PostScript

LETTERS TO THE EDITOR

Another case of serrated adenoma of the stomach

Adenomas of the stomach are histologically classified into tubular, villous and mixed (tubulovillous) adenoma. In the literature, in two previous studies, only six cases of serrated adenoma of the stomach have been reported. In this communication, we report a newly identified case. The patient presented with gastric complaints. The endoscopic examination showed a pediculated protruding tumour localised in the gastric corpus. Biopsies were reported as tubular adenoma with high-grade dysplasia. A surgical local excision of the tumour was performed. The histological examination revealed elongated fronds with lateral crenated, saw-tooth-like notches as a result of scalloped epithelial indentations. Areas with high grade dysplasia but without invasive carcinoma were demonstrated. This seems to be the first case of serrated adenoma localised in the gastric corpus in the literature.

Rubio¹ reported the first case of serrated adenoma of the stomach (cardia) in the literature. Since then, five additional cases in the cardia have been described by the same author.² In this report, we describe the first case of serrated adenoma localised in the gastric corpus.

The patient was an otherwise healthy woman in her 50s. For the preceding 2 years, she had experienced upper abdominal pain and anorexia.

Barium x ray examination revealed a protruding tumour in the gastric corpus (fig 1). The endoultrasonography showed a pediculated tumour in the greater curvature without infiltration of the gastric wall. Biopsy specimens were reported to have tubular adenoma with high-grade dysplasia.

Owing to the non-infiltration of the gastric wall, the surgeon decided to perform a local excision. After 2 years, the patient is well, without local recurrence or metastasis.

The surgical specimen comprised a tumour, measuring 9 cm, composed of finger-like fronds giving it a shaggy appearance.

Histological examination revealed a lesion composed of elongated fronds with lateral crenation caused by scalloped epithelial indentations. The nuclei covering the serrated glands were irregular and stratified (fig 2). Mitotic figures were increased. No invasive carcinoma could be demonstrated.

Discussion

The World Health Organization classification is the generally accepted histological classification of gastric adenomas of the stomach. It divides them into three subtypes: tubular, villous and tubulovillous. Serrated adenomas have not been found in the above-mentioned classification.

In 2001, Rubio¹ reported one case of serrated adenoma of the cardia. Since then, five additional cases have been found at his department.² Except for these six cases, no other case of serrated adenoma of the stomach has been reported. It is conceivable that, in

other series, similar cases have been classified as villous adenomas. It is possible that this type of lesion is of rare occurrence in the gastric mucosa although, in a span of 2 years, Rubio found four cases.²

The majority of gastric adenomas are localised in the antral region.³ On the other hand, the six serrated adenomas reported by Rubio were localised in the cardia.^{1,2} Our report seems to be the first to describe the case of gastric serrated adenoma localised in the corpus.

Nakamura⁴ found cancerous changes in 15.4% of 911 gastric adenomas. Rubio found that invasive carcinoma was already present at the time of diagnosis in five of six serrated adenomas.^{1,2} Thus, gastric serrated adenomas behave in an aggressive fashion. Rubio thinks that the propensity to evolve into invasive carcinoma seems to depend on size.² However, despite the big size of the tumour, no invasive carcinoma was demonstrated.

In conclusion, serrated adenomas of the stomach seem to have distinct location and morphological features, at variance with other histological adenoma phenotypes. It is possible that this type of lesion is of rare occurrence in the gastric mucosa. But, we think that its frequency is underestimated as similar cases may have been classified as villous adenomas.

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Figure 1 Barium x ray examination of the stomach showing an ulcerated protruding tumour in the gastric corpus.

Figure 2 Lesion showing serrated, indented dysplastic epithelium with stratified nuclei (H&E; original magnification, $\times 250$).

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Paraplegia due to a paravertebral extramedullary haemopoiesis in a patient with polycythaemia vera

In July 1985, a 43-year-old man was found to have polycythaemia vera. The peripheral blood counts were white cell count $14.15 \times 10^9/l$ (neutrophils 80%, lymphocytes 14%, monocytes 5%, eosinophils 1%), haemoglobin concentration 24.8 g/dl, haematocrit 0.7, red cell count $8.15 \times 10^{12}/l$ (neither anisocytosis nor poikilocytosis were observed), platelets $234 \times 10^9/l$. As only the erythroid lineage was affected significantly, he was treated with isovolaemic phlebotomy until April 2004. In May 2004, the patient suddenly developed a spastic paraplegia. Nuclear magnetic resonance imaging showed a posterior extradural tumour extending from T3 to T11 (fig 1A, B). The lesion expanded into the vertebral canal, inducing spinal cord compression. The occurrence of either a second neoplasm or a myeloid sarcoma (rare but possible during the clinical course of polycythaemia vera) was considered in the differential diagnosis. After thoracic laminectomy (from T2 to T11) and removal of the extradural lesion, all the symptoms resolved promptly and completely. A morphological and immunohistochemical analysis was then carried out to establish the diagnosis and to decide on the treatment. The tumour was composed of a heterogeneous cellular population resembling physiological haematopoiesis in all its components (fig 1G). The immunohistochemical analysis showed that the mass was composed of a cellular population resembling that of normal erythropoiesis and granulopoiesis, with cells at all stages of maturation. Glycophorin staining showed the erythroid population

(fig 1C) and myeloperoxidase, and linker of activation of T cells showed cells of the granulocytic series and megakaryoblasts/megakaryocytes (fig 1D, 1E), respectively. The number of blast cells, evaluated by CD34 staining, was not increased ($<5\%$; fig 1F), thus excluding the possibility of myeloid sarcoma with partial maturation.

The occurrence of extramedullary haemopoiesis is well known in cases of primary or secondary myelofibrosis. However, this phenomenon is extremely rare in association with other haematological diseases, such as inherited anaemias (especially thalassaemia) and chronic myeloproliferative disorders without evolution to myelofibrosis. Our case has unique and unexpected features. It should be underlined that immunohistochemistry was essential for a correct diagnosis, particularly for excluding myeloid sarcoma, which would have required intensive postoperative chemotherapy.

At the time of writing, after a follow-up of 13 months, the patient is well, with no neurological signs or symptoms. The peripheral blood counts were white cells $9.76 \times 10^9/l$ (neutrophils 78%, lymphocytes 16%, monocytes 4%, eosinophils 2%), haemoglobin concentration 13.2 g/dl, haematocrit 49.3%, platelets $179 \times 10^9/l$. His current treatment consists of isovolaemic phlebotomy and hydroxycarbamide (hydroxyurea),

Figure 1 The posterior extradural tumour extended from T3 to T11 (A–B). Immunohistochemical analysis demonstrated a cellular population resembling the normal hematopoiesis in all its components (C–G).

given to prevent possible new extramedullary haemopoiesis.

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Obesity-related glomerulopathy: another nail in the coffin of the epidemic of end-stage renal disease

The clustering of insulin resistance, dysglycaemia, dyslipidaemia, hypertension and central obesity represents the major features of metabolic syndrome. These clusters of factors may share common aetiology, each of which is a risk factor for cardiovascular disease. The metabolic syndrome seems to affect between 10% and 25% of adult populations worldwide. Several studies have described the association between metabolic syndrome, and diabetes and cardiovascular disease.¹ Although obesity is often associated with diabetes and hypertension, which are two of the most common risk factors for the development of end-stage renal disease (ESRD), it has been suggested that obesity in itself is an independent risk factor.

The prevalence of obesity-related glomerulopathy (ORG), which may lead to end-stage renal disease, has increased 10-fold over the past 15 years as a consequence of the spread of the obesity epidemic. The increasing prevalence of ESRD, with its associated high annual mortality and rates of cardiovascular complications, is a worldwide problem.² In the US alone, the prevalence of ESRD has more than doubled in the past decade and the population living with ESRD is projected to increase to 650 000 persons by the year 2010, with associated Medicare expenditures of \$28 billion.³ Identifying new and potentially modifiable risk factors for ESRD is critical in order to devise effective, population-based preventive strategies.

Massive obesity has been shown to produce nephrotic syndrome, and it has been reported that proteinuria and segmental glomerulosclerosis can be present in obese patients, even in the absence of diabetes.² In addition, a large-scale study including 6818 renal biopsies from 1986 to 2000 showed a 10-fold increase in renal lesion, such as glomerulomegaly and focal segmental glomerulosclerosis, which were associated with obesity.² ORG was recently defined morphologically as glomerulomegaly with or

without focal segmental glomerulosclerosis. The syndrome constitutes the triad of morbid obesity, marked proteinuria without oedema and normal serum albumin concentration. It can occur in any degree of obesity but is more common in the morbidly obese group—that is, body mass index $>40 \text{ kg/m}^2$. It often presents as proteinuria on urinary dipsticks, followed by the confirmation of gross proteinuria of up to 32 g/dl. ORG should be diagnosed by excluding the presence of hypertension or undetected type 2 diabetic renal diseases.² The pathogenesis is unknown (thought to be due to low renal nitric oxide production) and most of the available information comes from studies in Zucker fa/fa rats which often die from ESRD. These rats are a genetic model of obesity that results from a mutation in the leptin receptor gene.⁴ Homozygous Zucker fa/fa rats exhibit most of the metabolic picture seen in human obesity, including hypercholesterolaemia, hypertriglyceridaemia, hyperinsulinaemia and proteinuria.

Although the condition is said to be benign, a small proportion of patients will progress towards end-stage renal failure requiring replacement therapy, a further addition to the cost. The condition is readily reversible and ameliorated with weight loss, an important consideration in the management of this condition. In association with increasing prevalence of chronic kidney disease, this will inevitably result in increasing proportions of deaths from cardiovascular disease as well as increased prevalence and associated consequences of other complications of chronic kidney disease. A concerted, global initiative is required to deal with the ORG epidemic.

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Osseous metaplasia in ovarian tumours: a case with serous cystadenoma

In a recent paper in the *Journal of Clinical Pathology*, Godbole *et al*¹ reported a case of osseous metaplasia in a benign ovarian cyst in association with cloacal anomaly. These

Figure 1 The cyst wall is lined a single layer of cells and contains abundant osseous tissue. Ovarian stroma is seen on the right part of the picture. Original magnification, $\times 25$.

authors stated that only four published cases with osseous metaplasia in ovarian tumours exist, three in the literature,^{2–4} and the one they presented. The former three cases were associated with papillary serous carcinoma, thecoma and endometrioma in a supernumerary ovary, respectively. According to their data, Godbole *et al* concluded that osseous metaplasia is more common in anatomically abnormal ovarian tissue in women of reproductive age. However, a thorough search we made in the literature revealed that to date, the total number of cases with osseous metaplasia in an ovarian tumour reported in the literature has reached 10,^{1–10} (one of them⁵ was actually added after the report of Godbole *et al*, whereas one more case is described herein).

Our case concerns a 37-year-old woman who was subjected to hysterectomy with the right adnexa, owing to multiple leiomyomas. The right ovary measured 7 cm in diameter, and presented an osseous lesion that was hard in consistency and 3 cm in diameter. Histologic examination, after decalcification, showed a serous cystadenoma with extensive, circumferential osseous metaplasia of its wall (fig 1). The cyst wall was lined by a single layer of flattened or cuboidal cells, whereas the osseous tissue consisted of mature lamellar bone. The ovary was searched thoroughly to exclude the possibility of an underlying teratoma. The rest of the pathology of the present specimen revealed only the aforementioned uterine leiomyomas. This is the first reported case where osseous metaplasia has occurred in a benign ovarian serous cystadenoma.

Bone formation in the ovary, with the exception of developing in the setting of a mature cystic teratoma or a heterologous mixed mesodermal tumour, is exceedingly uncommon. Excluding the previous cases, so far, the ovarian neoplasms most commonly associated with osseous metaplasia are mucinous cystadenomas (three cases),^{6–8} followed by serous cystadenocarcinomas (two cases).^{2,9} A minority only seems to occur in anatomically abnormal ovaries (two cases). The most plausible explanation for bone formation in an ovarian neoplasm is a metaplastic process of the multipotential stromal cell. No prognostic significance has been attributed to this unusual phenomenon.

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Catecholamine and metanephrine excess in intracerebral haemorrhage: revisiting an obscure yet common “pseudophaeochromocytoma”

We prospectively recruited five patients with CT evidence of intracerebral haemorrhage (ICH), having excluded trauma, a history of phaeochromocytoma (PHEO) and sympathomimetics/antihypertensives capable of increasing catecholamines (CATS)/metanephrines (METS). Informed consent was obtained from the next of kin. Plasma METS are superior to plasma CATS, although both are unavailable locally. Urinary CATS/METS, which integrate CATS/

Figure 2 24 h urinary metanephrines (METS; ie, sum of metanephrine and normetanephrine) of five patients with intracerebral haemorrhage. Using a metanephrine cut-off of >8300 nmol/day, patients who exceeded these values would be deemed to have a positive screen for phaeochromocytoma. Pt, patient.

METS secretion and has greater sensitivity than plasma CATS in the absence of PHEO spells, was used.¹ 24 h urinary CATS/METS were sampled on days 1 and 7 and before discharge. Catheterised urine was transferred into bottles containing 10 ml 6 N HCl, and analysed by high-performance liquid chromatography (HPLC)–electrochemical detection. Patients with increases in CATS/METS underwent abdominal CT. ICH volume was estimated from CT. This research was ethically approved by our hospital's institutional review board.

Four of five cases had urinary METS and/or CATS exceeding twice the upper normal limit. On day 1, CATS were not measured for patients 2–4, and METS were not measured for patients 1 and 2 before discharge owing to logistic difficulties. Generally, CATS/METS peaked on day 7, and then declined (figs 1 and 2). On day 7, the average CATS/METS (reference intervals within parentheses) values were as follows: epinephrine 328.8 (9.3–122) nmol/day, norepinephrine 1079.3 (72–505) nmol/day, metanephrine 2075 (264–1729) nmol/day and normetanephrine 7029.8 (480–2424) nmol/day.

Patients 4 and 5 with massive “day 7” total CATS (1070 and 2505 nmol/day, respectively) and METS (10 365 and 12 392 nmol/day, respectively) had normal total CATS (44 and 165 nmol/day, respectively) and METS (2154 and 1189 nmol/day, respectively) when re-evaluated 2 years later.

The PHEO suspects revealed no adrenal/extra-adrenal lesions on abdominal CT and were unlikely to harbour PHEO. All four false

positives (patients 2–5) had larger ICH (cerebral haematoma >25 ml with or without intraventricular extension) requiring extra-ventricular drainage/craniotomy, whereas patient 1 with normal CATS/METS had a basal ganglia haematoma of 11.8 ml treated conservatively.

Syed et al² recently reported (n = 5) that urinary CATS/METS were insignificantly increased perioperatively, a state of profound stress. However, their results cannot be extrapolated to catastrophic stresses of ICH. Currently, there is a dearth of literature on the latter.^{3,4} We confirmed that CATS/METS excess occurs temporarily after ICH, probably from an autonomic storm analogous to sympathetic dysautonomia in traumatic brain injury.⁵ As patient 1 with minimal ICH had normal CATS/METS, the degree of dysautonomia seemed to be proportional to ICH size. The temporal trajectory of increases in CATS/METS provided an evidence-based optimal PHEO screening rationale, unconfounded by ICH and allowed differentiation from PHEO. Among those with increased METS, CATS were below the PHEO diagnostic threshold in patients 2 and 4. As METS are CATS derivatives, we believe the true “CATS peak” occurred before day 7, and could be higher between days 3 and 6.

In conclusion, screening patients with ICH for PHEO is best avoided in the first week and deferred for at least a month, although a PHEO should be excluded when CATS/METS are persistently raised. This has pragmatic implications to the medical community including chemical pathologists, neurosurgeons and endocrinologists.

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Figure 1 24 h urinary total catecholamines (CATS; ie, sum of epinephrine and norepinephrine) of five patients with intracerebral haemorrhage. Using a catecholamine cut-off of >1300 nmol/day, patients who exceeded these values would be deemed to have a positive screen for phaeochromocytoma. Pt, patient.

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Lengthy appendices

It is an established fact that the appendix is attached to the caecum; however, it is a rare occurrence that the appendix matches the caecum and ascending colon in length. The most recent edition of the *Guinness Book of Records* cites the longest appendix to have been removed as measuring 23.5 cm in length¹; the previous record was 21 cm.² It may be assumed that both these aforementioned appendices were acutely inflamed. I present a case that rivals these two appendices in length. I think that the appendix in this case presented which measured at least 22 cm may be one of the longest appendices encountered, at least in recent times. It was an incidental finding at

Figure 1 One of the longest normal appendices incidentally encountered at autopsy.

autopsy in an 80-year-old who died of unrelated causes (fig 1). However, the claims to fame of these three appendices may be both premature and late. Kelly and Hurdon, in their mammoth work *The vermiform appendix and its diseases* published in 1905, cite the case of an appendix measuring 33 cm in length, presented by F Grauer to the North-Western Medical and Surgical Society in 1890.³

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Limitations of transferability of absolute cut-points in non-standardised assays

We read the paper of Matull *et al*¹ on the biochemical markers of acute pancreatitis with much interest. We would, however, like to comment on some aspects that could be misleading.

First, absolute cut-off points as part of diagnosis or risk prediction need to be employed with great care.² This is especially true for enzyme assays such as alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase and amylase. For example, more than 200 methods of activity determination have been described for amylase.³ Amylase analytical methods vary with respect to the type of substrate and substrate concentration, use of auxiliary enzymes as well as assay conditions such as pH, temperature, incubation period and protein concentration.^{3,4}

Accordingly, reference intervals are method dependent, and it could be confusing to imply that values such as 600 or 1000 U/l have certain clinical sensitivities and specificities¹ without mentioning which analytical methods were employed, what the reference intervals were or that the figures will vary between laboratories owing to a lack in assay standardisation.^{2,4} Reference intervals for amylase range from 90–300 U/l (Phadebas, Magle AB,

Lund, Sweden) through 25–115 U/l (Dimension RxL, Dade Behring, Milton Keynes, UK) to 22–89 U/l (Olympus, Clare, Ireland). Not surprisingly, there are large differences between different assays when results from external quality assessment schemes are examined. The difference between the intermethod reference ranges is so significant that they have been flagged up as a clinical governance issue in some hospitals when changing routine clinical chemistry analysers.

The second, unrelated, aspect on which we wished to comment relates to interferences. Significant increase in serum triglyceride concentrations is a recognised interferent in some assays; however, it is unlikely to be an interferent or a competitive interferent in all 220+ amylase assays^{3–5} due to the inherent differences in assay formulation. Most modern amylase assays are not subject to such problems when the triglyceride concentration is <10 mmol/l.

It also needs to be noted that prognostic criteria such as Ranson and Glasgow are also affected by the above transferability limitations. Direct transfer without validation, especially when assays have not been standardised will lead to avoidable errors in diagnosis and assessing prognosis.

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