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 Grgurevic, Tatjana Pekmezovic, Slobodan Pantelic, Darija Kisic 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 Jagdish S Nachnani, Raja Gidwani, Esmat Sadeddin, Wendell K Clarkston, Russel 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 Kakharia, Nile 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 Eshratie, P Samadian, P Fani, Y Gorishi 297
Stomach cancer incidence among males in Golestan province, Iran Abdoljalal Marjani, Mohammad Javad Kabir, Shahriyar Semnani 299
Octreotide in congenital chylous ascites an avoid requirement of total parenteral nutrition Rakesh Mishra, Sanjeev Kumar 299

contd. on page iii ...

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Indian Journal of Gastroenterology 2007 Vol 26 November - December i
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
India Elsewhere 305

Announcements
Indian Journal of Gastroenterology J Mitra Memorial Award 268
Acknowledgment 295
News and Notices 304
Index to Advertisers 278
Instructions to Contributors 307
Transient neurotoxicity due to 5-fluorouracil

Besides the more common hematologic, gastrointestinal and dermatologic side effects, 5-Fluorouracil can rarely cause neurotoxicity. This may manifest acutely as cerebellar syndrome as well as encephalopathy, or delayed as subacute multifocal leukoencephalopathy.

A forty-one year old man diagnosed to have adenocarcinoma of sigmoid colon, Duke’s stage C, underwent anterior resection in December 2001 and completed post-opera-tive radiotherapy. He was started on adjuvant chemotherapy in March 2002 with bolus 5-FU 425 mg/m² and leucovorin 20 mg/m². On the fourth day of chemotherapy, he had a fainting spell associated with profuse sweating, vomiting and cold extremities. He was found to be dehydrated and was treated with antiemetics and intravenous fluids. Serum electrolytes and ECG were normal. He recovered completely.

Immediately following chemotherapy administration on the next day he developed slurred speech and inability to walk. On examination, he was alert and oriented but had apraxia. Optic fundi and ocular movements were normal. He had left upper motor neuron paresis of VII, IX and XII cranial nerves. He was unable to stand or walk without assistance and he also had cerebellar signs with normal motor power. Serum electrolytes, blood sugar, renal function tests and ECG were normal. He recovered completely from the neurologic deficits within four hours, hence imaging was not done.

The diagnostic criteria of 5-FU-induced acute neurotoxicity include development of encephalopathy during or shortly after completion of 5-FU administration, absence of biochemical abnormalities, organ failure, sepsis and brain metastases, and adverse effects by concomitant medications. Bygrave et al reported two patients with 5-FU neurotoxicity who had rapid onset of neurologic symptoms and complete spontaneous recovery, unlike paraneoplastic syndromes or central nervous system involvement by tumor. Occurrences of transient encephalopathy, cognitive disturbances, repeated seizures, and optic neuropathy have been reported. In one of the cases, cerebellar signs did not resolve completely after withdrawal of 5-FU.

Delayed 5-FU neurotoxicity causing leukoencephalopathy and presenting as gradually progressive impairment of cognitive function, abulia, ataxic gait, and/or akinetic mutism has also been reported. The underlying pathological mechanism remains unknown and a dose-effect relationship is unclear.

In conclusion, clinicians need to be aware of adverse acute neurological effect of 5-FU; these severe side effects occur rapidly, and on discontinuing the offending drug, complete spontaneous recovery is possible.

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