Gastrointestinal Stromal Tumor (GIST) with Glandular Component. A Report of an Unusual Tumor Resembling Adenosarcoma

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Summary

A case of gastrointestinal stromal tumor (GIST) with an unusual glandular component is reported. The tumor was found in the gastric fundus of a 93-year-old woman. Histologically, the lesion showed a biphasic adenosarcoma-like structure. Typical low-grade spindle cell patterns of GIST were intermingled with numerous and partly cystic glands. The glandular epithelium had pyloric/foveolar-like appearance, with foci of intestinal metaplasia and low-grade dysplasia. The stromal component was immunoreactive for CD117 (c-kit) and CD34, and negative for myoid and neuroid markers. The ultrastructural examination found nondescript and undifferentiated spindle cells. The gastric mucosa and submucosa near the tumor contained a small area with features of gastritis cystica profunda, with glands similar to those present inside the tumor. Therefore, a collision of GIST and gastritis cystica profunda is suggested in the histogenesis of the lesion.
Key words: **gastrointestinal stromal tumor – adenocarcinoma - gastritis cystica profunda – adenosarcoma – carcinosarcoma – stomach**

Súhrn

Gastrointestinálny stromálny tumor (GIST) s glandulárnou zložkou. Popis neobvyklého prípadu

Popísaný je neobvyklý prípad gastrointestinálneho stromálneho tumoru (GIST) s glandulárnou zložkou. Šlo o tumor gastrického fundu u 93-ročnej ženy. Histológia lézie bola tvorená diferencovanou vretenobunkovou štruktúrou typického GIST-u, v ktorej boli difúzne prítomné z časti cystické žliazky. Kolumnárny epitel žliazok bol podobný pylorickému a foveolárnemu typu, s ložiskami intestinálnej metaplázie a miestami s dyspláziami. Stromálna zložka tumoru bola imunohistochemicky pozitívna na CD117 (c-kit) a CD34, negatívne boli myoidné a neuroidné markery. Elektronmikroskopicky šlo o nediferencované vretenovité bunky. Sliznica a submukóza v blízkosti tumoru vykazovali fokálne známky gastritis cystica profunda so žliazkami podobnými ako vnútri tumoru. V histogenéze tumoru je predpokladaná kolízia GIST-u a gastritis cystica profunda.
Kľúčové slová: **gastrointestinálny stromálny tumor – adenokarcinóm – gastritis cystica profunda – adenosarkóm – karcinosarkóm – žalúdok**

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Gastrointestinal stromal tumor (GIST) is a tumor showing phenotypic characteristics of the interstitial cells of Cajal (17, 24). In these tumors various growth patterns were observed by the means of conventional light microscopy, such as epithelioid, spindle cell, intermediate, myxoid, schwannoma-like with nuclear palisading, and nested paraganglioma-like or carcinoid-like (10, 26). Some GISTs contain so-called skenoid fibers (14) composed of nodular tangles of collagen. Epithelial glandular structures do not belong to the recognized morphological spectrum of GIST, and this is not surprising as GIST is basically a neoplasm of mesenchymal origin. However, we have encountered recently an unusual GIST in which glandular structures were scattered inside an otherwise typical spindle cell population.

Clinical History

A 93-year-old female patient with ischemic coronary disease and with a history of several weeks of dyspepsia and recent vomitus was examined endoscopically for suspected gastric ulcer. In the gastric fundus a polypoid mass measuring 4.5x2.5x2 cm was found. It was removed endoscopically in several fragments. According to the clinician's information the polypoid lesion was excised completely. Seven weeks after the tumor excision, the patient was stabilized and without significant gastro-intestinal symptomatology. Clinical examinations did not find any tumor in other location.

Materials and Method

Biopsy specimens were fixed in formalin and embedded in paraffin. The sections were stained with HE, PAS, PAS with diastase, alcian blue at pH2.5 and Warthin-Starry silver stain for Helicobacter pylori. Primary antibodies used for immunohistochemistry are listed in table 1. Immunostaining was performed according to standard protocols using avidin-biotin complex labeled with peroxidase or alkaline phosphatase. Appropriate positive and negative controls were applied. For electron microscopic investigations, wet formol-fixed tissue was post-fixed in 4% paraformaldehyde, contrasted in 1% osmium tetroxide, and embedded in epoxy resin (Durcupan-Epon). Sections were cut 1 Ķm thick, stained with toluidine blue, and examined by light microscopy. Appropriate areas were selected, and thin sections were cut and stained with uranyl acetate and lead citrate, and examined with a Philips (Eindhoven, Netherlands) EM 208S electron microscope.

Results

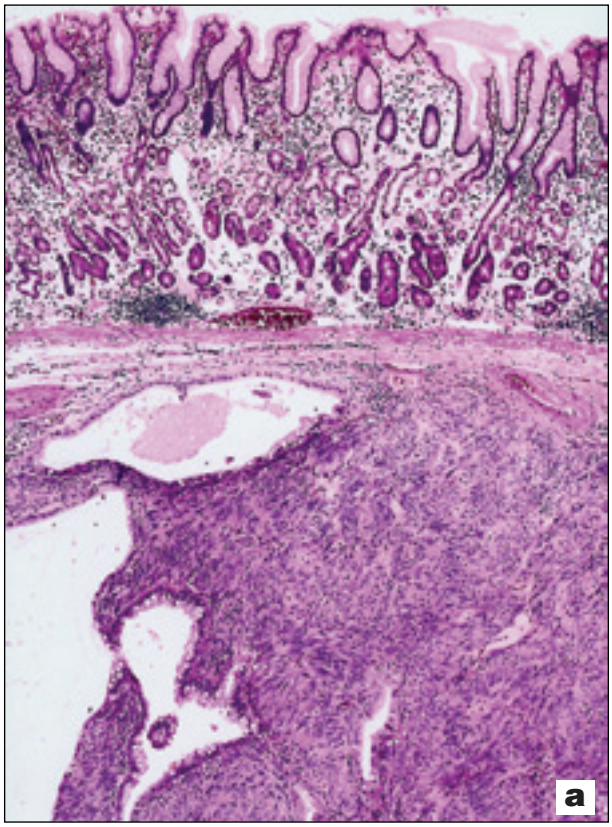
The excised tissue fragments were of irregular shape and measured from 5 to 14 mm. **Histologically**, they contained structures of polypoid mucosal/submucosal tumor and tissues of adjacent mucosa and submucosa. The tumor was composed of spindle cell fascicles with scattered and partly cystic glands (fig. 1). The spindle cell component had features of ordinary GIST with a slight atypia and with rare mitoses [1/50HPF] only. The glandular component contained cylindrical epithelium with a slightly eosinophilic cytoplasm and bland basal nuclei. Focally, the epithelium underwent complete intestinal metaplasia (IM). In addition, some glands showed low-grade dysplasia (fig. 1b). The

Table 1. Antibodies used for immunohistochemistry (*ASMA* α-smooth muscle actin, *AR* androgen receptor, *EMA* epithelial membrane antigen, *ER* estrogen receptor, *MSA* muscle specific actin, *MW* microwave pretreatment, *NSE* neuron-specific enolase, *poly* polyclonal, *PR* progesterone receptor)

Antibody specificity	Clone	Dilution	Pre-treatment	Source
cytokeratin	AE1-AE3	1:1000	MW	Neo Markers, Westinghouse
EMA	E29	1:1000	none	DAKO, Glostrup
ASMA	1A4	1:1000	none	DAKO, Glostrup
MSA	HHF-35	1:500	none	Neo Markers, Westinghouse
desmin	D33	1:1000	none	DAKO, Glostrup
S100 protein	poly	1:4000	none	DAKO, Glostrup
NSE	BBS/NC/IV-H14	1:3000	MW	DAKO Glostrup
synaptophysin	polyclonal	1:400	MW	Neo Markers, Westinghouse
chromogranin A	DAK-A3	1:400	pepsin	DAKO, Glostrup
gastrin	poly	1:500	pepsin	DAKO, Glostrup
c-kit	CD117	1:150	none	DAKO, Glostrup
CD34	QBEnd/10	1:800	none	Neo Markers, Westinghouse
CD10	56C6	1:40	MW	Neo Markers, Westinghouse
MUC1	Ma695	1:200	MW	Novocastra, Newcastle
MUC2	Ccp58C	1:400	MW	Novocastra, Newcastle
MUC5AC	CLH2	1:400	MW	Novocastra, Newcastle
MUC6	CLH5	1:400	MW	Novocastra, Newcastle
ER	ER1D5	1:1000	MW	Immunotech, Marseille
PR	1A6	1:50	MW	Immunotech, Marseille
AR	AR 441	1:2000	none	DAKO, Carpenteria
Ki 67	MIB1	1:1000	MW	DAKO, Glostrup

tumor was well-circumscribed and had a superficial ulceration. On the edge of the ulceration the inflamed corporal mucosa showed foveolar hyperplasia with complete intestinal metaplasia and with foci of low-grade dysplasia (fig. 2). Outside the ulcer margin, the mucosa showed features of mildly active chronic inflammation (fig. 1a) with pyloric metaplasia and with negativity for Helicobacter pylori. In addition, this mucosa and subjacent submucosa contained a small focus that resembled gastritis cystica profunda (GCP), with typical cystic glands in mucosa and submucosa near the tumor margin (fig. 3). The cystic glands were lined with cylindrical epithelium with clear to eosinophilic cytoplasm and bland basal nuclei. Except for the lack of IM and dysplasia, this epithelium was identical to that seen in glands inside the tumor.

The PAS and alcian stains showed typical mucin positivity in IM. The epithelium of the non-intestinalized glands inside the tumor as well as in the cystic glands near the tumor often showed luminal surface positivity for alcian blue and PAS-D whereas cytoplasmic positivity in both these stains was rare.



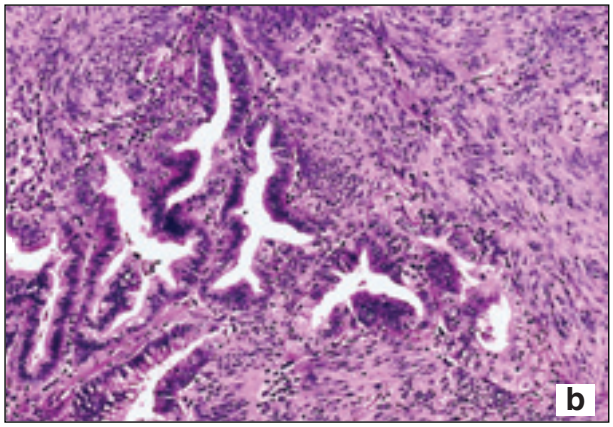
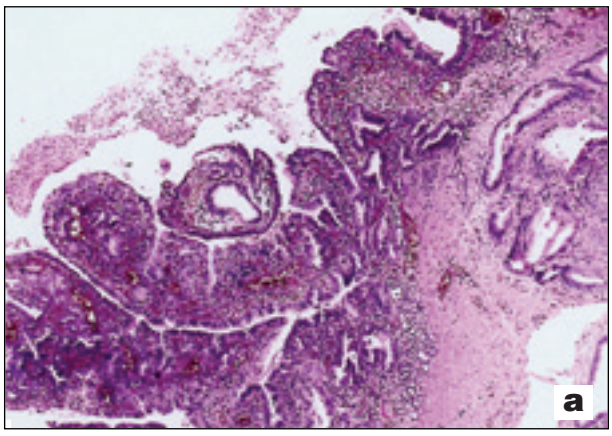


Fig. 1. GIST with glandular component a Low-power view shows well-circumscribed spindle cell tumor with bland appearing and partly cystic glandular component (HE, x25). b The spindle cell component had features of GIST. Some of the glands showed dysplastic changes (HE, x100)



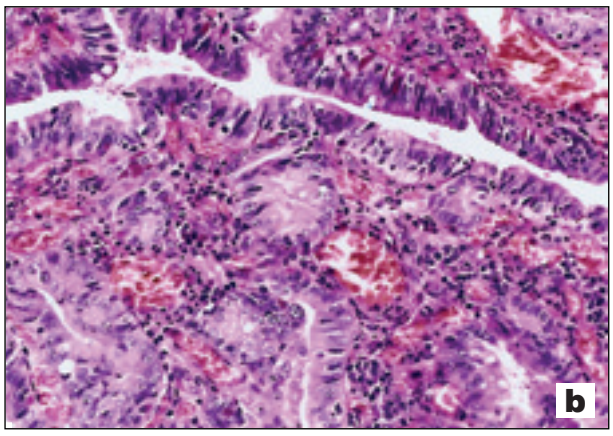


Fig. 2. The mucosa near the tumor margin. a Low-power view shows dysplastic mucosa near the tumor margin. Peripheral area of the tumor is seen as well (*right*) (HE, x25). b Low-grade dysplasia is well apparent in high-power view (HE, x400)

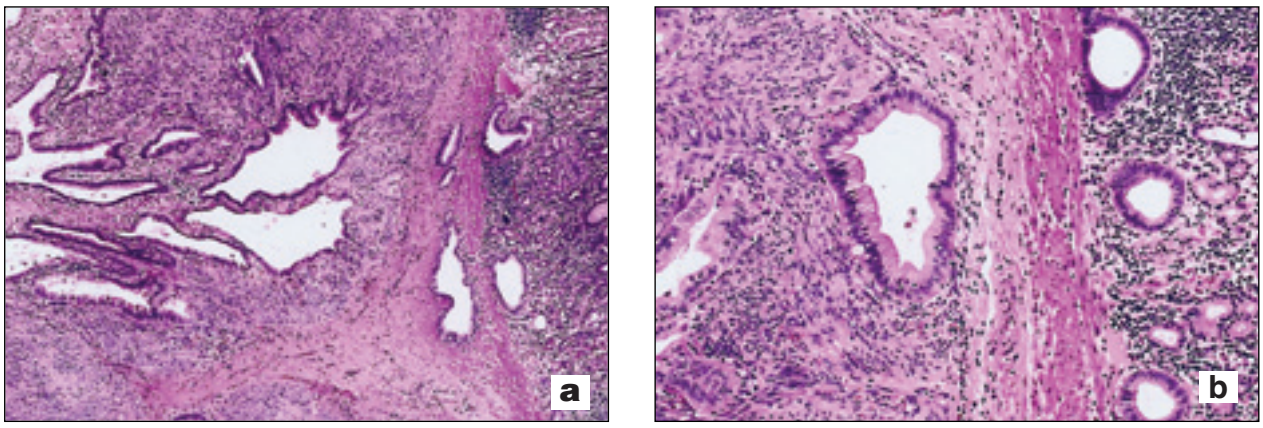


Fig. 3. A rare area suggesting a collision histogenesis of the lesion. a Features of gastritis cystica profunda in the mucosa/submucosa adjacent to the tumor (HE, x25). b The glandular epithelium had similar appearance both inside and outside the tumor (HE, x100)

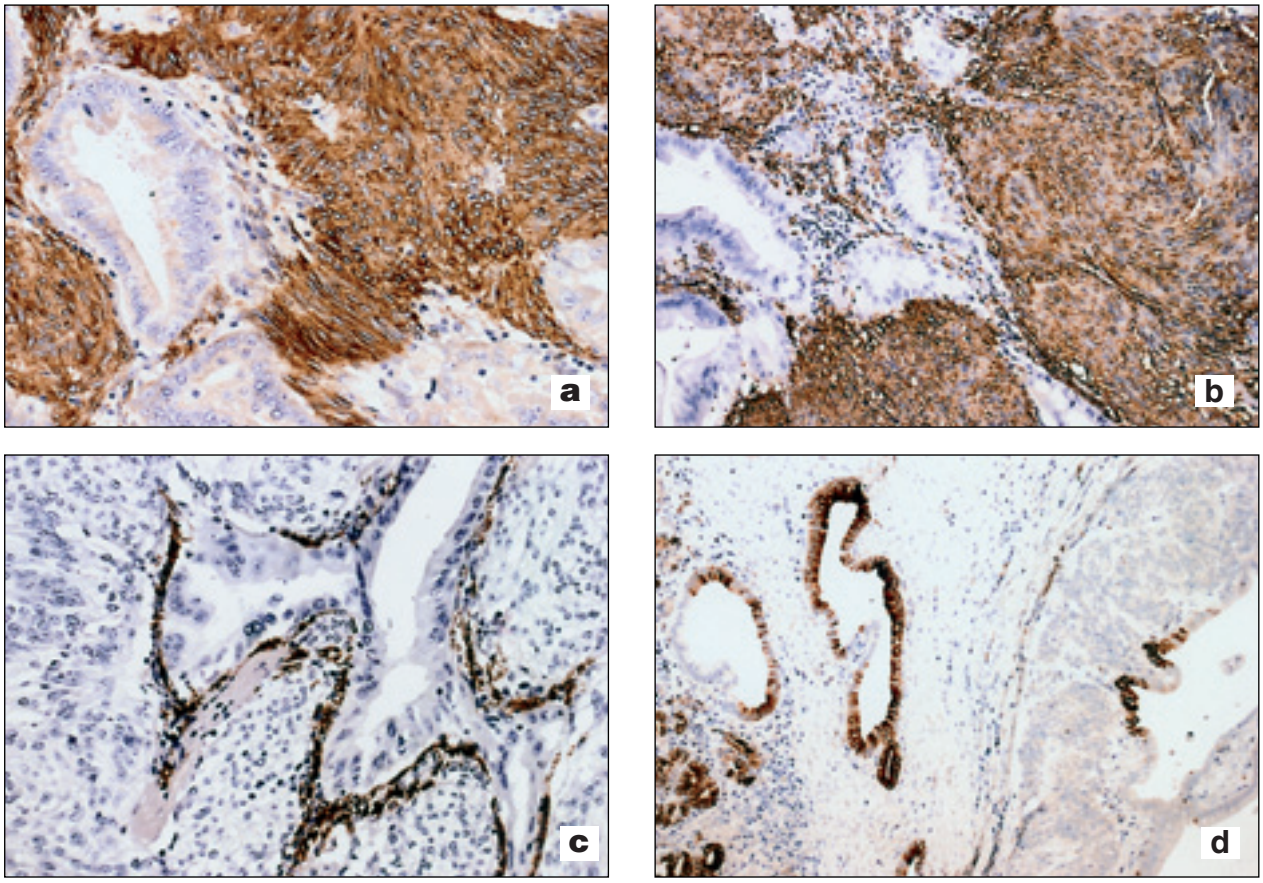
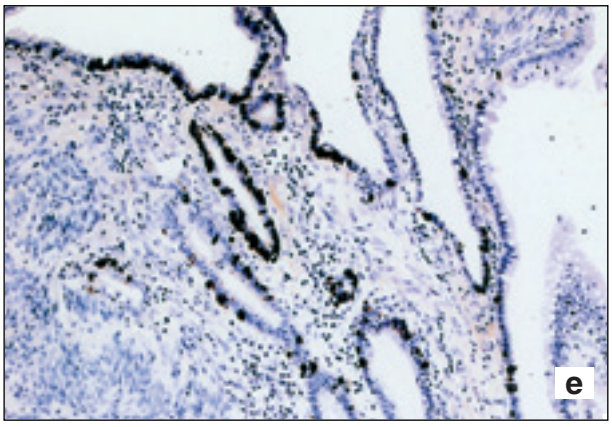


Fig. 4. Immunohistochemical features of the tumor. a Positivity of spindle cells for c-kit (ABC technique, x200). b Reactivity for CD34. A thin zone of CD34-negative stromal cells adjacent to the basement membrane of the glands is seen focally (ABC technique, x200). c Actin-positive stromal cells in a thin periglandular zone contrast with neoplastic actin-negative spindle cells of GIST (ABC technique, x200). d MUC6 reactivity in both GCP and intratumoral glands (ABC technique, x100). e Numerous chromogranin A-positive cells in the glandular epithelium (ABC technique, x100)



Immunohistochemically, the spindle cell component was strongly and diffusely positive for CD117 (c-kit) and CD34 (figs 4a and 4b), negative for cytokeratin, EMA, S100 protein, actin and desmin, and its MIB1 index was 3%. Anti-actin stained a few cells in a thin zone around some of the glands (fig. 4c). This zone was focally negative for CD117 and CD34. Anti-MUC6 (pyloric type mucin) stained many cells of glands inside the tumor and in cystic glands near the tumor (fig. 4d) as well as some cells in IM and dysplasia. Anti-MUC5AC (foveolar type mucin) also stained many cells in cystic glands both inside and outside the tumor as well as numerous cells in IM and dysplasia. MUC2 (intestinal type mucin) was positive in IM only. MUC1 was positive on luminal surface of some intratumoral glands, without any cytoplasmic reactivity. CD10 expression was limited to luminal cell surface in areas of intestinal metaplasia. Reactivity for chromogranin A (fig. 4e) and synaptophysin was seen in many cells of IM and dysplasia, but rare positive cells were scattered also in the undifferentiated cylindrical epithelium inside and outside the tumor, with a slight predominance in intratumoral glands. Immunostains for gastrin, ER, PR and AR gave negative results.

Ultrastructurally, the tissue available for examination was poorly preserved. The cells were elongated and some of them had dendritic appearing processes, especially in myxoid areas. In the cytoplasm numerous dark granules were seen, but the distinction between neuroendocrine granules and other granular structures [particularly lysosomes] was impossible due to the suboptimal tissue preservation. The nuclei were ovoid, with small nucleoli and granular chromatin. The cytoplasm contained intermediate filaments, granular endoplasmic reticulum and a few mitochondria. The only surface structure that could be identified was an infrequent desmosome-like cell junction. A various number of collagen fibers without skenoid features were seen in the extracellular space. Thus, the tumor cells were nondescript and undifferentiated, without any smooth muscle, schwannian or convincing GANT features (8).

Discussion

The diagnosis of GIST in the present case is indicated by the typical morphology of spindle cell pattern and the immunohistochemical positivity for CD117 and CD34 (17, 20, 21, 24, 26). Our ultrastructural finding of undifferentiated spindle cells is consistent with this diagnosis as well, and is in keeping with immunohistochemical negativity for myogenic and neurogenic markers (8). According to the contemporary classification, the tumor represents GIST without myogenic or neurogenic differentiation (10, 26). Measuring less than 5 cm, lacking significant atypia, and showing only rare mitoses and low MIB1 index, the tumor could be labeled as benign (10, 26). However, because of the presence of ulceration and the tumor diameter close to the 5cm threshold, along with a lack of an exact confirmation of a complete tumor removal, we preferred to diagnose it as "GIST of uncertain malignant potential, probably benign" with recommendation of a clinical follow-up.

The glands inside the tumor appear to be an extremely unusual finding. An exact classification of cylindrical epithelium of these glands was difficult. It resembled pyloric metaplasia (9), but in contrast with pyloric glands it showed cytoplasmic PAS positivity only in rare cells, although expression of MUC6 (pyloric type mucin) (15) was seen in numerous cells. Moreover, some of the cells expressed foveolar type mucin MUC5 (15). Thus, the glands did not show complete differentiation of any particular gastric cell type. We speculate that this epithelium is immature (i.e., containing adult stem cells) and capable of differentiation toward various cell types, and that in our case it differentiated toward pyloric (MUC6+), foveolar (MUC5+) and intestinal epithelium as well as it underwent initial neoplastic transformation toward dysplasia. Similar "totipotent" epithelial cells were labeled "ulcer associated cell lineage" by Wright et al. (28) who regard them as prototypic repair cell lineage. Recently Mukaisho et al. described and termed similar epithelium as "gut regenerative cell lineage" in animal experiment (23). The intratumoral glands in the present case were often dilated to cystic. This histological picture suggested initially an unusual biphasic epithelial-stromal neoplasm. However, we were capable to find, after an extensive sampling, similar epithelial cystic change, intestinal metaplasia and focal dysplasia (9) in the gastric mucosa adjacent to ulcerated tumor margin. Moreover, we have seen around some intratumoral glands actin-positive and CD117-negative myoid cells that differed from neoplastic cells and appeared as reactive cells of lamina propria entrapped into the tumor together with the gastric glands. Thus these findings indicate that the glands are not neoplastic and that they were "entrapped" into the tumor mass in consequence of a complex process combining the tumor growth, ulceration and exaggerated epithelial regeneration and proliferation in the area of that ulceration. The intestinal metaplasia and dysplastic changes of epithelium are probably related to ulceration as

well, as they usually are in an ordinary gastric ulcer (9, 23). The epithelial structure in our case was very similar if not identical to that of gastritis cystica profunda (11-13) which represents reactive lesion found in various gastric conditions such as ulcer, erosion, adenoma, carcinoma, carcinoid and previous gastric surgery (3, 12, 22, 29). In classical GCP the interaction between regenerated gastric epithelium and proliferating reactive fibroblastic and myoid cells leads to a peculiar histological picture of cystic glands intermingled with stromal cells. These glands contained cylindrical epithelium described as pyloric type (12). However, they showed sometimes an alcian blue positivity (11) which is unusual for pyloric glands, and it seems that the epithelium in GCP may be often immature and undefined, i.e. without differentiation toward any gastric cell type. In addition, some described cases of GCP contained intestinal metaplasia (13) and/or dysplasia (11) [like the epithelium inside the present tumor]. These observations support our view that the glandular component in the present tumor shows a phenotype consistent with GCP.

The rarely observed mixed pattern of carcinoma and GCP (3, 29) is explainable as a result of a "dynamic" relationship between the gastric mucosa and the neoplastic cells population. We think that histogenesis of the present structure is explainable in analogy, i.e. as a result of interaction between the neoplastic spindle cells of GIST and the adjacent non-neoplastic gastric epithelium.

In the differential diagnosis, several known primary "biphasic" gastric tumors were considered, such as gastric adenomyoma (6, 9, 19), gastric adenosarcoma (16) and gastric adenocarcinoleiomyosarcoma (7). Adenomyoma contains a mixture of benign smooth muscle cells and pancreatic ductal structures. In contrast with our case, the spindle cells of adenomyoma are actin and/or desmin positive and negative for CD117 (c-kit). Gastric adenosarcoma is not a well-established entity as an only one case was described by Kallakury et al. in 1993 (16). This lesion contained high-grade spindle cell leiomyosarcomatous component immunoreactive for desmin and benign glands with columnar-type epithelium. So-called gastric adenocarcinoleiomyosarcoma described by Dundas et al. (7) showed leiomyosarcomatous stroma and its epithelial component was clearly carcinomatous in contrast to gastritis cystica-like glands seen in our case. With regard to the differential diagnosis, we speculate that in the past, when spindle cell tumors of the gastrointestinal tract were classified either as leiomyomatous or schwannomatous as the category of GIST was yet not defined, the tumors similar to the present one could have been diagnosed as adenomyoma or adenosarcoma. Additional lesion that needs to be excluded in the differential diagnosis is a metastasis of biphasic epithelial-stromal tumor from other location (27), especially mullerian adenosarcoma (4) and mullerian stromal sarcoma with glandular differentiation (5). These tumors show different epithelium lacking intestinal metaplasia, and their stromal component has a little resemblance with benign or borderline GIST. Moreover, mullerian lesions express often estrogen and/or progesterone receptor (1, 2). Regarding CD117 positivity, it should be mentioned that it was observed in some mullerian sarcomas and carcinosarcomas, and therefore it cannot help in this differential diagnosis (18).

In conclusion, we have described an extraordinary case of GIST that contained heterologous glandular component. The glands were partly cystic and showed focal intestinal metaplasia and dysplasia. They were scattered inside an otherwise typical CD117+/CD34+ spindle cell population. The epithelial component resembled strongly that of gastritis cystica profunda. From the histogenetic point of view the lesion can be interpreted as a collision of GIST and GCP.

References

1. **Amant F., Schurmans K., Steenkiste E., et al.:** Immunohistochemical determination of estrogen and progesterone receptor positivity in uterine adenosarcoma. Gynecol. Oncol., 93, 2004, s. 680–685. – 2. **Ansink A.C., Cross P.A., Scorer P., et al.:** The hormonal receptor status of uterine carcinosarcomas (mixed mullerian tumours): an immunohistochemical study. J. Clin. Pathol., 50, 1997, s. 328–331. – 3. **Bogomoletz W.V., Potet F., Barge J., et al.:** Pathological features and mucin histochemistry of primary gastric stump carcinoma associated with gastritis cystica polyposa. A study of six cases. Am. J. Surg. Pathol., 9, 1985, s. 401–410. – 4. **Clement P.B., Scully R.E.:** Mullerian adenosarcoma of the uterus: a clinicopathologic analysis of 100 cases with a review of the literature. Hum. Pathol., 21, 1990, s. 363–381. – 5. **Clement P.B., Scully R.E.:** Endometrial stromal sarcomas of the uterus with extensive endometrioid glandular differentiation: a report of three cases that caused problems in differential diagnosis. Int. J. Gynecol. Pathol., 11, 1992, s. 163–173. – 6. **Derbyshire R.C.:** Studies of aberrant pancreas (thesis). University of Minnesota, Minnesota, 1940, U.S.A. – 7. **Dundas S.A., Slater D.N., Wagner B.E., Mills P.A.:** Gastric adenocarcinoleiomyosarcoma: a light, electron microscopic and immunohistochemical study. Histopathology, 13, 1988, s. 347–353. – 8. **Erlandson R.A., Klimstra D.S., Woodruff J.M.:** Subclassification of gastrointestinal stromal tumors based on evaluation by electron microscopy and immunohistochemistry. Ultrastruct. Pathol., 20, 1996, s. 373–393. – 9. **Fenoglio-Preiser C.M., Noffsinger A.E., Lantz P.E., et al.:** Gastrointestinal Pathology. An Atlas and Text, 2nd edition, Lippincott- Raven Press, 1999, Philadelphia PA; U.S.A. – 10. **Fletcher C.D., Berman J.J., Corless C., et al.:** Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum. Pathol., 33, 2002, s. 459–465. – 11. **Franzin G., Musola R., Zamboni G., Manfrini C.:** Gastritis cystica

polyposa: a possible precancerous lesion. Tumori, 71, 1985, s.13–18. – 12. **Franzin G., Novelli P.:** Gastritis cystica profunda. Histopathology, 5, 1981, s. 535–547. – 13. **Fonde E.C., Rodning C.B.:** Gastritis cystica profunda. Am. J. Gastroenterol., 81, 1986, s. 459–464. – 14. **Gall J.A., Chetty R., Kemp A.J., Penfold J.C.:** Multiple benign stromal cell tumours of the small bowel. J. Clin. Pathol., 46, 1993, s. 869–871. – 15. **Ho S.B., Shekels L.L., Toribara N.W., et al.:** Mucin gene expression in normal, preneoplastic, and neoplastic human gastric epithelium. Cancer Res., 55, 1995, s. 2681–2690. – 16. **Kallakury B.V., Bui H.X., delRosario A., et al.:** Primary gastric adenosarcoma. Arch. Pathol. Lab. Med., 117, 1993, s. 299–301. – 17. **Kindblom L.G., Remotti H.E., Aldenborg F., Meis-Kindblom J.M.:** Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am. J. Pathol., 152, 1998, s. 1259–1269. – 18. **Leath C.A. 3rd., Straughn J.M. Jr., Conner M.G., et al.:** Immunohistochemical evaluation of the c-kit proto-oncogene in sarcomas of the uterus: a case series. J. Reprod. Med., 49, 2004, s. 71–75. – 19. **Magnus Alselben E.I.V.:** Adenomyoma des pylorus. Virchows Arch. [A], 175, 1905, s. 137–156. – 20. **Mazur M.T., Clark H.B.:** Gastric stromal tumors. Reappraisal of histogenesis. Am. J. Surg. Pathol., 7, 1983, s. 507–519. – 21. **Miettinen M., Virolainen M., Sarlomo-Rikala M.:** Gastrointestinal stromal tumors – value of CD34 antigen in their identification and separation from true leiomyomas and schwannomas. Am. J. Surg. Pathol., 19, 1995, s. 207–216. – 22. **Morishita Y., Tanaka T., Kato K., et al.:** Gastric collision tumor (carcinoid and adenocarcinoma) with gastritis cystica profunda. Arch. Pathol. Lab. Med., 115, 1991, s. 1006–1010. – 23. **Mukaisho K., Miwa K., Kumagai H., et al.:** Gastric carcinogenesis by duodenal reflux through gut regenerative cell lineage. Dig. Dis. Sci., 48, 2003, s. 2153–2158. – 24. **Sarlomo-Rikala M., Kovatich A.J., Barusevicius A., Miettinen M.:** CD117: a sensitive marker for gastrointestinal stromal tumors that is more specific than CD34. Mod. Pathol., 11, 1998, s. 728–734. – 25. **Song S.Y., Park S., Kim S., et al.:** Characteristics of intramucosal gastric carcinoma with lymph node metastatic disease. Histopathology, 44, 2004, s. 437–444. – 26. **Suster S.:** Gastrointestinal stromal tumors. Semin. Diagn. Pathol., 13, 1996, s. 297–313 – 27. **Wick M.R., Swanson P.E.:** Carcinosarcomas: current perspectives and an historical review of nosological concepts. Semin. Diagn. Pathol., 10, 1993, s. 118–127. – 28. **Wright N.A., Pike C., Elia G.:** Induction of a novel epidermal growth factor-secreting cell lineage by mucosal ulceration in human gastrointestinal stem cells. Nature, 343, 1990, s. 82–85. – 29. **Yamagiwa H., Matsuzaki O., Ishihara A., Yoshimura H.:** Heterotopic gastric glands in the submucosa of the stomach. Acta Pathol. Jpn., 29, 1979, s. 347–350.

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Odborné akce v roce 2006

27.–29. ledna	Seminář: Patologie urogenitálního traktu – Plzeň
8. února	Meziregionální seminář patologů IAP – Olomouc
20.–24. března	Minikurzy u multihead mikroskopu – Plzeň
7.–8. dubna	Seminář mladých patologů – Litomyšl
26. dubna	Sklíčkový diagnostický seminář – Praha (1. LF UK)
4.–6. května	Sjezd českých patologů a sympozium molekulární patologie – Olomouc
září	Sjezd slovenských a českých patologů – Nitra
13.–14. října	Meziregionální seminář patologů IAP – Olomouc