Paris staging system for primary gastrointestinal lymphomas

Currently, much effort is put into the development of specific therapeutic approaches that are tailored to specific lymphoma entities. As a consequence, more specific information needs to be collected to support the choice of therapy. In gastric marginal zone B cell lymphoma of MALT-type, the need for specific staging is evident. With new techniques such as endosonography, this infiltration depth can be assessed with improving accuracy. However, the information cannot be translated into the current staging systems. The dissemination patterns of extranodal lymphomas are also essentially different from primary nodal lymphomas. As tumour stage is one of the most important guidelines in the choice of local therapy (surgery, radiotherapy) and chemotherapy, adequate documentation of tumour localisation in the organ related lymph nodes and beyond is essential.

The Ann Arbor staging system, developed for and routinely used in nodal non-Hodgkin’s lymphoma, is not optimal for documentation of the specific relevant features of primary extranodal lymphoma in the gastrointestinal tract. Several modifications and alternatives have been proposed. However, neither differentiation of stage I (confinement of lymphoma to the mucosa and submucosa) from stage I (tumour extension beyond the submucosa according to Radaszkiewicz and colleagues') nor discrimination of tumour localisation in the organ related lymph nodes and beyond is essential.

The Lugano classification was constructed by Roitber and colleagues' introducing stage IIIE for “serosa penetration” without lymph node involvement into the Ann Arbor system. This represents a change in meaning of stage II that originally indicated lymph node involvement. Therefore, the Lugano system is causing more confusion than benefit.

Table 1 Paris staging system for primary gastrointestinal lymphomas

<table>
<thead>
<tr>
<th>Code</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Lymphoma extent not specified</td>
</tr>
<tr>
<td>TO</td>
<td>No evidence of lymphoma</td>
</tr>
<tr>
<td>T1</td>
<td>Lymphoma confined to the mucosa/submucosa</td>
</tr>
<tr>
<td>T1m</td>
<td>Lymphoma confined to mucosa</td>
</tr>
<tr>
<td>T1sm</td>
<td>Lymphoma confined to submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Lymphoma involves muscularis propria or subserosa</td>
</tr>
<tr>
<td>T3</td>
<td>Lymphoma penetrates serosa (visceral peritoneum) without invasion of adjacent structures</td>
</tr>
<tr>
<td>T4</td>
<td>Lymphoma invades adjacent structures or organs</td>
</tr>
<tr>
<td>N0</td>
<td>No evidence of lymph node involvement</td>
</tr>
<tr>
<td>N1</td>
<td>Involvement of lymph nodes not assessed</td>
</tr>
<tr>
<td>N2</td>
<td>Involvement of lymph nodes not assessed</td>
</tr>
<tr>
<td>N3</td>
<td>Spread to extra-abdominal lymph nodes</td>
</tr>
<tr>
<td>M0</td>
<td>No evidence of extranodal dissemination</td>
</tr>
<tr>
<td>M1</td>
<td>Non-continuous involvement of separate site in gastrointestinal tract (eg, stomach and rectum)</td>
</tr>
<tr>
<td>M2</td>
<td>Non-continuous involvement of other tissues (eg, peritoneum, pleura)</td>
</tr>
<tr>
<td>BX</td>
<td>Involvement of bone marrow not assessed</td>
</tr>
<tr>
<td>B0</td>
<td>No evidence of bone marrow involvement</td>
</tr>
<tr>
<td>B1</td>
<td>Lymphomatous infiltration of bone marrow</td>
</tr>
<tr>
<td>pTNM</td>
<td>Clinical staging: status of tumour, node, metastasis, bone marrow</td>
</tr>
<tr>
<td>pN</td>
<td>Histopathological staging: status of nodal involvement</td>
</tr>
<tr>
<td>pM</td>
<td>The histological examination will ordinarily include 6 or more lymph nodes</td>
</tr>
</tbody>
</table>

*Valid for lymphomas originating from the gastro-oesophageal junction to the anus (as defined by identical histomorphological structure).

†Anatomical designation of lymph nodes as "regional" according to site:
(a) stomach: peri gastric nodes and those located along the ramifications of the coeliac artery (that is, left gastric artery, common hepatic artery, splenic artery) in accordance with compartments I and II of the Japanese Research Society for Gastric Cancer (1995);
(b) duodenum: pancreaticoduodenal, pyloric, hepatic, and superior mesenteric nodes;
(c) jejunum/ileum: mesenteric nodes and, for the terminal ileum only, the ileocolic as well as the posterior caecal nodes;
(d) colorectum: periocolic and perirectal nodes and those located along the ileocolic, right, middle, and left colic, inferior mesenteric, superior rectal, and internal iliac arteries.

As tumour stage is one of the most important guidelines in the choice of local therapy (surgery, radiotherapy) and chemotherapy, adequate documentation of tumour localisation in the organ related lymph nodes and beyond is essential.
A new case for CA19.9 elevation: heavy tea consumption

Serum carbohydrate associated antigen (CA19.9) is a reliable tumour marker of biliopancreatic malignancies. A number of benign diseases are also known to be related to CA19.9 elevation. Here we report a case of markedly raised levels of CA19.9 associated with heavy tea consumption.

Case report

A 52 year old woman was referred to our unit for epigastric pain and anorexia of two months’ duration. She also complained of nausea and a 2 kg weight loss. Her past medical history was unremarkable. She was a non-smoker and denied alcohol abuse or medication intake but remarked on overconsumption of warm black tea for several months (1.5–2 litres/day). Physical examination was normal.

Laboratory data demonstrated normal ranges for electrolytes, liver function tests, blood count, urea, creatinin, C reactive protein, amylase, and lipase. Fasting blood glucose, triglycerides, cholesterol, and thyroid function tests were normal. Autoantibodies were negative. Serum CA19.9 was 1432 U/ml (normal <37), and CEA was 2 ng/ml (normal <5).

Upper endoscopy, colonoscopy, and barium scan of the small bowel showed normal results. Abdominal ultrasonography and computed tomography scan found mild enlargement of the body of the pancreas without hepatobiliary abnormalities. Endoscopic ultrasonography showed no pancreatic malignancy or biliary abnormalities. The pancreas was homogenous and mildly enlarged in the body without pathological significance.

Spirometry, chest x ray, bronchoscopy, and bronchoalveolar lavage fluid examination were normal.

The patient was advised to stop tea consumption. Four weeks later she became symptom free and gained the 2 kg weight loss. Another serum CA19.9 assay showed a considerable drop in levels to 42 U/ml. A rechallenge test was then attempted. The patient restarted tea consumption as previously. Four weeks later, CA19.9 increased to 745 U/ml followed by a fall to 25 U/ml one month after withdrawal. Follow up one year later revealed no clinical abnormalities. Abdominal and chest computed tomography scan were normal.

Discussion

CA 19.9 is a monoclonal antibody against blood group substance b. It is present on normal biliary epithelium and is not expressed on normal hepatocytes. Other benign causes of CA19.9 elevation are shown in table 1. The common underlying mechanism for each is probably inflammatory hypersecretion of CA19.9 by normal epithelial cells.

To our knowledge, this is the first reported case of markedly raised levels of CA19.9 associated with heavy tea consumption. The mechanism of this relation remains unclear. In addition, the epithelial tissue target involved in CA19.9 secretion by tea overuse is unknown. Individual susceptibility to abnormal CA19.9 secretion triggered by tea overconsumption could not be excluded.

Table 1 Non-malignant causes of CA19.9 elevation (medline research)

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Mild elevation (&lt;200 U/ml)</th>
<th>High levels (&gt;1000 U/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive jaundice**</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acute liver failure and acute hepatitis**</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chronic liver disease**</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Alcoholic liver disease**</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Non-alcoholic liver disease**</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acute**</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chronic**</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Diabetes mellitus**</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Intestinal pulmonary disease**</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Collagen vascular diseases**</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Anecdotally reported: hydrenephrosis, endometriosis, splenic cyst, cholangiocyst, sigmoid diverticulitis, and hypothyroidism.

References


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References

Closely resembles syndrome X. Non-alcoholic steatohepatitis (NASH) may be associated with symptoms of syndrome X, including insulin resistance, hepatic steatosis, and a history of liver disease. Carbohydrate 19-9 antigen is a marker for non-malignant hepatocellular carcinoma. Transient hepatic inflammation was associated with transient hepatic inflammation. Serum levels of inflammation of the literature are not available.

Non-alcoholic steatohepatitis and hepatic steatosis in patients with adult onset growth hormone deficiency

Adult onset growth hormone (GH) deficiency closely resembles syndrome X. Patients with syndrome X often suffer from obesity, dyslipidemia, insulin resistance, and hypertension, and hepatic steatosis and non-alcoholic steatohepatitis (NASH) have also been characterised as symptoms of syndrome X. However, the relationship of GH deficiency to hepatic steatosis and NASH remains unclear.

We looked for the presence of hepatic steatosis using computer tomography (CT) in a study of 18 patients with adult onset anterior lobe pituitary hormone deficiency, with or without GH deficiency. We also performed a liver biopsy in one patient with adult onset GH deficiency. None of the patients was positive for hepatitis B surface antigen, hepatitis C virus antibody, antinuclear antibody, or antimitochondrial antibody. The criterion used for diagnosing hepatic steatosis was a ratio for liver/spleen CT value of less than 0.9. In 13 patients with GH deficiency, seven showed hepatic steatosis (53.8%) while in five patients without GH deficiency no hepatic steatosis was present (p=0.035). Body mass index (BMI kg/m²), serum triglyceride level (TG mg/dl), and serum total cholesterol (T-ch mg/dl) were similar in patients with or without GH deficiency (table 1). The significance of the hepatic steatosis was evaluated by χ² test. BMI, TG, and T-ch were analysed using an unpaired Students t-test. The male patient on whom we performed a liver biopsy was diagnosed with GH deficiency at 58 years old. He showed hepatic steatosis, measured by CT, at 64 years. Serum aspartate aminotransferase level fluctuated from 20 to 80 U/l. The patient did not have a history of alcohol abuse but was slightly obese (BMI 20 kg/m²). Liver biopsy was performed when the patient was 72 years old and this showed the presence of NASH (fig 1).

We have demonstrated that hepatic steatosis is more frequently observed in patients with GH deficiency than in those without GH deficiency. Furthermore, by liver biopsy, we have shown that a patient with GH deficiency also had NASH. These results indicate that adult onset GH deficiency is a possible risk factor for hepatic steatosis and NASH.

Table 1

<table>
<thead>
<tr>
<th>Hepatic steatosis (+/-)</th>
<th>Without GH deficiency</th>
<th>With GH deficiency</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>21.29(1.2)</td>
<td>23.54(2.21)</td>
<td>0.35</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>135.8 (25)</td>
<td>95.4 (10)</td>
<td>0.30</td>
</tr>
<tr>
<td>T-ch (mg/dl)</td>
<td>202.5 (18)</td>
<td>180 (6.0)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Values are mean (SD). BMI, body mass index; TG, serum triglyceride level; T-ch, serum total cholesterol.

Figure 1 Histology of the liver biopsy. Macrophages, pericellular and centrilobular fibrosis, and ballooned hepatocytes are all observed in this section. [Method: needle biopsy, haematoxylin-eosin staining.]

Expression of thiopurine methyltransferase in South Asians

Azathioprine and its metabolite 6-mercaptopurine (6-MP) are widely used in the treatment of Crohn’s disease, ulcerative colitis, autoimmune hepatitis, and a range of other inflammatory and autoimmune diseases, as well as for prevention of transplant rejection. Thiopurine methyltransferase (TPMT) converts 6-MP to 6-mercaptopurine (6-MP). Deficiency of its expression predisposes treated patients to bone marrow depression; it may also enhance the efficacy of thiopurines by increasing their metabolism to 6-mercaptopurine nucleotides. Previous reports in Caucasians have shown that approximately 0.3% are homozygous and 10% heterozygous deficient in TPMT. One study

References


suggests that the frequency of individuals with the mutant TPMT allele, TPMT*3A, is lower in Southwest Asians than in Caucasians. The mutant allele causes reduced enzyme activity in vitro. However, there are no data on the phenotypic expression of TPMT in South Asian populations.

We have compared expression of TPMT in South Asian and Caucasian patients attending gastroenterology, renal, rheumatology, and dermatology clinics who were being considered for treatment with thiopurines. TPMT activity was assayed by tandem mass spectrometry for 6-methylMP (assays kindly provided by Purine Research Laboratory, Guy’s Hospital, London SE1 9RT, UK). Homozygous deficiency of TPMT was defined as a level <10, heterozygous as 10–25, and normal as >25 pmol/h/mg haemoglobin.

Of 83 Caucasian patients, one (1.3%) was homozygously deficient, 10 (12%) were heterozygous, and 72 (86.7%) had normal expression of TPMT. The corresponding values in 77 South Asian patients were 0.7 (9%), and 70 (91%), respectively.

The prevalence of deficiency of expression of TPMT in South Asian patients resembles that in Caucasians. Use and monitoring of azathioprine and 6-MP should therefore follow similar principles in both ethnic groups.

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References


Fatigue is associated with high circulating leptin levels in chronic hepatitis C.

We read with great interest the recent paper from Piche and colleagues (Gut 2002;51:434–9) relating serum leptin levels to fatigue in chronic hepatitis C patients. On the surface, their observation that serum leptin levels correlate with the fatigue impact scale are very intriguing. However, leptin shows a gender based difference and women have circulating plasma leptin concentrations that are at least 2-fold higher than men, even when matched for body fat mass. Thus sex needs to be considered when investigating any association with leptin levels, and multivariate analysis is necessary to reduce the bias caused by this confounding variable. Indeed, in the study by Piche et al the fatigue impact scale was found to be significantly higher in females, without a multivariate analysis the authors cannot affirm that serum leptin levels are implicated in fatigue development in patients with chronic hepatitis C.

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Mutant K-ras2 in serum

Ryan and colleagues’ careful and well conducted study (Gut 2003;52:101–8) raises once again the interesting issue of whether molecular analysis and knowledge of mutations of the Kirsten ras gene in particular, have a role in the management of patients with colorectal cancer.

The two RASCAL (Kirsten Ras in Colorectal Cancer Collaborative group) studies1,2 which eventually enrolled data from 4266 patients from 42 centres in 21 countries showed that although the frequency of Kirsten ras mutations at codons 12 and 13 may vary a little between populations, overall they are only present in just over one third of patients. This is significantly less frequent than quoted by Ryan et al. In addition, the RASCAL study also showed that Kirsten ras mutations are not associated with sex, age, tumour site, or Duke’s stage.

Much more importantly, however, they also showed that of the 12 different possible specific point mutations at codons 12 or 13, only a guanine to thymidine mutation, which are found in less than 10% of all patients, is an independent variable for relapse and death. Indeed, the most common mutation, guanine to adenine, exerted an effect on survival barely different from wild-type ras. Others have shown there is a reasonable biological basis for these findings and that ras mutations collectively, rather than the mutation is not the same as the primary tumour, this raises many issues, not least that despite the very careful use of controls, nested polymerase chain reaction techniques may be too sensitive for clinical practice.

For an individual with colorectal cancer, a multitude of factors may shape the clinical course. To improve our knowledge, we must seek to study the most subtle variation in molecular profiles possible, as small differences may be very important. While rigorous small prognostic clinical studies may be intriguing, they may have significant limitations. Some of us have argued previously that there is only one way forward. All bodies funding prospective therapeutic studies in colorectal cancer should insist that a panel of molecular markers are measured and recorded in all patients using a standardised technique, even if they are not included as an end point, and make these results readily available for subsequent analysis. Studies in which these markers are performed prospectively carry the least risk of methodological flaws.

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BOOK REVIEW

Radiological Imaging of the Small Intestine


Springer Verlag are producing an extensive range of Radiology books under the general editorship of Professor AL Baert, and this volume on the small intestine is the latest in the line. Professor NC Gourtsoyiannis is its distinguished editor. This is not only a very well established series with topics which vary from organ based (that is, pancreas) to technique based (that is, spiral computed tomography (CT)) of the abdomen. As with all Springer publications, the illustrations are outstanding and the more than 800 in this book are no exception.

Imaging of the small intestine remains the last redoubt for the gastrointestinal radiologist due to the remorseless advance of endoscopy from both ends of the alimentary tract; a point noted in the foreword by Professor Baert. Virtual colonography has rekindled some interest but this is strictly a polyp/tumour detection exercise and the more subtle and interesting colonic abnormalities elude it. Study of the small bowel however retains that interest, both because of the myriad of processes which may affect it as well as those that it is not so easy to initiate the "knee jerk" response of biopsy it. Therefore remains more of a deductive radiological technique. This is also the most recent publication (2002 versus 1999) and in areas where there is rapid technical change—typically MR imaging—the reader can appreciate the difference.

It has to be said that both books fulfill their remit extremely well but for any radiologist with an interest in the gastrointestinal tract the USA will present new ideas and suggestions on pathophysiology, diagnostics, and therapy of liver diseases in ten programmes. Further details: Ms Veronika Rovicka. Tel: +420 241 445 759; fax: +420 241 445 806; email: veronika@congressprague.cz.

8th International Liver Symposium

This symposium will be held on 13 June 2003 in Manchester, UK. Leading speakers from the USA and Europe will present state of the art reviews on recent advances in hepatology. Further details: Professor TW Warnes, Department of Gastroenterology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK. Tel: +44 (0)161 276 4316; fax: +44 (0)161 276 8779; email: judith.harrop@cmcc.nhs.uk.

Falk Symposia—New Findings on Pathogenesis and Progress in Management of IBD

Two symposia and a workshop will be held on 10–14 June 2003 in Berlin, Germany. Further details: Falk Foundation e.V., Congress Division, PO Box 6529, 2800 Reichsburg, 05, 79041 Freiburg/Br, Germany. Tel: +49 761 15 140; fax: +49 761 15 14 359; email: symposia@falkfoundation.de; website: www.falkfoundation.de.

Gastroenterology and Endotheraphy: XXIst European Workshop

This will be held on 16–18 June 2003 in Brussels, Belgium. Further details: Nancy Beaupré, Administrative Secretariat of the Workshop, Gastroenterology Department, Erasme Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 (0)2 555 49 00; fax: +32 (0)2 555 49 01; email: beaupre@ulb.ac.be.

The Association of Coloproctology of Great Britain & Ireland

This annual meeting will be held on 7–10 July 2003 in Edinburgh, UK. Further details: Conference Secretariat, The ACGBI at the Royal College of Surgeons of England, 35–43 Lincoln’s Inn Fields, London WC2A 3PE. Tel: +44 (0)20 7973 0307; fax: +44 (0)20 7430 9235; email: acgbi@asgbi.org.uk; website: www.acgbi.org.uk.

European Helicobacter Study Group (EHSG)

This meeting, on Helicobacter infections and gastroduodenal pathology, will be held on 3–6 September 2003 in Stockholm, Sweden. Further details: Professor Torkel Wadstrom, President- EHSG, Lund University, Department of Infectious Diseases & Medical Microbiology, Division of Bacteriology, Solvegatan 23, SE-223 62 Lund, Sweden. Tel: +46 46 173 241; fax: +46 46 152 364; email: torkel.wadstrom@mmmb.lu.se; website: www.helicobacter.org.
Fatigue is associated with high circulating leptin levels in chronic hepatitis C

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Gut 2003 52: 915
doi: 10.1136/gut.52.6.915

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