Correspondence

Gastric glomangiomyoma: a pedunculated extramural mass with a florid angiomyomatous pattern

Sir: Glomus tumours are uncommon mesenchymal tumours with an incidence of about 1.6% among soft tissue tumours. The tumours are most commonly found in the peripheral soft tissues, especially in the distal parts of the extremities. Here, we describe a rare variant of the glomus tumour, glomangiomyoma, in the gastrointestinal tract with an unusual extramural location and a florid smooth muscle cell component.

A 54-year-old Chinese woman presented with recurrent epigastric pain for 2 years. Repeated endoscopies revealed no mucosal lesion but only vague bulging in the posterior wall of the gastric antrum. Computed axial tomography revealed a well-defined, 70-mm paragastric solid mass in the right upper abdomen connected to the stomach by a narrow stalk, extending just inferior to the liver to the level of the aortic bifurcation. The tumour was surgically removed and she has remained well during the last 3 months of follow-up after the operation.

The tumour was a circumscribed ovoid mass weighing 101 g and measuring $70 \times 60 \times 35$ mm with a solid tan-coloured cut surface (Figure 1A). There was no capsule, but the external surface of the tumour was smooth and covered by peritoneum.

Microscopically, the tumour showed a biphasic pattern (Figure 1B). The predominant component was eosinophilic spindle cells whorling around mostly capillary-sized vessels, forming an angiomyoma-like pattern (Figure 1C). These cells were strongly positive for smooth muscle markers including desmin (Figure 1D), smooth muscle actin and muscle-specific actin. The other component was the diagnostic glomus cells, comprising islands and sheets of small ovoid cells surrounding gapped or staghorn-like vessels. These cells possessed well-demarcated round basophilic nuclei and scanty cytoplasm (Figure 1E). Collagen IV and reticulin showed pericellular staining patterns around these cells. Only a few of these cells were positive for desmin (Figure 1F). Both components showed negative staining for AE1/AE3, CD34, C-kit (CD117), S100, HMB45, chromogranin and synaptophysin. Neither necrosis nor cytological atypia were present. The proliferative index of the tumour was low with rare mitotic figures (<1 per 50 high-power fields) and low MI B-2 (Ki67) staining (<1% for both cell components).

In conclusion, the tumour was a pedunculated, subserosal gastric glomangiomyoma with a predominant spindled smooth muscle cell component, resulting in a striking angiomyomatous pattern. The tell-tale glomus cell component was only confined to scattered small areas. Glomus tumours have a close growth association with vessels. Variable degrees of differentiation/transformation towards mature smooth muscle cells and a

Figure 1. A, Gross appearance of the solid tan-coloured cut surface of the glomangiomyoma. B, Low-power view of H–E section showing a small island of the basophilic ovoid glomus tumour cells (g) surrounded by the abundant smooth muscle cell component (sm). C, High-power view of H–E section showing the whorling pattern of the smooth muscle cells (sm) around vessels. D, Immunostaining of desmin (Dako M760, clone D33, dilution 1:150) showing the angiomyomatous pattern of this tumour with the strong staining of the smooth muscle cells (sm). E, High-power view of the H–E section showing the pericytoma-like glomus tumour cell component (g). F, Immunostaining of desmin showing the transition from negatively stained glomus tumour cells (g) to strongly stained smooth muscle cells (sm).
focal angiomylomatous pattern have previously been described. A predominant spindle cell component, as in the present case, however, has not been reported. Accordingly, differential diagnoses include gastrointestinal stromal cell tumour, haemangiopericytoma, solitary fibrous tumour, leiomyoma/leiomyoma of uncertain malignant potential, schwannoma and angiomylipoma (see Ref. 3 for review).

Miettinen and coworkers reviewed the largest series of 32 gastrointestinal glomus tumours. Most of them were circumscribed, intramural or intraluminal masses located in the gastric antrum. Typically, the presenting symptoms were those of gastrointestinal bleeding or ulcers. Most tumours were small and the patients fared well, except one with a large tumour (65 mm in size), who developed disease metastatic to the liver. The prognostic criteria of gastrointestinal glomangiomyoma or glomus tumours as a whole are not well established. With regard to the large size (70 mm) of the tumour of our patient, long-term follow-up is warranted. For glomus tumour affecting the extremities, location of the tumour in a deeper tissue plane is associated with a poorer prognosis. The depth of primary tumour, however, does not seem to play a significant role in the prognosis for gastrointestinal glomus tumour. Spindle cells in glomus tumours have been suggested to be associated with an adverse prognosis. However, it should be noted that among the few unfavourable cases reported, the ‘spindle’ cells were mostly sarcoma-like, resembling malignant fibrous histiocytoma or leiomyosarcoma. Thus, whether the cytologically bland, spindled smooth muscle component in the present case plays an additional adverse role in the clinical behaviour remains doubtful.

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Gastrointestinal zygomycosis: two case reports

Sir: Gastrointestinal zygomycosis is rare. We present one case of small intestinal mucormycosis and one case of colonic and hepatic entomophthoromycosis, documenting the dramatically different clinicopathological features caused by fungi of the two orders of the class Zygomycetes.

A 65-year-old Caucasian man with chronic obstructive pulmonary disease admitted with lobar pneumonia rapidly developed respiratory and renal failure. Subsequently, he had a major rectal bleed and emergency extended right hemicolecotomy revealed four separate well-demarcated perforations within otherwise normal ileum.

Microscopy showed florid acute inflammation and microabscesses at the perforation sites, associated with abundant multinucleate giant cells (Figure 1). Within the luminal necrotic debris and multinucleate giant cells were abundant irregularly shaped, non-septate hyphae, branching at right angles, morphologically consistent with Mucorales. Post-operatively, he was treated with 4 weeks of intravenous amphotericin B. Two years later, he is alive and well.

The second case was a 45-year-old Iranian farmer admitted with right iliac fossa pain. Computed tomography and subsequent right hemicolecotomy revealed a 90-mm solid caecal mass which histologically was a caecal abscess containing a striking number of eosinophils, multinucleated giant cells and multiple broad and sparsely septate fungal hyphae surrounded by characteristic ‘Splendore–Hoeppli’ precipitates (Figure 2). Six weeks later he developed multiple liver abscesses and fine needle aspiration again showed Entomophthorales hyphae surrounded by ‘Splendore–Hoeppli’ precipitates. Treatment with ketaconazole, together with cotrimoxazole, was successful and he was discharged 4 weeks later.

Mucorales and Entomophthorales, the two orders of the class Zygomycetes, are closely related fungi but have dramatically different disease manifestations. Mucorales are opportunistic fungi that cause rapidly disseminating, acute fulminating and often fatal infections in diabetic, debilitated or immunocompromised hosts. Fungi tend to invade blood vessels causing
mycotic emboli. Gastrointestinal mucormycosis is rare, with small intestinal involvement in immunocompetent adults described in only five cases in the literature, all of which were fatal, due to late diagnosis.

Entomophthorales are ubiquitous fungi causing generally chronic, subcutaneous or nasofacial infections in immunocompetent individuals in tropical and subtropical regions. The hyphae show no tendency for invading blood vessels.

Our first patient was severely debilitated with chronic obstructive pulmonary disease and chest infection and had received multiple different antibiotics prior to surgery, which probably predisposed to the fungal infection, perhaps via ingestion of fungus and invasion from the lumen into the intestinal wall. No apparent underlying intestinal disease was identifiable.

It is not possible to differentiate the various mucormycoses in tissue sections and isolation of Mucorales is difficult; material has to be cultured immediately. Fungal cultures were not performed for our first patient. However, morphologically the appearances of the fungus were consistent with Mucorales and the tissue macroscopy and histology characteristic of this infection. Although Aspergillus can occasionally produce a similar tissue reaction with multinucleated giant cells, it is readily distinguished by narrow hyphae with dichotomous branching at acute angles.

Entomophthoromycosis is histologically characterized by broad, branching and sparsely septate hyphae surrounded by ‘Splendore–Hoeppli’ precipitates. This microscopic picture is diagnostic and distinguishes entomophthoromycosis from other fungal infections, including mucormycosis. However, culture is necessary for species identification. The eosinophilic, periodic acid–Schiff-positive material of the ‘Splendore–Hoeppli’ phenomenon consists mainly of immune complexes and is an expression of the host immune response.

Fifteen cases of gastrointestinal entomophthoromycosis have been reported to date, with liver involvement in only two cases. Organisms, whenever identified, have been Basidiobolus haptosporus. Our second patient was a farmer without any evidence of immune deficiency, systemic illness or subcutaneous lesion. We suspect that ingestion of fungi led to abscess formation in the caecum, and the hemicolecotomy introduced fungi into the lymphatic and/or portal venous systems resulting in hepatic abscesses. Species identification was impossible because attempts at blood and liver aspirate cultures were unsuccessful.

Treatment of Zygomyces requires aggressive metabolic support, antifungal therapy and surgical resection and/or debridement of necrotic involved tissue. Early diagnosis, by histological examination, is important so that life-saving antifungal therapy can be initiated.

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Unusually close association of ectopic intrathyroidal parathyroid gland and papillary microcarcinoma of the thyroid

Sir: We here report the unusual case of a papillary microcarcinoma of the left thyroid lobe in close proximity to an ectopic intrathyroidal parathyroid gland. A bilateral nodal goitre had been removed from a 41-year-old woman. Clinically, an adenoma was suspected within the left lobe, and the right lobe showed a nodule with decreased hormonal function (‘cold’ nodule) on scintigraphic evaluation. There was no history of hyperparathyroidism.

On gross examination, the largest diameters of the two roughly spindle-shaped thyroid lobes were 62 and 48 mm. Cut surfaces revealed multiple nodules measuring up to 25 mm in largest diameter. Histological analysis showed the typical picture of a ‘struma colloides nodosa’ with focal regressive changes. However, the left-sided lobe contained an unusual histological finding with the close association of an encapsulated papillary microcarcinoma (follicular variant, maximum diameter 7 mm) and an ectopic (intrathyroidal) parathyroid gland (Figure 1a).

The papillary microcarcinoma showed characteristic cytological features with crowding and a ground-glass appearance of the nuclei (Figure 1b) but a completely follicular microarchitecture (‘follicular variant of papillary carcinoma of the thyroid’). Immunohistochemically, the parathyroid gland revealed a typical endocrine phenotype with expression of synaptophysin (Figure 1c). The papillary carcinoma strongly expressed S100 protein, while in the adjacent normal thyroid and the parathyroid only a few scattered reticulum cells were reactive with the anti-S100 antibody (Figure 1d).

The intrathyroidal localization of parathyroid glands in general seems to be a rare finding, but there are varying reports as to its true incidence. In several studies, some of which were concerned with surgery for primary hyperparathyroidism, the frequency of intrathyroidal parathyroid glands ranged from 2.4% to 8%. The incidence of occult papillary carcinoma in young adults (20–40 years) was 3% in an autopsy study of 138 patients.7 In people over 40 years of age, however, this incidence increases, leading to an overall incidence of 5–24% in the whole population.8,9 Thus, the present case of occult papillary microcarcinoma in close proximity to an intrathyroidal parathyroid gland is a most unusual incidental finding.

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Sir: We have read with interest the article entitled: 'Expression of HER-2/neu gene and protein in salivary duct carcinomas of parotid gland as revealed by fluorescence in-situ hybridization (FISH) and immunohistochemistry' by Skalova et al.¹ This work represents the first molecular assessment by FISH of HER2 gene status in this rare and aggressive neoplasm showing a histological resemblance to ductal carcinoma of the breast. The authors studied 10 cases by immunocytochemistry and FISH. They found strong immunohistochemical positivity (3+ score) in seven cases, four of which carried HER2 gene amplification (57%), while three were non-amplified (43%). In three cases the analysis was inconclusive.

We studied HER2 gene status in formalin-fixed paraffin-embedded tissue sections of 18 consecutive cases of salivary duct carcinoma collected in our institution, according to previous published methodologies.² Eleven cases showed a score 3+, eight of which carried HER2 gene amplification (73%), while three were non-amplified (27%). None of the immunohistochemically negative cases showed amplification.

In comparison with unselected breast carcinoma series, both the investigations outline a higher percentage of both HER-2 3+/amplified cases (25% versus...
and HER2 3+/non-amplified (i.e. false-positive) cases (3% versus 27–43%)\(^3\) in salivary duct carcinoma.

As far as the pattern of amplification is concerned, Skalova et al. described a homogeneously staining region (HSR) pattern in all amplified cases, while we observed three different patterns of amplification: (i) five cases presented amplified genes arranged as HSR, usually one or two per nucleus; (ii) one case showed multiple scattered single-copy HER2 signals and chromosome 17 polisomy (calculated ratio between HER2 and centromeric probe (CEP) 17 copy number was more than 2 in all tumour nuclei); (iii) two cases showed a pattern of hybridization consistent with double minutes (Figure 1), a very unusual occurrence in breast cancer.\(^4\)

Considering the breast model where the efficiency of herceptin-based therapy is restricted to HER2 3+ or amplified cases\(^5\) and assuming that in salivary duct carcinoma the biological basis of response to herceptin is the same as in breast cancer, we can anticipate successful use of this drug in salivary duct carcinoma. On the basis of the above-reported findings it might be expected that >50% of such patients could benefit from TKR-inhibitor therapy. However, the high rate of HER2 3+ non-amplified cases (>27%), likely to be unresponsive, necessitates FISH analysis for patient selection. Assessment by FISH is further supported by our preliminary data regarding the relationship between protein expression and the amplification pattern. Despite the presence of a 3+ immunohistochemical score, we found no HER2 protein by immunoprecipitation and Western blotting experiments in the two cases carrying double minute-related amplification. If this finding is confirmed by further experiments and since the lack of HER2 protein expression is correlated with an unsuccessful response to herceptin therapy, FISH is likely to become the assessment of choice in this salivary tumour type.

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Malignant mixed epithelial and stromal tumours of the kidney: a report of the first two cases with a fatal clinical outcome

Sir: Mixed epithelial and stromal tumour of the kidney (MESTK), a rare benign neoplasm of unknown aetiology, is a recently established entity unifying several neoplasms such as adult mesoblastic nephroma, cystic hamartoma of the pelvis, adult type cystic nephroma,
multilocular renal cysts, and solid and cystic biphasic tumour of the kidney. In cases reported as MESTK, recurrence or fatal outcome has, to date, never been reported. Here, we present two cases of malignant MESTK with local recurrences and fatal outcomes.

The first case was in a 43-year-old Japanese woman, who had undergone radical nephrectomy for a right renal tumour and developed a local recurrent tumour 2 years later. Nine months after extirpation of the recurrent tumour she developed another local recurrence, associated with severe haemorrhage which could not be sufficiently controlled even by three trials of transarterial embolization. The recurrent tumour was found to have invaded adjacent organs allowing only palliative surgery for mass reduction. The patient died 43 months after initial nephrectomy. The second case was in a 31-year-old Japanese woman who had undergone radical nephrectomy for a tumour in the upper pole of the left kidney. Four months after the operation, she developed a local recurrent tumour, accompanied by massive ascites. She died 11 months after nephrectomy.

In case 1, the primary tumour measured approximately 70 mm in diameter, was located mainly near the renal hilus and appeared to consist chiefly of solid components. In case 2 it measured 70 × 70 × 60 mm, was generally well circumscribed and extended beyond the renal capsule. It consisted of solid and cystic components; the former was yellowish and firm and the latter was filled with haematoma.

The primary tumours of both patients were composed of proliferating spindle-shaped cells and epithelial tubular structures of various sizes (Figure 1a). The epithelial components were intermingled with the stromal components throughout the tumours. In case 1, the spindle cells had bright eosinophilic cytoplasm and fusiform nuclei with moderate atypia, formed interlacing bundles and small fascicles with high cellularity (Figure 1b) and infiltrated the renal hilar fat extensively. In case 2, the stromal components were composed of varying numbers of atypical spindle cells with clear cytoplasm that formed fascicles or whorled around the small tubules. No blastema was present. In both cases, the sizes of the epithelial tubular structures were variable, from small tubules reminiscent of normal collecting ducts to cystically dilated ducts lined by cells with a hobnail appearance (Figure 2). All the cells of the epithelial components lacked cytological atypia. It is noteworthy that tubular structures could be seen even in the extrarenally invading part of case 2’s tumour and in the recurrent tumour of case 1, confirming that the tubules were not normal structures that had become involved but were integral neoplastic components of the tumours. Mitoses were conspicuous in both cases.

Immunohistochemically, the spindle cells of both cases were vimentin-positive, and those of case 1 were muscle-specific actin- and α-smooth muscle actin-positive. The cells of the epithelial structures of both cases were cytokeratin- and vimentin-positive and focally epithelial membrane antigen-positive.

The differential diagnoses include leiomyosarcoma, biphasic synovial sarcoma and related tumours. Although leiomyosarcoma is the most common mesenchymal tumour arising in the kidney, it contains neither neoplastic epithelial components nor entrapped tubules, because its growth is expansive rather than
infiltrative. Biphasic synovial sarcoma of the kidney is a rare neoplasm that contains both epithelial and stromal components. Even if typical biphasic synovial sarcomas occur in the kidney, their epithelial cells are usually cuboidal or polygonal and form solid nests and glandular or tubular structures, whereas the epithelial components in the present two tumours lacked obvious cytological atypia and were considered to be similar to those of the normal collecting ducts.

In conclusion, rarely, MESTK has a malignant histopathological appearance and behaves aggressively. In this situation, this tumour needs to be distinguished from leiomyosarcoma and synovial sarcoma arising in the kidney.

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Neuroendocrine carcinoma of the vulva with paraganglioma-like features

Sir: Neuroendocrine tumours (NTs) of the female genital tract are relatively uncommon. Particularly, NTs occurring in the vulva are extremely rare with the few cases reported in the English literature considered as Merkel cell carcinoma (MCC). Here we document a neuroendocrine vulvar carcinoma with peculiar microscopic, immunohistochemical and ultrastructural features reminiscent of a paraganglioma.

A 62-year-old woman presented with a 20-mm soft, painful lump located in the right upper portion of the labia majora. Abdominothoracic computed tomography (CT) scan excluded the possibility of it being a metastasis from a primary tumour elsewhere. An excisional biopsy was performed and a diagnosis of neuroendocrine carcinoma made. Three months later the neoplasm recurred locally and right inguinal lymphadenopathy was noted. Treatment consisted of radical vulvectomy followed by local radiotherapy. Eight months later a total body CT scan revealed an enlargement of the abdominal and mediastinal lymph nodes. Nineteen months after the original diagnosis the patient is still alive with multiple abdominal and thoracic metastases.

Histologically, the tumour involved the dermis and subcutis and showed a prevalent organoid or ‘Zellballen’ pattern of growth (Figure 1a). Occasionally, hypercromatic, slender cells, resembling sustentacular cells, outlined the neoplastic nests.

Tumour cells were medium in size, with abundant clear to eosinophilic cytoplasm; nuclei were round to oval with fine chromatin and occasional nucleoli. Mitotic figures, apoptotic bodies, foci of tumour necrosis, vascular invasion, and occasional glandular or pseudoglandular structures (Figure 1a, inset) were observed. Metastatic nodal disease was morphologically similar to the primary vulvar neoplasm.

Neoplastic cells were immunoreactive for cytokeratin 8 and 18, carcinoembryonic antigen (CEA), synaptophysin, PGP9.5 and neuron-specific enolase but were negative for cytokeratin 20, chromogranin A, and TTF-1. Protein S100 decorated occasional cells at the periphery of the ‘Zellballen’ (Figure 1b).

Electron microscopy was performed from a paraffin block. Tumour cells contained numerous dispersed cytoplasmic membrane-bound dense granules and exhibited features of epithelial differentiation including cell junctions. Moreover, electron microscopy showed the presence of long, slender sustentacular cells, outlining the epithelial nests.

On the basis of the morphological, immunohistochemical, ultrastructural and clinical findings a final diagnosis of neuroendocrine carcinoma of the vulva with paraganglioma-like features was made. The differential diagnosis included metastatic neuroendocrine carcinoma, malignant paraganglioma and MCC. Careful clinical evaluation and the absence of a previous history of a neuroendocrine neoplasm help to rule out a metastasis.

The ‘Zellballen’ growth pattern and the presence of sustentacular cells suggested a diagnosis of paraganglioma. A case of paraganglioma without malignant features occurring in the vulva has been reported. However, in the present case the presence of glands, the strong cytokeratin and CEA immunoreactivity, and the ultrastructurally evident desmosomal junctions strongly supported an epithelial origin of the lesion. Paraganglioma stains for neuroendocrine markers, but is not usually reactive for cytokeratin and CEA. Although occasional examples of paraganglioma have been reported to be immunoreactive for keratin, CEA immunostaining has never been described in this tumour. Moreover, it is noteworthy that the presence of sustentacular cells is not exclusive to paragangliomas.

Although the few reports describing primary neuroendocrine carcinoma of the vulva support its origin from epidermal Merkel cells, this case did not show the typical immunohistochemical and ultrastructural features of MCC.

Figure 1. a Neoplastic cells were mainly disposed in organoid nests. Inset: rare glandular structures were found in another microscopic field. b, Immunohistochemically, S100 protein outlined a residual stellate/dendritic cell at the periphery of a tumour nest (arrow).
The origin of primary vulvar neuroendocrine carcinomas is particularly intriguing.\(^7, 8\) In the present case the apparent lack of any relationship with vestibular glands and the absence of morphological features other than neuroendocrine strongly support an origin from solitary or aggregated cells of the diffuse/dispersed neuroendocrine system.

Whether the present case is simply a histological curiosity or has clinical significance is a moot point. We suggest that the diagnosis of neuroendocrine carcinoma, even with an unusual morphological appearance, should always be taken into account, since these tumours have a highly malignant clinical course, with disseminated disease usually occurring within 1 year following diagnosis.

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