CASE REPORT

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The importance of full tests of incidentally detected premalignant lesions

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Abstract

Early detection of asymptomatic phase or paraneoplastic manifestations in precancerous lesions and an early, correct and accurate diagnosis in terms of pathology of the lesion in question, makes important chances of healing and prolonged patient's life expectations. We present the case of a young patient who came to the emergency room and then admitted in the cardiology department with a heart rhythm disorder. The medical investigations that followed (gastric endoscopy, biopsy, histological and IHC exams), finds gastric polyps, which proved to be gastrointestinal stromal tumors (GIST).

Keywords: heart arrhythmia, gastric polyps, precancerous lesions, GIST.

Introduction

In the last 10 to 15 years [1, 2], the morbidity of gastrointestinal cancer, mostly gastric cancer, quickly elevated, becoming almost endemic. The multicenter project report CEEX 68/2006 [3] shows that 650 000 deaths occur annually all over the world, caused by the 750 000 newly diagnosed cases of gastric cancer, representing 9.9% of all newly diagnosed cancers in the world, as the second cause of cancer death worldwide after lung cancer [4, 5]. In the last 20 years in Europe, mortality from gastric cancer ranks third (8.1% of cancer deaths in 2004), after lung and colorectal cancer [3, 4]. In Romania [3, 6–8], gastric cancer mortality rate is two times higher than in EU countries, with 16.67 deaths/ 100 000 inhabitants/year for men and 8.6 deaths/100 000 inhabitants/year for women (10.8% of cancer deaths). Unfortunately, epidemiological studies performed in Romania, shows that 95.5% of patients were diagnosed with advanced stage gastric cancer and only 4.4% in the early stage, largely due to late presentation to the doctor [6, 8]. A significant variation on detecting disease incidence (6.6/100 000 in Transylvania and Walachia place-to-place 1.9/100 000) is mainly related to health education and the possibility of performing endoscopic investigations [9–11]. If 25–30 years ago, the top of the risk factors were smoking, burned fats and alcohol [12, 13], now it refer to stress and fast, messy meals ingested, changes in terms of food coloring additives, preservatives, sweeteners, preparation, fast food, fat, hot, genetically modified foods, along with increased alcohol consumption, and despite the anti-tobacco campaigns, increasing smoking in all age groups below [13, 14]. For this reason, early detection of asymptomatic phase or paraneoplastic manifestations precancerous lesions and early diagnosis, correct and accurate in terms of pathology of the lesion in question, makes important chances of healing and prolonged patient's life expectations [15–17]. Late disease diagnosis raises also socio-economic issues, related to high costs for diagnosis and treatment of these pathologic conditions and expenses that can amount more than EUR 7.2 billion annually in the EU [4, 18, 19]. It is therefore necessary to start some national programs for screening and monitoring early cancers, especially in communities and geographic areas with the highest morbidity for further improvement of gastric cancer mortality. Consequently, the detection, the monitoring and the treatment of premalignant lesions defined (chronic atrophic gastritis with dysplasia, gastric polyps, gastric adenomas, stomach ulcer, stomach resected and infection with *Helicobacter pylori* strains CagA-positive), can result in future favorable results outstanding long-term [18, 20, 21].

Patient, Methods and Results

In May 2012, a 38-year-old male, without previous medical history presented to the Emergency Department of "Filantropia" Municipal Hospital, Craiova, Romania, with palpitations, chest discomfort, epigastric pain,

anxiety, asthenia for the past two days, after an intense physical and intellectual effort. He is a smoker (25 cigarettes/day for about 15 years), and currently works in constructions (as a structural engineer). No others personal pathology knowned. Physical examination at the admission was notable for body temperature 36.8^{0}C, normal weight, blood pressure 150/90 mmHg (to an anxious, agitated patient), heart rate 180 beats per minute, arrhythmic heart sounds, systolic murmur 1st degree, no gallop, respiratory rate 22 breaths per minute, vesicular murmur harsher but without wet rales; the rest of the clinical exams was normal. Initial laboratory data showed at the emergency room: hemoglobin 13.9 g/dL, leukocytes 8520/mm^3 of which 77% segmented neutrophils, 1% eosinophils, 14% lymphocytes, 8% monocytes, platelets 257 000/mm^3, ESR 67 mm in one hour. ECG showed the presence of atrial fibrillations with ventricular 181–186 rate (Figure 1a).

Chest X-rays showed the aspect of a tobacco bronchitis with normal dimensions of the heart silhouette. In that stage, the patient was admitted for the department of cardiology. On presentation to our department, we complete the blood investigations with coagulation panel (serum fibrinogen 287 mg/dL, spontaneously INR was 1.02, Quick Time 12.9 s), and metabolic screening was normal (serum glucose 78 mg/dL, BUN 19 mg/dL, serum creatinine 0.53 mg/dL). We have also repeated the electrocardiogram, which showed us the same arrhythmia, atrial fibrillation, 181 beats per minute, thin (0.06 s) QRS complex (axis at 30^0), no right or left atrial or ventricular hypertrophia and without changes in the repolarization phase (Figure 1b).

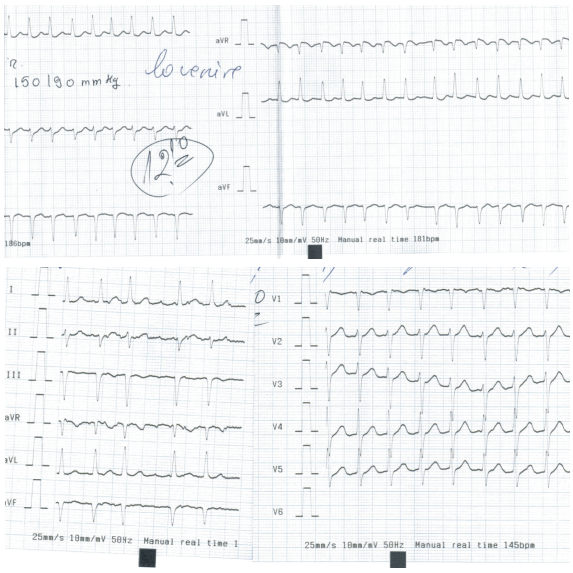

Figure 1 – ***Atrial fibrillation: (a) ECG at the admission in emergency room; (b) ECG at the admission in cardiology.***

The patient being stabile, we performed an echo-cardiographic exam, that revealed general hyperkinesis (due to the tachyarrhythmia), but normal dimensions and valvular aspects (Ao 28 mm, LA 31 mm, i.v. septum 9 mm, LVd 51 mm, LVs 42 mm, EFvs 59.5%). Given the fact that the arrhythmia seems recent and the fact that patient is young and stabile, with no cardio-vascular history, we decided to put on hold the electric defibrillation and to act classic. Therefore, we gave him: Amiodarone (5 mg/body weight/day, two times per day i.v. Glucose perfusion), anticoagulant (Enoxaparin sodium 40 mg/0.4, two times per day), sedative (Alprazolam 0.5 mg, two times per day), and ACE inhibitor (Quinaprilum 10 mg evening). One hour after, the ventricular rate was 89 beats per minute and B.P. 108/72 mmHg, still in atrial fibrillations, but much better as symptoms. We decided not to use beta-blockers because of pulmonary aspect of the patient. We continued the treatment with other perfusion in the evening. He remained all night arrhythmic. In the next morning, the first ECG we performed, showed a 69 ventricular rate sinus rhythm (Figure 2).

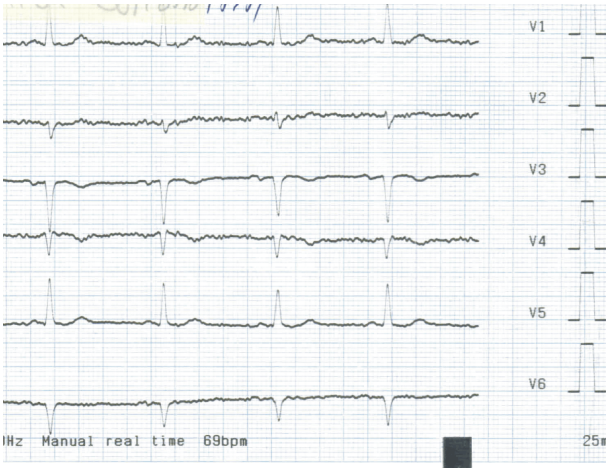

Figure 2 – ***Sinus rhythm: the next morning day ECG.***

Therefore, we began to reevaluate the patient to find out what caused the arrhythmia to further know how to treat him and how to prevent a new access of atrial fibrillation. All the tests (clinical, ECG, and echo heart) are normal, and the patient in sinus rhythm was asymptomatic. We could not do electrophysiology studies or watch the patient with Holter for arrhythmia to exclude the WPW syndromes (especially hidden ones), but all the ECG registrations have normal PR segment duration (0.10 for a 68–78 rate) and thin QRS complex (no more than 0.09 s). Therefore, we had to try to find something else. We reevaluate the history data gathered and focus on the digestive system. Some of gastric pathology usually interfere with cardiac symptoms or may trigger latent cardiovascular diseases. The upper abdominal pain and asthenia were over a year older and persisted after the arrhythmia resolution without a specific timetable, so we thought that it could be a hiatal hernia. A gastrointestinal endoscopy was performed at the gastroenterology department. Endoscopic examination of the upper digestive tract revealed multiple gastric polyps, 7–15 mm in size, in the gastric antrum. There were 5–6 sessile polyps covered with whitish yellow granules, 7 mm in diameter, arising from the greater curvature of the antrum (Figure 3). No malignant aspects: the surface of the polyps was smooth and without irregular area. The color of the polyps was almost uniform, but red spots could be seen in several places (Figure 4). Because the patient was young, and with risk factors for gastric diseases (stress, smoking, irregular meals, junk food) a

biopsy was made. *H. pylori* has been found negative. The patient was under cardiac observations for three days (Amiodarone, Clopidogrel) but the sinus rhythm was maintained. We also took care for the gastric condition (i.p.p., Sucralfate), as indicated the gastroenterologist physician. Two weeks after the discharge, we received the histological results: gastric stromal tumor.

Figures 5 and 6 (HE stain) highlighted the presence of a mixed GIST, with spindle and epithelioid cells that are characterized by short beams, uniform cells crossed by fibrillar eosinophilic cytoplasm. Perinuclear vacuoles and ovoid nuclei, stacked in spindle and epithelioid areas, present a solid growth pattern, with large cell vacuolated or clear cytoplasm. Either round or oval nuclei with finely dispersed chromatin and small nucleoli are observed. Figures 7–11 display images that demonstrate specific IHC positive markers for GIST tumors: CD117, CD34, S100 (cytoplasmic), Ki67 (intranuclear) and α-SMA (vessel walls).

Next week, the patient performed a partial gastric resection at the Emergency County Hospital of Craiova, Romania, and then he was taken in evidence to the Oncology Department in our hospital for further treatment and secondary prevention supervision.

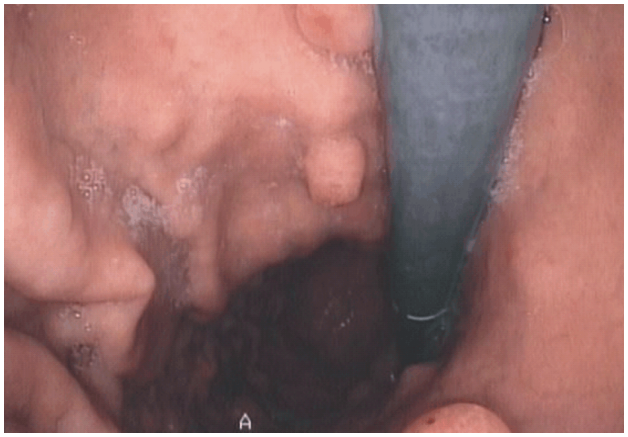

Figure 3 – ***Image from the gastric endoscopy: antrum's multiple polyps.***

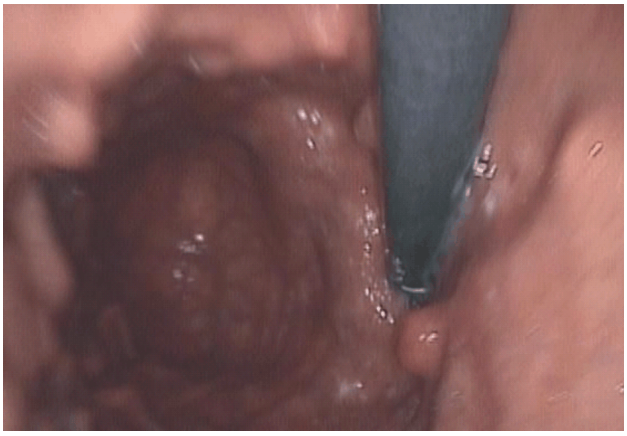

Figure 4 – ***No malignant aspects: smooth surface of the polyps, without irregular area.***

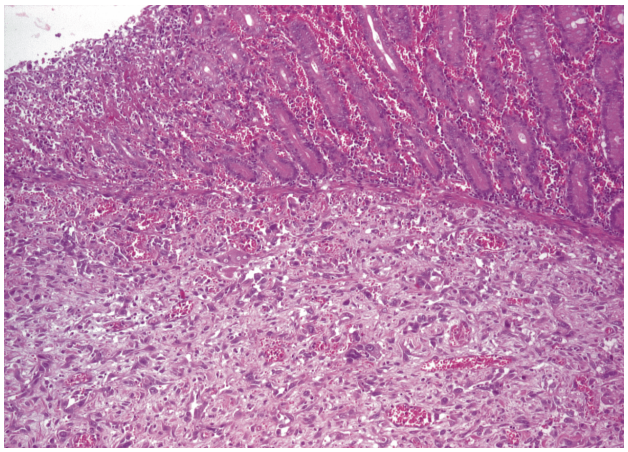

Figure 5 – ***GIST: gastric stromal tumor (HE stain, 40×).***

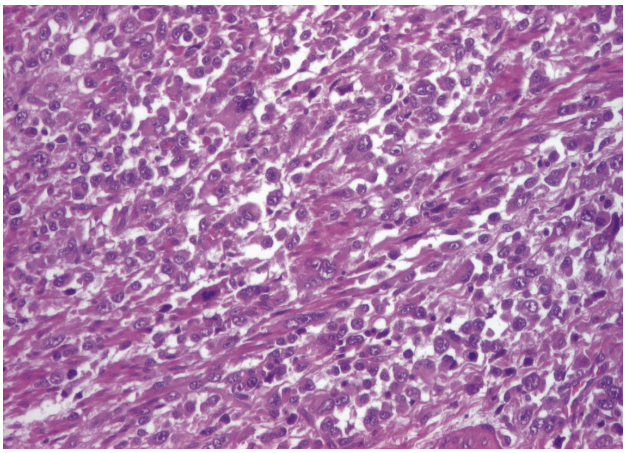

Figure 6 – ***GIST: tumor invasion into muscular tunica (HE stain, 100×).***

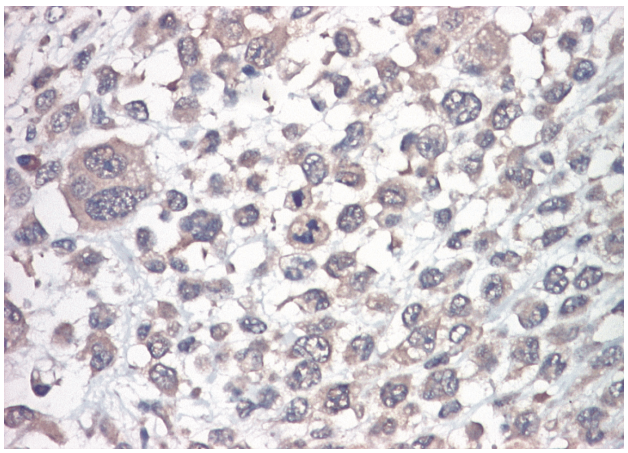

Figure 7 – ***GIST: CD117 positive cytoplasmic immunomarker (CD117 immunostain, 200×).***

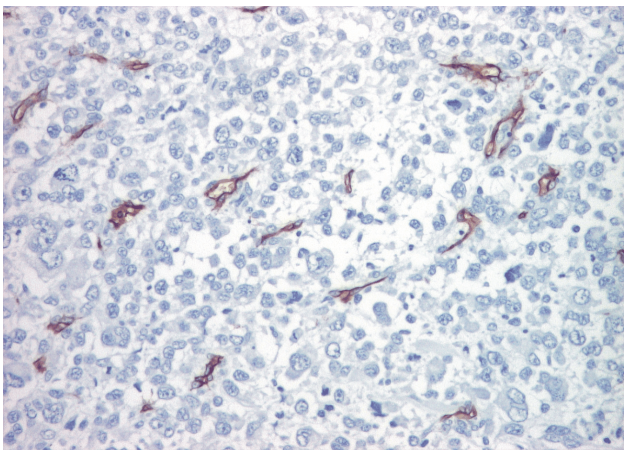

Figure 8 – ***GIST: rare CD34 positive cytoplasmic immunomarker (CD34 immunostain, 200×).***

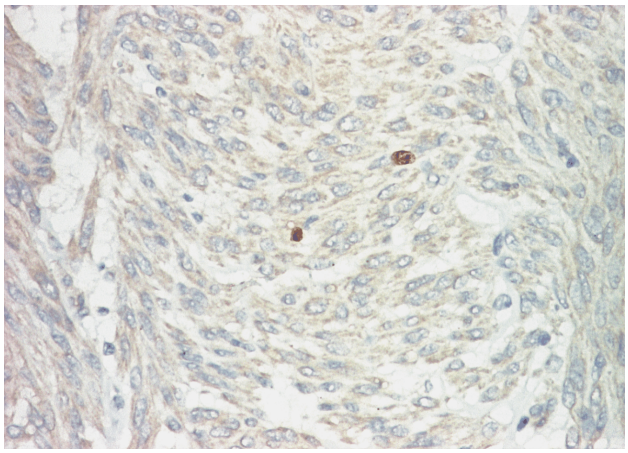

Figure 9 – ***GIST: Ki67 immunomarker positive in less 10% of tumor's cells (Ki67 immunostain, 200×).***

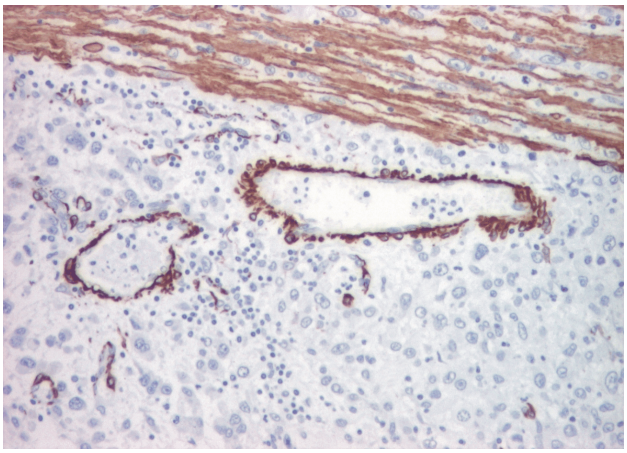

Figure 10 – ***GIST: positive alpha-smooth muscle actin immunomarker (α-SMA immunostain, 100×).***

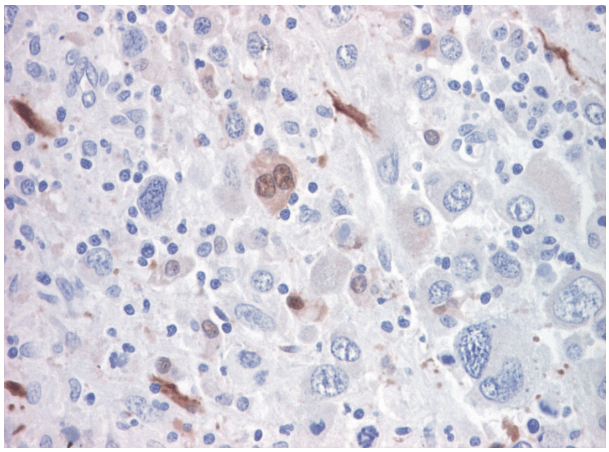

Figure 11 – ***GIST: S100 immunomarker positive in tumor's cells (S100 immunostain, 200×).***

Discussion

We found it educational to present this case because of the complexity and especially because of the combination of two complete different conditions, which improperly investigated could have negative effects for the well been of the patient. In this case, we have tried to find a correlation between paroxysmal arrhythmia and any digestive disease, but that proved to be false. We did not find any data in the literature, that a gastric polyp, regardless this location, might be the trigger for a heart rhythm disorder. However, things are different when we are dealing with a malignant polyp, because in paraneoplastic clinic syndromes, heart rhythm disorder could be, if not ordinary, but almost possible [21, 22]. Unable to perform endocrine and IHC tests for tracing the presence of specific hormones and/or peptides secreted by the carcinoid, we abandoned the idea of this possible etiology of paroxysmal atrial fibrillations. Thus, arrhythmia at this presented patient was secondary to his cardiovascular risk factors we had found (stress, smoking, addictions and messy food, alcohol), without any secondary digestive pathological implications. We had to go further. So we did not ignore the other symptoms, that did not fit in the clinical context of the apparent mainly disease, in this case the epigastric pain and asthenia. Also, finding a 'simple' polyp, uncomplicated and with small symptoms, we could have stopped investigations at this stage. If it was not, the accuracy of correctly and completely endoscopic examination, we have could miss a very important diagnosis for the patient's future [10, 16, 17].

Clinical issues

It is interesting that the clinical signs and symptoms of this pathological entity, is present in 72% of cases, direct related to the location of the tumor (most interest the stomach: 50–70%), to the growth rate and tumor diameter (a few mm) [16, 17, 19, 23]. Gastrointestinal stromal tumors may be clinical "silent" in small size [17, 21], or with minimal nonspecific symptoms as abdominal pain, or/and fatigue, as in our case. The large size up to 40 cm [17, 20], may be clinic palpable (50–70%) on physical exam, or may manifest symptoms due to their complications (upper GI bleeding/hemoperitoneum – 25% perforation tumor, intestinal obstruction or obstructive jaundice).

Pathogenesis

Gastrointestinal stromal tumors (GIST) have become a distinct clinically and histologically entity in the early 1980s when immunohistochemical techniques revealed that, some tumors shows characteristics not only of the smooth muscle differentiation, but also neuronal differentiation markers. Thus, initially were considered rare malignancy [22, 24–26] but soon, it turned out that their incidence was much higher than was expected before immunohistochemistry [27]. Literature data shows that GIST is 80% of gastrointestinal mesenchymal neoplasms and 0.1 to 3% of gastrointestinal malignancies in the U.S. [9, 18, 21, 25, 26]. The incidence is higher in males, and affects mostly the adults in the age group 4 to 7 [5, 10, 17, 18]. Pathogenesis of gastrointestinal stromal tumors originate from the interstitial cells of Cajal described (ICC), cell pacemaker – bowel, which generates slow electric waves and is willing inserted between intramural neurons and smooth muscle cells of the digestive tract [22, 26]; ICC is similar to cell fibroblasts, which express receptors CD117 (c-Kit+) [28]. Confirmation of diagnosis is by both histopathological and immunohistochemical examinations [22, 26]. Histological, the tumor sections, Hematoxylin

and Eosin colored, present morphological variations depending on tumor cells appearance: spindle cell type ("spindle-cell"), round/polygonal (epithelioid) cell type or mixed type, [15, 22, 26, 29]. Immunohistochemical examination involves evaluating the expression and the presence of tumor specific markers: c-Kit (94%), CD34 (82%), α-smooth muscle specific actin, S100 protein, desmin, Ki67 [22]. c-Kit (CD117) glycoprotein 145-kD is a defining diagnostic marker positive in 95% of GIST. Isolated positive immunohistochemical marking in absence of histopathological diagnosis (classic HE stain) might be considered false positive [22] because c-Kit is expressed also in other tumors. Miettinen's criteria [22, 26], explains that the malignancy is mainly given by the tumor size: over 10 mm and more than five mitoses per 50 HPFS. As secondary criteria, listed as specific for GIST tumors are: nuclear atypia, necrosis, ulceration, calcification, hyalinisation, organoid and palisaded pattern, and perinuclear vacuolation.

Particularities

In our case, the patient presented an unusual debut at the age that was under the age limit for the described disease, was poorly symptomatic because the macroscopical visible tumor, after endoscopy was small: about 25 mm (height polyp)/15 mm (diameter), without malignancy characters. Histological exam was the main method to diagnose the GIST gastric tumor (HE stain) related to immunohistochemical reveals, so both methods were positive as shown in the literature data cited in our presentation [30].

Conclusions

If any cardiac disorders occur to a young patient, he must be very carefully investigated to find the possible causes of those (including hiatal hernia and the paraneoplasic cardiovascular syndrome). When, after careful investigations found no other cause, only then it can be concluded that acute heart condition is due exclusively to personal risk factors. We did not find any data in the literature, that a gastric polyp, regardless this location, might be the trigger for a heart rhythm disorder. The combination of two complete different pathological conditions, improperly and incomplete investigated could have negative effects for the future health of the patient.

Contribution Note

All authors contributed equally to this manuscript.

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