and peri-hilar area.

Post operatively the patient had persistent biliary leakage from the drain site for which she underwent catheter placement under radiological guidance. The bile leak persisted beyond 4 weeks and she subsequently underwent ERCP +papillotomy and placement of a plastic biliary stent. She was put on combination chemotherapy of Albendazole and Praziquantel. She is now 13 months post surgery, is under regular follow up, has gained weight and is symptom free.

CASE 3 : Fig 5,6

A 75 year old female was referred to our clinic with complaints of pain upper abdomen since past few months. Physical examination was normal. Pre-operative LFT, KFT, hemogram and Tumor markers (CEA,AFP AND CA19-9)were within normal limits. CECT abdomen revealed two large heterogenous lesions, one in segments 4 and 5 and another lesion in segments 7 and 8. These lesions had irregular calcific foci with complex solid areas interspersed with areas of cystic degeneration. The reporting radiologist gave an impression of Intra hepatic cholangio-carcinoma vs a mesenchymal hepatic tumor. In view of a discordant diagnosis, a pre-operative biopsy was done which was suggestive of AE.

The patient was put on combination chemotherapy of Albendazole and Praziquantel. She is under our regular follow up. The lesion has remained stable for the past 8 months.

CASE 4 :

A 37 year old female, a known case of primary hypo-thyroidism was referred to our clinic with chief complaints of pain upper abdomen, and decreased appetite. Her past history was significant for pulmonary tuberculosis for which she had received full course of anti tubercular therapy. Physcial examination was normal. Tumor markers were not elevated. ELISA for hydatid was positive. USG showed a heterogenous lesion in segments 6 and 7. CT correlation revealed a heterogenous lesion with alternating cystic and solid areas. The lesion had no foci of calcifications.

She underwent open excision of the lesion and the final histopathology report revealed it to be a AE lesion. She is currently on two drug chemotherapy of Albendazole and Praziquental. She has completed 10 months of follow and is symptom free with no recurrence.

III. Discussion :

3.1 :NATURAL HABITAT, LIFE CYCLE AND GEOGRAPHIC DISTRIBUTION

Echinococcus Multilocularis(EM) is mainly confined to northern hemisphere. The belt stretches from Tundra zone in the north and extends southwards upto 40-45 degrees of latitude[7]. It has been reported from central Europe (Switzerland, Eastern France, West Austria, South Germany)and adjoining parts of Russia and Balkan states (Siberia, Azerbaijan, Turkey). The disease has also been reported from Central Asia (Northern Iran, Afghanistan, Northern India- Kashmir valley). North-west Canada, Alaska and North Japan has also reported many cases.

China is emerging as a new endemic focus with a large numbers of reported human cases. In many areas in China > 5% of human population has been reported to be infected with AE[8,9]. Such areas not only

have a high infestation rate in humans, but the dog population is also highly infected by the adult worm[10]. Presence of EM in the dog population may represent a quiescent stage of an increased transmission to humans. It has been warned that a major epidemic of EM may just be around the corner.

With wide variability in the quality of the data collected, and with no standardization of data collection, it is not surprising for the incidence of AE to be under-reported across all endemic countries.

All Echinococci species require two hosts for completion of their life cycle. Carnivores are the definitive hosts - they harbor the mature adult tapeworm and the reproduction is sexual in them. Meta-cestodes develop in liver and other organs of intermediate hosts and are then consumed by definite hosts for completion of life cycle. Humans are accidental, dead end intermediate hosts and do not complete the life cycle of EM.

Contrary to EG, EM is predominantly seen with a wild life cycle. For EM,carnivores like wolf, fox, coyotes and red foxesare the definitive hosts. Rodents like vole, lemming and muskrat serve as intermediate hosts. Dogs and cats can also become infected as definitive hosts, but their infection rates are low [11].Increasing fox populations in Europe are correlated with the greater numbers of cases of AE [12].

Eggs excreted by definitive hosts are consumed by intermediate hosts. A second larval stage begin and a meta-cestode containing proto-scoleces develops in the gut of the host. The metacestode is a fluid filled vesicle-like organism with an outer a-cellular laminar membrane and an inner cellular germinal layer. The inner germinal layermay give rise to brood capsules by asexual budding (also called daughter cysts). Proto-scoleces arise from the inner walls of the brood capsules. There may be thousands of proto-scoleces within an aggregation of EMvesicles. Each single proto-scolex has the potential to develop into a sexually mature adult worm[13]. EM has lower tendency to form cystic lesions unlike EG.

Humans get infected with EM by handling of infected fox carcasses or ingestion of fruits infected by cestode eggs. After the egg hatches in the small intestines, the oncosphere is released which is carried via portal circulation to the liver. In the liver, the meta-cestode divides asexually and undergoes lateral budding of germinal tissue and formation of multiple daughter vesicles. These secondary vesicles infiltrate liver parenchyma slowly and incitean intense host tissue reaction. The process of lateral budding of germinal membrane is more pronounced in EM than in EG. The resulting liver lesion may occasionalycavitateor may develop calcifications, although niether cavitation and calcification is pathognomonic for EM. Expansion in the liver occurs slowly and the disease can have a long latent period varying between 5-15 years[14].

Primary extra-hepatic lesions of EM are rare. Involvement of other organs occurs in context of metastatic or infiltrative disease[15,16].

3.2 :CLINICAL FEATURES

Symptoms of AE vary as per the organ involved. Liver especially the right lobe is the main site of disease[4,5]. Primary lesion size may vary from a few millimeters to 20 cm or more [17].Expansion of the lesion occurs slowly and the disease can have a long latent period[14]. The latent period for EM is longer when compared to EG. Spread may occur locally to involve adjacent organs or metastasize distantlyvia blood to brain, long bones, and lungs[18].

Presenting symptoms include abdominal pain, jaundice, weight loss, unexplained fatigue and signs of liver dysfunction. Rupture into biliary tree can present as cholangitis. Compression of vascular structures may present with signs of portal hypertension, biliary cirrhosis or even as Budd Chiari syndrome.

Symptoms in cases of lung involvement include hemoptysis, chest pain, cough with expectoration, and exertional dyspnea[19].

When left untreated or when treatment is inadequate, the prognosis is very dismal with liver failure, portal hypertension, and metastasis to other organs acting as sequelae to disease progression.

3.3 :IMAGING

Diagnosis mainly depends upon characteristic imaging findings and is aided by serology.

USG is the initial investigation of choice for liver lesions. USG reveals a complex mass having irregular borders with both hypo and hyper echoic areas. Areas of calcification and cavitation although being highly suspicious findings are neither pathognomonic nor universally found[20,21].

Wolfgang et al[22] reviewed USG findings of 185 patients of AE and proposed a sonographic classification for AE. They divided hepatic AE lesions into following sub-types :Hailstorm (54.1%); Pseudo-cystic (13.5%); Ossification (13.0%); Hemangioma-like (8.1%); and metastasis-like (6.5%).When presenting as a pseudo-cystic lesion with necrosis it can mimic hepatic cyst-adenomas, cyst-adenocarcinomas or even CE lesions. Addition of Doppler mode to USG aids in definition of vascular anatomy. Less than 5% of lesions cannot be assigned to any sono-morphological patterns.

CT remains the principle imaging modality for evaluation of AE lesions. It provides good demarcation of the lesion and is a good modality for evaluation of patterns of calcification. Number, size,and location of

lesions in the liver are well delineated. It also allows to study the relation and location of the lesion withrespect to vascular and biliary radicles, which are important in planning the operative strategy and the resection planes. CT also provides aone time concurrent imaging of adjacent as well as distantorgans and hence evaluation of extra-hepatic spread[23].

Characteristic findings of AE on CT include an infiltrating tumorwith irregular margins and heterogeneous contents of varied attenuation and calcifications. Hypo-attenuating areas corresponding to necrosis and parasitic tissueare highly characteristic findings. Both lobes of the liver can be involved diffusely. CT characteristics of AE have been well known to mimic both primary and metastatic malignancies of the liver[24]. CT also finds its role in calculation of FLR in patients who are scheduled to undergo extensive liver resections.

Tilman etal[25] reviewed the CT findings of 228 cases of confirmed AE and proposed a new CT based classification, EMUC-CT (EM Ulm Classification-CT) for hepatic AE lesions. They grouped the lesions into five main primary morphologies (A liver lesion can have more than one primary morphology or alternately the primary morphology of the largest lesion can be chosen). The categorization based on patterns of calcification is done separately as the extent, pattern and morphology of calcification has been known to evolve with the course and introduction of therapy. (Table 1A and 1B)

MRI as an imaging modality provides better soft tissue resolution. MRI provides better detail of central necrosis than CT but is less valuable in lesions with extensive calcifications and in small lesions[26].MRI helps to differentiate the parasitic and non-parasitic components of the lesion. It appreciates the multi-vesicular components of the lesion. It also provides mapping of the biliary and vascular radicles in relation to AE lesion and hence is effective in planning the operative strategy.

Extra-hepatic spread to other organs can also be appreciated well while using MRI as a single imaging modality. MRI thus finds its role in pre-operative evaluations, especially for patients who are supposed to undergo extensive hepatic resection or liver transplantation. Additionally, MRCPprovides a good non invasive appreciation of any suspicion of biliary communicationand has replaced percutaneous cholangiography in this regard[27].

A heterogeneous infiltrative mass with irregular margins and a necrotic center exhibiting low to intermediate signal intensity on T1-weighted images and heterogeneous signal intensity on T2-weighted images is characteristic of AE liver lesion. High T2 signal intensity corresponds to small cystic or necrotic components, whereas areas with low T2 signal intensity correspond to areas with intense fibrosis[28].

Based on MRI findings, Kodama et al [28] classified AE liver lesions into five types :

Type 1 : It consists of multiple small cysts without a solid tissue component. Comprise about 4% of total lesions.

Type 2 : These include lesions with a solid tissue component and associated with multiple small cysts. Comprise about 40% of all lesions.

Type 3 : Most common and comprise about 46 % of the total lesions. This type includes lesions consisting of a solid tissue component and associated with large irregular cysts.

Type 2 and Type 3 lesions may resemble cyst-adenomas, cyst-adenocarcinomas, peripheral cholangio-carcinomas or metastases producing peripheral bile duct dilatation. Presence of calcification and absence of enhancement usually differentiate the AE lesions from those malignant differential diagnosis.

Type 4 : Comprise about 4%.The lesions consist of predominantly solid tissue and no cystic components.

Type 5 : Comprise 6%. These lesions consist of a single large cyst without any appreciable solid tissue components. These type 5 lesions may mimic simple hepatic cysts.

The use of additional investigations like serological tests is advocated in lesions with low suspicion of AE(Types 1,4 and 5)[28,29,30].

3.4 :EXTRA-HEPATIC AE DISEASE

Extension to extra hepatic organs like peritoneum, diaphragm, peri-renal space, abdominal lymph nodes, pancreas, lungs, retro-peritoneum, abdominal wall, and spleen occurs mainly by extension of disease from the primary liver pathology. Dissemination also occurs via hematogenous and lymphatic pathways and may involve distant organs like the lungs, central nervous system, spine & long bones[31]. Most commonly involved organs in disseminated AE are the lungs and the brain. CT and MRI are the main imaging modalities used to evaluate extra-hepatic disease.

Dissemination to lungs occurs frequently, mainly by hematogenous spread in about 7–20% of patients[15,32]. Symptoms in cases with lung involvement include hemoptysis, chest pain, cough with expectoration, and exertional dyspnea[19]. AE lung lesions can be single or multiple, unilateral or bilateral, and they vary in size considerably. Differential diagnoses in cases with bilateral pulmonary lesions include pulmonary metastases, infection, and other granulomatous diseases.

Isolated soft tissue and bony involvement is exceedingly rare. The reported incidence of bony

involvement is< 1%[33]. Axial skeleton like sternum and vertebrae are the most common sites of involvement inAE[34]. Symptoms depend upon the site of involvement. AE bony lesions may predispose to pathological fractures.

CNS involvement has been reported in< 3% of patients with AE infestation and is a sign of widespread dissemination[15,32]. Anecdotal case reports of primary AE lesions of the brain have also been published[35,36]. Symptoms of CNS involvement include signs of increased intracranial pressure, seizures and focal neurologic deficits dependingupon the area of involvement.

To allow for effective communication between health care providers, staging of the disease burden, for evaluation and comparison of outcomes, the WHO Informal Working Group on Echinococcosis established a "PNM" classification system for AE[31]. The PNM classification(Table 2) system draws parallels from TNM classification system used in malignancies and describes the presence of a hepatic parasitic mass (P), involvement of neighboring organs (N), and involvement of distant sites (M).

Serological investigations are non invasive and help in supporting the diagnoses when clinical suspicion is high, especially in cases with suspiciousimaging features. These investigations also help in monitoring effectiveness of any treatment modality[37]. Serological investigations most commonly employed in AE diseases include ELISA and IHA tests. These tests are used against antigens EM2 and EMII/3-10 which are highly specific to AE[38]. However, ELISA against antigen EM2 may remain positive for years even in treated cases because EM2 antigen is present in inactive lesions also. Activity of EM16 and EM18 antigens present in the proto-scolexcan be obtained by titrating against those antigens byimmune-blot tests[39]. EM18 also serves to differentiate between CE and AE[40]. Several studies have revealed that AE patientshavehigh levels of IgG1 and IgG4 antibodies and that the IgG4 antibody levels decrease after treatment. An increase in IgG4 levels may thus act as a surrogate marker for reactivation of the parasite[41,42].

Demonstration of alveolar vesicles in the samples extracted by percutaneous needle biopsy also helps to confirm the diagnosis. PCR profiling of EM-DNA in liver biopsy samples has a very high positive predictive value, however negative results do not necessarily rule out the presence of an active lesion[16].

3.5 :TREATMENT

Treatment of AE mainly depends on the PNM stage of the disease[16]

Surgery and pharmacotherapy are the two main modalities used. Surgery is the treatment of choice in most cases. Radical surgery with complete resection of the lesion is consideredcurative. Palliative and conservative resections do not seem to offer any advantage over medical treatment.[43]

Liver transplantation is offered to patients with advanced stage, recurrent un-resectable disease, liver failure, and patients who are un-suitable for radical surgery. Extra-hepatic spread of AE during surgery is highly hazardous in liver transplant recipients because of drug-induced immunosuppression[16] which predisposes todissemination and relapse[44].

Peri-operative pharmacotherapy is widely used. Postoperative albendazole is recommended in all patients for a minimum of 2 yearsduration[43]. Alternative drugs used includemebendazole, praziquantel, and amphotericin[44,45]. Albendazole and praziquantel can be used in combination(as is the protocol at our institute). The optimal duration of albendazole treatment in patients not treated by surgery is however not clear. Albendazole has been continuously used for up to 20 years without any complications[16]. Use of albendazole in patients not undergoing surgery has been shown to have conflicting results, with some centers showing increase survival and some contradicting the same [46,47].

IV. Conclusion

Incidence of AE is increasing in the dog and fox population which precludes the expected increase in human AE cases. Handling the problem of AE requires implementation of vigorous preventive strategies, mass education, screening and treatment availabilityto exposed population groups. Extensive research is needed, focusing mainly on development of effective pharmaco- and immuno-therapy directed at confronting EM.

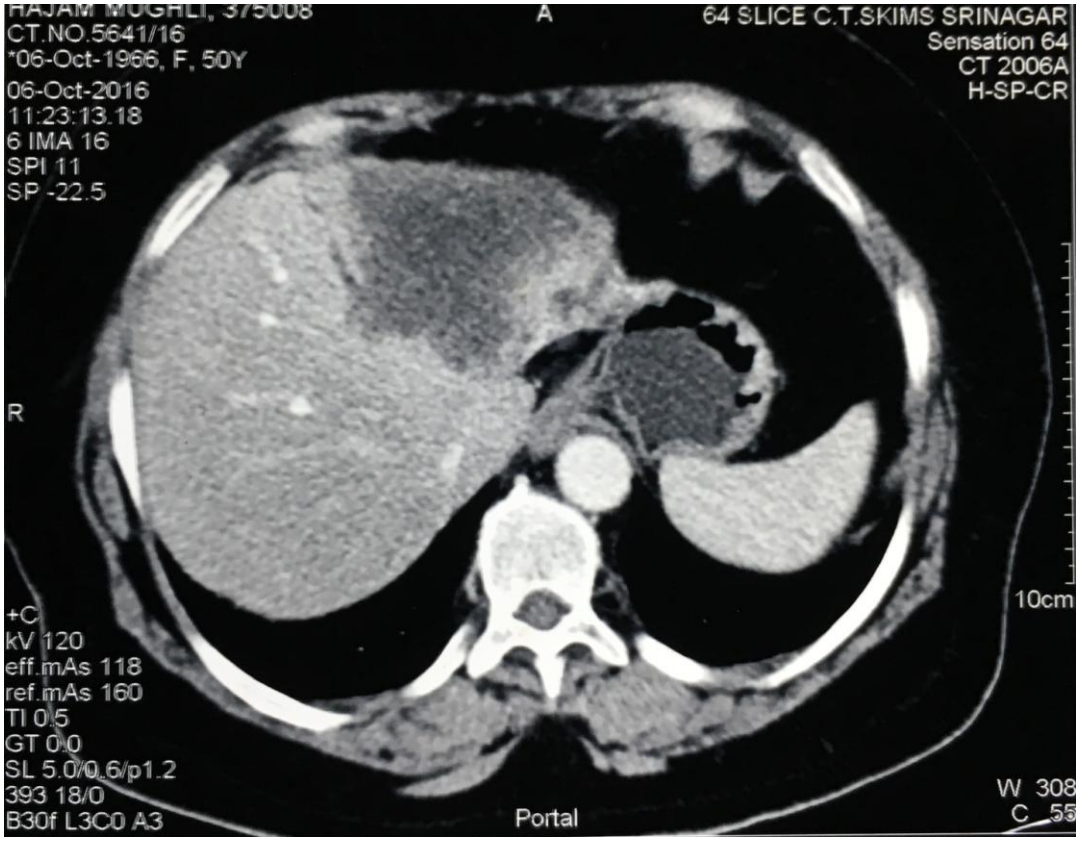

FIGURE1 : Left lobe complex lesion with extension into segment 5

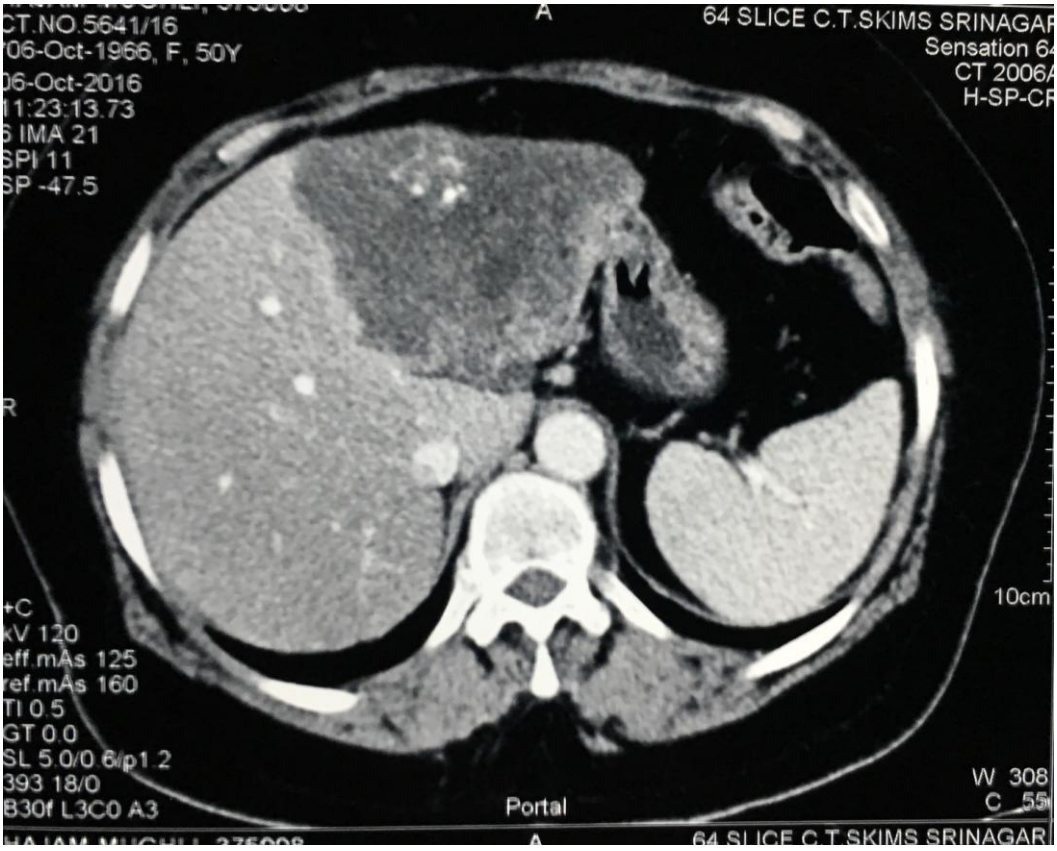

FIGURE2 : Left lobe complex lesion with foci of calcification

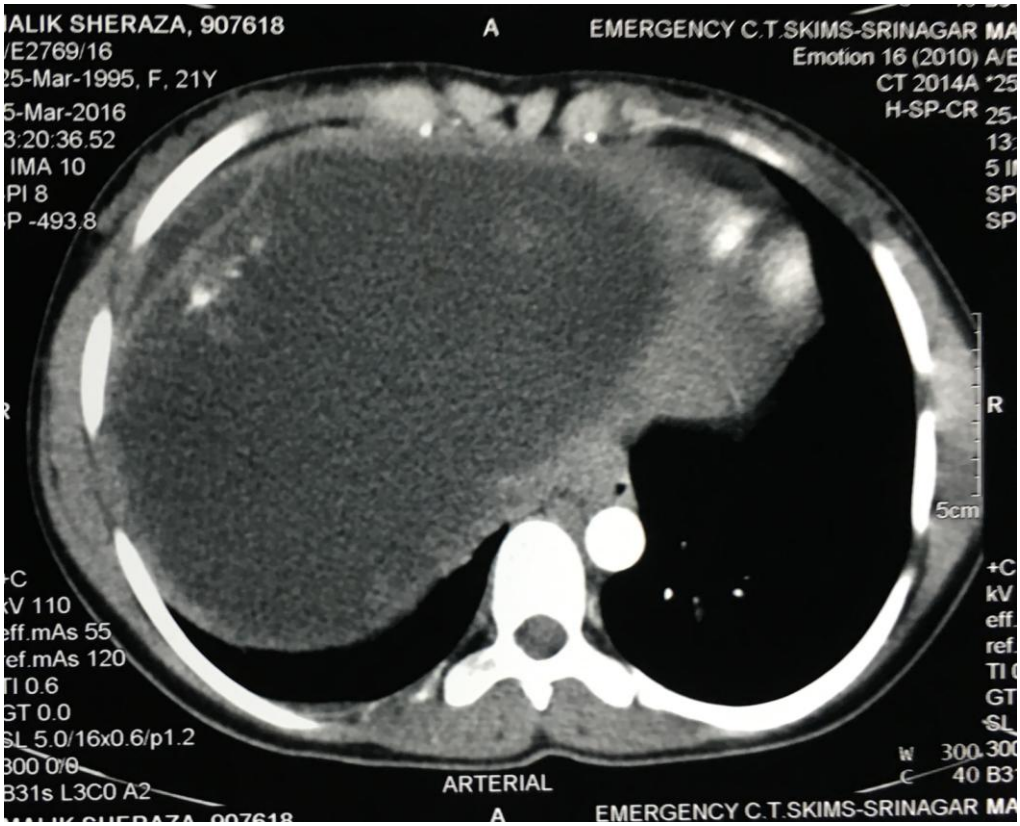

FIGURE3 :Large cystic lesion in right lobe with peripheral calcification and presence of a thin rim of normal liver rim around the lesion

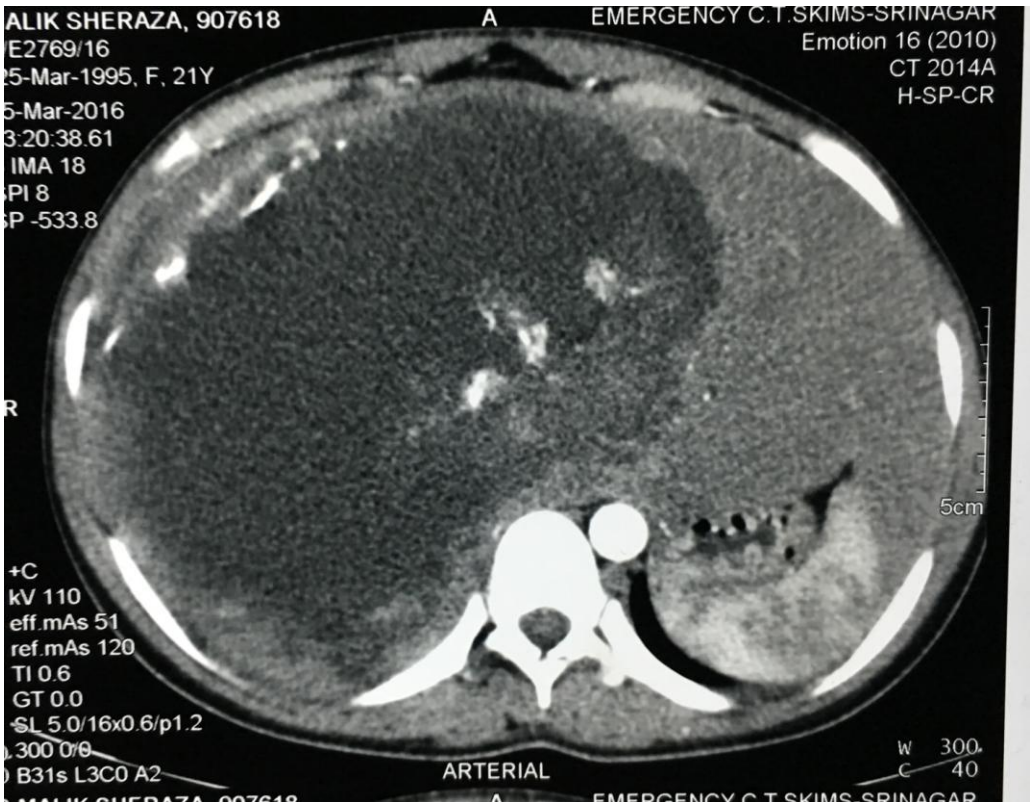

FIGURE4 :Large cystic lesion in right lobe of liver with multiple areas of scattered calcification and associated left lobe hypertrophy

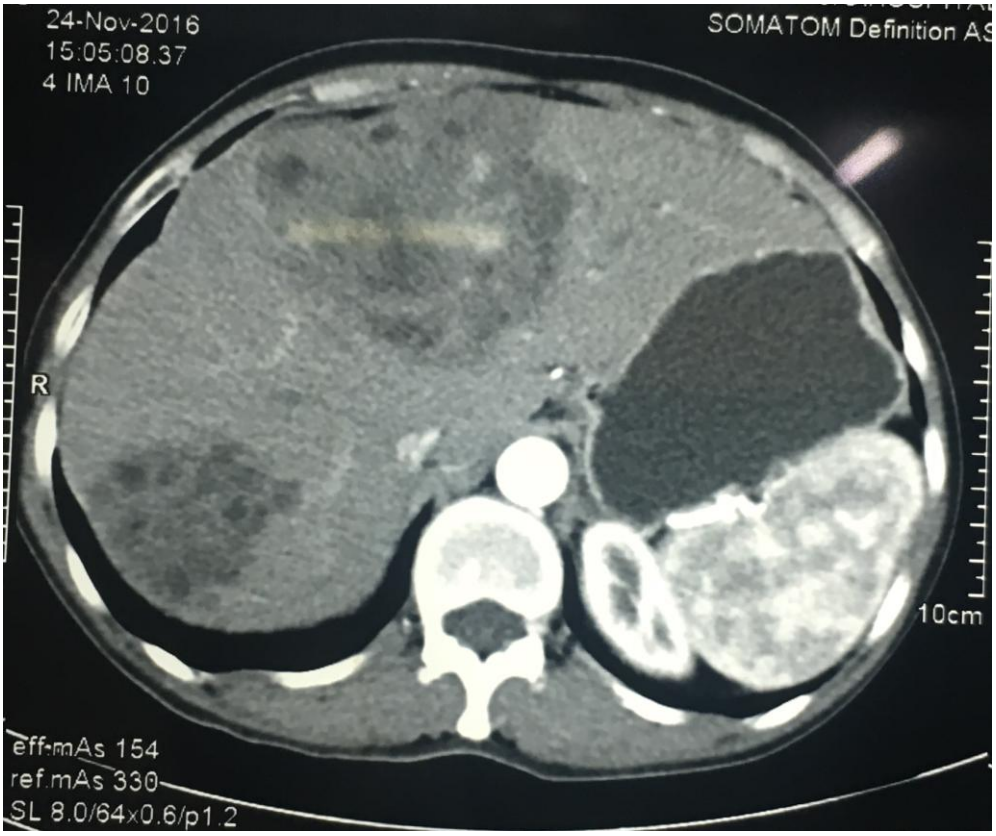

FIGURE5 :Complex lesions in segments 4,5 and 7,8. Areas of cystic degeneration and foci of calcification seen interspersed

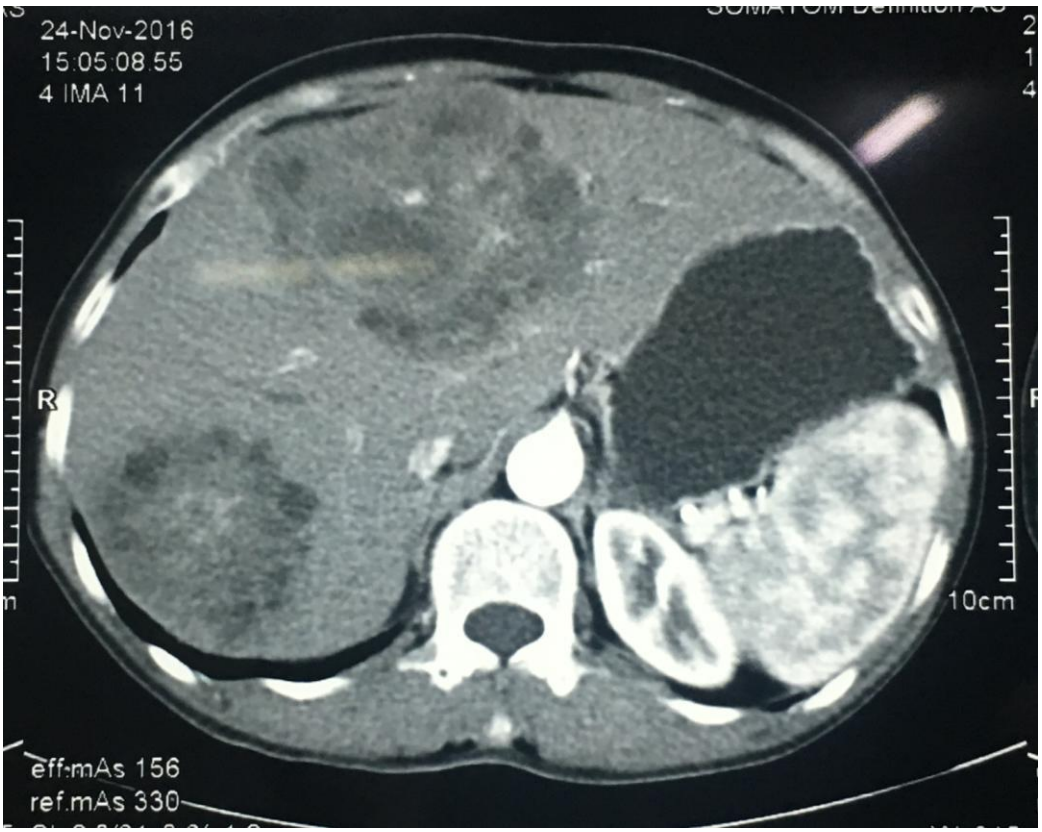

FIGURE6 :Complex lesions in segments 4,5 and 7,8. Areas of cystic degeneration and foci of calcification seen interspersed

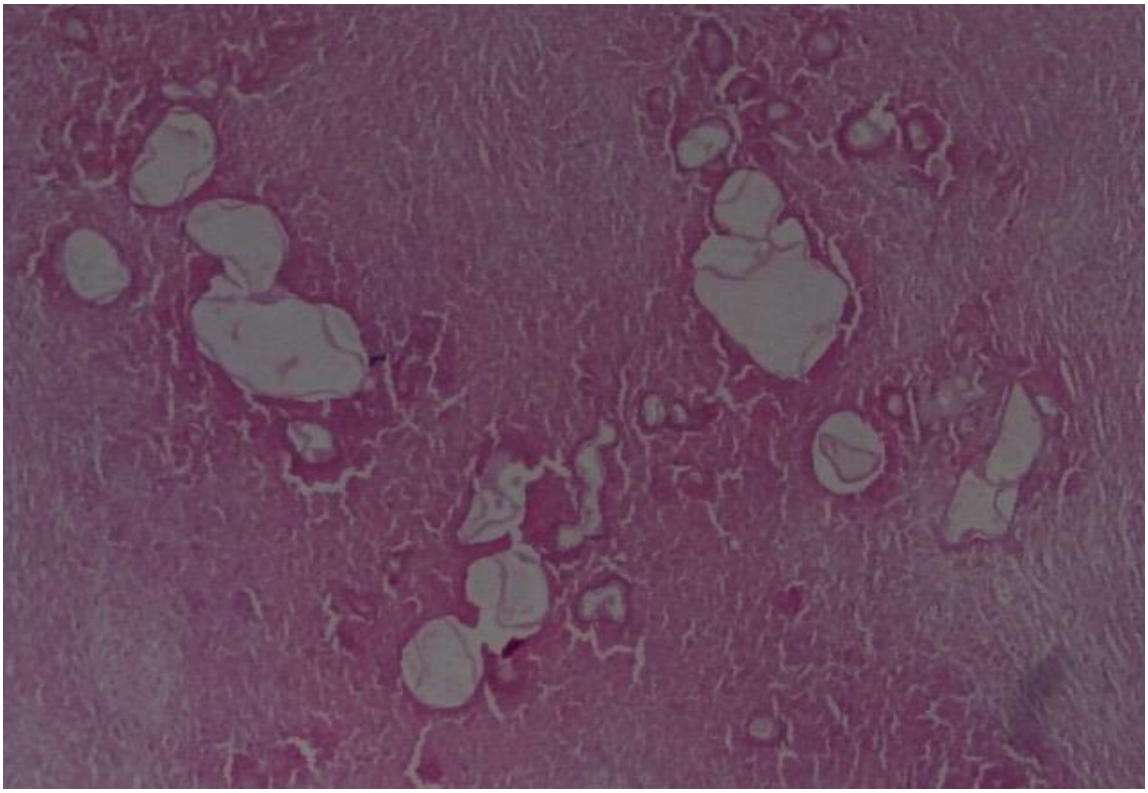

FIGURE 7 :

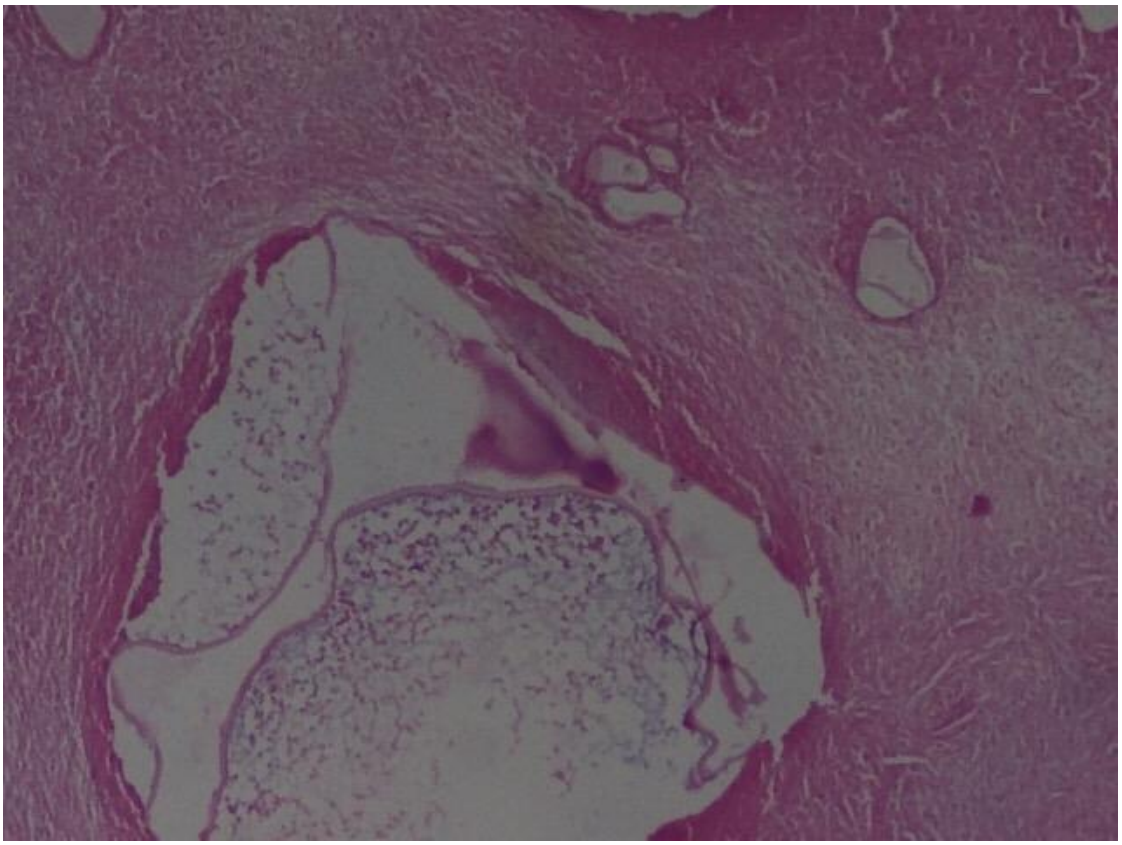

FIGURE 8:

FIGURES 7 AND 8 :

. PHOTO MICROGRAPHS SHOWING MULTIPLE CYSTIC STRUCTURES LINED BY THIN AVASCULAR AND EOSINOPHILIC LAMINATED MEMBRANES WITH NO NUCLEI.

. SURROUNDING LIVER PARENCHYMA IS DISTORTED AND SHOWS PORTAL ATROPHY WITH INFLAMMATORY INFILTRATE

. FIBROSIS AND CALCIFICATION INTER-SPERSED IN THE BACKGROUND

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