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A 16 Years Old Girl with Recurrent Hematemesis and Melena Diagnosed with Idiopathic Noncirrhotic Portal Hypertension (INCPH)

Case Report

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Author Details

Richmond R Gomes[1]*

Medicine, Ad-din Women's Medical College Hospital, Bangladesh

*Corresponding author

Richmond Ronald Gomes, Professor, Medicine Ad-din Women's Medical College Hospital, Dhaka Bangladesh

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Abstract

The term idiopathic non cirrhotic portal hypertension (INCPH) has been recently proposed to replace terms, such as hepatoportal sclerosis, idiopathic portal hypertension, incomplete septal cirrhosis, and nodular regenerative hyperplasia, used to describe patients with a hepatic presinusoidal cause of portal hypertension of unknown etiology, characterized by features of portal hypertension (esophageal varices, nonmalignant ascites, porto-venous collaterals), splenomegaly, patent portal, and hepatic veins and no clinical and histological signs of cirrhosis. Liver failure can occur in the context of precipitating factors. The development of portal vein thrombosis is common.

Physicians should learn to look for this condition in a number of clinical settings, including cryptogenic cirrhosis, a disease known to be associated with INCPH, drug administration, and even chronic alterations in liver function tests. Survival is manly limited by concomitant disorders. Currently, treatment of INCPH relies on the prevention of complications related to portal hypertension, following current guidelines of cirrhotic portal hypertension. No treatment has been studied aimed to modify the natural history of the disease. Here we present a 16 year old school girl presented with recurrent Hematemesis and melena who was subsequently diagnosed with INCPH after excluding all possible causes. She was managed conservatively with esophageal variceal band ligation (EVBL).

Keywords: Idiopathic Portal Hypertension, Esophageal Varices, Splenomegaly, Ascites, Cryptogenic Cirrhosis

Introduction

Idiopathic non cirrhotic portal hypertension is a disease characterized by periportal fibrosis and involvement of small and medium branches of the portal vein, resulting to intra hepatic portal hypertension in the absence of cirrhosis or other cause of liver disease and splanchnic venous thrombosis. 1 INCPH is more prevalent in Asia than in western country. In Asia, male and younger patient were more frequent diagnose had NCPH than in western country [1-4]. Histological features of INCPH comprise a wide spectrum of non-specific features, ranging from minor changes, sinusoidal dilatation, phlebosclerosis and portal fibrosis to nodular regenerative hyperplasia. Different conditions have been associated to this disorder including immune-based diseases, recurrent infections, HIV infection and antiretroviral treatment, trace metals, certain medications and prothrombotic factors [5-9]. The pathophysiological mechanisms causing INCPH remain largely unknown. Patients with INCPH usually present with signs and symptoms of portal hypertension (PH) such as splenomegaly, thrombocytopenia and variceal bleeding [5,10,11]. Patients can develop additional liver-related complications such as ascites, hepatic encephalopathy, portal vein thrombosis (PVT) or liver failure, that could eventually require liver transplantation (LT) [6,10,12-14].

Case Report

A 16years old unmarried school girl, hailing from rural Bangladesh, not known to have any co morbid illness, presented to us with

the complaints of recurrent passage of black tarry stool and bloody vomiting for last 6 months. For this she got admitted repeatedly in a local hospital and treated conservatively without any improvement. She complained bloody vomiting 4-5 times a day with each vomit and black tarry stool approximately 1 small cupful. She denied any abdominal pain, itching, steatorrhoea, weight loss, abdominal distension, leg swelling, joint pain, oral ulcer, skin pigmentation, previous jaundice or family history of liver disease. She had history of transfusion of total 6units of whole blood during her previous hospitalizations. History of consumed traditional potion, pain killer drugs, and alcohol and exposure to arsenic contaminated waster were denied. Her menstrual history was normal.

Physical examination revealed, she was pale, conscious, oriented, blood pressure 100/60 mmHg, pulse rate 105 beats/minute, respiratory rate 18 breaths /minute, axillary temperature 37.7°C, BMI 19.4 kg/m². She was mildly anemic, non icteric and there was no alopecia, pedal edema, skin pigmentation, malar rash, any petechiae, purpuric spot, ecchymosis, palmar erythema or spider naevus. Heart and lung were normal. In his extremities we did not find edema and there was no palmar erythema. Flapping tremor was absent. On abdominal examination, no engorged superficial abdominal veins. There was neither hepatomegaly nor any evidence of ascites but spleen was enlarged about 8cm along its long axis.

Laboratory tests showed hemoglobin levels of 7.8g/dl, MCV-69, MCH 22.1, leucocyte count 3.300/µL, platelet count 81,000/µL. Peripheral blood film revealed microcytic hypochromic anemia with target cells. Her serum albumin levels was normal (3.8g/dL). Her liver function, renal function, serum electrolyte, serum calcium, hepatitis B, C and HIV serology marker, ANA test, and hemostatic function (PT, aPTT) were within normal range. Thrombophillia screening including protein C, protein S, lupus anti coagulant, anti thrombin III, homocysteine level was normal. Chest X-ray within normal range, Abdominal USG revealed splenomegaly. Doppler USG revealed dilated portal vein (Figure1) but no thrombus in portal vein Endoscopy showed esophageal varices grade III (Figure 2). Liver biopsy could not be done due to lack of logistic support but fibroscan showed liver stiffness insufficient to define cirrhosis.

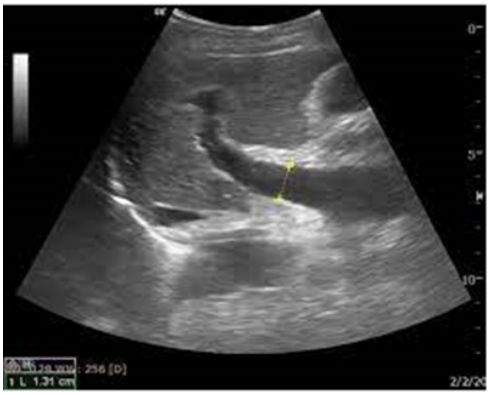

Figure 1: Doppler USG showing dilated portal vein without thrombus.

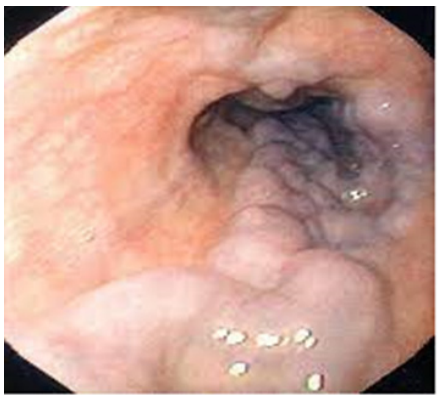

Figure 2: Endoscopy of UGIT showing varices grade III esophageal varices.

Patient was diagnosed with Idiopathic Non- Cirrhotic Portal Hypertension. She was transfused with 2units of whole blood. Finally we decided to do endoscopic band ligation of esophageal varices. She was discharged with 40mg propranolol two times daily and lansoprazole 30mg two times daily. There is a plan to follow her up after three weeks to do 2nd session of band ligation.

Discussion

In 1889, Guido Banti, an Italian pathologist, described a disease with splenomegaly and hypersplenism not associated with any known hematological disease [15]. In 1962, a syndrome distinct from both cirrhosis and extrahepatic obstruction of the portal vein was described in patients with portal hypertension from northern India [16]. The disease was called noncirrhotic portal fibrosis [17]. In 1965, Mikkelsen et al [18] identified a concentric thickening of the portal vein and its radicles and called this condition "hepatoportal sclerosis" while Boyer et al [19]. Studying cases of noncirrhotic portal fibrosis in India adopted the term idiopathic portal hypertension. Finally, in 2011, a group of European experts in portal hypertension proposed the term idiopathic noncirrhotic portal hypertension (INCPH) to be used in future collaborative studies [5].

Although INCPH has a worldwide distribution, it is particularly prevalent in Asia [20-22]. It is more frequent in socioeconomically disadvantaged individuals. Gender and age disparities have also been reported [20,23]. In Western populations, median age at diagnosis is 40years, with predominance in male gender. Conversely, Asian patients tend to be diagnosed at a younger age.

The etiology of INCPH is unknown [1,9,20,24,25]. Strikingly, small series and case studies show its association with an array of rare disorders; whether these associations are more than fortuitous remains unclear. The etiology of INCPH can be classified in five categories:

1) Immunological disorders (i.e. association with common variable immunodeficiency syndrome, connective tissue diseases, Crohn's disease, etc.)

2) Chronic infections

3) Exposure to medications or toxins (e.g. azathioprine, 6-thioguanine, arsenic)

4) Genetic predisposition (i.e. familial aggregation and association with Adams-Oliver syndrome and Turner disease)

5) prothrombotic conditions (e.g. inherited thrombophilias, myeloproliferative neoplasm antiphospholipid syndrome).

Diseases associated with INCPH are listed in table 1. A dual theory, implicating both intrahepatic vascular obstruction and increased splanchnic blood flow, has been suggested to explain portal hypertension in INCPH patients [5,12,26]. An increased intrahepatic resistance likely results from the obstructed intrahepatic vessels (i.e. phlebosclerosis) and distorted intrahepatic angioarchitecture (i.e. nodular regeneration). The mechanisms responsible for the obliteration of portal venules remain unknown. Several hypotheses have been proposed [5,26,27] including aberrant coagulation activation or thrombosis, acquired or inherited disorders of vascular remodeling, and endothelial injury from immune cells [28]. Similar to cirrhosis, the imbalance of different vasoactive mediators causing intrahepatic vasoconstriction could also be considered.

Table 1: Diseases associated with INCPH.

Disease Type	Disease Name or Cause
Acquired and congenital immunodeficiency	HIV
	Primary antibody-deficiency syndrome
Genetic disorders	Cystic fibrosis
	Adams–Oliver syndrome
	Turner's disease
Hematologic diseases	Myeloproliferative disorders (polycythemia vera, chronic myelogenous leukemia, essential thrombocythemia)
	Myeloid metaplasia
	Lymphoproliferative conditions (Hodgkin's disease, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and multiple myeloma)
	Spherocytosis
Autoimmune disease	Rheumatoid arthritis
	Systemic lupus erythematosus
	Systemic sclerosis
	Scleroderma
Gut diseases	Celiac disease
	Inflammatory bowel disease
Drug and toxins	Azathioprine, 6-thioguanine, arsenic as Fowler's, solution, oxaliplatin, busulfan, cytosine arabinoside, cyclophosphamide, thioguanine, bleomycin, chlorambucil doxyrubicin carmustine
Thrombophilia	Myeloproliferative neoplasm, protein S or C deficiency, antiphospholipid antibodies, lupus anticoagulant, factor V Leiden, prothrombin mutation.

Additionally to the increased intrahepatic resistance, a portal venous overflow secondary to splenomegaly has been linked to the development of portal hypertension in INCPH patients [29,30]. Overproduction of nitric oxide, released in the sinus lining spleen cells, could also justify the dilatation of splenic sinuses and subsequent massive splenomegaly frequently found in INCPH patients [5,31].

Complications related to portal hypertension dominate the signs and symptoms present in patients with INCPH [5,10,27]. The liver function is usually preserved. Variceal bleeding is the most common clinical feature. Unlike cirrhotic patients, prognosis of variceal bleeding in INCPH is usually good due to the preserved liver function. In those patients without variceal bleeding at diagnosis, over 75% had varices at the initial endoscopy [10,27]. A recent study has shown that the 1-year probability of developing small and large varices was 10% and 13%, respectively; this is similar to what is described in cirrhotic patients [10]. This study also showed that in patients with large varices, the 1-year probability of first bleeding episode despite primary prophylaxis was 9%.

In addition, the 1-year probability of re-bleeding despite combined secondary prophylaxis (i.e. beta blockers and endoscopic band ligation) was 22% [10]. Ascites is reported in up to 50% of cases, and it usually develops in the context of precipitating factors such as variceal bleeding or infections. Generally, it is easily controlled with low dose of diuretics and resolution of the trigger [5,13]. Hepatic encephalopathy is a rare complication and it is also related to precipitating factors. There are anecdotic reports of hepatopulmonary syndrome, por-

topulmonary hypertension and hepatocellular carcinoma. Over 95% of patients have splenomegaly and it can cause left upper quadrant's abdominal pain.

Portal vein thrombosis (PVT) is also common, with a reported prevalence that ranges from 13-46% [10,12,13]. A recent study found a 9% annual probability of developing PVT. HIV infection and the presence of variceal bleeding at diagnosis have been described as factors independently associated with a high risk of developing PVT [7,10]. Remarkably, most patients are asymptomatic at the time of PVT diagnosis. Therefore, it may be useful to screen for the presence of PVT in INCPH patients. It is unclear, however, the optimal frequency or best imaging modality in this context. In our patient, she had Hematemesis and melena that related to variceal bleeding (diagnosed with endoscopy) and also splenomegaly. She also did not show any sign of liver failure, eg; palmar erythema and also no edema in his lower extremity.

There is a lack of a specific positive test that leads to an INCPH diagnosis. It is based on clinical criteria and the formal exclusion of other causes of PH; this represents a clinical challenge, even in experienced liver units. Consequently, INCPH is frequently unrecognized, and in many instances patients are misdiagnosed with liver cirrhosis [32,33]. The diagnosis of INCPH is a diagnosis of exclusion, based on the following previously reported criteria [5].

a) Presence of unequivocal signs of portal hypertension (e.g., gastroesophageal varices, ascites, and/or splenomegaly)

b) Absence of cirrhosis, advanced fibrosis or other causes of chronic liver diseases that can cause PH by appropriate serological, biochemical tests and liver biopsy.

c) Absence of thrombosis of the hepatic veins or of the portal vein at imaging studies performed at diagnosis.

Therefore, the current diagnostic work up for INCPH should include:

A. detailed medical history to investigate concomitant diseases and exposure to drugs, medications or toxins

B. Liver imaging to evaluate the patency of the splanchnic venous axis

C. Laboratory tests to rule out other causes of liver diseases and/or PH

D. A mandatory liver biopsy to discard cirrhosis and other causes of chronic liver disease with or without PH.

As a result, a diagnosis of INCPH can only be made upon the exclusion of liver cirrhosis, portal vein thrombosis, Budd-Chiari syndrome, chronic liver diseases causing noncirrhotic portal hypertension (e.g. chronic viral hepatitis, primary biliary cirrhosis, non-alcoholic steatohepatitis, alcoholic steatohepatitis and autoimmune hepatitis) and conditions causing portal hypertension (congenital liver fibrosis, sarcoidosis and schistosomiasis).

Liver function test are normal, jaundice is rarely seen. Anemia, leukopenia and thrombocytopenia are common, because of hypersplenism. In our patient, liver function test was normal, ratio albumin and globuline normal, there is no hyperbilirubrinemia and also normal coagulation test. She had anemia, maybe related to hematemesis but also because of hypersplenism. She also had thrombocytopenia because of hypersplenism. Ultrasound is the first imaging modality study, in NCPH abdominal USG show normal liver, but sometime show chronic liver disease sign (nodularity), despite the lack of histological cirrhosis. Splenomegaly and echogenic thick walled portal vein. Contrast enhanced CT scan or MRI also can differentiated between cirrhosis and INCPH. From endoscopy we could find esophageal varices.

Liver biopsy is also an important diagnostic tool, to help differentiate between significant fibrosis (cirrhosis) and INCPH. In INCPH, we can find Hypoplastic or minute portal tracts, with a lumen of the bile duct or artery smaller than the surrounding hepatocytes are typical of INCPH [34]. and also minimal fibrosis. In the liver parenchyma, abnormalities that may be seen in the context of INCPH include sinusoidal dilatation, congestion and pericellular fibrosis, aberrant hepatic mvessels and dilatation of the central vein with or without perivenular fibrosis. A regenerative, compensatory response can be the result of a heterogeneous blood flow in the presence of circulatory abnormalities at different levels of the microcirculation. This might lead to nodular regenerative hyperplasia, showing micronodular transformation, with central hyperplasia and an atrophic rim in the absence of fibrosis [35,36].

Hepatic venous pressure gradient (HVPG) is normal (≤5 mmHg) or slightly increased (5-10 mmHg) but below the previously described cut-off for clinically significant portal hypertension in cirrhosis (CSPH; HVPG>10 mmHg) [23,37]. Also, liver stiffness value on transient elastography (Fibroscan®) is lower than the described cut-off values for diagnosing cirrhosis, varices and CSPH [7,10,37]. Thus, lower values for HVPG and liver stiffness than those described for cirrhosis and CSPH can be helpful by ruling out cirrhosis in a patient with signs of PH.

Management of INCPH is non specific, usually focus on management of its complication. The most common complication of INCPH is hematemesis cause by variceal bleeding. Data on management and prophylaxis of variceal bleeding in INCPH patients are scarce with a remarkable lack of randomized controlled trials. There are no specific guidelines for the management of PH in patients with INCPH. Nevertheless, expert opinion recommends following the guidelines of prophylaxis and management of PH in cirrhotic patients [5].

Briefly, primary and secondary prevention of variceal bleeding includes the use of non-selective beta-blockers and endoscopic variceal ligation. Trans-jugular intrahepatic portosystemic shunting (TIPSS) is an effective alternative in patients who fail to respond to medical and endoscopic therapy. Management of acute variceal bleeding includes early pharmacological treatment with vasoactive drugs (octeotride), intravenous proton pump inhibitor, early endoscopic control of bleeding, careful blood product replacement, and prophylactic antibiotics [38]. Guidelines also recommend withdrawing any drug potentially associated with INCPH (e.g. azathioprine) and treating any associated medical conditions [38].

Even though INCPH patients usually have well preserved liver function, and PH related complications are successfully controlled, some patients may require a liver transplantation(LT). Some of the reported indications for LT include unmanageable PH, progressive liver failure, chronic hepatic encephalopathy, hepatopulmonary syndrome and hepatocellular carcinoma. Post-LT outcomes of INCPH patients are good and the disease tends not to recur. However, data on this issue are limited and mostly based on small cohorts [5,36].

The use of anticoagulation in the management of PVT in INCPH is controversial, mainly due to the lack of

prospective data. Nevertheless, we believe that anticoagulation therapy must be considered in patients with underlying prothrombotic conditions and in patients who develop PVT. Another important point is whether anticoagulation may have a role in the prevention of PVT. Based on the high prevalence of thrombophilia, the frequent presence of thrombosis of small intrahepatic and main portal veins in INCPH, it would be even more important to determine whether anticoagulation could play a role to prevent disease progression.

Very few studies have evaluated the long-term prognosis of INCPH patients. Overall, prognosis is generally better than in patients with cirrhosis and a similar degree of portal hypertension. As mentioned

above, this may be due to the fact that most INCPH patients have well preserved liver function. However, a small subgroup of patients will develop liver failure and will require LT. Two recent European cohort studies evaluated prognosis of INCPH [10,13,39]. The Dutch study reported low overall and LT-free survival, 78% and 72% at 5years, respectively. However, it should be noted that only 13% of patients died from liver-related causes. Conversely, the Spanish cohort reported 86% of LT-free survival at 5years. Interestingly, ascites was identified as a poor prognostic factor in both studies. The presence of a concomitant severe disorder such as an immunological disease or malignancy was also identified as a poor prognostic factor in the Spanish study.

Conclusion

Over the last decade, numerous efforts have tried to clarify different aspects of INCPH. INCPH is probably under recognized and underestimated. It is not uncommon in Asia, sometimes we misdiagnosed it as cirrhotic patient, although initial treatment for complication is quite similar with cirrhosis patient, INCPH patient's had a better prognoses than in cirrhosis patient. Diagnosis of INCPH, is a diagnosis of exclusion, we must exclude other causes of hypertension portal before we diagnose INCPH. The diagnosis of INCPH still relies on clinical and histological elements; future research should provide diagnostic and prognostic biomarkers of the disease. Hopefully, future randomized trials will provide new tools to tackle this orphan disease and improve our understanding of its complex pathophysiology.

Conflict of Interest

None declared

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