

CASE REPORT

Metachronous gastrointestinal stromal tumor associated with other neoplasia – case presentation

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Abstract

The association of gastrointestinal stromal tumor (GIST), synchronous or metachronous with other tumors is reported in special literature, the most frequent being associated with other gastrointestinal tumors. GISTs are the most common mesenchymal neoplasm of the gastrointestinal tract with a malignant potential. We present a case of 68-year-old male patient diagnosed with GIST stage IV, unresectable due to liver metastases, treated with Imatinib, diagnosed at 13 months of prostate adenocarcinoma diagnosis [treated with hormonal therapy (HT) and external beam radiotherapy (EBRT)]; at 45 months from the first neoplasia diagnosis, the patient was diagnosed with the third neoplasia – lung squamous carcinoma – right inferior lobe, for which performed EBRT. The coexistence of GIST with other malignancies with different histology, remain a challenge for the clinician from etiological, and also from therapeutically actions point of view.

Keywords: gastrointestinal stromal tumor, prostate adenocarcinoma, lung squamous carcinoma.

Introduction

The presence of two or many primary neoplasia sites in one patient may be the results of susceptibility factors of patient meaning the genetic predisposition factors, acquired immunodeficiency, carcinogenetic influences, different risk factors accumulation on the same patient, may be a result of administrated treatments for the first malignancy or a simple chance [1–3].

Malignant diseases associated with gastrointestinal stromal tumor (GIST), reported in specialty literature, are gastric cancer and colon cancer, lymphoma and leukemia, gynecological carcinoma, prostate carcinoma, breast, lung, pancreas, liver, kidney, pancreas and gastric carcinoid [1, 2, 4].

The most frequent sites of GIST are gastric, duodenum, esophagus, colorectal and respective other gastrointestinal sites in 66%, 4.5%, 4.5%, 4.5%, and respective 14% of cases [1, 5].

We are presenting this case of a 68-year-old male patient, with three metachronous neoplasia – prostate, GIST and lung cancer.

The particularity of case is the association of three localizations, partial response at Imatinib treatment for GIST, with survival of 37 months. The prognosis was dictated by the neoplasia with the most unfavorable evolution. This case represents a challenge for the diagnosis of lung tumor, raising the question if the lung tumor was secondary tumor with starting point GIST, prostate or was the third primary cancer. This case, also, represents a challenge for diagnostic and treatment team who treat oncological patient in a multidisciplinary way

(oncologist, radiotherapist, surgeon, anatomopathologist, who represent an important link in this team).

Case presentation

We present a case of 68-year-old male patient, without significant family and personal medical history, with performance status (PS)=1. The first symptom occurred was dysuria. In February 2010, transrectal ultrasound was performed which evidenced: inhomogeneous configuration, difficult to delineate in the right site with high echogenic areas having 0.53 cm diameter in the right prostatic lobe and 0.66 cm diameter in the left prostatic lobe.

Histopathological (HP) examination was performed at "Fundeni" Clinical Institute, Bucharest, Romania, and the result was prostate adenocarcinoma, Gleason score 7 (3A+4B), with the following description: small glandular structures well individualized, infiltrative unregulated, focally with cribriform aspect formed by cubic cells with pale eosinophilic cytoplasm and hypertrophied nucleus with unregulated contour some of them, with prominent nucleolus (Figure 1, a and b).

Prostate specific antigen (PSA) value was 10 ng/mL. Chest X-ray examination was normal and abdominal and pelvic CT scan evidenced no secondary lesions.

After the distance extension evaluation (abdominal and pelvic CT scan was performed), the first neoplasia was staged. The first malignancy diagnosed was prostate tumor – T2aN0M0.

At this stage, therapeutically options were: Iodine-125 interstitial brachytherapy, external beam radiotherapy, radical prostatectomy and active surveillance. The patient has temporized the therapeutic decision.

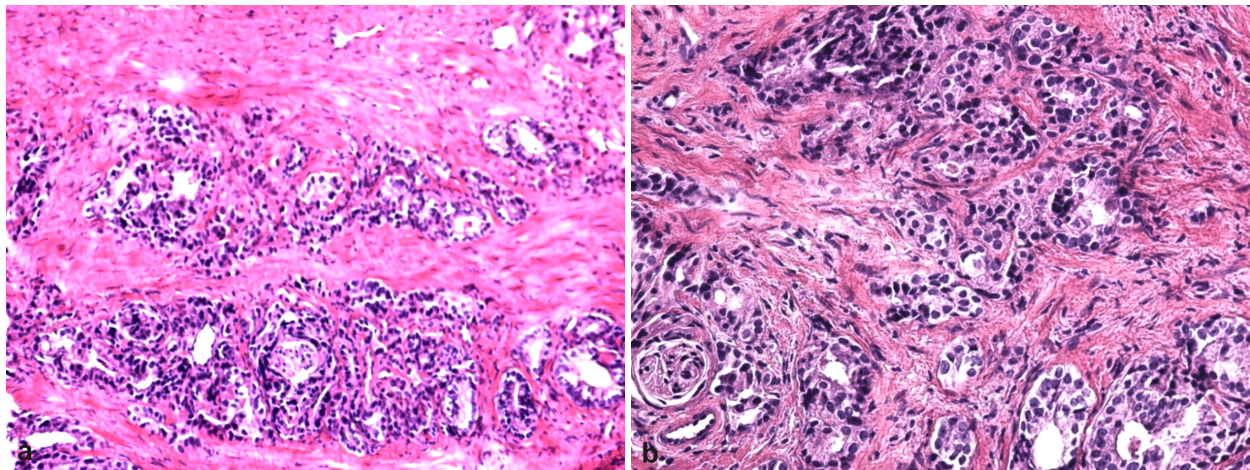


Figure 1 – Prostate adenocarcinoma, Gleason score 7 (3A+4B), pattern 5 focally, perineural invasion: (a) Mixed 3A and 4B patterns, perineural invasion, inflammatory background; (b) Glandular pattern 3A, perineural invasion. HE staining: (a) $\times 100$; (b) $\times 200$.

Between February 2010 and March 2011, the patient presented digestive symptomatology: postprandial abdominal pain, melena and physical asthenia, weight decreasing, important fatigability in the last three months.

In March 2011, the patient has performed an abdominal and pelvic CT scan (Figure 2), which reveals a voluminous tumor by 12/7/10 cm at the fornix, gastric body and small curve level in tight contact with diaphragm and left adrenal gland with expansion in pancreas; lymphadenopathy of 13 mm in perigastric and celiac areas. The liver has normal dimensions but the structure was heterogeneous with multiple expansive, hypodense lesions, with peripheral iodophilic reaction in both lobes, the biggest with 25 mm diameter; in kidney – bilateral cortical cysts (Figure 2).

The superior digestive endoscopy with biopsy was performed. The histopathological diagnosis was GIST with the following microscopic description: neoplastic tissue fragment constituted by a proliferation of fusiform cells with pattern fascicular, with moderate anaplasia and

numerous mitoses, >5 mitoses/50 consecutive high-power fields (>5 M/50 HPFs). Small foci of tumoral necrosis (Figure 3, a and b). Histopathological diagnosis was subsequently completed by immunohistochemistry (IHC) test.



Figure 2 – CT scan (March 2011): voluminous tumor by 12/7/10 cm at the fornix, gastric body and small curve.

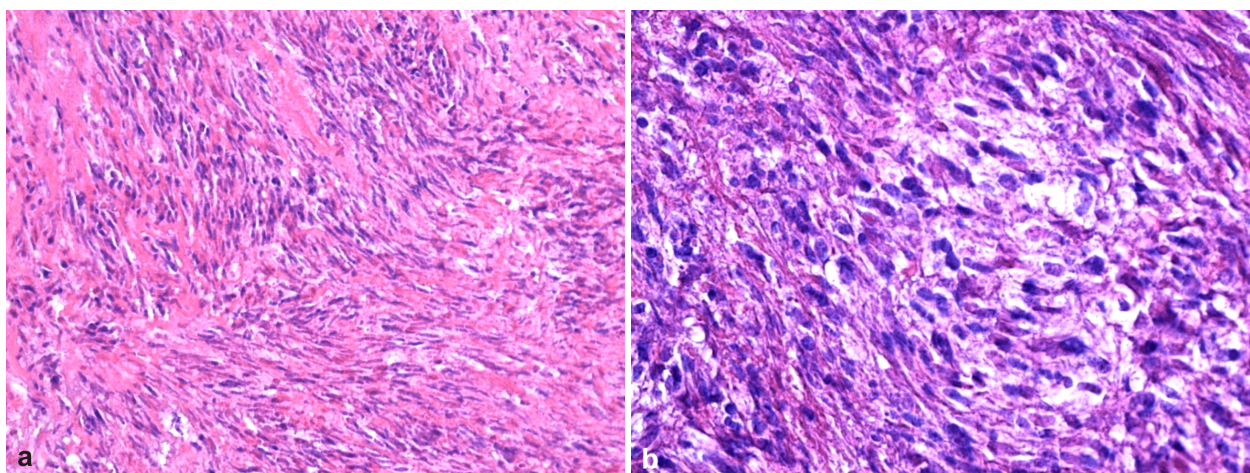


Figure 3 – (a and b) The histopathology images of GIST showed fusiform and epithelioid tumoral cells with mesenchymal aspect, perinuclear vacuolization and rare mitoses (three mitoses/50 HPFs). The structure is frequent lax, myxoid. HE staining: (a) $\times 100$; (b) $\times 400$.

Immunohistochemistry confirms the GIST diagnosis: numerous mitoses (>5 M/50 HPFs), alpha-smooth muscle actin (α -SMA) focal positive, desmin negative, CD117

(tyrosine-protein kinase Kit or c-Kit) diffuse positive, CD34 diffuse positive, Ki67 30%, D2-40 focal positive.

The patient was considered inoperable because of

unresectable tumor and the presence of liver metastases.

Due to lent evolution of prostate tumor with PSA doubling time >12 months, initial stage T2a, patient was fitted in favorable prognostic group, PSA 14 ng/mL at 121 months from diagnosis, absence of pelvic adenopathy, the liver metastases were considered being secondary to GIST and not secondary to prostate cancer.

The target molecular therapy with Imatinib, 400 mg

per day, was initiated and this treatment was monitored by CT scans at six months time interval (November 2011 and May 2012) performing. This examination indicated dimensional decreasing of tumor from gastric fornix and gastric body at 4 cm, without infiltration in pancreas; the secondary lesions in liver have stationary aspect respect of previous CT scan (Figure 4).

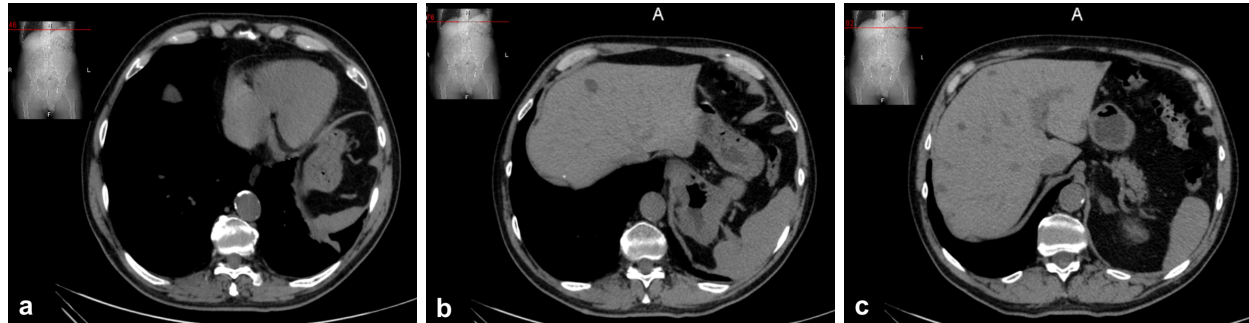


Figure 4 – CT scan, May 2012: (a and b) Dimensional decreasing of tumor from gastric fornix and gastric body at 4 cm respect of previous CT; (c) Liver secondary lesions with stationary aspect respect of previous CT.

The treatment continued without digestive side effects but occurs hematological toxicity with grade 1 anemia (hemoglobin 10.1 g/dL) and thrombocytopenia grade 1 (platelets 143 000/mm³).

The prostate ultrasound examination (April 2012) indicated an increased volume of prostate gland (40 cm³) with bilobar adenoma, periurethral and central calcifications, hypoechoic area about 18 mm in right lobe, preservation of prostate capsular confirmed also by inferior abdomen and pelvic magnetic resonance imaging (MRI) – increased volume of prostate gland, 5/6 cm with projection

of lobe 3 in bladder, with maintaining of cleavage plan with rectum and seminal vesicles, without pelvic lymphadenopathy. Biochemical constants were in normal limits, with the following exceptions: hemoglobin 10.9 g/dL, platelets 135 000/mm³, PSA 32 ng/mL.

Due to PSA dynamic (indicated in Table 1) the question was: Which is the best therapeutic decision for prostate cancer treatment: external beam radiotherapy (EBRT), hormonal therapy (HT) with luteinizing hormone-releasing hormone (LH-RH) analogs, Iodine-125 brachytherapy (I-125 BT) or association of EBRT+HT?

Table 1 – PSA dynamic before HT and EBRT

| Date | February 2010 | December 2010 | March 2011 | November 2011 | April 2012 | May 2012 | July 2012 |
|-------------|---------------|---------------|------------|---------------|------------|----------|-----------|
| PSA [ng/mL] | 10 | 11.5 | 12 | 17.9 | 26 | 32 | 20.6 |

PSA: Prostate specific antigen; HT: Hormonal therapy; EBRT: External beam radiotherapy.

In May 2012, the performing of HT with LH-RH analogs with Leuprorelin acetate, 11.25 mg, once at three months was decided.

In July 2012, after signing the informed consent for EBRT and for HT, the performing of EBRT in Department of Radiotherapy, “St. Apostle Andrew” Emergency Hospital, Galați, Romania was decided; PSA 20.68 ng/mL. The fractionation schema was: total dose (TD) 46 Gy/26 fractions/37 days, dose per fraction 1.8 Gy, on pelvic target volume and lymphatic areas, with an overdose in prostatic lodge until TD 66 Gy. Radiotherapy was difficult tolerated with secondary digestive toxicity manifested with grade 2 radiation proctitis for which symptomatic treatment was administrated.

Combined treatment, HT+EBRT, had a good response indicated by PSA decreasing values, monitored in December 2012 and May 2013 (Table 2).

Table 2 – PSA dynamic after HT and EBRT

| Date | December 2012 | May 2013 | February 2014 |
|-------------|---------------|----------|---------------|
| PSA [ng/mL] | 4.75 | 0.04 | 0.2 |

PSA: Prostate specific antigen; HT: Hormonal therapy; EBRT: External beam radiotherapy.

The CT scans performed in November 2012 and in

May 2013 confirmed a good treatment response of gastric tumor, showing the dimensional decreasing of gastric lesions, thickening of gastric body walls and fornix; dimensional and numerical decreasing of secondary liver lesions, liver cysts, multiple cortical kidney cysts and thickening of posterior perirectal fascia, probably of liquid nature (Figures 5 and 6).

It was recommended to be continued treatment with Imatinib – 400 mg per day + LH-RH analogs: Leuprolide – 11.25 mg once at three months.

Stage reevaluation from November 2013 ascertained the dimensional regression of gastric fornix's lesion, without pancreas infiltration, dimensional and numerical regression of secondary liver lesions and pulmonary nodule in right posterior segment, oval form, solitary with 3.5 cm diameter, iodophilic, with infiltrative margins, hilar adenopathy about 2 cm, pre-carinal and under-carinal (Figure 7).

The question has been raised at this moment was: What is the etiology of lung lesion: third primary neoplasia – lung tumor, metastases from GIST or metastases from prostate cancer?

In order to answer at this question, the patient performed bronchoscopy with biopsy; a histopathological result was squamous carcinoma.

Because the bronchoscopy examination was performed in other country (Unita Sanitaria Locale, Toscana, Italy), we have not access to the images from histopathological examination, but the bronchoscopy examination revealed presence of bloody vegetant mass in posterior sub-segment of right upper bronchia. Also, the patient performed in the same hospital, radiotherapy for lung cancer.

So, in November 2013 has been diagnosed the third metachronous neoplasia site: lung cancer, right inferior lobe, IIIA stage, T2N2M0, for which the patient performed external beam radiotherapy in 3D conformal technique, TD 66 Gy/33 fractions, on tumor target volume and mediastinal lymph node regions. Also, has been continued the treatment with Imatinib – 400 mg per day + LH-RH analogs – Leuprolide 11.25 mg once at three months.

In February 2014, the patient presented in Department of Oncology, “St. Apostle Andrew” Emergency Hospital, Galați, with physical asthenia, fatigability, PS=2. Biochemical and hematological constants were in limits, with exception of hemoglobin of 8.3 mg/dL, thrombocytopenia ($14\,000/\text{mm}^3$), erythrocyte sedimentation rate 40 mm/h, ferritin 30 ng/mL. It was decided to perform supportive care for anemia correction with iron medication in intravenous injection.

In May 2014, the patient performed the evaluation

stage with thoracic, pelvic and abdominal CT scan, which showed pleural effusion (8 cm), partial atelectasis in right superior lung lobe, which is not distinguished from heteroplasmy lesion and from hilar adenopathy, atelectasis in apical segment of right inferior lung lobe, subtotal occlusion of right superior lobar bronchia, obstructions of intermediary bronchia, medium lobar bronchia and right inferior lobar bronchia, right paratracheal segmental adenopathy, pre-carinal, under-carinal and pre-vascular (diameter of 30 mm superior respect of previous examination), celiac adenopathy of 13 mm diameter (Figure 8). Without bone secondary lesions in scanned segments and stationary aspect of liver secondary lesions, and gastric body lesions respect of previous exams.

Conforming to *Response Evaluation Criteria in Solid Tumors* (RECIST), we obtained partial response of GIST, after 37 months of treatment with Imatinib. But also, the patient had progressive disease of lung tumor. In July 2014, the patient presented in Emergency Unit of “St. Apostle Andrew” Emergency Hospital, Galați, with dyspnea, headache, visual disturbances with unknown causes, maybe stroke or pulmonary thromboembolism. The patient died in the same day.

The autopsy was proposed but the patient's family refused.

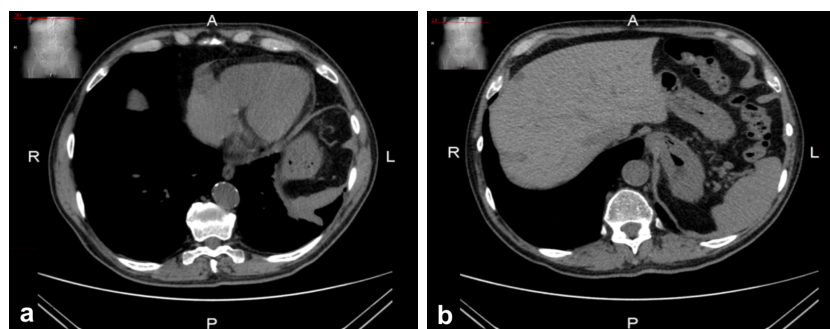


Figure 5 – CT scan, November 2012:
(a) Dimensional decreasing of gastric lesions, thickening of gastric body walls and gastric fornix; (b) Dimensional and numerical decreasing of secondary liver lesions.

Figure 6 – CT scan, May 2013:
(a) Stationary aspect of gastric tumor; (b) Regression of secondary liver lesions.

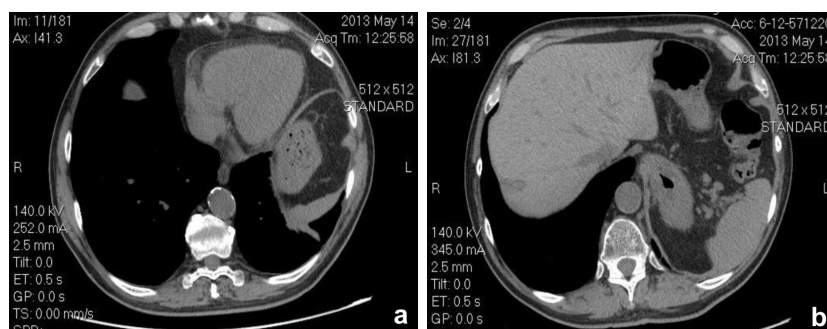


Figure 7 – CT scan, November 2013: (a) Pulmonary nodule in right posterior segment; (b) Dimensional decreasing of gastric lesions; (c) Dimensional and numerical decreasing of secondary liver lesions.

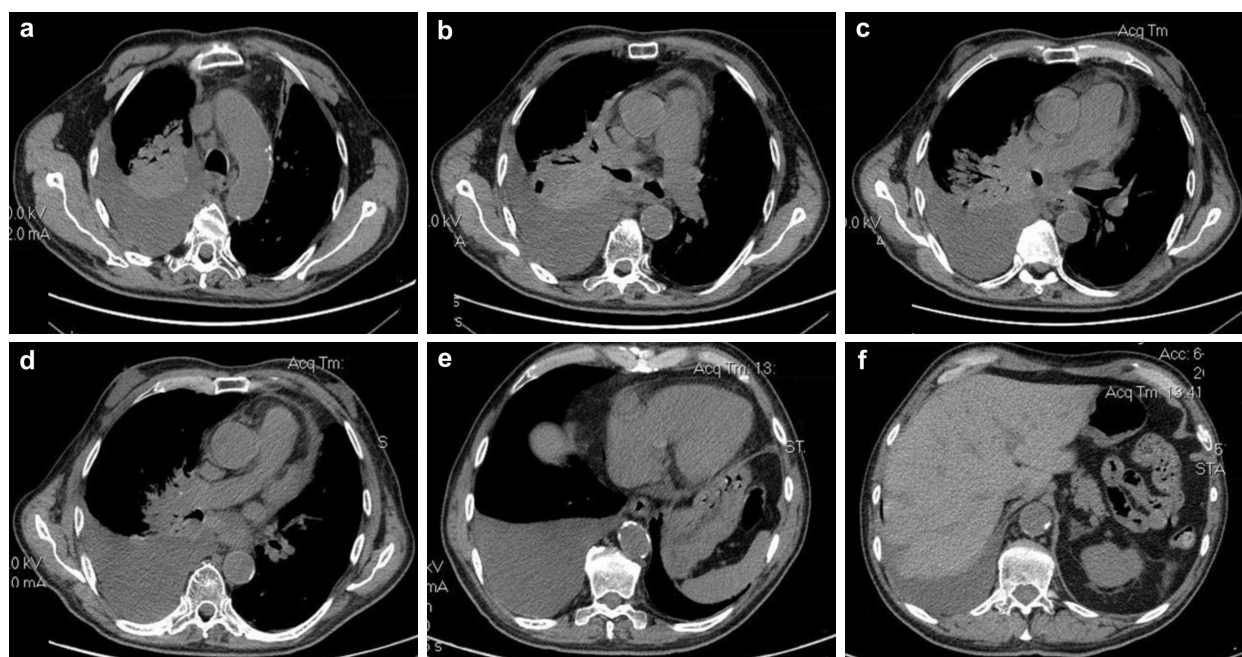


Figure 8 – CT scan, May 2014: (a) Pleural effusion (8 cm); (b) Partial atelectasis in right superior lung; (c) Atelectasis in apical segment of right inferior lung lobe, subtotal occlusion of right superior lobar bronchia, obstructions of intermediary bronchia; (d) Right paratracheal segmental adenopathy, pre-carinal, under-carinal and pre-vascular, celiac adenopathy of 13 mm diameter; (e and f) Stationary aspect of liver secondary lesions and gastric body lesions.

Discussion

Gastrointestinal stromal tumors are rare, in general are reported sporadic cases but also may belong to tumoral syndromes [2–4]. Less than 5% of GISTs are associated with one of the three tumoral syndromes: neurofibromatosis type 1 (NF1) – von Recklinghausen disease, Carney triad: GIST, functional extra-adrenal paraganglioma, familial GIST syndrome.

GISTs are most commonly located in the stomach (39–60%), small bowel (30–42%), colon-rectum (5–10%) and esophagus (5%) [5]. The most common symptoms of the patients in the current study were abdominal masses, pain and bleeding [6, 7]. The symptoms of these tumors depend on their size and location [7].

The disseminations ways in GIST are liver, peritoneal, lymphatic, bone, soft tissues and respective, lung in 65%, 21%, 6%, 6%, 2%, and respective, 2% of cases [1, 2].

Almost one-third of GISTs are discovered incidentally during investigative or therapeutic procedures for unrelated diseases [8]. GISTs may coexist with different types of cancer, either synchronous or metachronous. The frequency of this association and the spectrum of neoplasms involved have not been sufficiently analyzed.

A prognostic classification of GIST into four or five risk categories is based on tumor size, mitotic activity and/or site. Their therapeutic options include surgery and treatment with Imatinib mesylate [5, 9, 10].

The particularity of our study is the association between GIST, prostate adenocarcinoma and lung cancer, which is found in the specialty literature. However, the limit of this study is not having the IHC tests for lung cancer, K-ras mutations and epidermal growth factor receptor (EGFR) status.

There are data in literature, which does not indicate differences in IHC tests and molecular profile between single GIST and GIST coexisting with other tumors.

Several changes occurred in diagnostics, treatment and understanding of pathogenesis of GISTs, but their coexistence with other malignancies of different histogenetic origin still remains a challenging issue [11].

More, Imatinib treatment during 36 months significantly increased overall survival (OS) comparative with Imatinib treatment during 12 months [response rate – RR: 0.45 (0.22–0.89), $p=0.0187$]. A longer period of treatment (>36 months) may delay the other recurrence's occurrence; nevertheless, the impact of these data on overall survival remains unknown [10].

One study of Agaimy *et al.* [12] analyzed 486 patients with GIST associated with other neoplastic sites. The most frequent associations were: gastrointestinal carcinomas (47%), prostate carcinomas (9%), lymphoma/leukemia (7%), breast (7%), kidney (6%), lung (5%), female genital tract (5%), carcinoid tumors (3%), soft tissue and bone sarcomas (3%), malignant melanoma (2%), and seminoma (1%).

The potential association and causal relationship between GIST and other neoplasms remain to be investigated and occurrence of collision tumors and metastases of carcinoma or sarcoma into a GIST can be challenging diagnostic problems [12].

Also, Pandurengan *et al.* showed in one study of 783 patients, that approximately 20% of patients with GIST develop other types of cancers but it remains unclear if this is just an incidental coexistence or these two are related by a causal relationship [13]. Incidental GIST occurred mostly in males and coexisted most frequently with esophageal and gastric tumors (1.13% and 0.53%, respectively) and less with colorectal tumors (0.03%) [10].

There are few data about the etiology of this phenomenon, but many hypotheses have been proposed. The concurrence of GIST with other malignancies has raised the question of whether such an occurrence was coinci-

dental or whether both neoplasms were casually related. The development of these tumors may involve unknown carcinogenic agents, which influence other tissues, resulting in a simultaneous proliferation of different cell lines such as epithelial and stromal cells. Experimental evidence for this hypothesis has been provided [14–16]. Oral administration of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) in rats induced the development of gastric adenocarcinomas, almost exclusively localized in the pyloric region of the stomach or in the duodenum [14]. If combined with other agents that alter the gastric mucosal barrier (such as non-steroidal anti-inflammatory drugs, stress, and sodium taurocholate) leiomyosarcoma can be induced in association with the epithelial tumor [15].

There are other studies raising the hypothesis confirming which the synchronous development of GIST with other malignant diseases may involve commune carcinogenic agents, such as: enteral nitrosoguanidine may lead to adenocarcinoma and simultaneously exposure of nitrosoguanidine and acetylsalicylic acid determine the synchronous occurrence of gastric cancer and leiomyosarcomas [14, 17].

In the future, supplementary investigations, which include other genetics tests, may be useful, knowing that a great majority of GIST are determined by pathological activation of receptor tyrosine kinase protein (KIT) or platelet-derived growth factor receptor, alpha-polypeptide (PDGFRA) and by other genetics changes including activation of BRAF function and loss of succinate dehydrogenase (SDH) function, identified in a small group of GIST patients [9, 18].

Most GISTs are initiated by oncogenic mutations involving the receptor tyrosine kinase proto-oncogenes c-Kit and the PDGFRA gene [19, 20]. *In vitro* studies showed that concomitant KIT mutations with (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) KRAS mutations presented resistance at Imatinib. In GIST, KRAS mutations are presented in less than 0.2% of cases [9, 21]. Also, molecular biology studies are necessary in the future, in order to investigate the development simultaneously or metachronous tumors with different histology.

The molecular therapy development anti-c-Kit and PDGFRA with Imatinib and Sunitinib significantly modified the treatment of GIST. Once with antitumoral treatments increasing and consequently with survival increasing of oncological patients, many primary cancers represent more frequent entities [9].

✉ Conclusions

Multiple neoplasia occurrence rise different diagnosis and treatment problems. Non-randomized potential associations and also, causal problems between GIST association with other tumoral primary sites remain investigational. The coexistence of GIST with other malignancies with different histology, remain a challenge for the clinician from etiological, and also from therapeutically actions point of view.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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