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Case Series

Pleural effusion in hepatic vena cava disease

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Abstract
Pleural effusion is not uncommon in developing countries. It is usually considered to be due to tuberculosis and treated with anti-tubercular chemotherapy without much diagnostic workup. Hepatic vena cava disease (HVD), a disease caused by obliterative lesion of the hepatic portion of inferior vena cava induced by bacterial infection is common in developing countries. We report here the occurrence of pleural effusion in 10% of the cases of HVD. Four patients, one with acute and three with chronic HVD that presented with pleural effusion are described. Pleural effusion in HVD responded to treatment with antibiotic and diuretic. In developing countries HVD should be considered in the differential diagnosis of pleural effusion. It is postulated that bacterial infection and sodium retention resulting from acute caval obstruction are important in the pathogenesis of pleural effusion in HVD.

Key words: Pleural effusion, Hepatic Vena Cava Disease, Budd-Chiari syndrome, IVC obstruction

Hepatic vena cava disease (HVD) is a disease of the hepatic portion of inferior vena cava (IVC) caused by bacterial infection[1]. The lesion in acute stage is a localized thrombophlebitis just opposite the site of entry of the hepatic veins (Fig1). Patients with acute disease manifest clinically with fever, jaundice, hepatomegaly and ascites[2]. The acute lesion on resolution converts into stenosis or complete obstruction. The obliterative lesion commonly involves the ostia of middle and left hepatic veins. IVC and hepatic veins obstruction are followed by development of collaterals. Chronic disease progress insidiously and is characterized by features of caval obstruction like dilated superficial veins in the body trunk with upward flow, intermittent oedema of legs; or features of liver disease like hepatomegaly or splenomegaly, ascites or cirrhosis. An important feature of chronic disease is recurrent acute exacerbations characterized by ascites, fever, jaundice, or gastrointestinal bleed, precipitated by apparent or inapparent bacterial infection[3]. HVD is a common cause of ascites in Nepal[4]. Liver cirrhosis and hepatocellular carcinoma are important sequels the disease[5-10].

HVD is prevalent in geographic areas with low level of community hygiene and nutrition[11, 12]. It had occurred in the past in the West[13-17] and in Japan[5-8] but is now confined to developing countries. It was reported from South Africa[9, 10, 18], China[19], India[20-21] and Nepal[12, 22]. The disease was previously considered congenital[23] and labelled variously as Budd-Chiari syndrome affecting the hepatic portion of IVC, Asian-African type of Budd-Chiari syndrome, membranous obstruction of IVC (MOVC), obstruction of the hepatic portion of inferior vena cava, coarctation of IVC or hepatic cavopathy[25, 26].

Pleural effusion is not uncommon in developing countries. It is usually considered to be due to tuberculosis and commonly treated with anti-tuberculous chemotherapy. We report here the occurrence of pleural effusion in hepatic vena cava disease (HVD) which is not uncommon in developing countries and describe five patients of HVD with pleural effusion.

Materials and methods

Occurrences of pleural effusion in patients with HVD diagnosed during the period from 1989 to 1997 were studied. Diagnosis of HVD was based on clinical findings and ultrasound, supported by cavogram or liver biopsy. Markers of hepatitis B infection HBsAg by RPHA method, and anti-HBc by IHA method, and that of hepatitis C infection, anti-HCV by ELISA were assayed in all. History or occurrence of pleural effusion diagnosed clinically or by ultrasound and confirmed by X-Ray of the chest and aspiration of pleural fluid in patients with HVD and not related to other lung or heart disease or nephrotic syndrome was recorded.

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Four patients seen with significant effusion that did not have aspiration at other centre and had treatment with antibiotic or anti-tubercular chemotherapy before referral to out unit had diagnostic aspiration of the fluid. Diagnostic tap of the ascitic fluid was also done in patients with associated ascites. The aspirated fluids were inoculated at bed side for aerobic culture and the fluids examined for protein, albumin, total and differential WBC. Seven patients with effusion who presented with fever had blood culture for aerobic organisms.

Patients with pleural effusion were treated with oral antibiotic usually ciprofloxacin or ofloxacin or cefotaxim. Based on our past experience of treating HVD patient with bacterial peritonitis antibiotic was used initially in high dose and for period of 6 to 8 weeks[4]. Patients with massive effusion or ascites or oedema of legs also received diuretic, spirinolactone and or frusemide. Patients were informed of infection as a possible cause of effusion and were instructed to adopt good personal, food and water hygiene to prevent recurrence of the disease.

Results

Among 150 patients with HVD 16 (10 %) had pleural effusion. Of these 16 patients 5 had acute and 11 had chronic disease. None had cirrhosis. Eleven (73%) were male, and the average age of the patients was 22 years. IVC lesion was confirmed by cavogram in 14 patients (3 with acute and 11 with chronic disease). The obstruction in chronic disease was complete in 10 and a long segment stenosis in one. Three patients with acute disease showed long filling defects in the hepatic portion of IVC consistent with the localized presence of 'thrombophlebitis'. Eleven patients had liver biopsy (5 with acute and 6 with chronic disease). Congestive fibrosis was noted in 7, one had associated HCC. Three patients with acute disease showed changes in hepatocytes compatible with features of septicaemia[3].

Three patients (18%), one with acute and 2 with chronic HVD had repeated episodes of effusion over a period of 1 to 7 years. Of the 23 episodes of pleural effusion in 16 patients, 13 episodes were in right side and 10 in left side. Eight episodes in 6 patients were minimal (6 in the left and 2 in right) and were detected by chest X-Ray only. Reminder 15 episodes in 10 patients were moderate to massive effusions and were diagnosed clinically and confirmed by chest X-Ray and aspiration of the fluid.

Other associated clinical features in patients with pleural effusion

Ascites was present in 11 (69%) patients and was massive only in 2 and minimal in 3. One patient with chronic disease with massive ascites had only minimal effusion in the left side. Fourteen (87.5%) patients had fever, 13 (81%) had mild to moderate degree of hepatomegaly and 5 (31%) had jaundice. Splenomegaly was noted in 3; ankle oedema in 3 and dilated superficial veins in body trunk in 7 (44%) with chronic disease. One patient developed fever with chills a few hours after cavogram. Of the five patients with acute disease who had ascites, two had Staphylococcus aureus peritonitis following induced abortion, two were alcoholic with chronic diarrhoea had E.coli bacteraemia. The reminder fifth patient had history of prolonged pyrexia.

Two patients with chronic HVD had recurrent pleural effusion associated with fever but no identifiable source of infection. Both of these were young male and had three episodes each within 4 and 7 years and were treated repeatedly with anti-tuberculous chemotherapy, before they were referred to our unit after the detection of mild hepatomegaly. In both these patients the hepatic portion of the IVC was dilated and had complete obstruction.

Pleural fluid examined in 4 patients with no past history of antibiotic or anti-tubercular chemotherapy showed high protein content (4.5-4.7g/dl), and presence of WBC, mainly neutrophils and RBC. WBC count was about 250 cells per cubic mm except in one acute patient who had 3000 cells per cubic mm. Aerobic culture of pleural fluid grew coliform bacteria in this patient. Ascitic fluid study in 4 patients also showed high protein content (3.5-4.7g %). Mono-bacterial growth of E coli was noted in 3 and the reminder one had culture negative neutrocytic ascites. Blood culture done in 7 patients during febrile period, grew bacteria in 5- E.coli in 3 and Staphylococcus aureus in 2. All patients were sero-negative for HBsAg, anti-HBc and anti-HCV.

Response to treatment

Response to treatment with antibiotic and diuretic was good with no recurrence of pleural effusion in these patients.

Case reports

Case 1

TKL. A 20 year old young male adult from east Nepal, used to alcohol intake of about 250ml on alternate for last 5 years and chronic diarrhoea for last 1 year was admitted at Bir Hospital with high fever, puffy face, and shortness of breath, cough and upper abdomen pain. He had massive right side pleural effusion and 6cm enlarged smooth, firm liver. Pleural fluid had high protein content (4.5g %) and high count of WBC (3000/cumm), mainly neutrophils. Culture of blood and pleural fluid grew E.coli, liver tests showed mild elevation of serum bilirubin and ALT. Ultrasound showed enlarged liver with increased echo-texture and fresh and organized thrombus on posterior wall of the hepatic portion of IVC. Liver biopsy showed congestive fibrosis of the liver with extensive necrosis of the hepatocytes and one thrombosed hepatic vein radicle. Patient responded to treatment with ciprofloxacin 750mg twice a day and spirinolactone 100mg daily with control of fever and clearance of pleural fluid. The patient was discharged with advice to continue ciprofloxacin 500mg twice a day for a month. A repeat liver biopsy a year later showed advanced congestive cirrhosis.

Case 2

AP. A 23 young man from Kathmandu had consulted doctor for upper abdomen pain after food and on walking briskly and shortness of breath. He was detected to have right side pleural effusion and was treated with anti-tubercular chemotherapy for 9 months. Seven years later he had recurrence of the pleural effusion and consulted the same doctor. After consultation with chest specialist, study of pleural fluid and pleural biopsy he was put again on anti-tubercular chemotherapy including injection of streptomycin. Patient discontinued the treatment after 1 month. He had further recurrence of effusion after 4 years and this time he consulted another doctor who detected mild hepatomegaly and referred to Liver Unit for evaluation. He had a prominent superficial vein at upper abdomen with blood flow upward, mild hepatomegaly and normal liver tests excerpt for mild elevation of ALT. Ultrasound showed dilated hepatic portion of IVC with complete obstruction (Fig 3) which was confirmed by cavogram. He was non alcoholic and was sero-negative for HBsAg and anti-HCV. Liver biopsy showed congestive fibrosis of the liver. He responded to treatment with antibiotic. He was advised to adopt personal, food and water hygiene. He had been attending the follow-up clinic regularly since last 12 years and had no recurrence of effusion.

Case 3

NM. A 39 year young patient with past history of purulent discharge anal fistula with was admitted to Bir hospital with high fever, chills, upper abdomen pain of 2 weeks duration with sudden onset of shortness of breath. He had mild hepato-splenomegaly and massive left side pleural effusion. Investigation showed WBC count 10,000, 70% neutrophils, normal liver function tests, pleural fluid had high protein content, high WBC cell count, mainly neutrophils and presence of many RBC, culture failed to grow any organism. The patient had received antibiotic before admission to hospital. Ultrasound showed complete obstruction of the hepatic portion of IVC (Fig 4a). Patient was non-alcoholic, and was sero-negative for HBsAg, HBV DNA, anti-HCV, anti-HIV, anti-DNA, ANF, aldehyde test. Bone-marrow biopsy was normal. Liver biopsy showed intact lobular architecture with dense arachnoid fibrosis in perivenular areas and portal tracts slightly expanded by dense fibrosis. Cavogram showed complete obstruction of IVC at cavo-atrial junction (Fig 4b). The patient responded to treatment with Ciprofloxacin 750mg twice a day for 10 days followed by 500 mg twice a day for one month. Anal fistula was surgically treated. Long term follow-up for last 18 years showed no recurrence of effusion.

Case 4

BS. This 59 year old elderly lady was diagnosed of liver cirrhosis in the past and was admitted to a local hospital with sudden development of cough and shortness of breath, puffy face and swelling of hands and feet in 2004. The pleural fluid was found exudative and she was put on anti-tubercular chemotherapy. As she became more short of breathe even after one and half month of treatment she came to our clinic. She is non-alcoholic and was HBsAg and anti-HCV negative. In the past she had acute non A-E hepatitis in 2000, intermittent chronic diarrhoea from 2001 to 2003 and two episodes of fever in 2002 and 2004. Ultrasound showed presence of IVC stenosis which confirmed by cavogram. She responded to treatment with antibiotic and spirinolactone. However she had recurrence of two episodes of pleural effusion in 2006 precipitated by bacterial diarrhoea. She was admitted to a nearby nursing home during the first episode where she was aspirated of 3L of fluid. The third episode responded to treatment with antibiotic and diuretic and she was put on long term prophylactic antibiotic ciprofloxacin 750 mg once a week.

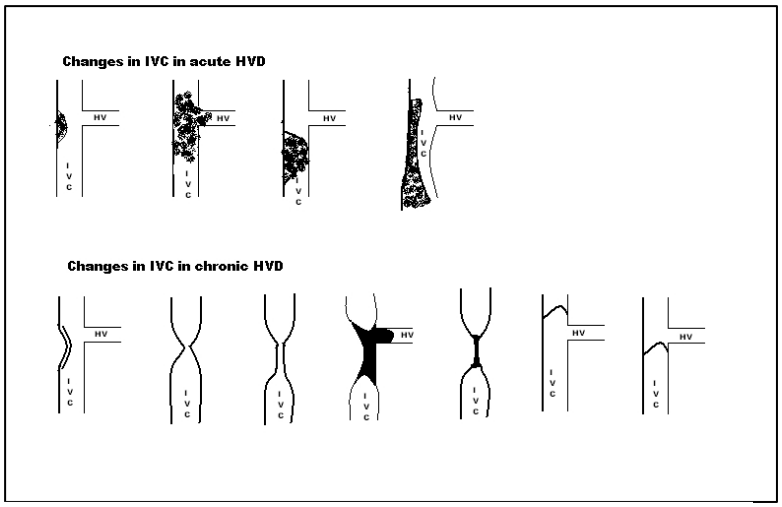

Fig 1: Changes in IVC in acute and chronic HVD

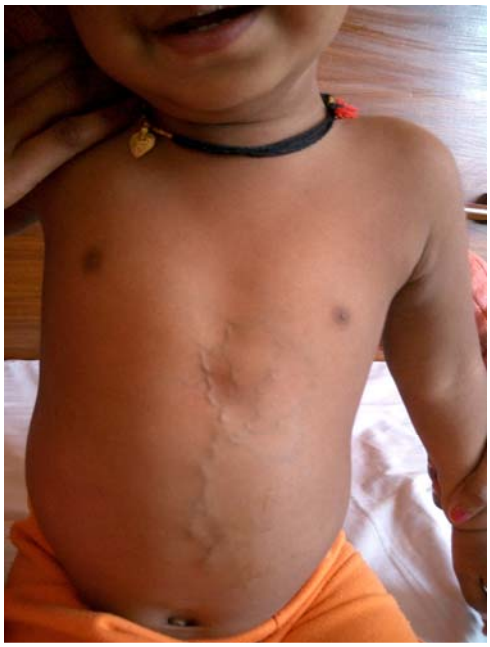

Fig 2: Presence of dilated superficial veins in abdomen and ascites in HVD

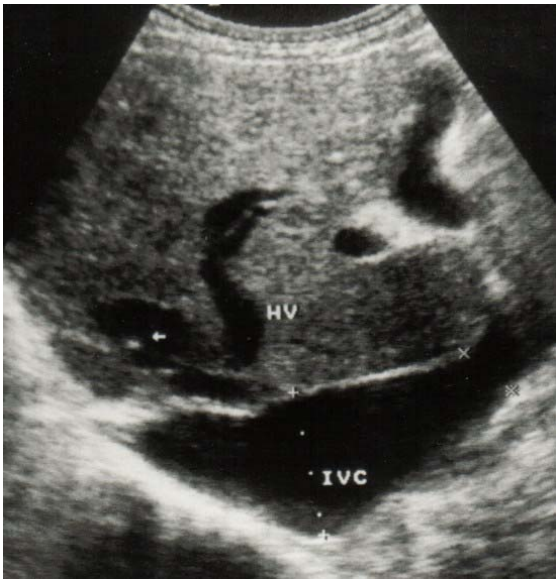

Fig 4: Ultrasound of liver showing complete obstruction of IVC

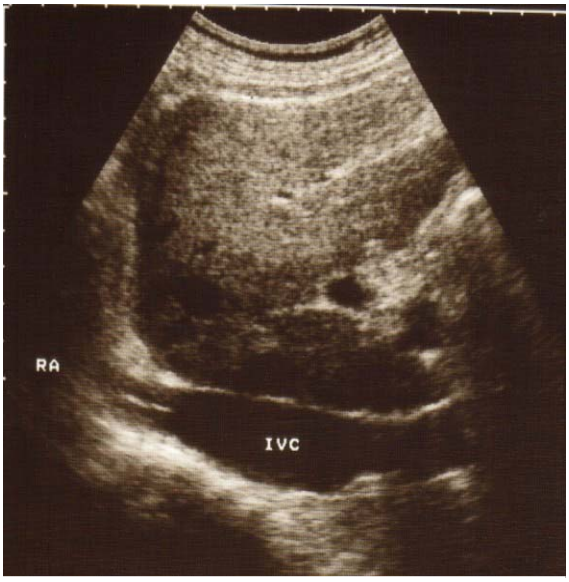

Fig 3a: Ultrasound of liver showing complete obstruction of IVC

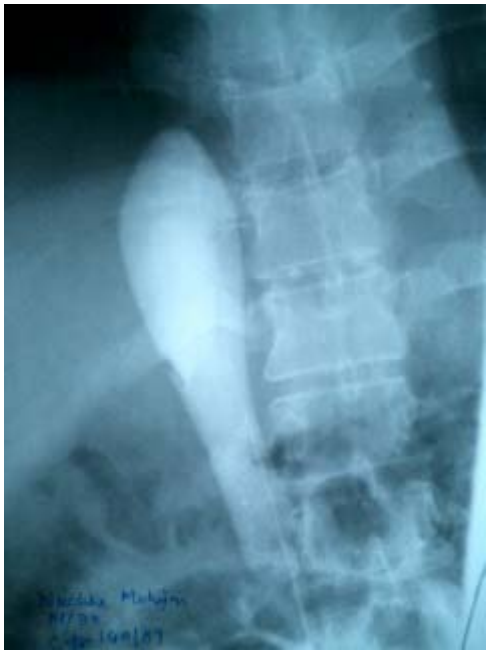

Fig 4b: Cavogram of the same patient showing complete obstruction of IVC

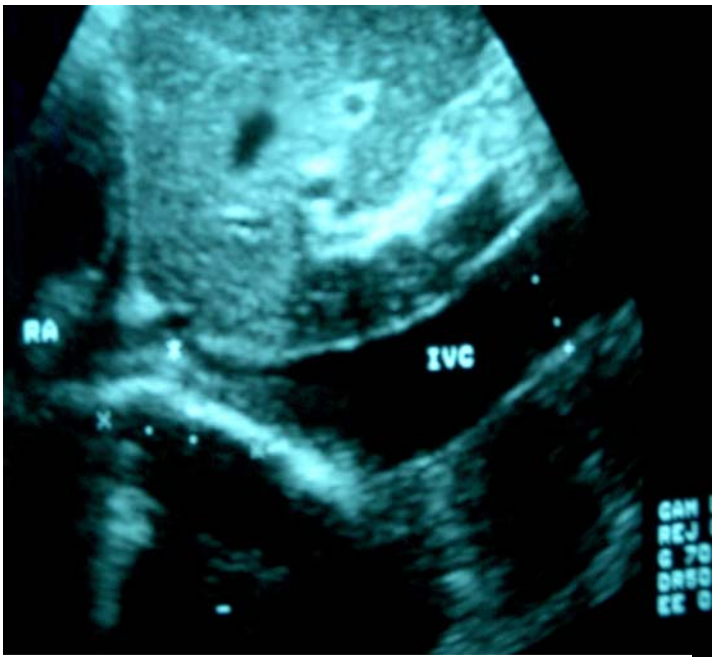

Fig 5: Ultrasound showing deposition of fresh thrombus in a patient with chronic HVD with IVC stenosis

Discussion

Sixteen patients, 10% of 150 patients with hepatic vena cava disease (HVD), none of whom had cirrhosis or cardiac failure or lung disease had pleural effusion. HVD in patients with pleural effusion were confirmed by cavogram and or liver biopsy. Pleural effusion in HVD occurred in acute stage or during acute exacerbation of chronic disease. Saundby in 1989 and Dixon Mann and Walker Hall in 1904 had reported the presence of pleural effusion in patients with chronic obstructive disease of the IVC[14, 24].

Another liver disease known to have associated pleural effusion is cirrhosis[27]. Pleural effusion occurs in about 5% patients with cirrhosis. It is mostly seen in right side, and is known as hepatic hydrothorax. It is thought to be due to direct passage of ascitic fluid from abdomen into pleural space through acquired defect in the diaphragm[28]. None of our patient except case number 4 reported above had cirrhosis. The recurrent pleural effusion in this patient was however not associated with ascites but with bacterial diarrhoea. Thus pleural effusion in HVD is different from hepatic hydrothorax.

What may be the cause of pleural effusion in HVD? It was not related to ascites as in cirrhosis. As pleural effusion in HVD occurred in acute stage or during acute exacerbation of chronic disease both of which are related to bacterial infection and deposition of fresh thrombus at the hepatic portion of IVC[3, 29], roles of these two factors- presence of infection and aggravation of caval obstruction need to be looked into in the pathogenesis of pleural effusion in HVD. Pleural effusion in this disease occurred in either side, was minimal to massive and not directly related to presence or severity of ascites. Most of these patients however had evidence of presence of active infection as shown by high incidence of fever (85%), bacteraemia in 5 out of 7 presenting with fever and bacterial peritonitis in 4. It is likely that the effusion was caused by infection. Detection of bacteraemia in 5 patients suggests that bacterial seeding of the pleural cavity as a likely event. Direct evidence of bacterial infection of pleura however was noted in only one patient seen during the acute stage who had presence of E.coli bacteria in the blood and pleural fluid. Right side pleural effusion of moderate degree had been noted in patients with pyogenic abscess of the liver situated close to the sub-diaphragmatic position that has not ruptured into the pleura. Infection probably spread to the pleural cavity through the lymphatics. The bacterial spread to the pleural cavity may be haematogenous or through lymphatics from adjoining liver or IVC. Rapid clearance of pleural effusion both in HVD and in that associated with pyogenic liver abscess with antibiotic

treatment appears to support the concept that effusion in these condition are probably caused by bacterial infection.

Levy and Wexler in 1987 found that the experimental constriction of sub-diaphragmatic portion of IVC in dogs resulted in decrease in sodium excretion by the kidneys[30]. Sodium retention in this condition was mediated by hepatic baroreceptors and followed increase in sinusoidal pressure. Acute HVD or acute exacerbation of HVD clinical mimics experimental caval obstruction. It is likely that as in experimental caval constriction, acute or acute on chronic caval disease results in sodium retention, as is suggested by the occurrence of puffy face and swelling of hands at the onset of pleural effusion in some patients. Bacterial infection and associated sodium retention may play a role in the pathogenesis of pleural effusion in HVD. Sodium retention results in fluid accumulation in body and bacterial seeding in the localization the fluid in the pleural cavity. Response to treatment with antibiotic and diuretics of patients even with massive effusion appears to support this assumption.

In conclusion, hepatic vena cava disease should be considered in the differential diagnosis of pleural effusion in developing countries. It is easily diagnosed by ultrasound examination[31, 32]. HVD is likely if effusion is associated with hepatomegaly or prominent superficial veins in body trunk or ascites or jaundice or elevated level of ALT. It should always be suspected in patient with bacterial infections. Patients of pleural effusion should not be straight way put on anti-tubercular chemotherapy. It is not only unwise but potentially hazardous to subject a patient of HVD with pleural effusion to long term anti-tubercular chemotherapy, especially in the presence of chronic liver disease or cirrhosis.

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