Intraductal papillary mucinous neoplasm with more than one histologic type of epithelium

To the Editor,

I read with great interest the recent paper by Sanada and Yoshida on benign intraductal papillary mucinous neoplasm (IPMN) of the pancreas containing two major subtypes [1]. In this case report the authors describe the coexistence of a gastric type IPMN with an intestinal type. The former was composed of benign pyloric-type mucosa (hence, IPM adenoma) and was located mainly in the branch pancreatic ducts. This lesion then transitioned into the main pancreatic duct that also harbored an intestinal type IPMN of borderline cytological atypia. In addition, the small ducts contained lesions of PanIN 1A and 1B which communicated with the gastric type IPMN. The morphologic features were supplemented by MUC staining which clearly delineated gastric and intestinal type mucosae constituting the entire lesion [1].

These are indeed interesting observations and Sanada and Yoshida are to be complimented for their meticulous sampling of the lesion and documentation of the histopathologic findings. However, they state combinations of the different histologic types of IPMN within the one lesion are uncommon. In the paper by Adsay et al, they delineated a category, which they deemed "unclassifiable" [2]. This category was reserved for cases that could not specifically be placed into one of the 3 major types or comprised areas of intestinal or pancreaticobiliary epithelium, neither of which was considered the dominant histologic type. Most importantly, this paper goes on to say, "many of the intestinal and pancreatobiliary types had null (gastric type) type components" [2]. In the Discussion section of this paper, the authors conclude that the null or gastric type "is often present in the background of the other two types" [2]. Furthermore, in the consensus paper of 2005, it is also stated, that "areas with gastric-type epithelium can be associated with the other subtypes, implying that the gastric type might be a common precursor of the other types" [3].

In a review of our own material of over 50 IPMNs, gastric type IPMN coexisting with the other types was frequent (seen in approximately 30-35% of cases), and in fact, coexistence of intestinal and pancreatobiliary, intestinal and oncocytic and pancreatobiliary with oncocytic subtypes were also encountered.

The nomenclature used to designate an IPMN is based on the dominant histologic pattern seen. In the case described by Samada and Yoshida it would seem perfectly acceptable to consider the IPMN to consist of two types of epithelium because neither type appeared to predominate, although this is not stated explicitly in the description. However, the crux of the issue is that the different types of epithelium that constitute IPMNs frequently coexist, although one type tends to predominate and the IPMN should be labeled after the predominant epithelial type.

Also of major interest and great speculation is the association between gastric type IPMN and PanIN. Not only do they share locations (localized to branch and small ducts), they are lined by similar if not identical pyloric-type epithelium and share the same MUC expression profile. The arbitrary cut off figure of ducts 1cm or more harboring IPMN and ducts smaller than 1cm housing PanIN, is purely for the convenience of separating the two lesions. It does not take into account a possible temporal sequence of events where IPMNs at sometime may have been less than 1cm in size, despite being lined by similar epithelium as PanIN. Several have commented on the extreme difficulty separating the two lesions and perhaps there is a continuum between PanIN and gastric type IPMN.

Runjan Chetty, MB BCh, FRCPA, FRCPath,
FRCPC, DPhil, Department of Pathology,
University Health Network
University of Toronto,
Toronto, Canada

J Gastrointestin Liver Dis
June 2009 Vol.18 No 2, 251-259

References

1. Sanada Y, Yoshida K. A case of benign intraductal papillary mucinous neoplasm of the pancreas containing two major subtypes. J Gastrointestin Liver Dis 2008;17:457-460.
2. Adsay NV, Merati K, Basturk O, et al. Pathologically and biologically distinct types of epithelium in intraductal papillary mucinous neoplasms. Am J Surg Pathol 2004;28:839-848.
3. Furukawa, T, Kloppel G, Adsay NV, et al. Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. Virchows Arch 2005;447:794-799.

Perihepatic adipose tissue thickness

To the Editor,

This letter is in relation to the recent article which appeared in your journal titled "Perihepatic adipose tissue thickness: a new non-invasive marker of NAFLD?" by Lirussi et al [1].

The aim of this work was to develop tools which can be used to diagnose one of the most common liver diseases in the world, non-alcoholic fatty liver disease (NAFLD), with non-invasive testing. This goal has great importance given the vast numbers of individuals at risk for NAFLD and the infeasibility and unattractiveness of performing an invasive test such as liver biopsy in all suspected cases.

The authors draw from previous work by our group and others where ultrasound examination including measurement of the subcutaneous tissue thickness was used to predict NAFLD cases [2, 3]. The authors describe using the perihepatic adipose tissue thickness (PATT) defined by the adipose layer measured between the liver surface and the abdominal muscle layer. By excluding the skin and muscle layer the authors argue they only include the metabolically related component of the subcutaneous tissue thickness measurement. In a similar fashion to the subcutaneous thickness they are able to show that the PATT has a cutoff of 11.2 mm where below NAFLD is unlikely to be present (the subcutaneous cutoff is 20 mm).

This type of non-invasive measurement either by PATT or subcutaneous tissue thickness by ultrasound perhaps in combination with clinical risks, physical exam and laboratory panels could help to define those that are at greatest risk and serve to select a group that needs to go on to further invasive studies such as liver biopsy. Given the magnitude of the NAFLD problem and the global healthcare system impact NAFLD poses, future research in non-invasive, cost effective tools such as these are warranted.

Thomas Riley
3rd Department of Medicine
The Penn State Hershey Medical Center
Hershey, PA 17033, USA

References

1. Lirussi F, Vitturi N, Azzalini L et al. Perihepatic adipose tissue thickness: a new non-invasive marker of NALFD? J Gastrointestin Liver Dis 2009;18:61-66.
2. Riley TR, Bruno MA. Sonographic measurement of the thickness of subcateous tissues in nonalcoholic fatty liver disease versus other chronic liver diseases. J Clinical Ultrasound 2005;33:439-441.
3. Riley TR 3rd, Mendoza A, Bruno MA. Bedside ultrasound can predict nonalcoholic fatty liver disease in the hands of clinicians using a prototype image. Dig Dis Sci 2006;51:982-985.

Plasmodium falciparum and hepatitis B virus co-infection –a rare cause of acute hepatitis

To the Editor,

Falciparum malariae is endemic in India and causes jaundice and fever. There are case reports of the association of malaria with viral hepatitis [1,2]. Coexistence of the two diseases may cause diagnostic difficulty. We report a case which had co-infection with plasmodium falciparum and hepatitis B.

A 65-year-old female patient presented with jaundice for 10-12 days and fever for 5 days. The jaundice was preceded by prodormal symptoms of nausea, vomiting, malaise and fatigability. Jaundice was progressive in nature and associated with pruritus but no clay-colored stools. She had had high-grade fever associated with chills and rigor for 5 days. There was no past history of jaundice, blood transfusion, high risk behavior or alcohol use. On examination she was drowsy, had tachycardia, pallor and deep icterus. Her liver was palpable 3 cm below right costal margin without splenomegaly. Chest and cardiovascular system were unremarkable.

Investigation revealed hemoglobin12.8g/dl, total leukocyte count 6,450/ml, platelet 80,000/ml, prothrombin time prolonged by 3 seconds, blood glucose 105mg/dl, serum bilirubin 18.9mg/dl (conjugated 8.4mg/dl), serum total protein 7.6g/dl (albumin 3.3g/dl), alanine aminotransferase (ALT) 2036U/L and aspartate aminotransferase (AST) 1887 (normal <40), alkaline phosphatase 411 IU/L; serum urea and creatinine normal. Peripheral blood smear was positive for Plasmodium falciparum and malarial antigen was positive (histidine rich protein II based kits). Her viral markers showed a positivity for HbsAg and IgM anti-HBc and were negative for IgM anti-HEV, anti-HAV and anti-HCV. Her ultrasound showed hepatomegaly and a thickened gallbladder wall. The Dengue serology and Widal test were negative.

The patient was started on intravenous quinine (30mg/kg/day in 3 divided doses), ursodeoxycholic acid (600mg/day), ceftriaxone initially - later stopped, 10% dextrose, and paracetamol whenever fever more than 101F. Fever subsided on the second day and quinine was continued for 10 days. Over the next ten days platelet count and coagulation parameters normalized. Her bilirubin and transaminases normalized at 12 weeks.

Our patient had acute hepatitis B and malaria. The diagnosis of acute hepatitis was based on positivity for HbsAg and IgM anti-HBc.

Jaundice in malaria occurs in 5.3-62% of patients and is due to severe hemolysis or hepatic involvement [3].

Malaria hepatitis is usually described in patients with plasmodium falciparum infection.The patient presents with nausea, vomiting, fever and jaundice with abnormal liver biochemistry. Malarial hepatitis is characterized by a rise in serum bilirubin along with the rise in ALT to more than three times the upper limit of normal. However, liver histology shows malarial pigment, swollen hepatocytes, inflammatory infiltrate, and centrizonal necrosis and is termed malarial hepatopathy [4]. Hepatic dysfunction is reversible, if recognized early, in all patients developing malarial hepatopathy who respond to antimalarial therapy as was seen in our patient.

Chronic liver disease due to hepatitis B may be a risk factor for severe malaria as 23.77% of patients suffering from malaria have HBsAg positivity [5]. But our patient had acute hepatitis B, the first to be reported to be associated with malaria.

In our opinion, both malaria and viral hepatitis are frequent in this part of the world. Patients with fever and jaundice with splenomegaly, normal prothrombin time and low platelet should be investigated for malaria and those with transaminases in thousands and coagulopathy should undergo tests for viral markers.

Ramesh Roop Rai, Pankaj Jain
SMS College Hospital, Jaipur, India

References

1. Ghoshal UC, Somani S, Chetri K, Akhtar P, Aggarwal R, Naik SR. Plasmodium falciparum and hepatitis E virus co-infection in fulminant hepatic failure. Indian J Gastroenterol 2000; 20: 111.
2. Bansal R, Kadhiravan T, Aggarwal P, Handa R, Biswas A, Wali JP. Plasmodium vivax and hepatitis E co-infection - a rare cause of malarial jaundice. Indian J Gastroenterol 2002; 21: 207-208.
3. Bhalla A, Suri V, Singh V. Malarial hepatopathy. J Postgrad Med 2006; 52: 315-320.
4. Anand AC, Puri P. Jaundice in malaria. J Gastroenterol Hepatol 2005; 20: 1322-1332.
5. Barcus MJ, Hien TT, White NJ, et al. Short report: hepatitis B infection and severe Plasmodium falciparum malaria in Vietnamese adults. Am J Trop Med Hyg 2002; 66: 140-142.

Gallstone ileus as first presentation of a gallbladder carcinoma

To the Editor,

A 75-year-old woman was admitted to our hospital with a 3-week history of abdominal discomfort, vomiting and diarrhoea. On physical examination a non-generalized abdominal tenderness and distension was encountered. Laboratory findings revealed leukocytosis of 19.8 x 10^6/L. There was no deranged liver biochemistry.

An abdominal contrast enhanced CT showed a thick walled, air-filled gall bladder, a distended stomach and dilated loops of small intestine (Fig.1). Although no gallstone could be identified, these findings suggested the presence of a cholecysto-enteric fistula and gallstone ileus. At laparotomy, three obstructive gallstones were removed from the ileum (Fig. 2). The gallbladder showed a thickened wall and pericystic inflammation. Considering the critically ill elderly patient, the gallbladder was left in place.

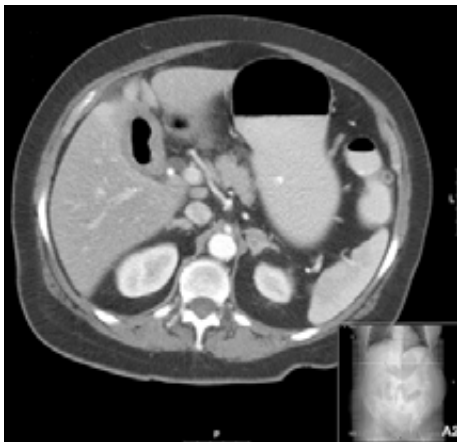

Fig 1. CT scan: a thick-walled, air-filled gall bladder, a distended stomach and dilated loops of small intestine.

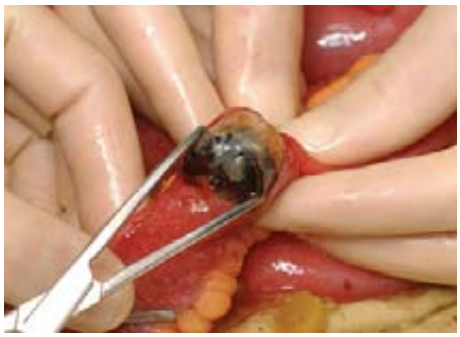

Fig 2. At laparotomy, three obstructive gallstones were removed from the ileum.

Recovery was initially uneventful. However, two months later the patient presented with general sickness, high fever (39°) and jaundice. The blood tests showed an inflammation, elevated liver enzymes and hyperbilirubinemia. The ERCP showed a slightly dilated common bile duct without an obvious obstructive gallstone. An endoprosthesis was placed and the patient showed some recovery. The fever however persisted and the clinical course deteriorated. A subcostal laparotomy was performed finding a firm gallbladder with malignant aspect. Various focal lesions were found in the liver of which intra-operative frozen sections confirmed the diagnosis of adenocarcinoma. Palliative treatment was started.

As a result of a trend to early operative management of symptomatic cholecystolithiasis, late complications of long-standing cholecystitis such as gallstone ileus are becoming exceedingly rare. Controversy exists whether initial surgery for gallstone ileus should be a one-stage procedure including stone removal, cholecystectomy and closure of the bilio-enteric fistula [1, 2], or should be limited to removal of obstructive stones [3]. Cholecystoduodenal fistula is the most common cause of gallstone ileus [4]. Gallstone ileus due to

primary gallbladder carcinoma is even more infrequent. This case *elevates* the awareness for gallbladder carcinoma as an underlying cause for biliary-enteric fistula and subsequent gallstone ileus in 6% of the cases [5].

Jeroen Heemskerk[1], Simon W Nienhuijs[2]
Departments of Surgery,
1) Laurentius Hospital Roermond;
2) Catharina Hospital Eindhoven, The Netherlands

References

1. Rubin M, Asseo G, Shimonov M, Pakula R, Mahagna Z, Antebi E. Management of gallstone ileus-a controversial issue. Isr J med Sci 1993; 29: 680-682.
2. Clavien PA, Richon J, Burgan S, Rohner A. Gallstone ileus. Br J Surg 1990; 77: 737-742.
3. Hesselfeldt P, Jess P. A review of 39 cases with emphasis on surgical treatment. Acta Chir Scand 1982; 148: 431-433.
4. Kasahara Y, Umemura H, Shiraha S, Kuyama T, Sakata K, Kubota H. Gallstone ileus. Review of 112 patients in the Japanese literature. Am J Surg 1980; 140: 437-440.
5. Day EA, Marks C. Gallstone ileus. Review of the literature and presentation of thirty-four new cases. Am J Surg 1975; 129: 552-558.

Hepatocellular carcinoma in membranous obstruction of the inferior vena cava - a causal or a casual presentation

To the Editor,

Membranous obstruction of the inferior vena cava (MOIVC) is associated with an increased risk of development of hepatocellular carcinoma (HCC).

We present the case of a 26-year old female admitted with progressive abdomen distension and edema of the lower extremities for 2 months. On examination she had tortuous and dilated veins over the anterior abdominal wall and at the back. The liver was enlarged and hard. There was tense ascites. Ultrasound and Doppler study of the portal venous system showed an enlarged caudate lobe with narrowing of the IVC at the level of the diaphragmatic hiatus. The right hepatic vein was thinned and occluded while the left and middle hepatic veins were patent in most of their length and drained into collateral veins at their terminal portions. Contrast enhanced CT scan of the abdomen showed a diffusely enlarged liver with ill defined hypo dense lesions, involving both the lobes of the liver and enhancing with contrast. Serum alpha fetoprotein was 884 ng/mL. Fine needle aspiration cytology of the lesion was positive for malignancy. Chest x-ray showed multiple cannon ball lesions suggestive of lung secondaries. 5-FU was administered for palliation.

For the relief of the tense ascites, a therapeutic angiogram was attempted. An opposing venogram (Fig.1) revealed a thick oblique membrane in the suprahepatic segment of the IVC with multiple venovenous collaterals. Transatrial balloon angioplasty resulted in immediate relief of ascites and the patient was relieved of ascites for the next 3 months.

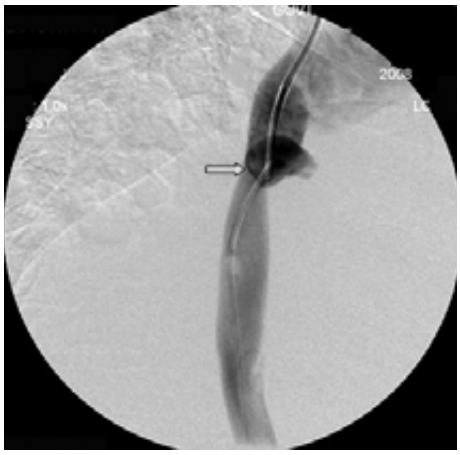

Fig 1. Opposing venogram showing a thick oblique membrane (arrow).

Membranous obstruction of inferior vena cava is a common cause of hepatic venous outflow obstruction in Africa, Japan, India and Nepal where it is frequently observed. The natural history of MOIVC depends on the nature of the occlusive lesion, adequacy of the collateral circulation and the development of HCC. The etiology of HCC in patients with MOIVC is unclear. Hepatitis B virus infection [1], chronic liver congestion [2], portal fibrosis and cirrhosis [1, 3] have been hypothesized as possible factors responsible for hepatocarcinogenesis.

The incidence of HCC in MOIVC varies between 4.7% and 47.5% [4-6]. Those affected are often younger and have a poorer prognosis. The link between MOIVC and HCC has been fairly established [4, 5]. In Simson's series [6], 48 out of 101 patients with MOIVC seen over a 9-year period had primary liver cell cancer. He considered caval obstruction as an important oncogenetic factor and not a simple promoter. The obstruction rendered patients susceptible to one or more environmental carcinogens. Hepatitis B virus which was thought to be an initiator and its markers were seen in 22.1% with HCC and 66.6% in those with cirrhosis and cancer. However this prevalence was far less in all African blacks with HCC of comparable age to those with MOIVC.

Kew et al [5] reported 6 out of 162 (3.7%) South African black patients with HCC had MOIVC – the incidence exceeded that occurring in the general population.

It is the centrolobular necrosis and regeneration resulting from the hepatic venous hypertension and congestion and not the occlusive lesion that directly causes malignant transformation. They act as a tumor promoter predisposing the individual to one or more environmental hepatocarcinogens in regions where HCC often complicates MOIVC [7].

Management of MOIVC due to thin membranes is by transluminal angioplasty. Transatrial membranotomy

on cardiopulmonary bypass may be required for thicker membranes. Tumor recurrences have also been reported.

In the present case, the patient manifested as MOIVC in the first instance. Hepatocellular carcinoma was documented during evaluation and transatrial balloon angioplasty was made to relieve the tense ascites. An aggressive approach towards HCC was not possible in our patient as there was widespread dissemination in the lung parenchyma even at the initial presentation. An early diagnosis and correction of the obstructive pathology in MOIVC may alleviate some of the serious complications like cirrhosis and HCC.

Pazhanivel Mohan, Sukumar R, Surendran R,
Sathyabhama C, Venkataraman Jayanthi
Department of Gastroenterology,
Stanley Medical College, Chennai, India

References

1. Takayasu K, Muramatsu Y, Moriyama N, et al. Radiological study of idiopathic Budd-Chiari syndrome complicated by hepatocellular carcinoma. A report of four cases. Am J Gastroenterol 1994; 89: 249–253.
2. Kawaguchi T, Sata M, Ono N, et al. Budd-Chiari syndrome complicated by hepatocellular carcinoma with no evidence of infection with hepatitis virus: a case report. Hepatogastroenterology 1999; 46: 3237–3240.
3. Matsui S, Ichida T, Watanabe M, et al. Clinical features and etiology of hepatocellular carcinoma arising in patients with membranous obstruction of the inferior vena cava: in reference to hepatitis viral infection. J Gastroenterol Hepatol 2000; 15: 1205–1211.
4. Simson IW. Membranous obstruction of the inferior vena cava and hepatocellular carcinoma in South Africa. Gastroenterology 1982; 82: 171–178.
5. Kew MC, McKnight A, Hodkinson J, Bukofzer S, Esser JD. The role of membranous obstruction of the inferior vena cava in the etiology of hepatocellular carcinoma in Southern African blacks. Hepatology 1989; 9: 121–125.
6. Dilawari JB, Bambery P, Chawla Y, et al. Hepatic outflow obstruction (Budd-Chiari syndrome). Experience with 177 patients and a review of the literature. Medicine (Baltimore) 1994; 73: 21–36.
7. Kew MC, Hodkinson HJ. Membranous obstruction of the inferior vena cava and its causal relation to hepatocellular carcinoma. Liver Int 2006; 26: 1-7.

Acute non-typhoid Salmonella mycotic aneurysm of the thoracic aorta

To the Editor,

A 39-year-old man presented with acute onset of epigastric pain radiating to left lower and the back, preceded by diarrhea. His past history revealed acute biliary pancreatitis, laparoscopic cholecystectomy, chronic hepatitis C and a recent admission (discharged 3 days previously) because of fever and delirium, during pegylated interferon-alpha and ribavirin, due to a staphylococcal aureus cystitis and bacteraemia with Salmonella Enteritidis. Anti-viral therapy was stopped and ceftriaxone intravenously was started, subsequently followed by ciproxin orally. Physical examination revealed a male patient in severe pain with a normal temperature and no signs of peritonitis. Laboratory tests were similar to those tested previously at the outpatient clinic (CRP 20 mg/L), except for the lactate level of 2.5 mM (normal range: 0.6-2.4mM). ECG, abdominal ultrasound, and plain abdominal x-ray's were normal. CT-angiography of the abdominal and thoracic arteries showed a leaking saccular mycotic aneurysm of the descending aorta at the level of thoracic vertebra 12 (Fig. 1). Emergency placement of an endovascular stent, ending 2 cm above the celiac artery (Fig. 2) was performed. After 5 days he was discharged in a good clinical condition.

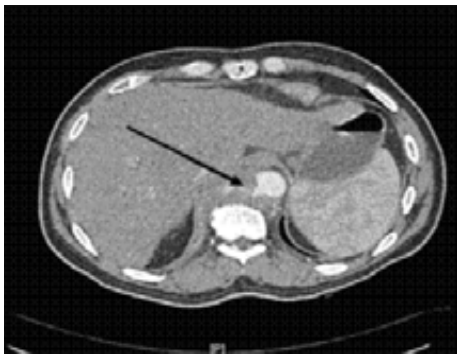

Fig 1. Transverse CT image of leaking mycotic aneurysm.

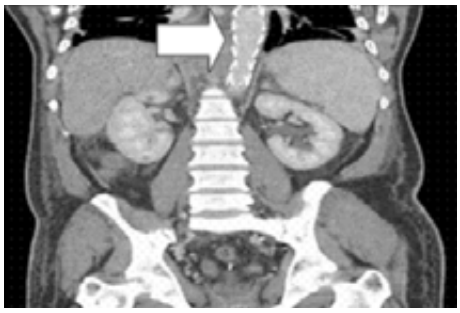

Fig 2. Sagittal CT image of leaking mycotic aneurysm.

The incidence of endovascular infections in patients with non-typhoid Salmonella bacteraemia ranges from 9 to 16.2% [1]. These species appear to have a predilection for invading damaged endothelium in the heart and arterial walls leading to a spectrum of cardiovascular infections [1, 2]. Mycotic aneurysms account for 2.6% of all aortic aneurysms and in 50% of these cases Salmonella species are the cause [2]. Standard treatment consists of a combination of surgical intervention and antibiotic treatment. The mortality for untreated patients is greater than 90%, compared to 40% in surgically treated patients, in the latter extensive debridement is (almost) always indicated [2]. Evidence and experience with thoracic endovascular procedures and their long-term results is poor, a maximal follow-up of 48 months and no mortality [3]. Therefore, in immunocompromised patients presenting with sudden onset of backpain, positive cultures with Salmonella species should arise suspicion of a leaking aortic mycotic aneurysm.

Erwin-Jan M. van Geenen, Tim C.M.A Schreuder,
Carin J.M. van Nieuwkerk , Chris J.J. Mulder
Department of Gastroenterology and Hepatology
VU Medical Centre, Amsterdam, The Netherlands

References

1. Niesen H, Gradel KO, Schonheyder HC. High incidence of intravascular focus in nontyphoid Salmonella bacteraemia in the age group above 50 years: a population- based study. Acta Pathol Microbiol Immunol Scand 2006;114:641-645.
2. Bayer AS, Scheld WM. Endocarditis and intravascular infections. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 5th ed. Philadelphia: Churchill Livingstone 2000:888-892.
3. Kotzampassakis N, Delanaye P, Masy F, Creemers E. Endovascular stent-graft for thoracic aorta aneurysm caused by Salmonella. Eur J Cardiothorac Surg 2004; 26:225-227.

Pegylated interferon/ribavirin-induced sudden sensorineural hearing loss in a patient with chronic hepatitis C

To the Editor,

Weekly pegylated interferon (PEG-IFN) plus daily ribavirin is currently considered the standard therapy for patients with chronic HCV infection. Sudden hearing loss has been frequently reported in HCV patients undergoing interferon alpha monotherapy [1]. We describe here the case of a patient with chronic HCV infection and sensorineural hearing loss associated with PEG-IFN alpha and ribavirin combination therapy. The patient ultimately made a full recovery from this condition after discontinuation of therapy. To the best of our knowledge, there have been only three reports of acute sensorineural hearing loss associated with combination therapy of PEG-IFN and ribavirin for chronic HCV infection [2-4].

A 47-year-old man with a history of chronic hepatitis C was referred to our department for further evaluation. His ALT value on admission was 95 U/L (normal < 41 U/L). His viral load was 3,590 027 RNA copies/mL and the genotype was 1a. Liver biopsy revealed chronic hepatitis with mild activity and stage I fibrosis. Combination therapy was started with of PEG-IFN-α-2a subcutaneously (180 μg per week) and ribavirin (1000 mg/day). The patient responded well, his aminotransferase levels normalized, and HCV-RNA was undetectable at week 24. Thirty-two weeks after initiation of therapy, he suddenly developed severe hearing loss in the left ear. Pure tone audiometry confirmed a sensorineural hearing loss (left ear: air/bone: 80/78 dB; speech reception threshold (SRT): 95 dB; speech discrimination: 32%; MCL: 100 dB; UCL: 12 dB; right ear: air/bone: 12/5 dB; speech reception threshold (SRT): 30 dB; speech discrimination: 100%; MCL: 75 dB; UCL: 100 dB). The PEG-IFN and ribavirin combination therapy was discontinued immediately. One month later, hearing loss showed a complete recovery. One month after initial discontinuation, combination therapy with PEG-IFN and ribavirin was restarted. After 48 weeks, the patient's liver biochemistry normalized and HCV-RNA was undetectable. The hearing loss did not recur.

In previous papers on auditory disability (hearing loss, tinnitus, or both) occurring during combination therapy of chronic HCV infection with PEG-IFN and ribavirin, seven patients treated with PEG-IFN and ribavirin developed hearing loss [2-4]. Formann et al reported that hearing loss did not recover completely following discontinuation of combination therapy, but notably no worsening was observed [2]. Our patient developed unilateral sensorineural hearing loss associated with PEG-IFN and ribavirin combination therapy. Interestingly, our case fully recovered after discontinuation of PEG-IFN-alpha and ribavirin therapy and did not relapse upon the reinitiation of the same combination regimen. The rapid improvement of auditory function following discontinuation of PEG-IFN suggests a microvascular pathogenesis of hearing loss in our patient. Accordingly, thrombocytopenia may lead to intracochlear hemorrhage, resulting in sensorineural hearing loss. It is also worth noting that the drug itself may be directly toxic to the auditory nerve hairy cells [4, 5]. No cases of sensorineural hearing loss caused by ribavirin alone have yet been described. The role of ribavirin in the development of sensorineural hearing loss in our patient is unclear, and there are no published reports of hearing loss due to ribavirin monotherapy.

In conclusion, PEG-IFN may cause sudden hearing loss that can fully recover after discontinuation of therapy, and may not recur upon reinitiation of the combination regimen with ribavirin. Physicians should be aware of the possible ototoxic effects of IFN-PEG requiring appropriate surveillance.

Ozlen Atug[1], Hakan Akin[1], Yusuf Yilmaz[1],
Murat Sari[2], Nurdan Tozun[1]
1) Department of Gastroenterology;
2) Department of ENT,
Marmara University School of Medicine,
Istanbul, Turkey

References

1. Kanda Y, Shigeno K, Kinoshita N, Nakao K, Yano M, Matsuo H. Sudden hearing loss associated with interferon. Lancet 1994; 343: 1134-1135.
2. Formann E, Stauber R, Denk DM, et al. Sudden hearing loss in patients with chronic hepatitis C treated with pegylated interferon/ ribavirin. Am. J.Gastroenterol 2004; 99: 873-877.
3. Wong VK, Cheong-Lee C, Ford JA, Yoshida EM. Acute sensorineural hearing loss associated with peginterferon and ribavirin combination therapy during hepatitis C treatment: outcome after resumption of therapy. World J Gastroenterol 2005; 11: 5392-5393.
4. Le V, Bader T, Fazili J. A case of hearing loss associated with pegylated interferon and ribavirin treatment ameliorated by prednisone. Nat Clin Pract Gastroenterol Hepatol 2009; 6: 57-60.
5. Cole RR, Jahrsdoerfer RA. Sudden hearing loss: an update. Am J Otol 1988; 211-215.

Metastasis of ulcerative colitis in peristomal skin – an extremely rare case

To the Editor

A 75-year-old Caucasian man with a longstanding history of ulcerative colitis (UC) and proctocolectomy with ileostomy presented with a few months' history of peristomal skin lesions. He reported recurrent itchy erythematous blisters, which at times were quite painful, weeping of the peristomal skin, and occasional ulceration. After an unsuccessful initial treatment with topical steroid creams, he was referred for a gastroenterology review.

Examination of peristomal skin (Fig.1) revealed a scaly erythematous rash with excessive granulation tissue and ulceration. Skin scrapings ruled out fungal infection, and a skin biopsy ruled out suspected pyoderma gangrenosum; the findings were of large bowel mucosa with ulcerated colonic glands, mucin depletion, extensive Paneth cell metaplasia, and cryptitis/crypt abscesses with surrounding moderate acute-on-chronic inflammatory cell infiltrates (Fig. 2), which are suggestive of active UC. As this is extremely unusual after a proctocolectomy, the patient underwent an ileoscopy. The ileal mucosa showed mucosal erythema and multiple polypoid lesions peristomally, without any evidence of neoplasia on histology. The diagnosis of metastatic ulcerative colitis was made.

The stoma itself appeared in healthy condition, hence refashioning was disregarded as a therapeutic option. Further topical steroid, 5-ASA and liquid nitrogen failed to improve the patient's symptoms. The condition eventually responded to topical sucralfate powder.

Inflammatory bowel disease (IBD) can also affect the skin; two major lesion types may develop during its course (15-20% in Crohn's and 10% in UC) [1, 2]. 'Specific lesions' reflect disease activity and their histological findings of granulomatous inflammation with epitheloid cells are similar to the intestinal ones. 'Reactive lesions' (erythema nodosum and pyoderma gangraenosum) can be found in other systemic diseases, but they are more frequently associated with IBD. Dermatoses such as epidermolysis bullosa acquisita and acne fulminans have a questionable connection with IBD [3].

Metastatic UC, defined as the occurrence of specific cutaneous lesions remote from the intestinal disease, is a rare complication. It seems unrelated to bowel disease activity, and manifests as subcutaneous nodules or ulcers, mainly at the lower extremities or at the peristomal skin in patients who had surgery. To the best of our knowledge, there are no reports of this condition in English literature.

Peristomal skin is usually irritated secondary to the leakage of urine or faeces, but can also be affected by preexisting skin diseases, i.e. psoriasis, seborrhoeic dermatitis and eczema, infections, allergic contact dermatitis, and pyoderma gangrenosum. The differential diagnosis of these skin manifestations may be very difficult and skin biopsy remains the only reliable discriminator test [4]. In our case, the presentation was similar to common peristomal skin conditions, and it remains unclear why the disease was active in the skin when no activity was found in the bowel.

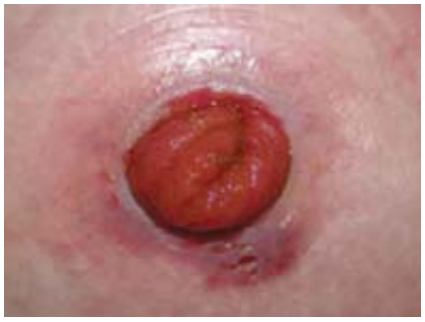

Fig 1. Macroscopic appearance of peristomal skin, with small ulcer.

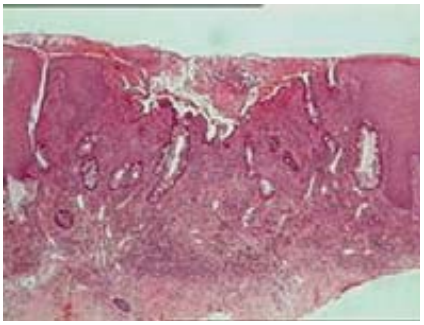

Fig 2. Histology of peristomal skin biopsy.

Although the IBD-related skin lesions often respond to the treatment of the bowel disease, sometimes additional therapy is required, in the form of corticosteroids, antibiotics, azathioprine or methotrexate. More recently, infliximab and tacrolimus have been used successfully in steroid resistant cases. Relocation of the stoma is reserved for persistent ulceration failing all other therapy [5].

Iftikhar Ahmed[1], Anastasios Koulaouzidis[2]
Javaid Iqbal[2], Terrence Wardle[1]
1) Countess of Chester Hospital NHS Foundation Trust;
2) Edinburgh Royal Infirmary, Edinburgh, UK

References

1. Tavarela Veloso F. Review article: skin complications associated with inflammatory bowel disease. Aliment Pharmacol Ther 2004; 20 (suppl 4): 50-53.
2. Lyon CC, Smith AJ, Griffiths CE, Beck MH. The spectrum of skin disorders in abdominal stoma patients. Br J Dermatol 2000; 143: 1248–1260.
3. Karolyi Z , Eros N , Ujszaszy L, Nagy G. Cutaneous and mucosal manifestations of inflammatory bowel diseases. Ovr Hetil 2000; 141: 1391-1395.
4. Ciubotaru V, Tattevin P, Cartron-Savin L , et al. Cutaneous metastatic Crohn's disease. Rev Med Interne 2003; 24; 198-201.
5. Kiran RP, O'Brien-Ermlich B, Achkar JP, Fazio VW, Delaney CP. Management of peristomal pyoderma gangrenosum. Dis Colon Rectum 2005; 48: 1397-1403.

Magnifying endoscopy with narrow-band imaging or confocal laser endomicroscopy for in vivo rapid diagnostic of Barrett's esophagus

To the Editor,

We read with great interest the article by Boeriu et al [1] regarding the utility of the magnifying endoscopy and chromoendoscopy in the evaluation of the upper gastrointestinal tract.

Barrett's esophagus (BE) is a metaplastic disorder in which specialized columnar epithelium replaces normal squamous epithelium, being recognized as a precursor of esophageal carcinoma. The diagnosis of BE by conventional endoscopy can be difficult. Fewer than 50% of the cases of endoscopic findings of BE are confirmed by the histopathology examination of the biposy samples [2]. In our center, only 22.34% from all BE detected endoscopically proved to have intestinal metaplasia at biopsy sample examination.

Lately there has been special concern regarding the development of new endoscopic diagnostic techniques for the recognition of intestinal metaplasia at the gastroesophageal (GE) junction. Magnifying endoscopy with methylene blue staining has been reported to improve the diagnostic accuracy of BE [3]. However, recently a high level of interobserver variability with a low accuracy of this technique in detection of intestinal metaplasia at the GE junction has been demonstrated [4]. Furthermore, it has been proved that using methylene blue for the detection of BE could accelerate carcinogenesis by induction of oxidative damage of DNA when photosensitised by white light during endoscopy examination [5]. For this reason, using a potential mutagenic dye for the examination of a premalignant condition of the gastrointestinal tract should be avoided.

Narrow-band imaging (NBI) is a new endoscopic diagnostic technique, being capable of providing virtual chromoendoscopic images only by a simple button touch. The NBI system consists of an electronic endoscope system and a source of light equipped with a narrow band filter, yielding very clear images of microvessels on mucosal surfaces. This system, in combination with a magnifying endoscope, can emphasize the microvasculature and mucosal pattern (Fig. 1). The magnifying endoscopy with NBI has been proven to have a high accuracy, reproducibility and repeatability in detecting intestinal metaplasia at the gastric and esophageal level, when used by both experienced endoscopists in the use of NBI and those unfamiliar with it [6].

Confocal laser endomicroscopy (CLE) is a newly developed endoscopic imaging technology that provides 1000-fold magnification cross-sectional images of the gastrointestinal mucosa during routine endoscopy. The histopathological criterion of intestinal metaplasia is the presence of goblet cells. Endomicroscopically, goblet cells appear as homogeneous dark spots at the level of epithelial columnar cell (Fig. 2). ECL can detect with high accuracy the presence of intestinal metaplasia at esophageal and gastric level, and can predict with high accuracy BE associated neoplastic changes [7]. In our experience, intestinal metaplasia at esophageal and gastric level could be predicted with a sensitivity, specificity, positive predictive value, and negative predictive value of 92.8%, 96.8%, 86.6%, and 98.39% respectively. The kappa index for the agreement between endomicroscopy and histopathology was 0.87 and the interobserver reliability index was 0.96.

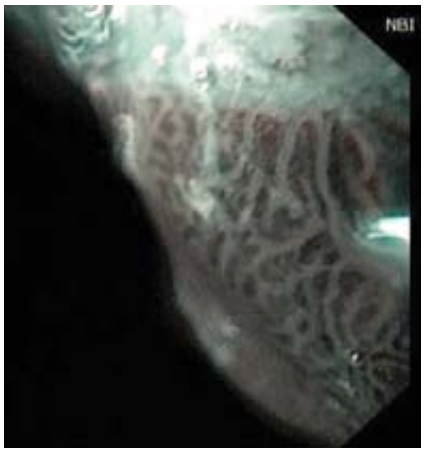

Fig 1. Magnifying endoscopy with NBI - Barrett's esophagus, villous pattern.

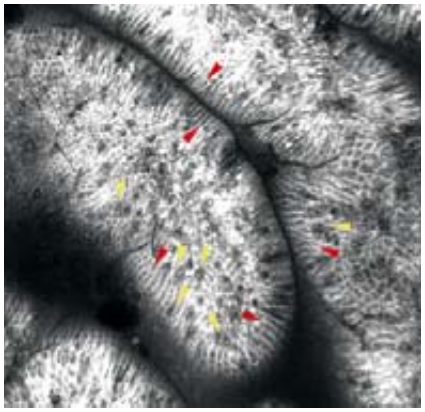

Fig 2. Confocal laser endomicroscopy – Barrett's esophagus. Columnar-lined epithelium (red arrows) with intermitent dark mucin goblet cells (yellow arrows) in the distal esophagus.

In conclusion, so far, magnifying endoscopy with NBI and CLE represent easy to use, reliable endoscopic techniques that can provide valuable information regarding gastrointestinal mucosa and should be used for the evaluation of gastrointestinal conditions in general, and for BE in particular.

Bogdan Cotruta, Cristian Gheorghe, Ion Bancila
Center of Gastroenterology and Hepatology,
Fundeni Clinical Institute, Bucharest, Romania

References

1. Boeriu AM, Dobru DE, Mocan S. Magnifying endoscopy and

chromoendoscopy of the upper gastrointestinal tract. J Gastrointestin Liver Dis 2009; 18: 109-113.
2. Eloubeide MA, Provenzale D. Does this patient have Barrett's esophagus? The utility of predicting Barrett's esophagus at the index endoscopy. Am J Gastroenterol 1999; 94: 937-943.
3. Endo T, Awakawa T, Takahashi H, et al. Classification of Barrett's epithelium by magnifying endoscopy. Gastrointest Endosc 2002; 55: 641-647.
4. Meining A, Rosch T, Kiesslich R, Muders M, Sax F, Heldwein W. Inter- and intra-observer variability of magnification chromoendoscopy for detecting specialized intestinal metaplasia at the gastroesophageal junction. Endoscopy 2004; 36: 160-164.
5. Olliver JR, Wild CP, Sahay P, Dexter S, Hardie LJ. Chromoendoscopy with methylene blue and associated DNA damage in Barrett's oesophagus. Lancet 2003; 362: 373-374.
6. Singh R, Anagnostopoulos GK, Yao K, et al. Narrow-band imaging with magnification in Barrett's esophagus: validation of a simplified grading system of mucosal morphology patterns against histology. Endoscopy 2008; 40: 457-463.
7. Kiesslich R, Goetz M, Vieth M, Galle PR, Neurath MF. Confocal laser endomicroscopy. Gastrointest Endoscopy Clin North Am 2005; 15: 715-731.

The role of chromogranin A in irritable bowel syndrome

To the Editor,

Enterochromaffin cells (EC) are a major source of circulating chromogranin A (CgA). CgA belongs to a family of highly conserved acidic proteins that are produced, stored, and secreted by the diffuse neuroendocrine system, polymorphonuclear neutrophils, and the myocardium. CgA serves as a prohormone for a range of peptides with potential regulatory functions, but is best known to clinicians as a marker for neuroendocrine tumors. CgA is also implicated in the pathophysiology of functional gastrointestinal disorders.

Recently, in two studies CgA has been assessed in patients with irritable bowel syndrome (IBS). In the last issue of this journal, Sidhu et al [1] presented the prevalence of CgA in diarrhoea predominant Rome II IBS patients. Serial CgA levels were measured using a competitive radioimmunoassay with the use of purified full-length human CgA. The normal adult concentration is between 2-20u/L. The authors chose the level of >60u/l as significant, based on the range usually being given as 2 standard deviations from the mean. This could suggest that patients with levels greater than 60 have a significant and unexplained level of serum CgA.

Eighty one percent of IBS patients (n=177) had normal CgA levels (0-20u/L). Whilst 12.3% (n=27) had values between 20-60u/L, 6.8% (n=15) had CgA levels >60u/l. It could therefore be postulated that patients with diarrhoea predominant IBS have enterochromaffin hyperplasia which results in their elevated CgA levels. However the reason behind the elevated CgA in only a proportion of patients with IBS remains unclear.

Elevated serum concentrations of CgA are seen in most neuroendocrine tumours (most notably phaeochromocytoma and carcinoid). Serum concentrations show a strong correlation with tumour mass within the individual patient, and thus can be used for monitoring response to treatment. Other causes of raised CgA include small cell lung cancer, prostate, breast and colon cancer.

In patients with gastrinoma (the Zollinger-Ellison syndrome) elevated CgA levels appear to reflect the associated gastrin-mediated enterochromaffin-like cell hyperplasia. Interestingly, enterochromaffin cell hyperplasia has also been demonstrated on rectal biopsy in patients with post-infective IBS (stool culture positive for Campylobacter). Enterochromaffin cells are a plausible mediator of diarrhoea predominant symptoms as they are known to play a pivotal part in the control of gut motility and secretions

In another recent study, Valeur et al [2] assessed serum CgA in patients with selfreported food hypersensitivity most of them (89%) having IBS according to the Rome II criteria. In this study, CgA was measured using an enzyme immunoassay. A nearly 40% lower than normal serum CgA levels was found in these patients (n = 18), and this was in marked contrast to the elevated serum CgA levels found in the subgroup of diarrhoea predominant IBS patients studied by Sidhu et al.

The cause of this reduction could include both intestinal (e.g. loss of EC cell functions or enteric neuropathy) and extra-intestinal (e.g. effects of stress or altered sympathoadrenal activity) abnormalities. The low serum CgA observed in IBS patients with self-reported food hypersensitivity opens a new approach for our understanding of this functional gastrointestinal disorder. These findings may therefore have important clinical implications.

Intriguingly, a non-specific, 48% decline in plasma CgA has been reported in response to infusion of somatostatin. Increased meal-stimulated plasma levels of somatostatin have indeed been reported in patients with IBS. Hypothetically, an above normal release of somatostatin could account for the reduced serum CgA in IBS.

It seems that both elevated and reduced levels of CgA can be found in subgroups of irritable bowel syndrome.

Trygve Hausken
Institute of Medicine, University of Bergen
Bergen, Norway

References

1. Sidhu R, McAlindon ME, Leeds JS, Skilling J, Sanders DS. The role of serum chromogranin A in diarrhoea predominant irritable bowel syndrome. J Gastrointestin Liver Dis. 2009;18: 23-26.
2. Valeur J, Milde AM, Helle KB, Berstad A. Low serum chromogranin A in patients with self-reported food hypersensitivity. Scand J Gastroenterol 2008;43:1403-1404.