

Short reports

A renin secreting ovarian steroid cell tumour associated with secondary polycythaemia

M R Stephen, G B M Lindop

Abstract

A 67 year old woman presented with dry skin, facial hair, hoarse voice, and weight gain. She was hypertensive (168/96 mm Hg), her haemoglobin concentration was 19 g/l, and haematocrit was 55.7%. The diagnosis of probable secondary polycythaemia was made. Blood testosterone concentration was 44 nmol/l (normal < 5) and was not suppressed by dexamethasone, suggesting a neoplastic source rather than a pituitary abnormality. Transvaginal ultrasound revealed a hypoechoic solid mass in the left ovary suggestive of a solid ovarian tumour. Hysterectomy and bilateral salpingo-oophorectomy were performed following which testosterone concentration returned to normal. Immunocytochemistry provided evidence of renin synthesis. This is a case of an unusual steroid cell tumour that caused virilisation accompanied by symptoms of secondary polycythaemia presumably as a result of erythropoietin production. This is the second case of a steroid cell tumour with an erythropoietic effect and the first that shows evidence of renin synthesis.

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Keywords: ovarian steroid cell tumour; polycythaemia; renin secretion.

Ovarian steroid cell tumours were first described by Scully in 1979.¹ Steroid cell tumours are now included in the World Health Organisation classification and account for approximately 0.1% of all ovarian neoplasms. Ovarian steroid cell tumours comprise three groups: stromal luteomas, Leydig cell tumours (hilus cell tumours, and Leydig cell tumours non-hilar type), and steroid cell tumours not otherwise specified (NOS). The last group accounts for about 60% of steroid cell tumours.²

Steroid cell tumours NOS are androgenic in about half the cases, oestrogenic in about 10%, and in a few cases there is evidence of a progestogenic effect.^{3,4} There are five reports of cortisol secreting steroid cell tumours causing Cushing's syndrome, and three further cases with increased plasma cortisol concentrations but without Cushing's syndrome.^{3,4} One case

was associated with aldosterone secretion.⁵ To our knowledge, there is a single reported case associated with polycythaemia.⁶ We present a case of a steroid cell tumour NOS that was probably synthesising erythropoietin, renin, and inhibin.

Case report

A 67 year old woman presented with dry skin, facial hair, hoarse voice, and weight gain. Her symptoms had begun two years earlier with loss of her "singing voice". Her vocal cords at that time were normal. She was hypertensive (168/96 mm Hg), her haemoglobin concentration was 190 g/l, and haematocrit was 55.7%. A blood film, other haematological indices, and examination of aspirated bone marrow were normal. The diagnosis of probable secondary polycythaemia was made. Blood urea and electrolytes, in particular serum potassium, were normal as were arterial blood gases, thereby excluding chronic pulmonary disease and renal disease as causes of the secondary polycythaemia. Abdominal ultrasound was also normal. Investigation of her virilisation was initiated.

Blood testosterone concentration was 44 nmol/l (normal < 5) and was not suppressed by dexamethasone. This suggested that a neoplastic source of testosterone secretion was more likely than a pituitary abnormality. Transvaginal ultrasound revealed a hypoechoic solid mass in the left ovary suggestive of a solid ovarian tumour. Hysterectomy and bilateral salpingo-oophorectomy were performed and omental biopsies and peritoneal washings were submitted for pathological examination. Following surgery her testosterone concentrations returned to normal. They remained normal (1.3 nmol/l) at follow up. Haemoglobin was normal at 143 g/l and haematocrit at 44%. She remained mildly hypertensive at 165/110 mm Hg and 150/90 mm Hg on two separate follow up visits.

PATHOLOGICAL FINDINGS

The specimens consisted of a symmetrical normal uterus, both tubes and ovaries, omentum, peritoneal fluid, and peritoneal washings. The uterus and right ovary were unremarkable. The left ovary (60 × 38 × 30 mm) was replaced by a lobulated mass. On section an attenuated capsule surrounded lobules of bright yellow firm

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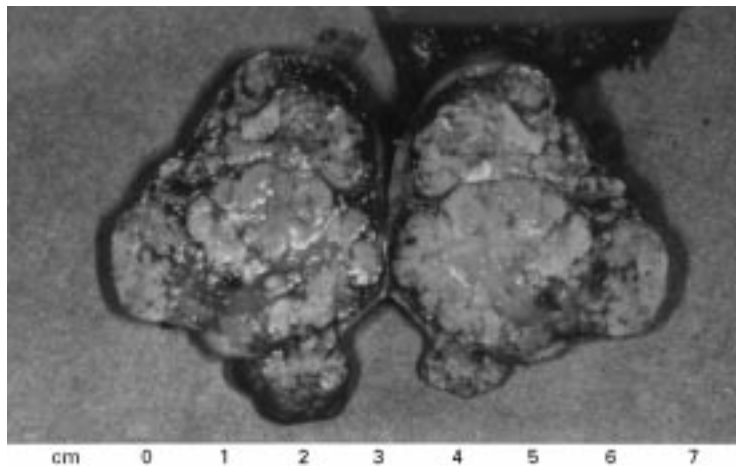


Figure 1 Ovary replaced by a lobulated mass (60 × 38 × 30 mm) of bright yellow firm tissue.

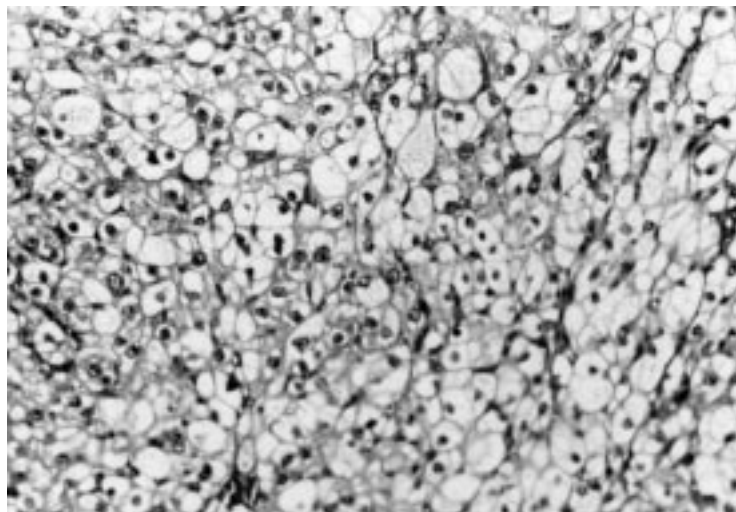


Figure 2 The cells lack a pattern and are separated by fine strands of fibrovascular stroma. The vesicular nuclei show some atypia and have prominent large nucleoli surrounded by clear cytoplasm. (Haematoxylin and eosin; original magnification ×80.)

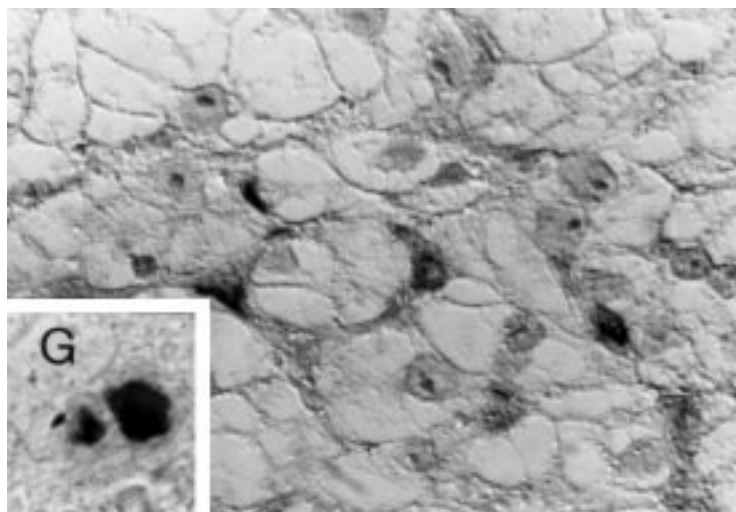


Figure 3 In situ hybridisation reveals positive staining for renin in scattered small spindle cells. Insert shows control kidney section of a case of renal artery stenosis. There is strong staining adjacent to a glomerulus (G). (Visualised with nitro blue tetrazolium/bromo-chloro-indolyl-phosphate counterstained with periodic acid Schiff; original magnification ×600.)

tissue. The largest lobule measured 16 × 13 × 10 mm and the overall appearance resembled adrenal gland tissue (fig 1). There was no necrosis or haemorrhage.

Microscopy of this ovary showed sheets of clear cells surrounded by delicate fibrovascular stroma. The tumour cell nuclei were vesicular and varied in size and shape. Most cells had a single large nucleolus (figs 2 and 3). The nuclear atypia was assessed as grade 2.² There was no necrosis and the mitotic count was less than two per 10 high power fields. There was almost complete penetration of the capsule of the ovary and tumour bulged into vascular channels with probable vascular invasion. There was no evidence of tumour in the omentum, the peritoneal fluid or peritoneal washings.

Oil Red O staining confirmed a high lipid content in the tumour. Immunocytochemistry revealed strong staining for inhibin in the lipid rich tumour cells (antibody source Serotec, Kidlington, Oxford, UK; dilution 1/50). In situ hybridisation for renin mRNA (600 base pair probe in plasmid PGem I; digoxigenin labelled⁷ riboprobe) demonstrated sparse focal positivity (fig 3). The renin secreting cells were small and had a perivascular distribution. They were spindle shaped or stellate and were much smaller than the lipid rich tumour cells. The nuclei were small and had inconspicuous nucleoli. Whether these renin secreting cells were tumour cells or stromal cells is uncertain. In situ hybridisation for erythropoietin using a commercial oligoprobe was unsuccessful (R & D Systems, Abingdon, Oxford, UK; oligo cocktail 5' and 3' end labelled with digoxigenin-11-dUTP).

Discussion

The malignant potential of this ovarian tumour is uncertain but its diameter of 6 cm (tumours > 7 cm are prognostically poor), nuclear grade 2, low but significant mitotic activity, capsular penetration, and vascular invasion all point to this tumour having metastatic potential.

The peptide hormone inhibin is a physiological product of ovarian granulosa cells that modulates folliculogenesis.⁸ In postmenopausal women it is synthesised by activated non-neoplastic sex-cord stroma. Accordingly, inhibin may be synthesised by sex-cord stromal neoplasms.⁹ The strong staining with inhibin antibodies may be a useful pointer in the diagnosis of metastatic steroid cell tumours; however, inhibin is not a specific marker of ovarian tumours and its clinical use as a tumour marker has been disappointing.

The permanent fall in haematocrit caused by removal of the tumour suggests that the tumour was responsible for the erythrocytosis. It is uncertain whether our inability to demonstrate erythropoietin in the tumour cells was because of technical problems with the probe or because of the secretion of erythropoietin precursors in the tumour with conversion to erythropoietin elsewhere.

The presence of renin synthesis in this tumour is interesting. Similar to inhibin, prorenin probably also has a physiological role

in modulating folliculogenesis.¹⁰ In this case we were unable to determine whether the renin secreting cells were tumour cells or perivascular ovarian stromal cells. A similar problem has been encountered in renin secreting renal cell carcinoma; the evidence has been reviewed.¹¹ The ovary secretes prorenin into the blood, and ovarian tumours may also secrete prorenin and active renin and cause hypertension. Tumours secreting active renin cause severe hypertension and hypokalaemia. Our patient had only mild hypertension and normal blood potassium levels. Hence it is probable that the mild rise in blood pressure was caused by the raised haematocrit rather than secretion of active renin by the tumour. We did not find evidence of renin synthesis in two other cases of sex-cord stromal tumours (unpublished observations). Plasma prorenin concentration is a good tumour marker for Wilms's tumour and other renin secreting tumours, but its role in other neoplasms is not clear. The investigation of biologically inactive prorenin as a tumour marker in ovarian tumours may prove rewarding.

We thank Dr D Millan for permission to report this case.

- 1 Scully RE. Tumours of the ovary and maldeveloped gonads. In: Scully RE, ed. *Atlas of tumor pathology. Second series, fascicle 16*. Washington, DC: Armed Forces Institute of Pathology, 1979:215–20.
- 2 Hayes MC, Scully RE. Ovarian steroid cell tumour (not otherwise specified): a clinicopathological analysis of 63 cases. *Am J Surg Pathol* 1987;11:835–45.
- 3 Young RH, Scully RE. Ovarian steroid cell tumours associated with Cushing's syndrome: a report of three cases. *Int J Gynaecol Pathol* 1987;60:40–8.
- 4 Kasperlik-Saluska AA, Sikorowa L, Ploch E, et al. Ectopic ACTH syndrome due to bilateral ovarian androblastoma. *Eur J Obstet Gynecol Reprod Biol* 1993;52:223–8.
- 5 Kulkarni JN, Mistry RL, Kamat MR, et al. Case report of autonomous aldosterone-secreting ovarian tumour. *Gynaecologic Pathology* 1990;37:284–9.
- 6 Montag TW, Murphy RE, Belinson JL. Virilizing malignant lipid cell tumour producing erythropoietin. *Gynaecol Oncol* 1984;19:98–103.
- 7 McKenzie KJ, Ferrier RK, Howatson AG, et al. Demonstration of renin gene expression in nephroblastoma by in situ hybridisation. *J Pathol* 1996;180:71–3.
- 8 Yamato M, Minami S, Nakano R, et al. Immunohistochemical localization of inhibin/activin subunits in human ovarian follicles during the menstrual cycle. *J Clin Endocrinol Metab* 1991;74:989–93.
- 9 Flemming P, Grothe W, Maschek H, et al. The site of inhibin production in ovarian neoplasms. *Histopathology* 1996;29:465–8.
- 10 Lumbers ER. The ovary. In: Robertson JIS, Nicholls MG, eds. *The renin angiotensin system*. London: Gower Medical Publishing, 1992:(chap 46)1–12.
- 11 Lindop GBM, Leckie BJ, Mimran A. Renin-secreting tumours. In: Robertson JIS, Nicholls MG, eds. *The renin angiotensin system*. London: Gower Medical Publishing, 1992:(chap 54)1–12.

Sequential malt lymphomas of the stomach, small intestine, and gall bladder

M R Stephen, M A Farquharson, R A Sharp, R Jackson

Abstract

Low grade lymphomas of mucosa associated lymphoid tissue (MALT) are indolent neoplasms that, although tending to remain localised for many years, may spread to other mucosal sites. A 53 year old woman treated by total gastrectomy for low grade MALT lymphoma of the stomach developed a recurrence in the small bowel 18 years later, and a further recurrence involving the gall bladder after three years in complete clinical remission after chemotherapy. In situ hybridisation showed that the small intestine and gall bladder recurrences had the same pattern of light chain restriction. Tumour from all three sites was shown to be derived from a single clone by the demonstration of an identical immunoglobulin heavy chain gene rearrangement by the polymerase chain reaction. The case illustrates the propensity of MALT lymphomas to "home" to mucosal sites and gives an insight into their behaviour over an extended follow up.

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Keywords: MALT lymphoma; extranodal marginal zone lymphoma; stomach; small intestine; gall bladder.

Low grade mucosa associated lymphoid tissue (MALT) lymphomas behave in an indolent fashion, remain localised to the site of origin for many years before dissemination, and respond favourably to local measures. A 10 year survival rate of 75% is quoted for low grade gastric tumours¹ but there is little information on the behaviour of this tumour over a longer period of follow up. Involvement of two mucosal sites either concurrently or sequentially is a well recognised characteristic of these tumours. Examples include simultaneous involvement of the small bowel and stomach, bilateral presentation of salivary gland tumours, and recurrence of MALT lymphoma of the thyroid in the duodenum after three years.^{2–4} Involvement of the gall bladder by MALT lymphoma is rare, there being only two previously reported cases to our knowledge in the literature.^{5–6} We report a case of recurrent MALT lymphoma of the stomach involving multiple mucosal sites, including the gall bladder, over 21 years.

Case report

A 53 year old woman presented in 1973 with anorexia and vomiting. At gastroscopy, the mucosa was atrophic and showed multiple areas of haemorrhage. A histamine test meal revealed complete achlorhydria. At laparotomy

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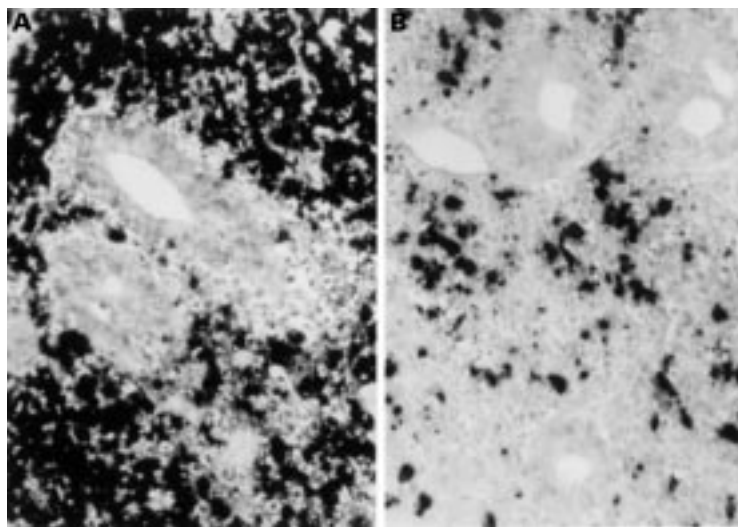


Figure 1 In situ hybridisation of the jejunal biopsy for (A) κ light chain and (B) λ light chain.

a frozen section was reported as lymphosarcoma and total gastrectomy was performed with anastomosis of the jejunum to the oesophagus and enteroanastomosis between the afferent and efferent loops of the small bowel. The patient made a full recovery and remained in good health for 18 years.

In 1991 she presented with symptoms of malabsorption including a low serum albumin of 20 g/dl, low zinc, magnesium, and calcium. A barium follow through was suggestive of diffuse lymphomatous involvement of the jejunum and proximal ileum, which was confirmed by endoscopic biopsy. Complete resolution of clinical symptoms followed a low grade chemotherapy regimen. Three years later she presented with nausea and vomiting. She was slightly jaundiced and an abdominal ultrasound showed an enlarged gall bladder containing multiple gall stones. Cholecystectomy was performed and four gall stones were extracted from the common bile duct. During the procedure a few enlarged lymph nodes were observed in the porta hepatis. The spleen

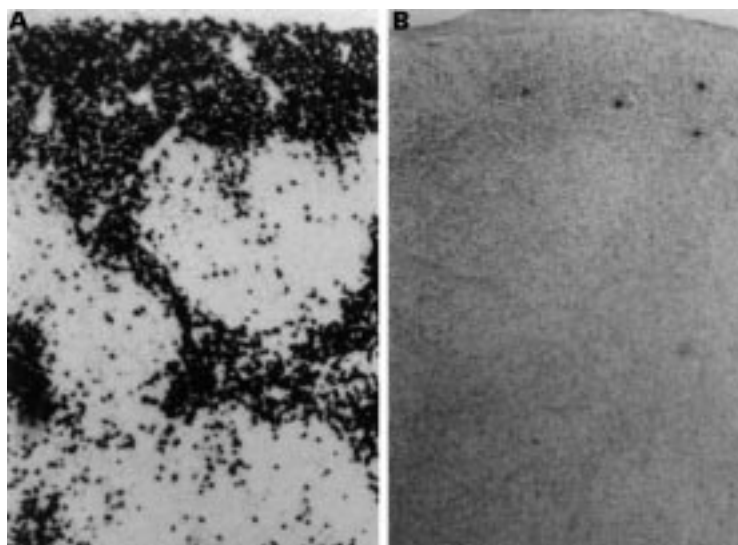


Figure 2 In situ hybridisation of the gall bladder for (A) κ light chain and (B) λ light chain.

was normal. Histological examination revealed low grade MALT lymphoma involving the gall bladder and local lymph nodes. She was treated with a low grade chemotherapy regimen and was disease free 36 months later when last reviewed.

Materials and methods

Sections (4 μ m) stained with haematoxylin and eosin from all three specimens were retrieved from the archives of the Victoria Infirmary, Glasgow, and reviewed. In situ hybridisation (ISH) for light chain mRNA was performed using the method described by Hell *et al* with slight modification.^{7,8} The probes used were double digoxigenin labelled oligodeoxynucleotide probes (R&D systems, Abingdon, Oxfordshire, UK) to κ and λ chain mRNA. Detection was achieved using an alkaline phosphatase labelled antidigoxigenin antibody (Boehringer Mannheim, Lewes, East Sussex, UK) with NBT/BCIP (Sigma, Poole, Dorset, UK) as substrate. The slides were counterstained with haematoxylin and mounted using Faramount (Dako, High Wycombe, Bucks, UK).

For the polymerase chain reaction (PCR) a 10 μ m section was cut from each specimen and placed in separate tubes. After dewaxing, the sections were digested overnight at 37°C with proteinase K (Sigma) at 500 μ g/ml. The proteinase K was inactivated at 95°C for 10 minutes and 5 μ l from each sample was used in the PCR. The PCR was a semi-nested procedure using Fr3 and LJH primers in the first round, and Fr3 and VLJH primers in the second. The products were analysed on a 10% polyacrylamide gel that was poststained with ethidium bromide and viewed under ultraviolet light.

PATHOLOGICAL FINDINGS

The initial gastrectomy specimen was described as being diffusely thickened with a macroscopic appearance suggestive of linitis plastica. The mucosa was roughened and irregular. Histological review revealed the typical features of a low grade B cell lymphoma of MALT type. There was pronounced mucosal atrophy associated with diffuse lymphocytic infiltration of the lamina propria and submucosa. There was focal infiltration of the muscularis propria and serosa. The infiltrate consisted mainly of small lymphocytes and centrocyte-like cells surrounding and over running residual reactive follicles. Plasma cell differentiation was noted focally in the superficial aspect of the lamina propria. Lymphoepithelial lesions were not demonstrated in the available blocks. No lymph nodes were available for assessment. There was evidence of lymphomatous involvement of both the duodenal and oesophageal resection margins. Light chain restriction was not convincingly demonstrated by ISH. Examination of the duodenal biopsy revealed broadening of villi, crypt atrophy, a diffuse lymphoplasmacytic infiltrate within the lamina propria, and lymphoepithelial lesions formed by centrocyte-like cells. Kappa light chain restriction was demonstrated by ISH in the tumour cells showing plasmacytic differentiation (fig 1).

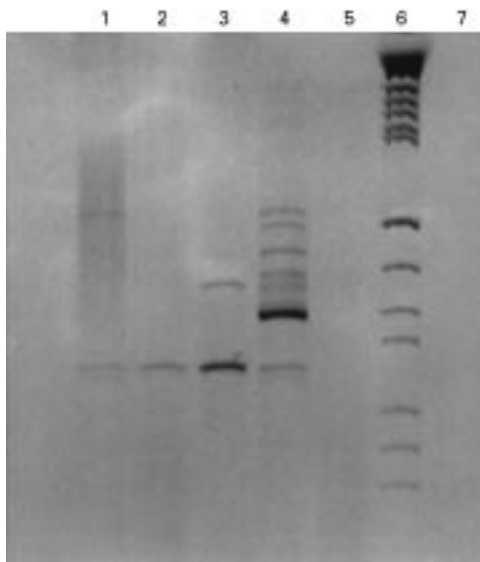


Figure 3 PCR products visualised by ethidium bromide showing an identical immunoglobulin heavy chain gene rearrangement in the three tumours. Lane 1, gall bladder lymphoma; lane 2, duodenal lymphoma; lane 3, gastric lymphoma; lane 4, positive control (known B cell lymphoma); lane 5, negative control; lane 6, DNA molecular weight markers; lane 7, negative control.

On macroscopic examination the gall bladder wall was diffusely thickened and the mucosa displayed a rather polypoid appearance. Histological examination revealed a diffuse lymphomatous infiltrate identical to that seen in the previous duodenal biopsy and gastric resection. The tumour involved the entire thickness of the gall bladder wall and was composed of centrocyte-like cells with extensive plasma cell differentiation. Occasional lymphoepithelial lesions and residual reactive germinal centres were identified. Kappa light chain restriction in the plasma cell component was again demonstrated by ISH (fig 2). The lymph nodes from the porta hepatis showed marginal zone involvement by centrocyte-like cells, typical of spread from an extranodal B cell lymphoma of MALT type. All three tumours displayed an identical immunoglobulin heavy chain gene rearrangement on analysis by PCR (fig 3).

Discussion

We have described a case of low grade MALT lymphoma of the stomach sequentially involving multiple mucosal sites over a period of 21 years. The lymphoma has behaved in a relatively indolent fashion and the patient was in remission at latest follow up. The supposition that the small intestine and the gall bladder tumours were recurrences rather than new primaries is supported by the demonstration of common clonality of the three tumours by PCR. It is noteworthy that the recurrences have continued to display the low grade pattern of the original gastric tumour with no suggestion of transformation to a higher grade over such a long follow up. The pattern of involvement of the small bowel in this case is unusual. The patient presented after 18 years of relative well-being with severe weight loss and clear evidence of severe malabsorption. Barium studies

showed diffuse small bowel infiltration and the biopsy confirmed MALT lymphoma. The clinical features described resemble those seen in Mediterranean lymphoma (immunoproliferative small intestinal disease (IPSID)) the most common manifestation of MALT lymphoma in the Middle East but rare in the West.⁴ In Europe, small intestinal MALT lymphoma more commonly presents as a localised tumour mass resulting in obstruction. The similarity to IPSID was also apparent on histological examination of the small bowel biopsy where plasma cell differentiation was prominent. Light chain production, as identified in our case, however, is rare in IPSID. The malabsorption responded dramatically to chemotherapy.

Involvement of the gall bladder by low grade MALT lymphoma is rare, there being only two previously described cases.⁵⁻⁶ As in the other published cases, our patient presented with a typical history of cholelithiasis and the diagnosis of lymphoma only became obvious on histological examination. The reason for recurrence in this case may have been as a direct consequence of incomplete resection at initial gastrectomy, albeit after an interval of 18 years. Disease free resection margins however may be no guarantee of future protection from local relapse as recurrences have been described in patients thought to have had an initial curative resection.⁹ This phenomenon is thought to be due to the presence of multiple microscopic foci of tumour within the gastric mucosa distant from the main tumour mass.¹⁰ Moreover, plasma cells derived from a small intestinal MALT lymphoma have been detected in the apparently normal gastric mucosa of the same patient, indicating the ability of this tumour to colonise distant mucosal sites.²

This case illustrates many of the properties of low grade MALT lymphoma. The tumour was slow growing, produced a variety of clinical problems, and demonstrated a propensity for spread to other mucosal sites rather than for systemic dissemination. The late recurrence after an 18 year interval has implications for the definition of cure especially in younger patients.

- Cogliatti SB, Schmid U, Schumacher U, *et al.* Primary B-cell gastric lymphoma: a clinicopathological study of 145 patients. *Gastroenterology* 1991;101:1159-70.
- Spencer J, Diss TC, Isaacson PG. A study of the properties of a low grade mucosal lymphoma using a monoclonal antibody specific for the tumour immunoglobulin. *J Pathol* 1990;160:231-8.
- Hyjek E, Smith WJ, Isaacson PG. Primary B cell lymphoma of salivary gland and its relationship to myoepithelial sialadenitis. *Hum Pathol* 1988;19:766-76.
- Isaacson PG, Norton AJ. *Extranodal lymphomas*. Edinburgh: Churchill Livingstone, 1994:114.
- McCluggage WG, Mackel E, McCusker G. Primary low grade malignant lymphoma of mucosa-associated lymphoid tissue of the gallbladder. *Histopathology* 1996;29:285-7.
- Mosnier JF, Brousse N, Sevestre, *et al.* Primary low-grade B-cell lymphoma of the mucosa associated lymphoid tissue arising in the gallbladder. *Histopathology* 1992;20:274-5.
- Hell K, Pringle JH, Hansmann ML, *et al.* Demonstration of light chain mRNA in Hodgkin's disease. *J Pathol* 1993;171:137-43.
- Farquharson MA, Foulis AK, Lee FD, *et al.* Comparison of polymerase chain reaction (PCR) and in situ hybridisation (ISH) in the diagnosis of B cell lymphoma [abstract]. *J Pathol* 1996;179(suppl):40A.
- Green JA, Dawson AA, Jones PF, *et al.* The presentation of gastrointestinal lymphoma; study of a population. *Br J Surg* 1979;66:798-801.
- Wotherspoon AC, Dogliani C, Isaacson PG. Low grade gastric B-cell lymphoma of mucosa-associated lymphoid tissue (MALT): a multifocal disease. *Histopathology* 1992; 20:29-34.

Familial pancreatic lymphoma

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Abstract

Non-Hodgkin's lymphoma is not commonly a familial condition. This is believed to be the first two cases of primary pancreatic lymphoma within a single family. The two cases, a brother and sister, both presented in their 60s and were diagnosed histologically as having high grade B cell lymphoma affecting the pancreas, an uncommon primary site. Both responded well to treatment with chemotherapy and were in remission at the time of writing. On further investigation it was found that their mother also presented with a malignant lymphoma of cervical nodes 30 years earlier and subsequently died of the disease.

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Keywords: pancreas; lymphoma; familial; non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma is not commonly a familial condition. We report two cases, a brother and sister, of primary pancreatic lymphoma that we believe to be the first within a single family.

Case 1

A 66 year old man presented in July 1992 with a two month history of central abdominal pain, constipation, poor appetite, and weight loss of over 6 kg. On admission he was thin, pale, had a small pleural effusion, and a tender epigastric mass. Gastroscopy was normal, but ultrasound revealed massive enlargement of lymph nodes in the pancreatic and para-aortic regions with an enlarged spleen containing two abnormal foci. An initial percutaneous biopsy was non-diagnostic and at laparotomy an 8 cm mass was found in the body and tail of the pancreas with extensive surrounding lymph node involvement. The tumour was composed of immunoblast-type cells with large nuclei, and single or multiple nuclei with moderate amounts of cytoplasm. There were high mitotic and apoptotic indexes. Immunostaining (fig 1) confirmed B cell lineage (CD20+, CD3–). Appearances were in keeping with a large B cell diffuse lymphoma (REAL classification¹).

The patient was treated with CHOP chemotherapy (cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone) and received two courses, the second at half dose because of neutropenia and sepsis. Following the second course he showed little clinical improvement and ultrasound assessment of the mass four months after presentation showed only minimal improvement. In view of this, his intolerance to chemotherapy, and poor general condition he was referred for palliative care.

More than a year later he was referred back by his family doctor. He was in remarkably good health with no clinical evidence of disease and had gained 17 kg in weight. Computed tomography (CT) confirmed the improvement with no evidence of residual pancreatic lymphoma and complete resolution of the splenic lesions. He was given two further courses of CHOP chemotherapy as consolidation, which he tolerated well. He remains in complete remission 34 months later.

Case 2

The sister of case 1 presented in November 1993, also aged 66, with a short history of weight loss, pale stools, and painless jaundice. Abdominal CT revealed massive pancreatic enlargement with lymphadenopathy in the para-aortic and porta-hepatis regions causing biliary obstruction. Initial attempts at CT guided percutaneous biopsy were unsuccessful but an endoscopic retrograde cholangiopancreatography of the ampulla of Vater yielded adequate material for histological assessment. This showed a diffuse infiltrate of large lymphoid cells with singly or multiply nucleolate rounded nuclei with uncondensed chromatin. There were frequent apoptotic and mitotic bodies and the Ki67 score was high. The tumour was of large B cell origin (CD20+, CD79a+, CD3–) and was of high grade diffuse type (REAL classification¹) (fig 2).

The patient's jaundice was initially relieved by percutaneous stenting of the bile duct and her exocrine pancreatic dysfunction was treated with enzyme supplements. She then entered a BNLI trial and was randomised to PACEBO chemotherapy (12 weeks of cyclical prednisolone, hydroxydaunorubicin, cyclophosphamide, etoposide, bleomycin, and vincristine). Her response was good; CT four months later showed complete resolution of the pancreatic enlargement.

She remained well for three months after chemotherapy but then developed lower back pain and numbness of the right leg. Radiography showed collapse of the L2 vertebra and a magnetic resonance imaging (MRI) scan showed probable lymphomatous infiltration of all the lumbar vertebrae that was treated with local radiotherapy.

Two months later she developed a left vocal cord palsy. CT and MRI scans were essentially normal, but cerebrospinal fluid showed raised protein concentration with atypical lymphoid cells suspicious of leptomeningeal lymphomatous involvement. By this time she was also unwell with fever and weight loss and therefore she recommenced systemic chemotherapy. She received six cycles of CHOP together with

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cranial irradiation and monthly injections of intrathecal methotrexate.

The patient is now well 24 months after completing treatment and subsequent abdominal CT has shown no evidence of disease. Her neurological symptoms have also largely resolved.

On further investigation it was discovered that their mother also had a malignant lymphoma that was diagnosed in 1955. She initially presented with deafness and cervical lymphadenopathy and was successfully treated with local radiotherapy. Unfortunately she relapsed in 1967 with an enlarged spleen and ascites that failed to respond to radiotherapy and she died the following year. We were able to obtain the original blocks and review the histology. This demonstrated an appearance very similar to the first two cases (large B cell diffuse lymphoma, REAL classification) and CD20+, CD3-. Two other siblings remain well, a further sibling died 15 years ago of renal carcinoma.

ADDITIONAL INVESTIGATIONS

To look for common features between the three tumour samples a number of additional inves-

tigations were performed. Some results were incomplete because of the poor quality of the DNA isolated from the stored material. We were unable to demonstrate any features in common between the three cases. In particular we were unable to demonstrate a common pattern of expression of p53, RB or bcl-2. No evidence for t(14;18) translocation was found using a polymerase chain reaction technique for the MBR or mcr. Allele imbalance studies were only possible in one patient (case 1). The tumour suppressor loci examined were APC, p53, DCC, NM23, and RB1. Abnormalities were noted only at the APC locus.

Discussion

Pancreatic lymphoma is a rare disease with a reported incidence of 0.3–2.2% of all lymphomas.^{2,3} Small series of up to 20 patients have been reported.^{2–6} Both clinically and radiologically it is difficult to distinguish from the more common carcinoma of the pancreas, but it may represent up to 4% of all pancreatic malignancies.^{3,5,6}

The reported cases of pancreatic lymphoma have usually been older patients who often present with only a short history of symptoms. Presenting symptoms commonly reported are weight loss, abdominal pain, nausea, and less commonly fever and night sweats.^{3,4,6} If the pancreatic head is involved there may be bile duct obstruction with jaundice but pancreatic duct dilatation is rare.^{5,6} Hart *et al* also reported one case as having lumbar spine involvement, as in case 2.⁴

Two reports^{4,5} examined the role of radiology in the diagnosis of pancreatic lymphoma by retrospective review of CT in subsequently proven cases. Although typical CT features have been identified—that is, a large homogeneous mass usually infiltrating and surrounding the pancreas, with or without significant regional lymphadenopathy, especially below the renal vein, they conclude that as atypical features are frequently identified in histologically proved disease, biopsy is essential in making the diagnosis. Percutaneous guided biopsy is usually the first method attempted but unfortunately, as in one of our cases, the success rate is often poor (< 50%)^{2,6} and thus laparotomy is usually required to make a definitive diagnosis.

Pancreatic lymphoma is generally responsive to chemotherapy, the most common regimen reported being CHOP.^{2,4,6} Remission rates range from 30% to 60%^{2,6} and the median survival is approximately two years.^{4,6}

The cases presented here are believed to be the first within a sibship. In addition, it is interesting that their mother also had a non-Hodgkin's lymphoma, although not involving the pancreas.

Several studies have looked at family links in cases of lymphoma and other malignancies.^{7,8} These have shown that although there is a strong family link in cases of Hodgkin's disease, this is much weaker in non-Hodgkin's lymphoma accounting for fewer than 1% of cases.⁸ In the largest review that examined 38 families with lymphoma involving more than

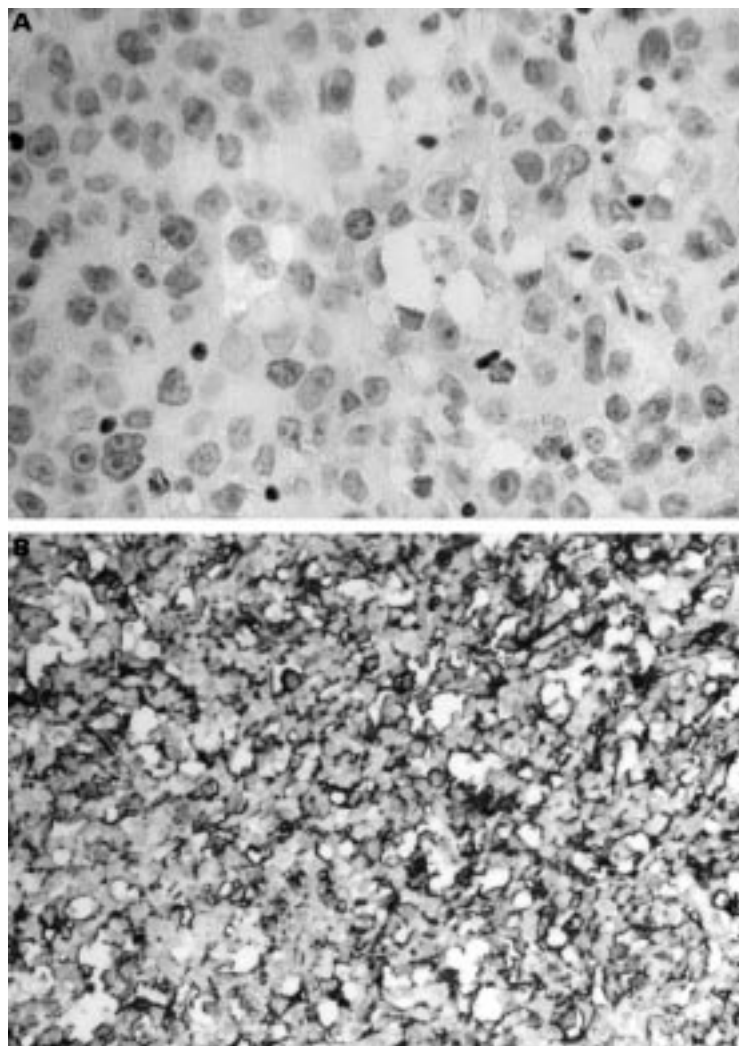


Figure 1 (A) A high grade large cell diffuse lymphoma from case 1 with a predominance of large nucleated nuclei (haematoxylin and eosin; original magnification $\times 420$). (B) Strong staining with the B cell marker CD20 (original magnification $\times 300$).

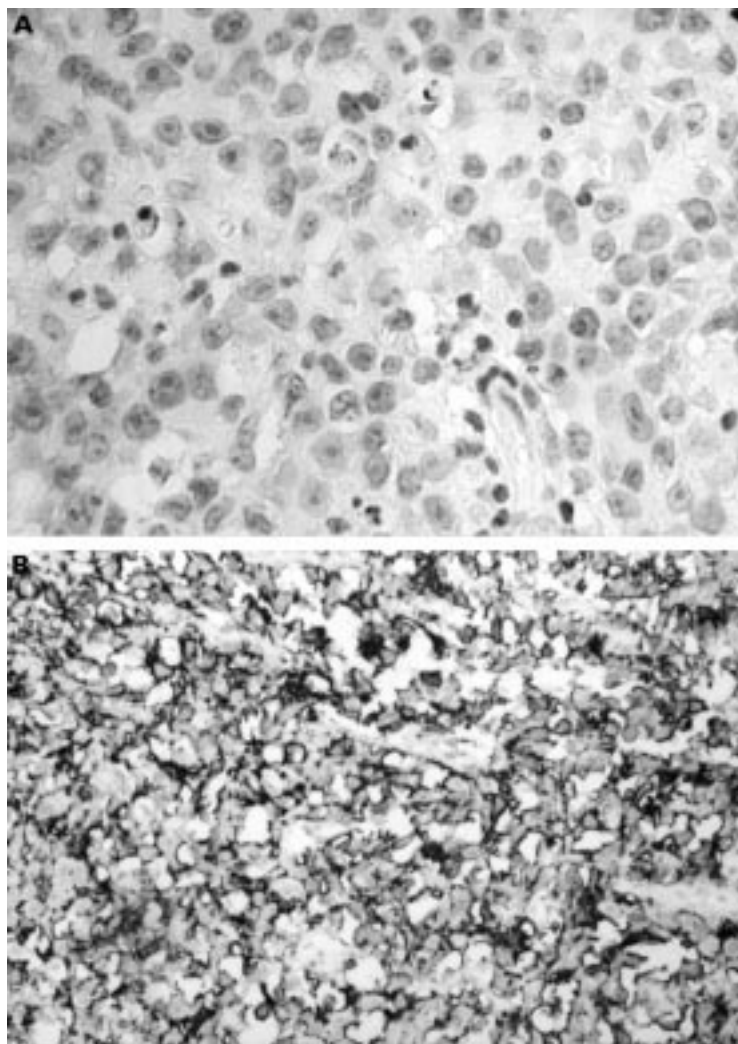


Figure 2 (A) Biopsy of Ampulla of Vater from case 2. Appearances identical to case 1 (haematoxylin and eosin; original magnification $\times 420$). (B) Strong staining with anti-CD20 (original magnification $\times 300$).

one family member,⁹ 80% of the cases were in siblings. Two distinct patterns have been identified, the first involving male adolescents, the second, as in this report, occurring in older adults with an equal sex distribution.⁹ The risk of developing non-Hodgkin's lymphoma if a sibling has the disease is increased three to

fourfold^{9 10} and there is a small increase in risk (relative risk 1.3) if a first degree relative has any haematological malignancy.^{8 10} In some instances other non-affected family members have been shown to have an inherited immune dysfunction and this is more common in young male patients.^{7 9 10} The aetiology of the familial association in non-Hodgkin's lymphoma remains unclear but it is likely that there is an increased genetic susceptibility to environmental and other factors.⁹ It may be of relevance that both patients reported here and their mother lived or worked on farms and a weak association has been noted between agrochemical use and lymphoma.¹⁰

In summary, although we cannot prove either genetic or other aetiological factors linking these two cases, the probability of such a rare condition occurring by coincidence in two members of the same family, even one prone to the development of haematological malignancies, must be minimal. Both cases exhibited features typical of pancreatic lymphoma consistent with those previously reported in the literature; however, it is pleasing to note that both of these patients remain in remission, at a length of time already well in excess of the reported median survival.

- Harris N, Jaffe ES, Stein H, *et al.* A revised European-American classification of lymphoid neoplasms. *Blood* 1994;**84**:1361–92.
- Brown PC, Hart MJ, White TT. Pancreatic lymphoma, diagnosis and management. *Int J Pancreatol* 1987;**2**:93–100.
- Cappell MS, Yao F, Cho KC, Axiotis CA. Lymphoma predominantly involving the pancreas. *Dig Dis Sci* 1989;**34**:942–7.
- Hart MJ, White TT, Brown PC, Freeny PC. Potentially curable masses in the pancreas. *Am J Surg* 1987;**154**:134–6.
- Van Beers B, Lalonde L, Soyer P, Grandin C, Trigaux J-P, *et al.* Dynamic CT in pancreatic lymphoma. *J Comput Assist Tomogr* 1993;**17**:94–7.
- Webb TH, Lillemoe KD, Pitt HA, Jones RJ, Cameron JL. Pancreatic lymphoma: is surgery mandatory for diagnosis or treatment? *Ann Surg* 1989;**209**:25–30.
- Greene MH. Non-Hodgkin's lymphoma and mycosis fungoides. In: Schottenfeld WB, Fraumeni JF, eds. *Cancer epidemiology and prevention*. Philadelphia: WB Saunders, 1982:754–71.
- Haim N, Cohen Y, Robinson E. Malignant lymphoma in first-degree blood relatives. *Cancer* 1982;**49**:2197–200.
- Linet MS, Pottern LM. Familial aggregation of hematopoietic malignancies and risk of non-Hodgkin's lymphoma. *Cancer Res* 1992;**52**(suppl):5468S–73S.
- Cartwright RA, McKinney PA, O'Brien CO, Richards DG, Roberts B, *et al.* Non-Hodgkin's lymphoma: case control epidemiological study in Yorkshire. *Leuk Res* 1988;**12**:81–8.