

Distribution of constitutive (COX-1) and inducible (COX-2) cyclooxygenase in postviral human liver cirrhosis: a possible role for COX-2 in the pathogenesis of liver cirrhosis

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Aims: Prostaglandins produced by the action of cyclooxygenases (COX) are important mediators of systemic vasodilatation and inflammation in liver cirrhosis. The aim of this study was to investigate the distribution of COX-1 and COX-2 in postviral cirrhosis.

Methods: The immunohistochemical expression of the constitutive (COX-1) and the inducible (COX-2) isoenzymes was investigated in 15 patients with cirrhosis after hepatitis B and C infection; three normal control livers were also analysed.

Results: COX-2 was absent from normal liver but was highly expressed in cirrhosis, mainly in the inflammatory, sinusoidal, vascular endothelial, and biliary epithelial cells. Low amounts of COX-1 were expressed in both normal and cirrhotic livers, exclusively in sinusoidal and vascular endothelial cells, with no differences seen between normal and cirrhotic livers.

Conclusions: COX-2 is overexpressed in liver cirrhosis, and possibly contributes to prostaglandin overproduction, which may be a major component of the inflammation and hyperdynamic circulation associated with cirrhosis. Because COX-2 is thought to contribute to tumour development, high COX-2 production could be a contributor to hepatocellular carcinoma development in cirrhosis. The finding of COX-2 and not COX-1 upregulation in cirrhosis could provide a possible new role for selective COX-2 inhibitors in reducing inflammation and minimising the occurrence of hepatocellular carcinoma in patients with cirrhosis.

Cyclooxygenase (COX) is the rate limiting enzyme involved in the conversion of arachidonic acid to prostaglandin H₂ (PGH₂), the precursor of various compounds including PGs, prostacyclin, and thromboxanes, which are important inflammatory mediators.¹ Two COX isoforms, COX-1 and COX-2, have been found to share more than 60% identity at the amino acid level. COX-1 is constitutively expressed in many tissues and responsible for various physiological functions, including cytoprotection of the stomach, vasodilatation in the kidney, and the production of a proaggregatory prostanoid, thromboxane A₂, by platelets. In contrast, COX-2 is an inducible immediate early gene originally found to be induced by various stimuli such as mitogens and growth factors.^{2–5} Therefore, COX-2 is responsible for the release of PGs during inflammatory conditions, but COX-1 produces those PGs needed for the maintenance of normal physiological body functions. This has led to the concept that inhibition of COX-2 may explain the therapeutic usefulness of non-steroidal anti-inflammatory drugs (NSAIDs) as anti-inflammatory agents, whereas the inhibition of COX-1 may explain the unwanted renal and gastrointestinal side effects associated with their use. Overexpression of COX-2 has been demonstrated in various chronic inflammatory diseases, such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, gastritis caused by *Helicobacter pylori*, and chronic venous leg ulcers.^{6–9}

"The in vivo profile of both cyclooxygenase isoforms in human liver is unknown"

The liver has emerged as the major organ participating in the degradation and elimination of arachidonic acid products of systemic origin.¹⁰ PGE₂ specifically regulates important

liver functions, such as portal blood pressure, glucose homeostasis, delivery of nutrients to liver parenchymal cells, and pathogenesis of liver fibrosis.¹¹ In vitro studies have shown that primary Kupffer cells express only COX-1; however, lipopolysaccharide treated Kupffer cells express both COX-1 and COX-2.¹² The in vivo profile of both COX isoforms in human liver is unknown. Therefore, our study aimed to investigate the expression of COX-1 and COX-2 in patients with liver cirrhosis using immunohistochemical staining in liver tissues to determine which isoform could be involved.

MATERIALS AND METHODS

Patients

We studied a total of 15 patients, 12 men and three women, with a mean (SD) age of 42.3 (14.3) years, from the department of tropical medicine, Minia University Hospital, Minia, Egypt. All patients were subjected to thorough clinical examination, routine laboratory investigations (blood picture, urine, and stool), liver function tests, abdominal ultrasonography, upper gastrointestinal endoscopy, sigmoidoscopy, and liver and rectal biopsies. Eleven¹¹ patients had chronic hepatitis C virus (HCV) infection, as shown by serum HCV polymerase chain reaction (PCR) positivity, and four patients had chronic hepatitis B virus (HBV) infection, as shown by serum HBV surface antigen positivity; three patients (two with HCV and one with HBV) had coexistent schistosomiasis. The severity of the liver cirrhosis was graded

Abbreviations: COX, cyclooxygenases; HCC, hepatocellular carcinoma; NSAID, non-steroidal anti-inflammatory drug; PG, prostaglandin; TBS, Tris buffered saline

clinically according to the Child-Pugh classification.¹³ All patients had a grade B score: this scoring depended on the presence or absence of ascites, total bilirubin, and serum albumin, in addition to the degree of encephalopathy and nutritional status of the patients. Patients received no vasoactive drugs (nitrates, β blockers, or antibiotics). None of the patients showed combined liver disease, diabetes, renal disease, arterial hypertension, congestive heart failure, or severe extrahepatic diseases

Pathological examination

We used 15 liver biopsies from patients with cirrhosis whose expression of nitric oxide synthase has been described previously.¹⁴ Informed consent was obtained from all patients whose biopsies were used in our study, after ethical approval by the local committee. Liver sections were stained with haematoxylin and eosin and pathological diagnosis was confirmed by a pathologist (RFTMcM). The presence of active inflammation, cirrhotic nodules, and fibrosis was confirmed. The Ishak necroinflammatory total score¹⁵ and the individual interface (A), lobular (C), and portal (D) components were assessed, and the Ishak fibrosis stage was confirmed as either 5 or 6. None of the cases had evidence of active schistosomiasis. Three liver biopsies with normal liver histology, from the histopathology department, Manchester Royal Infirmary, taken during cholecystectomy, were used as controls.

Immunohistochemistry

Paraffin wax embedded liver biopsies were used. Sections (5 μ m thick) were cut on to poly-L-lysine coated slides. Sections were dewaxed and antigen retrieval was performed by adding 0.1% trypsin (Sigma; Poole, Dorset, UK) in calcium chloride to the section for one hour at 37°C. The slides were then processed for immunohistochemistry. Before immunolabelling, endogenous peroxidases were quenched by treatment with 0.5% H₂O₂ in methanol, with subsequent washing in Tris buffered saline (TBS; 0.7% Tris HCl, 0.2% Tris base, 0.02% NaCl, 1% Triton \times 100). Non-specific binding of IgG was blocked using normal goat serum diluted 1/50 in 0.1% bovine serum albumin in TBS for one hour. The sections were incubated with 1/200 (COX-2) and 1/500 (COX-1) diluted primary antibodies (polyclonal rabbit anti-COX-2 and anti-COX-1 (Cayman, Ann Arbor, Michigan, USA)) at 4°C overnight, washed, and incubated for a further 60 minutes with biotinylated secondary antibodies (goat antirabbit; Vector Laboratories, Burlingame, California, USA; diluted 1/500). After incubation for a further 60 minutes with the Vectastain ABC kit, the substrate, diaminobenzidine tetrahydrochloride (Sigma), was added for 10 minutes. Positive cells were labelled brown. For the negative control, the primary antibodies were replaced with normal goat serum (the host species used to raise the secondary antibody). Haematoxylin was used as a counterstain to show the nuclei.

RESULTS

COX-2 expression was not seen in the control livers (fig 1A). The expression of COX-2 was greatly upregulated in cirrhotic liver (fig 1B–F), where it was localised in inflammatory cells infiltrating the liver (fig 1B), mainly mononuclear-like cells (fig 1D), vascular endothelial lining cells (fig 1C), Kupffer cells seen in sinusoidal spaces (fig 1E), and the epithelial lining of bile ducts (fig 1F). COX-2 was expressed only in the cytoplasmic compartment of the positive cells. It was completely absent from hepatocytes.

COX-1 was seen in normal (fig 2A) and in cirrhotic livers (fig 2B,C). It was mainly expressed in Kupffer cells and vascular endothelial lining cells (fig 2A,B). There was no

significant difference in COX-1 expression between normal and cirrhotic livers.

The negative control, in which the primary antibody was replaced by normal serum from the host species used to raise the secondary antibody, showed complete absence of staining (fig 2D), indicating the high specificity of the antibodies used.

DISCUSSION

In our study, we have shown that COX-1 is expressed both in normal and cirrhotic livers. In contrast, COX-2 was not seen in normal liver, but showed de novo synthesis and pronounced upregulation in liver cirrhosis. This induction of COX-2 may be the result of active inflammation in cirrhosis, secondary to hepatitis. Interestingly, high COX-2 expression has been reported to be highly correlated with the degree of inflammation¹⁶ and the development of fibrosis.¹⁷ This is reasonable, considering the fundamental action of COX-2 as a mediator of inflammation. In liver cirrhosis, the induction of COX-2 is probably multifactorial. The ischaemic environment in liver cirrhosis¹⁸ could be one of the inducers of COX-2 because there is evidence that ischaemia and hypoxia can induce COX-2.¹⁹ Moreover, COX-2 may be induced in the liver by growth factors.^{2–5} Endotoxins are also major inducers of COX-2. Dinchuk *et al* showed that COX-2 mediates endotoxin induced liver injury in COX-2 deficient mice.²⁰ There is direct interaction between Kupffer cells and endotoxins that are removed from the circulation primarily by Kupffer cells, which subsequently become activated and increase prostaglandin synthesis.^{21–23} This may imply a role for endotoxins in the induction of COX-2 in cirrhosis.

Many of the known biological effects of PGs are mediated through their interaction with specific receptors. PGs are the key mediators of cell signalling between Kupffer cells and hepatocytes.^{24–25} They act on receptors on hepatocytes, increasing triglyceride synthesis and accumulation in liver. This was confirmed by the finding that COX inhibition reduces hepatic lipid accumulation.²⁶ In a study of rat liver, Suzuki-Yamamoto *et al* demonstrated COX-1 staining in hepatic endothelial cells,²⁷ whereas Yasojima *et al* revealed COX-1 and COX-2 expression by measuring both mRNA and protein,²⁸ with more COX-1 than COX-2 in human livers from patients with brain diseases, including Alzheimer's disease.

“This induction of COX-2 may be the result of active inflammation in cirrhosis, secondary to hepatitis”

There is thought to be a link between hepatitis and liver cirrhosis and the development of hepatocellular carcinoma

Take home messages

- The expression of COX-2 is increased in liver cirrhosis, and possibly contributes to prostaglandin overproduction—which may be a major component of the inflammation and hyperdynamic circulation associated with cirrhosis
- COX-2 is thought to contribute to tumour development, so that high COX-2 production might be important in the development of hepatocellular carcinoma (HCC) in cirrhosis
- Because COX-2 but not COX-1 is upregulated in cirrhosis, selective COX-2 inhibitors might be useful in reducing inflammation and minimising the occurrence of HCC in patients with cirrhosis

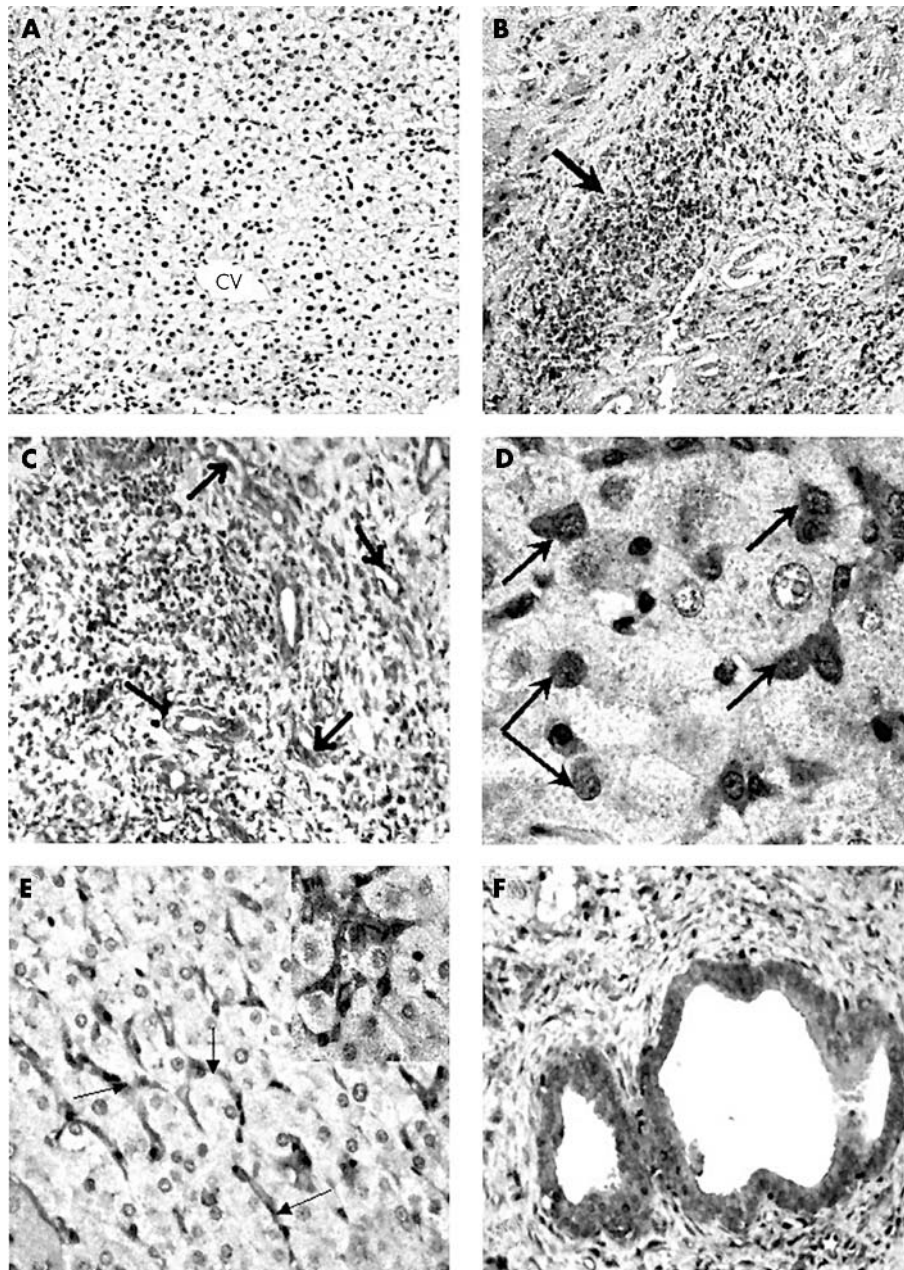


Figure 1 Immunoperoxidase showing COX-2 expression in (A) normal and (B–F) cirrhotic liver samples. (A) Normal human liver showing complete absence of COX-2 immunoreactivity. CV, central (terminal hepatic) vein region; original magnification, $\times 10$. (B) A cirrhotic liver showing infiltration with inflammatory cells, which show dense COX-2 immunoreactivity (arrow); original magnification, $\times 25$. (C) Large number of blood vessels seen in a cirrhotic liver showing COX-2 expression (arrows); original magnification, $\times 50$. (D) Macrophage-like cells (arrows) infiltrating between hepatocytes show high COX-2 immunoreactivity; original magnification, $\times 100$. (E) COX-2 immunoreactivity is seen in sinusoidal cells (arrows) in cirrhotic liver. The COX-2 positive sinusoidal cells are seen surrounding negatively stained hepatocytes; original magnification, $\times 50$. (F) A liver cirrhosis sample showing COX-2 expression in the epithelial lining of bile ducts; original magnification, $\times 100$.

(HCC) because liver cirrhosis is seen in up to 90% of patients with HCC.²⁹ High COX-2 expression was found in various types of carcinoma including HCC.^{30–31} Kondo *et al* looked at the expression of COX-2 in HCC and non-tumorous tissue by immunohistochemistry using the same antibody as that used in our study.¹⁶ Expression was greatest in established cirrhosis compared with normal and non-cirrhotic liver, and was also greater than in dysplastic nodules and HCC. It was also suggested that COX-2 could play a role in the relapse of HCC. Morinaga *et al* have shown COX-2 overexpression in non-tumorous liver compared with HCC and demonstrated a correlation with the histological activity index, transaminase values, and proliferative activity,³² suggesting that COX-2 is related to the background necroinflammatory and regenerative activity. It has been suggested that COX is a carcinogenic agent and COX inhibitors (NSAIDs) were found to have anti-tumour activities.^{33–34} In an animal model, selective COX-2 inhibitors prevented carcinogenesis by the induction of apoptosis in tumour cells.^{35–36} Moreover, PGs have a vasodilatory

action³⁷ and COX-2 facilitates angiogenesis via the enhanced release of angiogenic growth factors, such as vascular endothelial growth factor,³⁸ which was found to be increased in cirrhosis.³⁹ Therefore, COX-2 may play a role in the vasodilatation and angiogenesis associated with hepatocellular disease. Thus, in liver cirrhosis, COX-2 could contribute to the pathogenesis of HCC by increasing necroinflammatory activity and promoting proliferation,³² enhancing angiogenesis,³⁹ and inhibiting apoptosis.^{40–42}

In human liver cirrhosis and carbon tetrachloride (CCl₄) induced liver cirrhosis in rats, there is increased renal synthesis of vasodilator PGs, which counteract the actions of endogenous vasoconstrictors such as angiotensin II, norepinephrine, and antidiuretic hormone on the renal vascular and tubular systems.⁴³ Therefore, administration of NSAIDs in cirrhosis could induce renal failure by inhibiting renal COX and blocking PG synthesis. Interestingly, NSAIDs suppressed cirrhosis and subsequent malignant transformation in an animal model.⁴⁴ However, these drugs are not

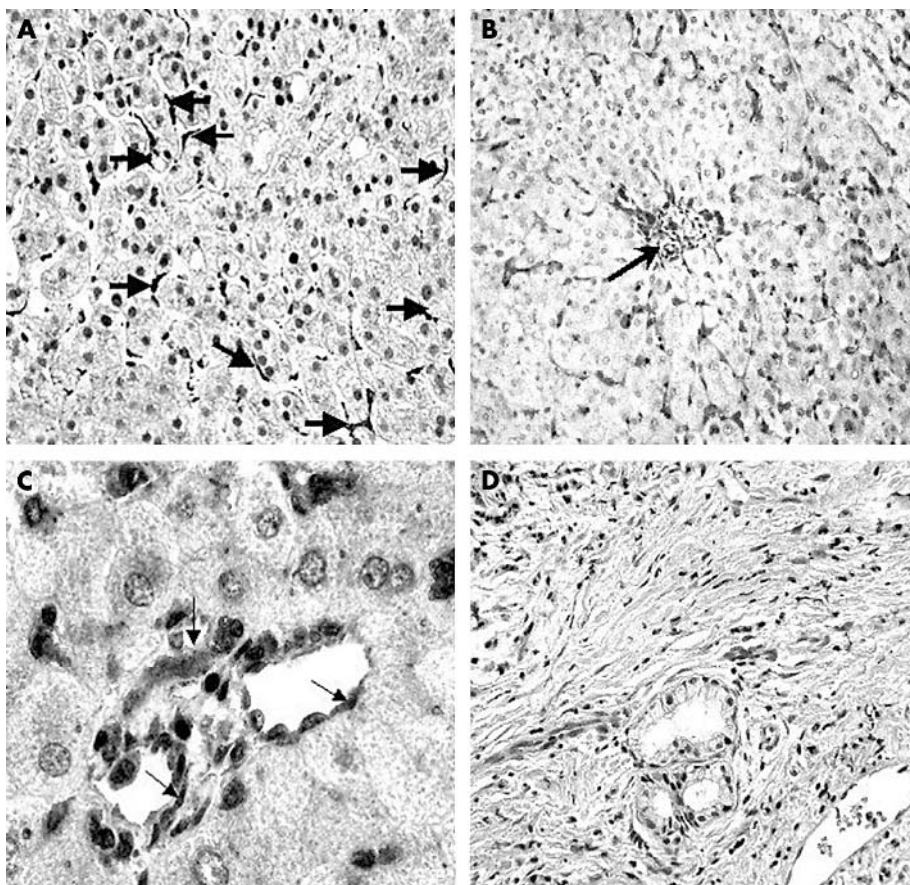


Figure 2 Immunoperoxidase staining showing COX-1 distribution in (A) normal liver and (B,C) human cirrhotic liver. (A) COX-1 is seen in normal liver, localised in the sinusoidal cells (arrows); original magnification, $\times 50$. (B) In cirrhotic liver, COX-1 immunoreactivity is seen in the perivenular region (arrow) and in sinusoidal cells extending from the terminal hepatic vein; original magnification, $\times 25$. (C) COX-1 is localised to the endothelial lining of two blood vessels seen in cirrhotic liver (arrows), with no expression in hepatocytes; original magnification, $\times 100$. (D) A negative control in which the primary antibodies (COX-1 and COX-2) were omitted from the staining procedure, showing complete absence of staining and indicating the high specificity of the antibody used in our study; original magnification, $\times 50$.

recommended in patients with liver cirrhosis because of the renal side effects. This limitation could be overcome by the recent findings concerning selective COX-2 inhibitors and their possible use in some human diseases.² Recently, it has been shown that selective COX-2 inhibitors did not impair renal function in a rat model of liver cirrhosis.⁴⁵ This suggests that effective treatment by selective COX-2 inhibitors may be possible and confirms that the maintenance of renal function is attributed mainly to PGs derived from COX-1.⁴⁵ Therefore, the fact that the main source of COX in liver cirrhosis is COX-2, with little contribution from COX-1, suggests that the use of selective COX-2 inhibitors in these patients may help to reduce inflammation and provide a potential preventive measure for malignant transformation.

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This study was presented to the British Society of Gastroenterology at Birmingham in March 2002 and has been published in abstract form (*Gut* 2002;50suppl II:A31).

Sadly, Dr N A Mohammed has died since this paper was written.

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Lymphadenoma of the salivary gland: a rare tumour

Lymphadenoma of the salivary gland is a very rare (or possibly even under-reported) tumour with only sparse reports found in the literature. It is not mentioned in most textbooks on salivary gland tumours or head and neck pathology.^{1–3} The 1996 Armed Forces Institute of Pathology fascicle briefly discusses the entity as a variant of sebaceous lymphadenoma ("lymphadenoma that lacks sebaceous differentiation").⁴ We report a case of lymphadenoma arising from the parotid gland.

A 74 year old man presented with a solitary mass in his parotid gland. A computed tomography scan suggested the possibility of pleomorphic adenoma. Fine needle aspiration was subsequently done, raising the possibility of a Warthin's tumour. A superficial parotidectomy was then carried out for a definitive diagnosis, including a small amount of sternocleidomastoid muscle to ensure clearance.

Grossly, the tumour was a well demarcated, solid grey/white mass measuring 1 cm in diameter. Microscopic examination revealed anastomosing islands of epithelial cells within a dense lymphoid stroma (fig 1). A few glandular lumina and cysts containing dense eosinophilic secretions were seen at the periphery of the nodule. No sebaceous glands were identified. There was no evidence of

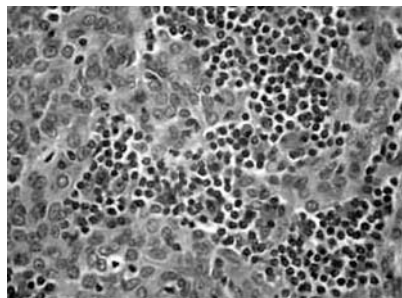


Figure 1 Islands of epithelial cells accompanied by a prominent lymphoid stroma.

cytological atypia or abnormal mitotic activity. On immunohistochemistry the anastomosing cells were positive for epithelial and basal cell markers (epithelial membrane antigen, MNF116, 34BE12, and S100). The absence of sinuses and nodal capsule excluded the possibility of the tumour arising from an intraparotid lymph node.

Ma *et al* in 2002 reported three patients with lymphadenoma of the salivary gland, all males, with ages ranging from 13 to 57 years.⁵ They noted the difficulty of diagnosing this entity, as a result of the indistinct appearance without sebaceous cells. Therefore, other tumours such as Warthin's tumour, lymphoepithelial cysts, sebaceous lymphadenoma, metastatic carcinoma, and malignant lymphoma also need to be considered.^{4,5} Proper recognition of this rare tumour is necessary to avoid confusion in the diagnosis. Our diagnosis in this case was confirmed by Chan, a co-author of the previously mentioned case report. Too few cases have been documented to comment on its behaviour.

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Gastric precancerous lesion follow up based on pathological evidence

We read with interest the article by Dinis-Ribeiro *et al* addressing the follow up of "atrophic chronic gastritis and intestinal metaplasia (IM)".¹ The authors conclude that: (1) "in patients with atrophic chronic gastritis or with type I IM, a three yearly follow up could be suitable"; and (2) "patients with type III IM may benefit from 6–12 monthly (follow up)".

How precancerous lesions are histologically assessed and followed up are fields of our interest and we would raise some methodological concerns about the published study.

In assessing atrophy, it would be advisable to adopt the classification(s) proposed by the current international literature. The original Sydney system was recently revised by a group of specialists in gastrointestinal pathology (including the authors of the original classification), prompting important changes in the previous diagnostic criteria.^{2,3} The new version was also validated by testing its

interobserver consistency. The adoption of such internationally shared criteria facilitates comparisons between studies.

As for the histological classification of dysplasia, the Dinis-Ribeiro study applied the Vienna criteria, which include category 4.3 (suspicious for invasive carcinoma) among the non-invasive neoplasia categories (NiN). From a biological standpoint at least, this category is quite distinct from the NiN categories. Recently, two classifications have been proposed for gastric NiN arising in the stomach; here again, adopting the World Health Organisation criteria would enable an easier comparison between this and other studies.^{4,5}

Finally, the authors report that the two pathologists assessing the slides agreed in 85% of cases; it would have been better to express interobserver consistency properly, in terms of *K* statistics.

To define the "entry biopsy" as "first or intermediate" is a contradiction in terms, which may introduce a bias in the calculation of the follow up time and which influences the validity of the results. The authors state that 144 patients were included in the study and, a few lines later, that 239 pairs of endoscopy biopsies were considered. In view of the fact that they also say that no less than two biopsy samples were taken at each endoscopy, the numbers become bewildering.

In dealing with precancerous lesions, extensive sampling protocols (always including the angular mucosa) are mandatory.^{5,6} To say that "more than 15% of patients had more than four biopsies for each endoscopy" is not satisfactory, either for the patient's safety or for any speculation vis-à-vis the "follow up model"—particularly because the follow up ranged from 3.2 to 36.2 months in 41 of the 144 patients.

An important outcome of the study would be the demonstration that low grade NiN can progress to more severe lesions (invasive or non-invasive?), but the clinical value of this observation is considerably reduced by the short follow up and the difficulty in correlating the number of biopsy samples (239) with the number of patients (144).

On the whole, we found the message emerging from the Dinis-Ribeiro study a valuable contribution to our understanding of the natural history of gastric carcinogenesis. Our critical comments are intended simply as a reminder that caution is needed in recommending follow up protocols unless all the essential conditions can be met to support such recommendations.

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CALENDAR OF EVENTS

Full details of events to be included should be sent to Maggie Butler, Technical Editor JCP, The Cedars, 36 Queen Street, Castle Hedingham, Essex CO9 3HA, UK; email: maggie.butler2@btopenworld.com

ACP Management Course for Pathologists, 2004

8–10 September 2004, Hardwick Hall Hotel, Sedgefield, County Durham, UK

Further details: V Wood, ACP Central Office, 189 Dyke Road, Hove, East Sussex BN3 1TL, UK. (Tel: +44 (0) 1273 775700; Fax: +44 (0) 1273 773303; Email: Jacqui@pathologists.org.uk)

Combined Adult and Congenital Cardiovascular Pathology Course

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11–15 December 2004, New Delhi, India

Further details: Dr V Malhotra (General Secretary) or Dr P Sakhuja (Treasurer and Pathology Coordinator), Room 325, Academic Block, Department of Pathology, GB Pant Hospital, New Delhi 110002, India. (Tel: +91 11

23237455; Email: welcome@apaslindia2004.com; Website: www.apaslinzdia2004.com)

BOOK REVIEW

Medical Microbiology

Edited by C H Collins, P M Lyme, J M Grange, *et al.* Published by Hodder Arnold, 2003, £45.00 (paperback), pp 456. ISBN 0 34080 896 9

If ever asked the question “what are flippers, springers, and hard swells?” in the pub quiz then this book, the eighth edition of a venerated text that first appeared in 1964, is where you should turn for the answers. The new edition has enlisted the help of an American editor and author in a bid to include a North American perspective and, although there are nods in this direction (NCCLS susceptibility testing—for example), this is essentially a text that will appeal to a mostly UK centric audience. The book acknowledges that many microbiology laboratories, clinical or otherwise, still rely to a very great extent on traditional hands on benchwork and the detail in which this type of working is covered has always been this book’s strong point. However, in this new edition one senses a reluctance to bow to change and wave farewell to some old friends. Do we really need to know about the care and maintenance of glass Petri dishes (“still popular in some areas”); does anyone still use Stamp’s method for preserving cultures or the Henry technique in isolating listeria? Nevertheless, the book does cover automated and molecular techniques, but some are given more weight than others—for example, there is an in depth discussion of impedance instrumentation, whereas real time polymerase chain reaction is dealt with in a single paragraph. Diagrams to illustrate the principles behind some less widely known techniques might also have been of value.

The book has never confined itself to methods used by medical microbiologists and has always placed a strong emphasis on techniques used in food, water, and environmental laboratories. This is no bad thing because there is a considerable degree of overlap between the disciplines—clinical laboratories may wish to perform air or environmental sampling when investigating

outbreaks of nosocomial infection—for example, and biomedical scientists and medical microbiologists (especially those in training) would benefit from knowledge of how to assess foodstuffs for microbiological safety. Conversely, however, there are other areas where the clinical and non-clinical disciplines diverge a little too much, and the clinical fraternity is unlikely to find much interest in, for instance, performing spore counts on gelatin used in canned ham production or in sampling vats, hoppers, and pipework. Coverage of non-clinical methods has also encroached on the space devoted to culture and identification of medically important pathogens—methicillin resistant *Staphylococcus aureus* is breezed over in two short paragraphs and reference to glycopeptide resistance in enterococci is restricted to two statements that *Enterococcus casseliflavus* and *Enterococcus gallinarum* manifest low level resistance to vancomycin. Perhaps future editions of the book could have two iterations—one for food/water/environmental microbiologists, with less emphasis on clinical methods, and one for workers in clinical laboratories in which the food and other sections are reined in to a more appropriate level.

Despite these criticisms, there really is much to recommend this book, with handy chapters on laboratory safety, quality assurance, sterilisation and disinfection, enumeration of bacteria, and others, which are relevant to all laboratories. It would certainly be a worthwhile purchase for many laboratories (although not for virology laboratories: the book is a virus free zone), especially those where trainees are to be found. And flippers, springers, and hard swells? They are all types of can deformation produced by gas producing food spoilage organisms.

J R Kerr

CORRECTION

Distribution of constitutive (COX-1) and inducible (COX-2) cyclooxygenase in postviral human liver cirrhosis: a possible role for COX-2 in pathogenesis of liver cirrhosis. Mohammed N A, El-Aleem S A, El-Hafiz H A, *et al.* *J Clin Pathol* 2004;**57**:350–4. The second author’s name should have been Abd El-Aleem S A.

PostScript

CORRESPONDENCE

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Adenocarcinoma arising in villous adenoma of the ampulla of Vater with synchronous malignant gastrointestinal stromal tumour of the duodenum: a case report

An association between ampullary adenoma and adenocarcinoma has been reported previously.¹ However, we believe that this is the first report of the synchronous occurrence of adenocarcinoma of the ampulla of Vater and a gastrointestinal stromal tumour (GIST).

A 41 year old woman was admitted to our hospital for the evaluation of jaundice. Her liver function tests were as follows: alanine aminotransferase, 37 U/litre (normal range, 0-31); aspartate aminotransferase, 32 U/litre

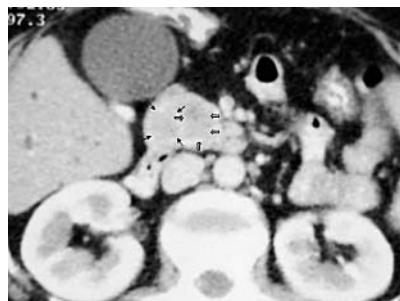


Figure 1 Computed tomography (CT) showed a solid mass, located inferiorly to the pancreatic head and uncinate process. The mass enhanced similarly with pancreatic parenchyma at the early arterial phase. Preoperatively, the mass was interpreted as being located in the pancreatic head. CT images were evaluated retrospectively with the findings at surgery and two different lesions were differentiated (arrows).

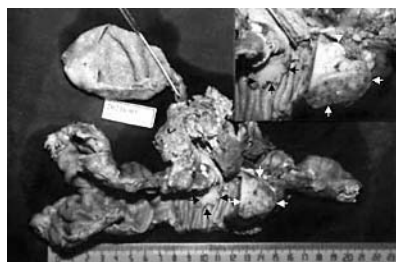


Figure 2 Grossly, a polypoid tumour is located at the duodenal ampulla (black arrows) and another solid subserosal tumour is seen in the second portion of the duodenum (white arrows).

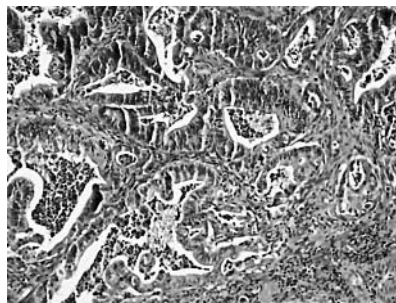


Figure 3 Histological examination of the ampullary tumour revealed moderately differentiated adenocarcinoma; haematoxylin and eosin stain; original magnification, $\times 100$.

(normal range, 0-32); alkaline phosphatase, 598 U/litre (normal range, 0-240); total bilirubin, 203.2 mg/litre (normal range, 1-11); direct bilirubin, 151.6 mg/litre (normal range, 0-3).

Ultrasonography, computed tomography, and magnetic resonance imaging studies showed intrahepatic and extrahepatic bile duct dilatation. Termination of the com-

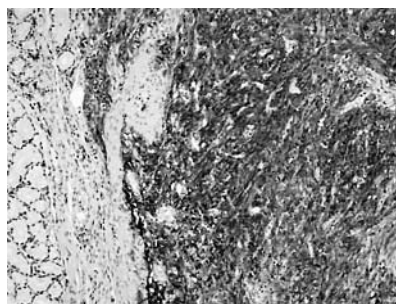


Figure 4 Tumour cells showed a diffuse and strong positive immunoreaction for CD117 in the gastrointestinal stromal tumour; original magnification, $\times 100$.

mon bile duct at the distal end by a mass was noted (fig 1). The initial radiological differential diagnosis included pancreatic head tumour and periampullary carcinoma.

Endoscopic procedures were not performed before surgery. Pancreaticoduodenectomy, cholecystectomy, and distal gastrectomy with lymph node dissection were performed.

Grossly, there was a polypoid tumour (1.5 \times 1.5 \times 1 cm) at the duodenal ampulla with a solid subserosal tumour (3 \times 3 \times 2 cm) in the second portion of the duodenum (fig 2). On cut section, there was no transition between these two different tumours and no invasion of surrounding tissues and pancreas.

Histologically, the tumours showed a moderately differentiated adenocarcinoma associated with a villous adenoma, which was limited to the ampulla of Vater and a GIST (figs 3 and 4). The GIST was sharply demarcated from the surrounding tissue and it was mainly located at the serosa and muscular layers. Cytologically, the tumour cells had spindle shaped, blunt ended or oval nuclei, with evenly distributed chromatin and moderate pleomorphism; the cells exhibited a fascicular or storiform growth pattern, and had invaded the submucosal layer. Nine atypical mitotic figures for each 10 high power fields (HPF) were present. Immunohistochemically, the tumour cells of the GIST showed diffuse and strong positive immunoreactivity against CD117 (T595; 1/20 dilution; Novocastra, Newcastle, UK), CD34 (QBEND/10; 1/50 dilution, Dako, Glostrup, Denmark).

Stromal tumours involving the small intestine are far less common but seem to have greater malignant potential.² The expression of CD117 has emerged as the most important defining feature and probably the gold standard for diagnosing GISTs.² High mitotic index (more than five mitoses/10 HPF) and larger tumour size (> 5 cm) are generally accepted as the best indicators of malignancy in GIST.² Despite the small size of the tumour, nine atypical mitotic figures/10 HPF, submucosal invasion, and mild pleomorphism of the tumour cells were present in our case.

The possible cause of multiple malignancies include: reduced immunological competence, constitution, genetic factors, chemotherapy, radiation exposure, surgery, or smoking.³ In our patient, a family history of malignancy and other risk factors were not present. It can also be hypothesised that the duodenum was influenced by the same unknown carcinogen, resulting in a simultaneous proliferation of different cell lines (epithelial and stromal cells).⁴

The literature includes case reports of gastric collision tumour composed of GIST intermixed with adenocarcinoma, synchronously occurring GIST and carcinoid tumour, GIST and lipoma, and GIST and mucosa associated lymphoid tissue lymphoma.⁴⁻⁵ To our knowledge, our case is the first

report of the synchronous occurrence of adenocarcinoma of the ampulla of Vater with a GIST.

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Intra-abdominal fibromatosis of the jejunum and mesentery

A 24 year old woman presented with a painless abdominal lump of six months' duration. She had no history of colonic polyps. A mobile, non-tender, globular mass was felt in the umbilical region. A

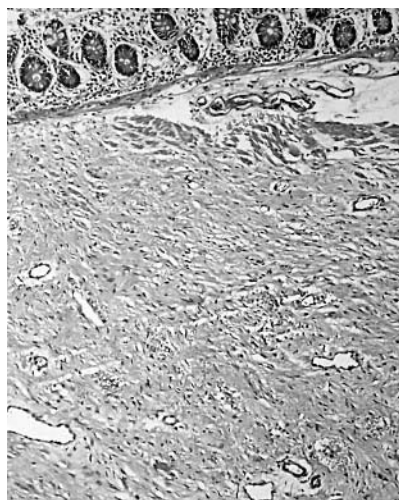


Figure 1 Spindle cell neoplasm infiltrating the muscularis propria of the jejunum.

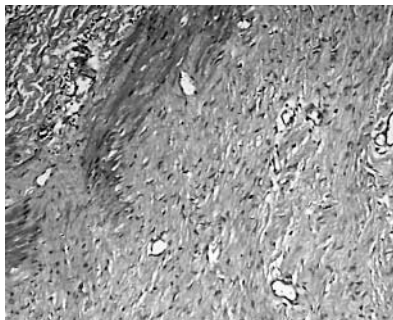


Figure 2 Bland spindle cells and many thin walled vessels forming the neoplasm.

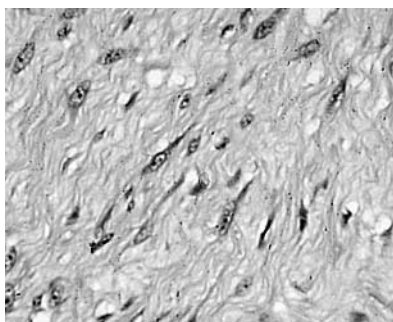


Figure 3 Spindle cells with tapering ends and oval, vesicular nuclei.

computed tomography scan showed a homogenous, non-enhancing mass, possibly arising in the small bowel mesentery.

The tumour was resected entirely with a loop of jejunum. The tumour measured 14 × 12 × 10 cm and was intimately related to the bowel wall. The cut surface was tan, whorled, and firm, without necrosis, cystic change, or haemorrhage. Microscopy showed loosely and haphazardly arranged spindle cells with bland, oval nuclei and minimal cytoplasm (figs 1 and 2). There were also plump spindle cells with tapering ends with oval, vesicular nuclei and moderate amounts of eosinophilic cytoplasm (fig 3).

There were many thin walled vessels of varying calibre (fig 2). There were no cells with epithelioid features, inflammatory cells, calcification, osseous metaplasia, necrosis, or mitoses. The tumour infiltrated the muscularis propria and had infiltrating margins. The tumour cells were negative with antibodies to CD117, S100, CD34, and smooth muscle actin (Dako, St Louis, Missouri, USA; dilutions of 1/200, 1/200, 1/50, and prediluted, respectively) and positive for desmin (Labvision, Fremont, California, USA; 1/200 dilution).

The patient has no evidence of disease 16 months after surgery.

The differential diagnosis of a bland spindle cell tumour involving the gastrointestinal tract and mesentery includes gastrointestinal stromal tumour (GIST), fibromatosis, and inflammatory myofibroblastic tumour.¹ Inflammatory myofibroblastic tumours are more common in children and are characterised by a dense inflammatory cell component among a myofibroblastic proliferation. GIST was considered an unlikely diagnosis because of the whorled

appearance on cut surface; histological evaluation confirmed this. We made a diagnosis of fibromatosis of the jejunum and mesentery.

Intra-abdominal fibromatosis, in its classic presentation, as a mesenteric mass, does not pose a diagnostic problem because of its distinctive gross and microscopic features. However, when it presents primarily as an intestinal wall tumour, the diagnosis of GIST may seriously be considered. Importantly, as many as five of 13 cases of bowel wall fibromatosis in one series had been labelled initially as low grade sarcomas, whereas 13 of 25 in another study mimicked GIST.^{2,3} Distinguishing between the two entities is important because of the different treatment protocols and biological behaviour. GISTs are malignant neoplasms that may be treated by Imatinib mesylate if they are unresectable or if there is a distant metastasis.⁴ They are soft, lobulated, and fleshy on cut surface. Epithelioid cells, skeinoid fibres, mitoses, and necrosis are common.^{1–3} Fibromatosis is a low grade neoplasm that may recur but never metastasises. Recurrence is often related to incomplete excision. Tamoxifen has been used in the management of a recurrent or unresectable tumour.⁵ GISTs usually express CD117 and often CD34 also, whereas fibromatosis is always negative for CD34 and may or may not express CD117.^{1–3} However, fibromatosis is essentially a haematoxylin and eosin diagnosis. The gross appearance—that is, a fibrous mass without necrosis or haemorrhage—gives a clue to the diagnosis.

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CORRECTION

Distribution of constitutive (COX-1) and inducible (COX-2) cyclooxygenase in postviral human liver cirrhosis. N A Mohammed, S A El-Aleem, H A El-Hafiz, et al. *J Clin Pathol* 2004;**57**:350–4. The second author's name should have been S A Abd El-Aleem.

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BOOK REVIEWS

Zoonoses: infectious diseases transmissible from animals to humans

Edited by H Krauss, A Weber, M Appel, et al. Published by ASM Press, 2003, \$79.95 (paperback). ISBN 1 55581 236 8

We are constantly being bombarded with advice on how to ensure that we lead a healthy life—eat less, drink less, and take more exercise. Reading this book adds to this litany in that we are exhorted not to crack chestnuts with our teeth, to avoid eating ants and, of course, not to apply raw chopped frogs to our wounds if fasciolopsiasis, dicrocoeliasis, and sparganosis, respectively, are to be avoided.

Despite their acknowledged importance, zoonoses are often tucked away at the end

of standard infectious disease textbooks almost as an afterthought, and there have been few texts devoted exclusively to this group of infections. This book, the English language version of the third edition of a book originally published in Germany, is intended to redress the balance. The quality of translation is very good and there are only occasional reminders as to the book's provenance—for example, we are told that the main means of transmission of many zoonotic pathogens is through “smear infection”.

The authors take an essentially organism based approach to the topic, with descriptions of the epidemiology, clinical manifestations, diagnosis, management, and prevention of each infection. Given the sheer number of zoonoses, this means that space that could have been devoted to a more in depth discussion of the major zoonoses is taken up with sections dealing with spectacularly rare conditions, such as lagochilascariasis. Furthermore, several conditions, which have questionable zoonotic origin—such as pneumocystosis—are considered, sometimes at length.

Although the book is crammed with painstakingly collected information, it is still not clear to me how the book is intended to be used. Although the A–Z compendium of common and not so common infections is useful, many potential readers would have appreciated at least one chapter that adopted a more syndromic approach to the patient with unexplained fever. Moreover, a more in depth discussion of the problems in treating zoonoses arising from antimicrobial resistance would have been beneficial. Similarly, clinicians and jobbing diagnostic laboratory workers are unlikely to find page after page of polymerase chain reaction primers for the reverse transcription polymerase chain reaction of oropouche, colti, and other viruses of much value. These are more the province of the research or reference laboratories, which will turn to the primary literature for this information. Those who like textbooks to take a view of the subject in the round might also have appreciated a section dealing with the epidemiology of zoonoses and the profound influence that the climatic, geopolitical, and socioeconomic changes of the last 50 years has had, and will continue to have, on our risks of acquiring these infections.

Nevertheless, this book would be a worthwhile purchase for any departmental library and would be a useful reference for pathologists and clinicians alike. Chopped frog vendors, however, may beg to differ.

K Kerr

Histopathology Specimens: Clinical, Pathological and Laboratory Aspects

Authored by D C Allen, R I Cameron. Published by Springer, 2004, pp 518. ISBN 1 85233 740 0

When reviewing a book of this nature it is difficult to be critical because there are several different methods of specimen handling and processing. The method used is often dependent on personal preference and accepted protocols in individual laboratories. As the authors state in the preface, there is no one correct method; however, irrespective of the method used, maximum information must be obtained from the macroscopic and microscopic examination.

In an era where great importance is placed on the information obtained from macroscopic examination of the specimen and optimal processing of tissue for histological examination, a book to guide pathologists is welcome.

This book covers specimens from 11 anatomical regions, each including numerous specific sites and one miscellaneous section. Each section covers anatomy (including lymphovascular supply, where applicable), clinical presentation, clinical investigations, pathological conditions (both non-neoplastic and neoplastic), clinical aspects of surgical pathology specimens, and laboratory aspects of surgical pathology specimens. The sections on laboratory aspects of surgical pathology specimens provide extensive coverage of specimen types, points to consider in the description of specimens, appropriate selection of blocks, and the essentials of an adequate histopathology report. The last chapter on miscellaneous specimens and ancillary techniques discusses needle core biopsies, fine needle aspirations, cytospin and liquid based cytology, specimen photography, specimen radiography, frozen sections, immunohistochemistry, flow cytometry, in situ hybridisation, electron microscopy, cytogenetics, molecular genetics, and proteomics.

Although there are references to fixatives in specific sections, future editions would benefit by the inclusion of sections on fixatives and optimal fixation, decalcification of specimens, lymph node identifying fluids, and transport media for immunofluorescence biopsies.

The authors intended to provide a book based on their current practice protocols “to educate and better equip all those involved in the histopathology specimen process”, and this they have achieved.

D Govender