Contents

Editorial

Surveillance of Indians with liver cirrhosis for treatable hepatocellular carcinoma: another enigma  K M Mohandas 261

Original Articles

Risk factors for esophageal cancer in Serbia
Zorana Gledovic, Anita Grguřević, Tatjana Pekmezovic, Slobodan Pantelic, Darija Kisić 265

Time to recognize atypical celiac disease in Indian children
Abhinav Sharma, Ujjal Poddar, Surender Kumar Yachha 269

Incidence of hepatocellular carcinoma among Indian patients of cirrhosis of liver: an experience from a tertiary care centre in northern India  Shashi Bala Paul, Vishnubhatla Sreenivas, Manpreet Singh Gulati, Kaushal Madan, Arun Kumar Gupta, Sima Mukhopadhyay, Subrat Kumar Panda, Subrat Kumar Acharya 274

Clinicopathological predictors to predict sustained viral response rates in patients with chronic hepatitis C infection  J agdish S Nachnani, Raja Gidwani, Esmat Sadeddin, Wendell K Clarkston, Rusell Fiorella, Laura M Alba 279

Short Report

Portal venous thrombosis after umbilical vein catheterization
Seddigheh Hosseinpour Sakha, Mandana Rafeey, Mohammad Khazem Tarzamani 283

Review

Epidemiology of inflammatory bowel disease in Asia  Ajit Sood, Vandana Midha 285

Case Report

Extensive gastrointestinal tract and thyroid involvement with Wegener’s granulomatosis
Raja Shekhar Reddy, Sappati Biyyani, Privi Pauskar, Nabil M Fahmy, James F King 290

Case Snippets

Acral and palmo-plantar hyperpigmentation in a patient with disseminated hepatocellular carcinoma  Rohit Goyal, Sreenivasa Baba Chalamalasetty, Kaushal Madan, Shashi Bala Paul, Raman Arora, Rajni Safaya, Subrat K Acharya 292

Primary intestinal lymphangiectasia as a component of autoimmune polyglandular syndrome type I: a report of 2 cases  Govind K Makharia, Nikhil Tandon, Neil de Jesus Rangel Stephen, Siddhartha Datta Gupta, Rakesh K Tandon 293

Letters

Iron deficiency anemia in Asians and Caucasians -- Any differences? Pierre Ellul 296

HBeAg negative chronic hepatitis B with persistently normal serum transaminase and low HBV DNA can cause significant liver disease  Mamun-Al-Mahtab, Salimur Rahman, Mobin Khan, Md. Kamal, Ayub Al Mamun 297

Screening for hepatocellular carcinoma in hepatitis B and C chronic carriers in Iran
A Fani, I Fani, B Eshtatieh, P Samadian, P Fani, Y Gorishi 297

Stomach cancer incidence among males in Golestan province, Iran
Abdoljalal Marjani, Mohammad Javad Kabir, Shahriyar Sennani 299

Octreotide in congenital chylous ascites an avoid requirement of total parenteral nutrition
Rakesh Mishra, Sanjeev Kumar 299

For online submission of articles and viewing full text of publications, visit the Journal website at www.indianjgastro.com

contd. on page iii...
Contents (contd.)

Mantle cell lymphoma (multiple lymphomatous polyposis) of gastrointestinal tract
M Murugesh, Veerendra Sandur, Niraj Sawalake, Madhu Sasidharan, Sanjay Altekar, Umang U Rathi, Mukta R Ramadwar, Pravin M Rathi 300

Transient neurotoxicity due to 5-fluorouracil
B Selvamani, Reena George, J Subhashini 301

Portal hypertension associated with sickle cell disease. Is there a coexistent liver disease?
Saju Xavier 302

Images

Mediastinal masquerade S Sankar, M Subramanian, K R Balakrishnan, Richard Saldanha 303

Detection of gall bladder cancer metastases in rare sites by PET scan Parul J Shukla, Savio G Barreto, Shailesh V Shrikhande, Mohandas KM, Purandare N, Rangarajan V 303

Gastroenterology Elsewhere 305

India Elsewhere 306

Announcements

Indian Journal of Gastroenterology J Mitra Memorial Award 268
Acknowledgment 295
News and Notices 304
Index to Advertisers 278
Instructions to Contributors 307
Surveillance of Indians with liver cirrhosis for treatable hepatocellular carcinoma: another enigma

Hepatocellular cancer (HCC) is a leading cause of cancer worldwide.⁰ Symptomatic cases with HCC usually live for less than a year.¹ Hence, screening for HCC has been proposed for populations with high incidence rates, such as patients with liver cirrhosis.³ However, data on the clinical utility and cost effectiveness of such screening are limited.³ The National Cancer Institute, USA recently summarized that, based on fair evidence, screening would not result in decreased mortality from HCC.³ In a large randomized trial from China, a country with one of the highest incidence rates for HCC, that included 18816 subjects aged 35 to 59 years with chronic hepatitis B (HBV) infection, screening using alfa-fetoprotein (AFP) and ultrasound (US) every 6 months reduced mortality due to HCC from 131.5/100,000 population to 83.2/100000.⁴ However, this study did not use intention-to-treat analysis. Another randomized trial from Qidong County, China in which 5581 men were screened with six-monthly AFP failed to show a reduction in mortality.⁵

The evidence favoring periodic surveillance in high risk subjects is limited. A recent systematic review on surveillance of patients with liver cirrhosis for HCC using standard methodology failed to identify any study that met the quality criteria;⁶ a combination of AFP testing and US at 6-monthly intervals was found to be the most effective surveillance strategy. This strategy was estimated to identify nearly 3-fold more people with operable HCC at the time of diagnosis and almost halve the number of deaths from HCC.⁶ However, such surveillance was costly, when subsequent liver transplant and post-transplant care were added to the cost of surveillance. Etiology of cirrhosis is also a determinant, with screening being more cost-effective in those with HBV-related cirrhosis, and less so in those with ALD-related cirrhosis.

In India, the epidemiology of HCC is quite enigmatic. Most HCC occur in patients with liver cirrhosis caused by chronic HBV infection, hepatitis C virus (HCV) infection or alcohol.⁷ In addition, contamination of food items, grains and oil seeds with aflatoxin is widespread in India.⁷ Paradoxically, the incidence of HCC has been low in all the population-based registries, as well as in data from hospital registries and autopsy studies from India.⁷ In contrast, the incidence of HCC in Indian immigrants to USA and mortality rates of HCC among Indians in Canada are similar to the rates reported in the native Caucasian population.⁷,⁸,⁹

Many researchers have attributed the low incidence rates in India to under-reporting, whereas others argue that the difference is real, because HCC is a rapidly fatal cancer and cannot be missed. This issue can be settled only by prospective studies on natural history of cirrhosis in the Indians. Such epidemiological studies are long due, given the huge burden of chronic hepatitis in India. The study by Paul et al in this issue of the Journal therefore provides much needed information.¹⁰

Paul et al conducted a prospective observational study to determine the incidence of HCC in northern Indian patients with liver cirrhosis but no evidence of HCC at enrolment.¹⁰ They screened 301 patients with Child class A or B cirrhosis over 44 months. After excluding those who had HCC at entry using US, triple phase computed tomography (TPCT) and AFP, 194 patients were followed up with US and AFP every 6 months and TPCT every year. The male:female ratio among the participants was 6:1 and 15% of them had elevation of AFP at the time of enrolment. During a cumulative follow up of 563 person-years, 9 cases of HCC (all males) were detected, with an incidence rate of 1.6 (95% CI 0.07-3.0) per 100 person-years. The authors concluded that the incidence rate of HCC in Indian patients with liver cirrhosis is intermediate between the high rates in Japan and the low rates seen in Europe. The authors could not identify any risk factors associated with the development of HCC due to the small sample size.¹⁰ The strengths of this study include a prospective study design, the use of intensive imaging techniques to exclude HCC at entry and an intensive follow up of the high risk study subjects for a reasonable duration.

The risk of HCC and cost effectiveness of a surveillance program depend on several factors,⁶ including age and gender of patients, and etiology of cirrhosis. Pooled data from cohort studies from Europe and USA in patients with cirrhosis have shown that the annual rate of progression to HCC is about 2.2% in HBV-related cirrhosis, 3.8% in...
HCV-positive patients and 1.7% in alcohol-related cases.\textsuperscript{6,11} The rates for development of HCC in the Far East are even higher.\textsuperscript{12,13} Results of the current study suggest that HCC develops less frequently in Indian patients with cirrhosis. However, some important issues need discussion.

First, one cannot exclude the possibility of selection bias, as has been partly alluded to by the authors too. The high screen failure rates at entry (36%) and the lower (43%) percentage of patients with HBV-related cirrhosis are important. Furthermore, 85% of patients were men, possibly due to a strong gender bias in seeking health care. The second point is whether the enrolled subjects were truly free of HCC at entry, since 15% had elevated AFP including two having AFP over 300 ng/mL; none of these patients developed HCC during follow up. In contrast, among 9 patients who developed HCC, AFP was elevated over 100 ng/mL in only three and above 300 ng/mL in only one patient at the time of development of HCC, although the detected HCC were large in three patients. These findings highlight the limitations of using AFP levels alone for HCC surveillance; these can be considerably elevated in patients with active hepatitis without HCC, and may be low in patients with small tumors. AFP levels vary widely among different populations.\textsuperscript{14}

A noteworthy finding in this study was the high HCC detection rate (5 cases) in the first 13 months after enrolment, with incidence rate of 3.53 per 100 person years in the newly diagnosed patients with liver cirrhosis. In screening studies, the initial rounds of testing can detect more cases (prevalent cases) than in the subsequent screening rounds. However, this is less likely in this study because the investigators had used a highly sensitive method (TPCT) to exclude small HCC before enrolment. These five cases may thus be a chance finding (due to a small sample size) or due to faster growth potential of these cancers resulting in what is known as length-bias in screening studies. A corollary is that the HCC incidence rates may decrease further if the cohort is followed up for longer periods.

All screening studies must evaluate clinical benefit in the population.\textsuperscript{6} Because almost all HCC occur in patients with advanced cirrhosis which is rapidly fatal, the cost-effectiveness of HCC screening programs should be assessed by life-years saved and not in terms of cases detected. The options for curative treatment in patients with cirrhosis and early HCC are limited by the residual liver function, and hence mortality rates for HCC continue to be high in the absence of liver transplant.\textsuperscript{2} In the current study, six of the nine patients died within one year of detection of HCC, and survival of the HCC cases detected by screening was similar to that in the absence of surveillance.\textsuperscript{15} Surveillance for HCC in cirrhotic patients has resulted in variable findings in Europe, US, and Asia.\textsuperscript{3,6,11,16} A controlled study using frequent (three-monthly) and intensive imaging (Lipiodol-CT) from Hong Kong,\textsuperscript{16} a region with high incidence of HCC, reported results similar to those of Paul et al. Though there was a high incidence of small HCC detected in HBV carriers, the surgical resection rates were low and no clinical benefit accrued from early detection.\textsuperscript{16}

It is important to note that surveillance is not always innocuous. It may induce anxiety among subjects and their caregivers, and changes in individual behavior in an attempt to avoid cancer. False-positive and false-negative findings may occur, resulting in serious consequences. Further, although Paul et al have not done a formal cost analysis, they rightly point out that a screening program in India will be prohibitively expensive.

The cost of six monthly AFP and US, and annual TPCT will be huge, particularly when seen in the light of very few HCC cases detected each year by screening men in their middle age. The cost of adding each extra life-year by surveillance will be even bigger since most of the patients detected with HCC did not live long. Thus, this study suggests that the tax payer’s money should not be used for routine surveillance of all Indian men suffering from liver cirrhosis. However, it does not rule out a possibility that screening in older patients or patients in Child class A may be rewarding. Although speculative and not supported by Indian data, patients who are likely candidates for liver transplant may put on a surveillance program. Needless to state, efforts aimed at primary prevention of HBV infection using universal vaccination of children, universal precautions in all health care settings and secondary prevention by early diagnosis and treatment of chronic viral hepatitis should continue.

**The Indian enigma**

The lower incidence rates of HCC in Indian patients with liver cirrhosis compared to US, Europe and other Asian countries remains enigmatic. The International Agency for Cancer
Research (IRAC) had estimated 13,630 cases of primary liver cancers in India (9,153 males, 4,477 females) in India in 2002 (including intrahepatic cholangiocarcinoma which constitute a large proportion of primary liver cancers in northern India). In contrast, the number of primary liver cancers from seven population cancer registries included in the Cancer Incidence in five continents (volume 9, 1998 to 2002) was 3,023 cases during 179 million person years. Uniformly low incidence rates of HCC recorded by population-based cancer registries from all parts of India and among Indian immigrants to US and Canada is note-worthy. On the other hand the estimated burden of HCC in India is huge. If we ignore the HCC arising from HCV, alcohol and other causes, we would have had a HCC burden of 68,000 new cases each year from the HBV carrier pool alone assuming that 15% of our 45 million HBV carriers are HBeAg positive and 0.01% of this pool to develop HCC each year. This five-fold difference between observed and estimated incidence rates for HCC merits discussion.

Several factors could explain the lower incidence of HCC in Indian patients. The first reason may be an overestimation of HBV burden in India. A recent systematic review of 54 Indian studies reported the true prevalence rates of HBV infection in non-tribal and tribal populations to be 2.4% (95% CI 2.2-2.7) and 15.9% (11.4-20.4), respectively. Also, a large proportion of these HBV-infected persons may be negative for HBeAg, and hence at a low risk of developing HCC. Another important reason for low HCC rates could be the competing causes of mortality in the Indian population. The average life expectancy at birth for Indians is still relatively low at 64 years, while the population-based incidence of HCC peaks at 75 years. The incidence rates for HCC in 100,000 males by age groups 40-44, 50-54, 60-64 and 70-74 years are 1.6, 5.7, 12.9 and 22.6, respectively. The low age-specific incidence of HCC in middle-aged Indian men may also be because of predominance of horizontal transmission of HBV. However, these measurement biases can explain only a part of the story, and other confounding mechanisms could also play a role.

Cofactors that modulate hepatic carcinogenesis could be one such reason. Aflatoxin B-1 (AFB-1) is an important co-factor in hepatic carcinogenesis in countries where contamination of food grains with Aspergillus fumigatus is common. The relative risk for HCC in unexposed controls, AFB-1 alone, HBsAg alone and combination of AFB-1 and HBV were 1, 3.4, 7.3 and 59.4, respectively, indicating multiplicative interaction between AFB-1 exposure and HBV infection. Ingested AFB-1 is metabolized by the glutathione S-transferase (GST) group of enzymes; inability to detoxify AFB-1 is an important risk factor for HCC. Several studies from East Asia and Africa have shown that genetic polymorphisms of GST (GST-µ1 and GST-01) may influence the susceptibility to aflatoxin-induced hepatic carcinogenesis. In a nested case-control study in Taiwan the effect of AFB-1 exposure on HCC risk was more pronounced among HBV carriers with null genotype (OR 3.7, 95%CI 1.5-9.3). Notably, in this study, AFB-1 exposure alone did not increase the risk for HCC. Several studies have reported low prevalence of GST null genotype among Indians. A diet rich in chlorophyll may also reduces the carcinogenic effects of AFB1 on the liver.

Iron has been implicated in the induction of hepatic inflammation and carcinogenesis. Iron overload, elevated transferrin saturation and liver iron deposits have been associated with more active and severe liver disease in patients with non-cirrhotic chronic HBV infection. Also, phlebotomy has been shown to reduce the risk of HCC in patients with chronic hepatitis C. Iron deficiency is very common in India with a prevalence of >85% in pregnant women.

The natural history of liver cirrhosis in Indians is indeed enigmatic. The study by Paul et al suggests that though the rate of development of HCC in Indian patients is lower, these tumors progress faster than those in other parts of the world. Further well-designed epidemiological studies on these enigmatic findings in Indian patients may offer useful clues for secondary prevention of HCC in them.

K M Mohandas
Department of Digestive Diseases and Clinical Nutrition, Tata Memorial Hospital, Mumbai 400 012

References
3. National cancer institute. Liver (Hepatocellular) cancer