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Case Report / Приказ болесника

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Synchronous adenocarcinoma and gastrointestinal stromal tumor (GIST) in the stomach – report of two cases

Синхрони аденокарцином и гастроинтестинални стромални тумор желуца (ГИСТ) – приказ два случаја

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SUMMARY

Introduction Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor that occurs in the gastrointestinal tract, most commonly in the stomach or small intestine. The surgery of stomach is the dominant way of treatment of these tumors. The synchronous detection of adenocarcinoma and gastric GIST is not so common condition, which is often diagnosed intraoperatively and has a significant impact on the prognosis of these patients.

Case outline We herein report two cases of gastric GIST with synchronous adenocarcinoma tumors who, while undergoing surgery for a primary gastric adenocarcinoma, were incidentally, intraoperatively detected to have a synchronous gastric GIST. The first case is of a 76-year-old female patient. The histopathological analysis of the operative specimen showed in the first place, a poorly differentiated advanced gastric adenocarcinoma. The second tumor, from the gastric serosa, was a spindle cell gastrointestinal stromal tumor of low risk. It was diffusely positive for DOG1, CD34 and CD117. Its proliferative index was established using Ki67 antibody. The number of mitoses was 1 mitosis per 5 mm^2.

The second case is of a 65-year-old male patient. The histopathological analysis revealed an early, well-differentiated, intestinal type adenocarcinoma of gastric mucosa. The synchronous tumor from the serosa of the stomach was a spindle cell gastrointestinal stromal tumor (CD34, DOG1 and CD117 diffusely positive) of low risk. The proliferative index of this tumor, labeled with the Ki67 antibody was very low. Necrosis was not present, as well as mitoses

Conclusion Synchronous adenocarcinomas and GIST stomach are not so common a association of two tumors, that are usually detected intraoperatively and after immunohistochemical analysis. Recognition of this condition is very important role in differential diagnostic value and the exclusion of metastases of malignant tumor deposits. Based on these tumor severity we determine the radicalness of surgical intervention which has an impact on the outcome of these patients.

Keywords: gastrointestinal stromal tumor; gastric adenocarcinoma; synchronous tumor

САЖЕТАК

Увод Гастроинтестинални стромални тумори (ГИСТ) су најчешћи мезенхимални тумори, који се јављају у гастроинтестиналном тракту, најчешће у желуцу и танком цреву. Операција је доминантан начин лечења ових тумора. Синхроно јављање аденокарцинома и ГИСТ-а желуца је не тако честа асоцијација два различита типа тумора, које се често дијагностикује интраоперативно и има значајан утицај на прогнозу болести ових пацијената.

Приказ случаја У овом раду дат је приказ два случаја синхроних аденокарцинома и гастроинтестиналних тумора желуца, који су дијагностиковани случајно у току операције примарног аденокарцинома желуца. Први случај је пацијенткиња стара 76 година, код које је хистопатолошка анализа оперативног препарата показала узнапредовали слабо диферентованиадено карцином, као и гастроинтестинални стромални тумор вретенастих ћелија желуца, ниског ризика. Други тумор са желудачне серозе је био дифузно позитиван на *DOG1, CD34* и *CD117*, а пролиферативни индекс је установљен антителима *Ki67*. Број митоза је био 1/5 mm^2. Други случај је пацијент стар 65 година оперисан због раног добро диферентованог аденокарцинома интестиналног типа, код кога је интраоперативно установљено постојање синхроног ГИСТ вретенастих ћелија (*DOG1, CD34* и *CD117* дифузно позитивни) са ниским ризиком. Пролиферативни индекс био је веома низак, а некроза и митозе нису биле присутне.

Закључак Синхрони аденокарциноми и ГИСТ желуца су не тако честе асоцијације два различита типа тумора, који се обично откривају интраоперативно и након имунохистохемијске анализе. Препознавање овог стања има диференцијално дијагностички значај у искључивању метастаза и депозита малигног тумора. На основу узнапредовалости туморских процеса одређује се радикалност оперативног захвата, што има утицаја на исход лечења ових пацијената.

Кључне речи: синхрони тумори; гастринтестинални стромални тумори (ГИСТ); аденокарцином желуца

INTRODUCTION

A gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor that occurs in the gastrointestinal tract (GI), most commonly in the stomach or small intestine. More than half of GISTs start in the stomach. Most of the others start in the small intestine, but GISTs can start anywhere along the GI tract [1]. The tumors are thought to grow from specialized cells found in the gastrointestinal tract called interstitial cells of Cajal (ICCs) or precursors to these cells. ICCs are cells of the autonomic nervous system, the part of the nervous system that regulates body processes such as digesting food. ICCs are sometimes called the "pacemakers" of the GI tract because they signal the muscles in the digestive system to contract in order to move food and liquid through the GI tract. GISTs are usually found in adults between ages of 40 and 70, children and young adults rarely develop these tumors. The tumors can be with a unclear malignant potential and metastatic risk [2].

Small tumors may cause no signs or symptoms. However, some people with GISTs may experience pain or swelling in the abdomen, nausea, vomiting, loss of appetite, or weight loss. Sometimes, tumors cause bleeding, which may lead to low red blood cell counts (anemia) and, consequently, weakness and tiredness. Bleeding into the intestinal tract may cause black and tarry stools, and bleeding into the throat or stomach may cause vomiting of blood [3].

Adenocarcinoma is the most common histological type of gastric tumor, accounting for approximately 95% of all gastric carcinomas. It has been determined that adenocarcinoma is the aggressive tumour based on histologic features. Although collision tumors of the stomach are uncommon, several cases have been reported. Most collision tumors of the stomach are composed of an adenocarcinoma intermixed with a gastric lymphoma. Some are composed of an adenocarcinoma intermixed with a carcinoid tumor. However, gastric collision tumors composed of a GIST and adenocarcinoma are exceedingly rare [4, 5, 6].

Synchronous tumours in the stomach are rarely diagnosed preoperatively. We herein report two cases of gastric GIST with synchronous adenocarcinoma tumors.

CASE REPORT

We herein report two cases of gastric GIST with synchronous adenocarcinoma tumors who, while undergoing surgery for a primary gastric adenocarcinoma, were incidentally, intraoperatively detected to have a synchronous gastric GIST. The first case is of a 76-year-old female patient. She was evaluated for her complains of fatigue and upper epigastric pain. Laboratory test results showed low levels of Fe. EHO examination of the abdomen did not verify significant deviations from normal findings. CT examination of the abdomen, showed on the fundus of the stomach along to the large

curvature, a soft tissue tumor, with no significant post-contrast opacification, measuring up to 20 mm, which contains the small calcifications (Figure 1).

Esophagogastroduodenoscopy revealed on the large curve in the distal part of the corpus of the stomach, the circular recess with irregular edges about 3 cm in diameter, on a wide basis, which is infiltrative changed. On the same level, but along the rear wall, gastroduodenoscopy showed a submucosal nodule, about 20 × 15 mm in diameter. The patient was treated surgically; the operation of choice was subtotal gastrectomy with D2 lymphadenectomy. Intraoperatively changes on a large curvature of the stomach were verified, 3cm in diameter, which penetrated serosa and omentum. The nodule was verified on the serosa of gastric fundus, 1 cm in diameter. The histopathological analysis of the specimen showed in the first place, a poorly differentiated advanced gastric adenocarcinoma (histological grade 3), that infiltrated half of the stomach muscular wall thickness (Figure 2).

The final diagnosis was made by immunohistochemical analysis, and the tumor was positive for cytokeratins. The second tumor, from the gastric serosa, was a spindle cell gastrointestinal stromal tumor of low risk. It was diffusely positive for DOG1, CD34 and CD117. Its proliferative index was established using Ki67 antibody (+, in less than 3% of the tumor cells). The number of mitoses was 1 mitosis per 5 mm^2 (Figures 3 and 4).

The second case is of a 65-year-old male patient was evaluated for his complaints of dysphagia, loss of appetite, pain in the upper abdomen and 2 episodes of melena. Laboratory test results showed low levels of hemoglobin. Esophagogastroduodenoscopy verified hyperemic mucosa of antrum, with subepithelial polypoid tumor, with central recess, about 3–4 mm in diameter. Biopsy was taken and histopathological examination showed a high degree of dysplasia. The patient was treated surgically; the operation of choice was subtotal gastrectomy. Intraoperatively, little tumor was verified on serosa of the stomach corpus, 10x13mm in diameter, and tumor on stomach antrum, 5 mm in diameter, which didn't penetrate serosa.

The gastric tumor was located in the fundic part of the stomach. It was an ulcerative lesion, 5mm in diameter. The serosal tumor weighted 0.6 grams, measuring 13 × 10 × 10 mm.

The histopathological analysis revealed an early, well-differentiated, intestinal type adenocarcinoma of gastric mucosa that invaded superficially the lamina propria. Signs of chronic atrophic gastritis with intestinal metaplasia in the surroundings of the above-mentioned tumor were noted.

The tumor from the serosa of the stomach was a spindle cell gastrointestinal stromal tumor (CD34, DOG1 and CD117 diffusely positive) of low risk. The proliferative index of this tumor,

labeled with the Ki67 antibody was very low (about 1% of Ki67 positive tumor cells). Necrosis was not present, as well as mitoses (0 mitosis / 50 high power fields, or 0 mitosis / 5 mm^2).

DISCUSSION

The emergence of two histologically different neoplasms in the same organ is not so common. Adenocarcinoma is the most common malignant stomach tumor, while on the other side GIST is stromal tumor of the digestive tract that occurs in less than 1% of all gastrointestinal malignancies [7]. Synchronous tumors are not that common tumor association, and are usually detected only during the histopathological evaluation [8]. When the GIST is submucosal or subserosal the gastric mucosa may not be invaded and the endoscopic biopsies can be normal. In most of the reported cases of synchronous gastric adenocarcinoma and GIST, the preoperative biopsy fragments showed only adenocarcinoma and the GIST were detected only following laparotomy and examination of the resected stomachs[9]. In our first case, gastroduodenoscopy showed submucosal nodule, about 20x15mm in the diameter. In our second case, the total gastrectomy was performed primary for the gastric adenocarcinoma and a small GIST was found incidentally with the histopathological examination of the specimen. The coexistence of primary gastric adenocarcinoma and GIST has often been detected incidentally on gastric mucosa or serosa, or occasionally intramurally, at surgery or gastroscopy for other reasons [10]. Some authors have found that 10% of GIST is in association with other neoplasms, usually cancer [11]. The incidence of synchronous occurrence of adenocarcinoma and GIST is 0.25%. According to literature, co-existence of GISTs with the other tumours ranges from 4.5% to 33%. Maiorama has found that out of 52 patients there were 6 cases of GIST association with other tumor (5 with adenocarcinoma and 1 with carcinoid) [12, 13].GIST is most common in the stomach (60%), jejunum and ileum (30%), duodenum (5%), colorectum (<5%), while a few individual cases described in the esophagus and the appendix (<1%) [14].

The literature describes the phenomenon of synchronous GIST with different tumors, adenocarcinoma, lymphoma, leukemia, lung cancer, prostate cancer, pancreatic cancer, adrenal adenoma [15, 16, 17]. In most cases, GIST and adenocarcinoma are described indifferent parts of the stomach, but in the literature, there are cases where are they in collision [18]. Patients treated for synchronous tumour should receive adjuvant therapy for the more advanced or aggressive tumour type [19]). Synchronous adenocarcinomas and GIST stomach are not so common a association of two tumors, that are usually detected intraoperatively and after immunohistochemical analysis. Recognition of this condition is very important role in differential diagnostic value and the exclusion of metastases of malignant tumor deposits. Based on these tumor severity we determine the radicalness of surgical intervention which has an impact on the outcome of these patients [18, 19].

GIST is positive for CD117, CD34, and occasionally for actin, but always negative for desmin and S-100 protein [20]. In our cases, GIST is from the category of low risk, with spindle cells, with no signs of atypia, necrosis, or bleeding. Immunohistochemical staining was positive for the DOG-1, CD34, CD117, and Ki67 (1–3% of the tumor cells). Many studies highlight the positivity of CD117 and CD34 in GIST tumors. According to the literature CD117 is expressed in 80-95%. The definitive diagnosis is not possible if the tumor is negative for CD117, CD34, SMA and S100 [20]. A novel marker DOG-1 has been found in GIST tumors, which can be used for definitive diagnosis. DOG-1 is a membrane calcium dependent chloride channel expressed specifically and strongly at GIST [21, 22].In our cases, definite diagnosis of GIST was possible because the tumour cells were diffusely and strongly positive for DOG1, CD34, and CD117.

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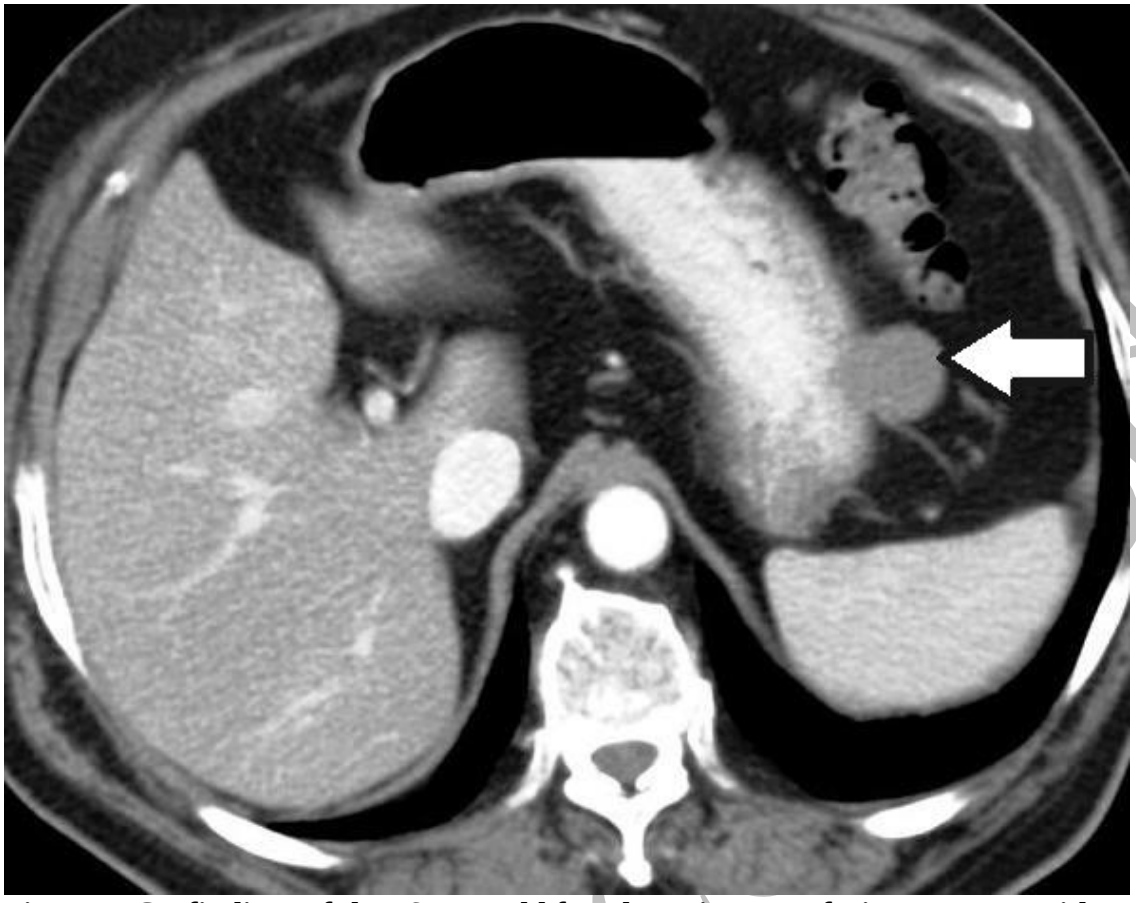

Figure 1. CT findings of the 76-year-old female patient: a soft tissue tumor, with no significant post-contrast opacification along the large curvature of the stomach fundus (arrow)

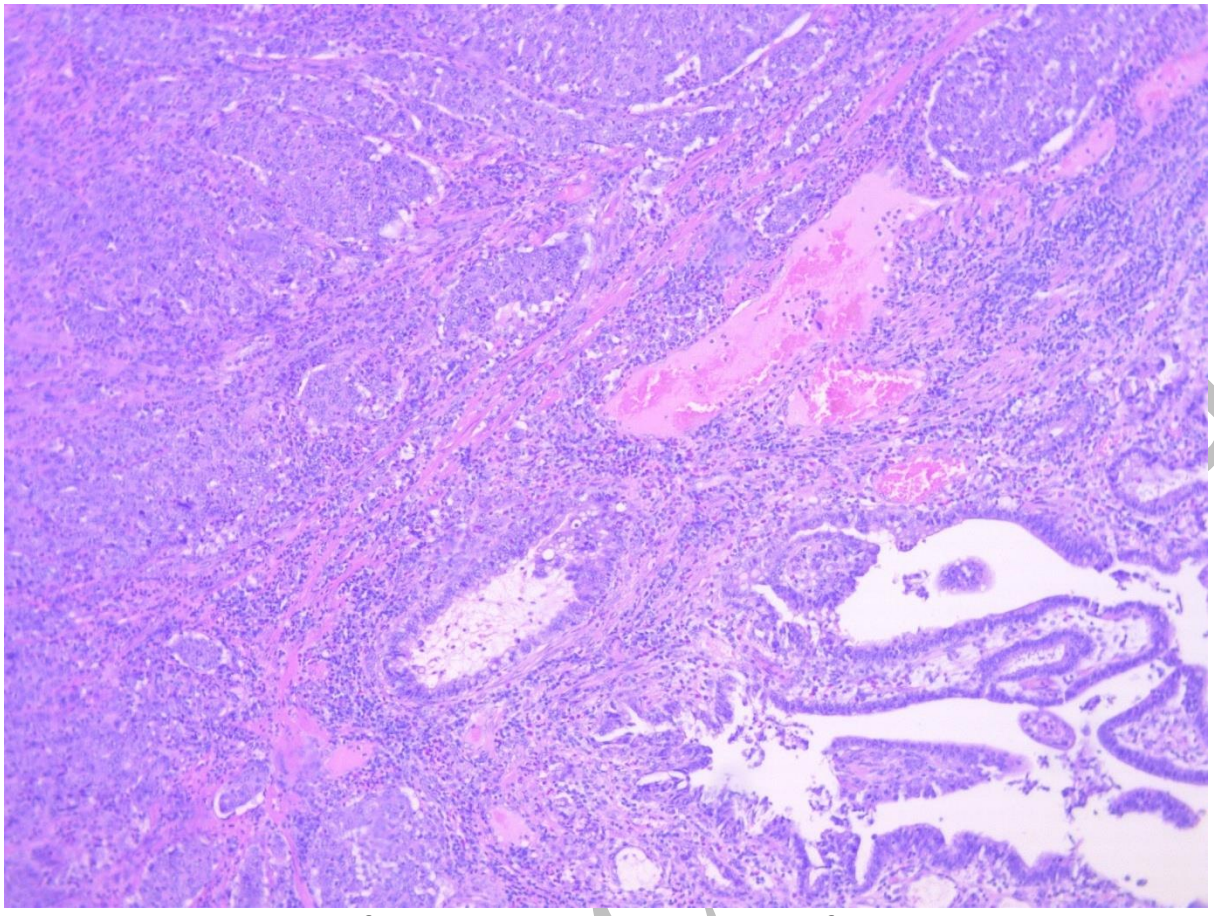

Figure 2. The 76-year-old female patient: adenocarcinoma of the stomach, poorly differentiated, intestinal type, H&E, ×100

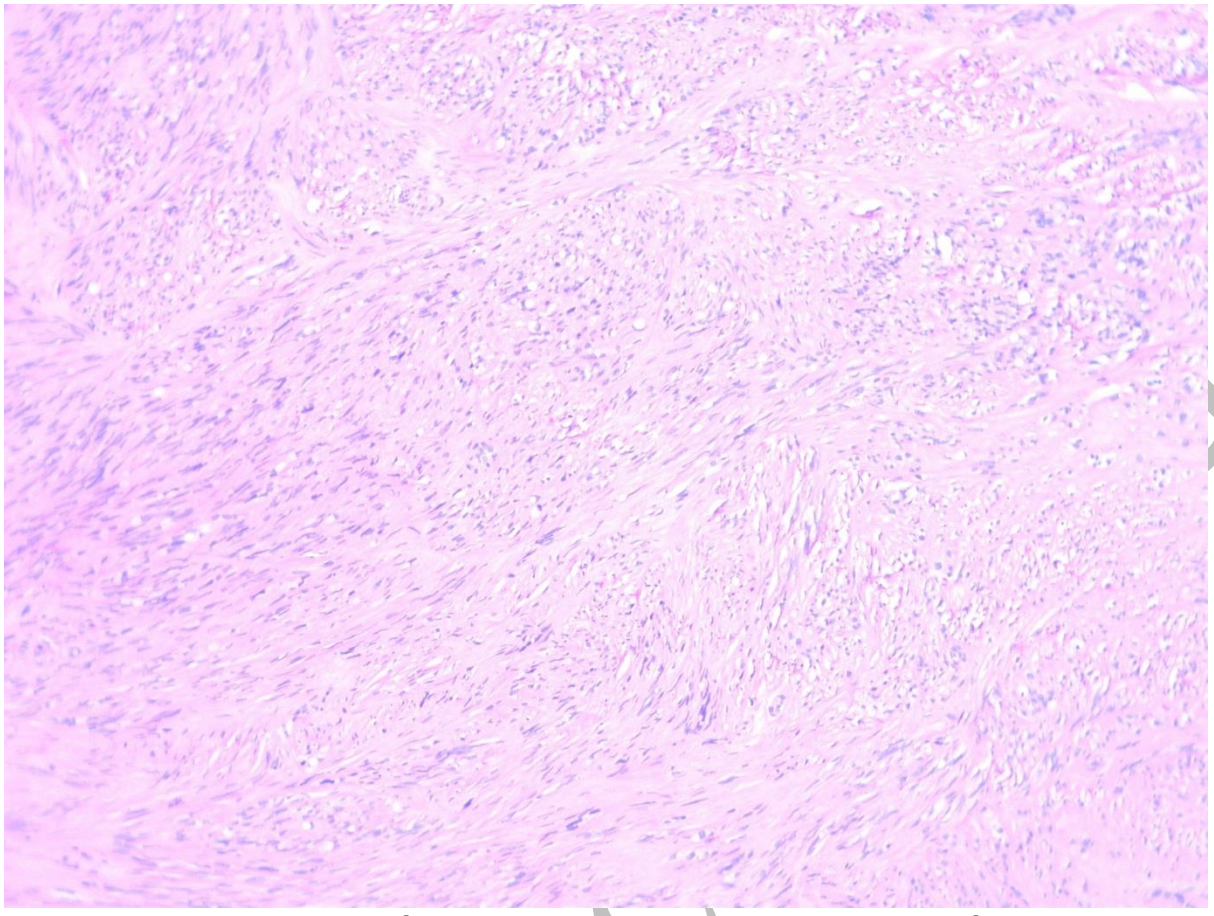

Figure 3. The second tumor, from the gastric serosa in the 76-year-old female patient: gastrointestinal stromal tumor, spindle cell type, H&E, ×200

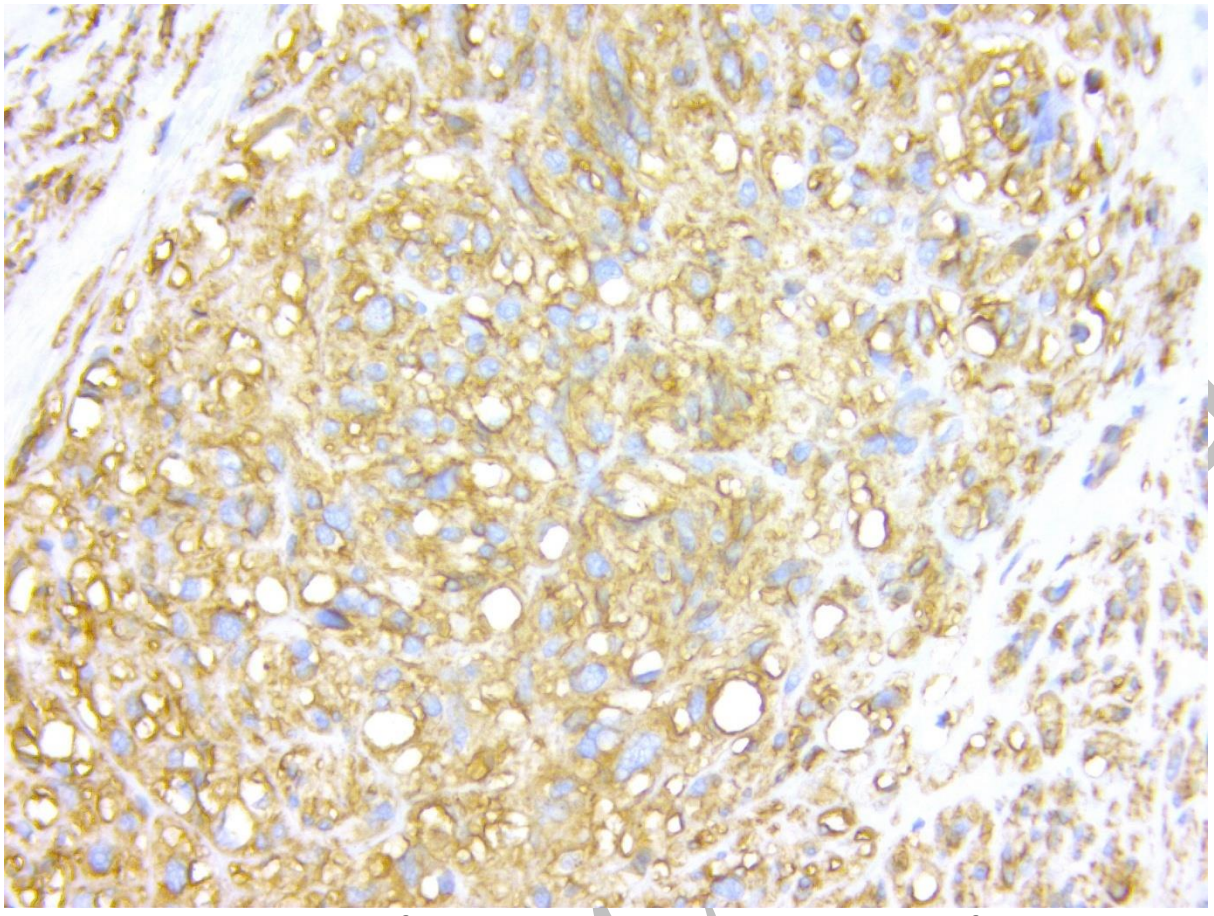

Figure 4. The second tumor, from the gastric serosa in the 76-year-old female patient: gastrointestinal stromal tumor, spindle cell type, antiDOG1 antibody, ×400

Table 2. Comparison of categorical variables between patients with schizophrenia and controls, the results of Pearson Chi-Square test

Morphological features		Patients (N = 126)	Control group (N = 124)	p	OR	95% CI
		N (%)				
Hair	Fine hair – going up soon after combing[1]	68 (54.0%)	41 (33.1%)	0.001**	2.373	1.422–3.963
	Fine hair – not going down after combing[1]	64 (50.8%)	23 (18.5%)	0.000**	4.533	2.559–8.030
	Two or more hair whorls[1]	82 (65.1%)	15 (12.1%)	0.000**	13.542	7.054–26.001
Eyes	Epicanthus[1]	7 (5.6%)	2 (1.6%)	0.116	3.588	0.731–17.624
	Eyebrows fused[2]	41 (32.5%)	17 (13.7%)	0.001**	3.036	1.612–5.718
	Heterochromia[2]	4 (3.2%)	1 (0.8%)	0.215	4.033	0.444–36.599
Nose	Wide nose basis[3]	65 (51.6%)	21 (16.9%)	0.000**	5.226	2.911–9.382
	Nostrils anteverted[2]	30 (23.8%)	31 (25%)	0.827	0.938	0.526–1.670
Ear	Low-seated ears – the lowest point of the earlobe in line with mouth or lower[4]	74 (58.7%)	20 (16.1%)	0.000**	7.400	4.079–13.425
	Low-seated ears - the lowest point of the earlobe in line with the area between nose and mouth[4]	48 (38.1%)	67 (54%)	0.012	0.524	0.316–0.867
	Adherent earlobes[1]	67 (53.2%)	59 (47.6%)	0.377	1.251	0.761–2.056
	Lower part of earlobes towards back	7 (5.6%)	2 (1.6%)	0.116	3.588	0.731–17.624
	Malformed ears[1]	5 (4%)	0	0.999	-	-
	Asymmetrical ears[1]	6 (4.8%)	4 (3.2%)	0.538	1.500	0.413–5.450
	Soft and pliable ears[1]	64 (50.8%)	55 (44.4%)	0.308	1.295	0.787–2.130
	Preauricular skin tag[3]	0 (0%)	3 (2.4%)	0.999	-	-
Palate	High-steepled palate[1]	72 (57.1%)	31 (25%)	0.000**	4.000	2.335–6.852
	High flat palate[1]	38 (30.2%)	21 (16.9%)	0.015	2.118	1.158–3.875
Tongue	Continuous longitudinal	38 (30.2%)	40 (32.3%)	0.752	0.917	0.537–1.567

	fissure[4]					
	Discontinuous longitudinal fissure[4]	**41 (32.5%)**	**40 (32.3%)**	**0.927**	**1.025**	**0.603–1.742**
	One central and two shorter longitudinal fissures[4]	**12 (9.5%)**	**11 (8.9%)**	**0.843**	**1.091**	**0.462–2.575**
	Only transverse fissures[4]	**9 (7.1%)**	**3 (2.4%)**	**0.093**	**3.129**	**0.827–11.847**
	Transverse fissures in the last third of the tongue with a longitudinal fissure apically[4]	**10 (7.9%)**	**5 (4%)**	**0.196**	**2.070**	**0.686–6.240**
	Vertical fissure running along the midline and few fissures diffusely distributed across the dorsal tongue surface[4]	**20 (15.9%)**	**3 (2.4%)**	**0.001****	**7.683**	**2.220–26.583**
	Fissures diffusely distributed across the dorsal tongue surface[4]	**18 (14.3%)**	**4 (3.2%)**	**0.004**	**5.047**	**1.656–15.380**
	Without any fissures[1]	**12 (9.5%)**	**14 (11.3%)**	**0.663**	**0.834**	**0.370–1.884**
	With rough spots[1]	**44 (34.9%)**	**39 (31.5%)**	**0.531**	**1.184**	**0.698–2.007**

[1]Waldrop et al. [5]; [2]Ismail et al. [33] ; [3]Gourion et al. [6]; [4]New/modified items;
OR – odds ratio; CI – confidence interval;
***p ≤ 0.0018 (Bonferroni correction);**
****p ≤ 0.001**

Table 3. Two-way MANOVA (Gender X Group) of selected continuous variables

Variable	Gender	Group	Mean	SD	p	η_p^2
Body height	female**	Research	163.37	6.12	0.000**	0.532
		Control	169.07	6.94		
	male**	Research	179.64	7.14		
		Control	183.59	7.94		
Head circumference	female**	Research	53.60	2.31	0.000**	0.178
		Control	55.33	1.92		
	male	Research	56.60	2.46		
		Control	56.68	2.32		
(Inner canthus distance + outer canthus distance)/2	female**	Research	6.61	0.84	0.002*	0.044
		Control	5.47	0.71		
	male	Research	6.71	0.80		
		Control	6.10	1.00		

SD – standard deviation; η_p^2 – partial eta-squared;
***p ≤ 0.007 (Bonferroni correction);**
****p ≤ 0.001**

Table 4. Multiple univariate logistic regression model for prediction of group status of schizophrenic patients and normal comparison subjects based on minor physical anomalies

Variable	Beta estimate	SE	χ^2 (df = 13)	p
Inner canthus distance	3.906	0.773	25.558	0.000**
Outer canthus distance	-1.156	0.320	13.050	0.000**
Fine hair – not going down after combing	0.853	0.501	2.894	0.089
Fine hair –going up soon after combing	0.098	0.464	0.044	0.833
Two or more hair whorls	2.049	0.521	15.475	0.000**
Eyebrows fused	0.318	0.552	.332	0.565
Wide nose basis	0.545	0.519	1.104	0.293
Low-seated ears – the lowest point of the earlobe in line with mouth or lower	1.257	0.470	7.162	0.007
High-steepled palate	1.698	0.532	10.191	0.001**
High flat palate	1.225	0.593	4.268	0.039
Vertical fissure running along the midline and few fissures diffusely distributed across the dorsal tongue surface	1.425	1.001	2.028	0.154
Fissures diffusely distributed across the dorsal tongue surface	1.847	0.983	3.529	0.060
Constant	-4.882	1.625		

SE – standard error; df – degree of freedom;
***p ≤ 0.0038 (Bonferroni correction);**
****p ≤ 0.001**

