

## CASE REPORT

## EGIST of the greater omentum – case study and review of literature

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### Abstract

The development of immunohistochemical methods has outlined a particular group of tumors, with very specific features and treatment, originating in the Cajal cells of the muscularis propria or related stem cell-like precursors present in the wall of the digestive tract called gastrointestinal stromal tumors (GISTs). A sub-segment with similar features may develop outside the digestive tract, namely extra-gastrointestinal stromal tumors (EGISTs). From the small category of EGISTs, we report on a case of a primary epithelioid EGIST of the greater omentum, which is seldom reported in literature. The tumor was diagnosed in a man with non-specific symptoms who presented for abdominal enlargement. The tumor was characterized and there was a preoperative suspicion of a non-digestive tumor located in the greater omentum. The tumor was surgically removed showing no contact with adjacent organs. Immunohistochemical examination was consistent with a primary EGIST of the greater omentum. Treatment with Imatinib mesylate was started and at two-year follow-up, the patient is disease free. The case raises problems regarding pathogenesis, immunohistochemical features, behavior, evolution and prognosis of omental EGIST, for which no significant or conflicting data are available in the literature.

**Keywords:** extra-gastrointestinal tumors, tumors of the omentum, gastrointestinal stromal tumors.

### Introduction

Gastrointestinal stromal tumors (GISTs) represent a distinct group of tumors having their origin in Cajal interstitial cells (CIC), which normally express CD117 – the tyrosine kinase component of the mass factor receptor in the stem cell [1, 2]. In 1983, following the immunohistochemical investigations, Mazur & Clark proposed the term GIST, while differentiations related to the malignant features and predictions on the tumoral behavior came later [3–5]. Extra-gastrointestinal stromal tumors (EGISTs) are rare tumors developing apart from the digestive tract, representing less than 10% of all stromal tumors, most of them originating in lesser or greater omentum, mesentery and retroperitoneum [6–8]. The incidence of primary EGIST in the greater omentum has been reported to be less than 1% [9–11]. Omental EGISTs were reported as solitary or multiple tumors, their aggressiveness ranging from benign to metastatic behavior [12, 13]. Histological and immunohistochemical characteristics of EGISTs and GISTs are identical, both types expressing the CD117/CD34 immunophenotype, which is the pathological diagnostic hallmark of GIST [14]. Same as their digestive counterpart, most of the EGISTs have mutually exclusive gain-of-function KIT/platelet-derived growth factor receptor alpha (PDGFRA) mutations [11, 15]. There are three hypotheses regarding the development of EGISTs: the first asserts their origin in the digestive tract, with exophytic development and subsequently acquisition of autonomy; the second supports the idea that EGISTs are peritoneal metastases of an undiagnosed GISTs; the third hypothesis, asserted by Sakurai *et al.*, proposes the mesothelial origin

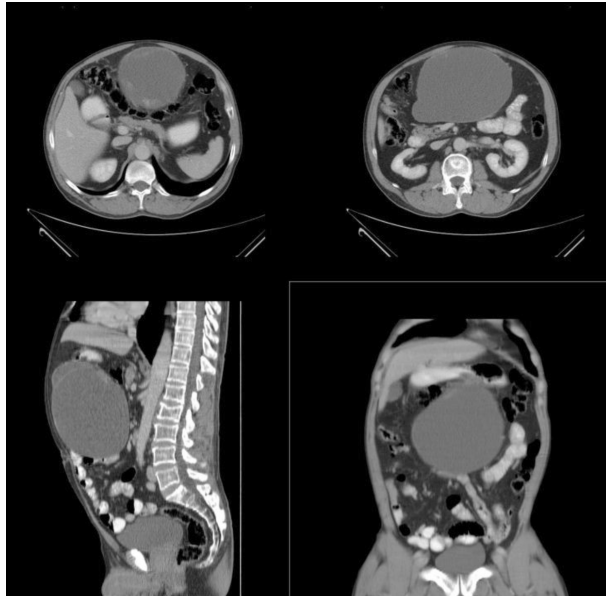
by demonstrating similar characteristics to Cajal cells (CD117 on their surface) [12, 16–18]. We describe herein a rare case of a primary epithelioid EGIST of greater omentum that presents slightly positive CD117 expression and negative alpha-smooth muscle actin ( $\alpha$ -SMA) expression. We discuss the pathogenesis, immunohistochemical features, clinical behavior and prognostic factors with a review of the literature.

### Case presentation

A 64-year-old male patient with no personal either familial significant past medical history presented for an insidious abdominal enlargement and slight discomfort. Clinical evaluation revealed a large mass in the epigastrium and was characterized on an outpatient ultrasound scan as a cystic expansive mass 122/165 mm with septa inside and a solid mass of 30/18 mm on the rear wall. The ultrasound examination could not determine a relationship to an organ.

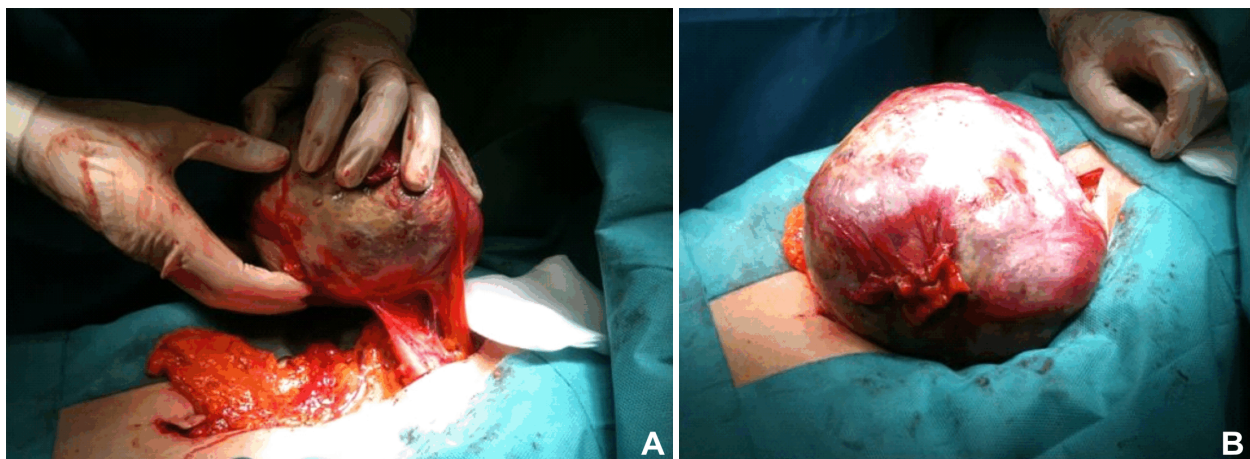
The patient was admitted in the Regional Institute of Oncology, Iassy, Romania, where the clinical examination revealed a 170/160 mm tumor located in the epigastrium and right hypochondrium, which seemed fixed on initial examination, but could be shifted with a change in body position. The computed tomography (CT) scan confirmed that the cystic tumor was located just under the abdominal wall, having thin walls and septa as well as significant enhancement after i.v. contrast administration (Figure 1). Despite the large dimensions, 122/170/165 mm (anterior-posterior/transversal/cranio-caudal diameter), it was possible to assert the origin in the greater omentum and gastro-colic ligament as well as the origin of the

vascularization in the vessels of the omentum and gastroepiploic arcade. There was an evident mass effect on the transverse colon and bowel loops and a direct contact with the anterior gastric wall, where invasion could not be excluded. Description raised the suspicion of a cystic tumor growing in the omentum or mesentery, possibly a GIST, cystic lymphangioma or mesenteric cyst. Tumoral markers (carcinoembryonic antigen and carbohydrate antigen 19-9) were within normal values.



**Figure 1** – CT scan examination: voluminous (122/170/165 mm) cystic tumor located just under the abdominal wall, with thin walls and septa enhancement after i.v. contrast administration; mass effect on bowel loops.

Surgical procedure involved a midline laparotomy, which allowed for easy mobilization of the tumor outside the abdominal cavity. As seen in Figure 2, the tumor was attached to the omentum and there were no signs of connection with adjacent organs, while all vascular structures that supplied the tumor originate in the vascular arcades of the greater omentum allowed for easy tumor excision. The tumor was completely excised along with the adjacent omentum. The postoperative course was uneventful and patient started Imatinib mesylate treatment. Six months after the procedure the clinical, biological and imagistic evaluations indicated no signs of recurrence.



**Figure 2** – (A and B) Intraoperative images showing the tumor attached to the greater omentum with no signs of connection with adjacent organs and with all vascular structures originating in the arcades of the greater omentum.

Macroscopic evaluation confirmed a 165/160/100 mm cystic unilocular tumor, with hemorrhagic content and necrotic debris adhering to the inner wall. Optical microscopy revealed a connective tissue tumoral growth, with predominant epithelioid shape, with areas of fusiform cells and moderate nuclear pleomorphism within tumor proliferation. Cells present homogenous eosinophilic cytoplasm or ample vacuolization. Mitotic activity was estimated as low, with a mean of two mitoses per 50 high-power fields (HPF) (Figure 3). Microscopic aspects, associated with tumor dimensions described above were suggestive of an extra-gastrointestinal stromal tumor (EGIST).

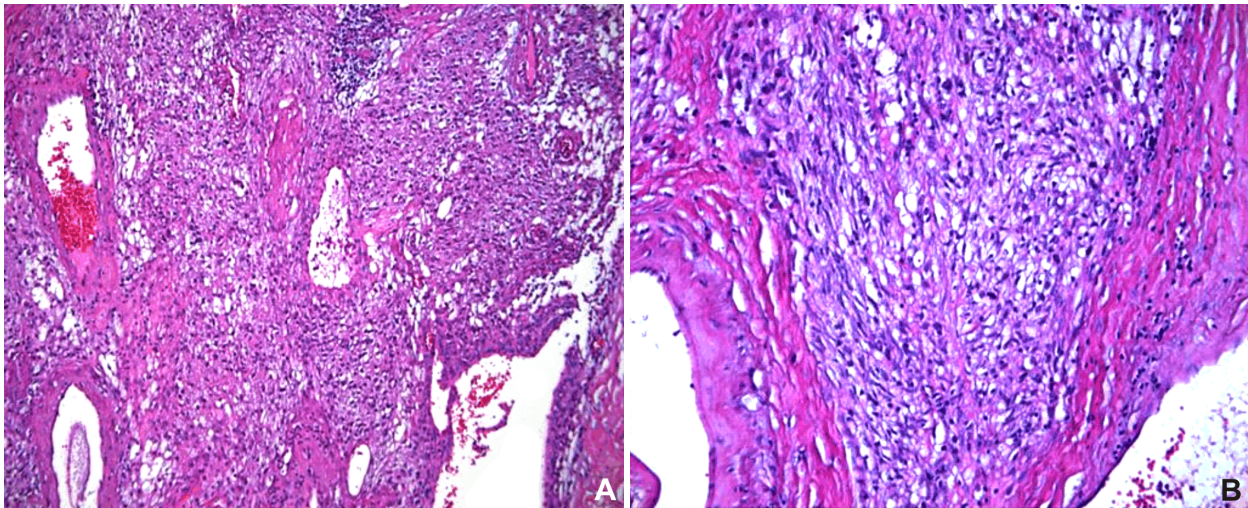
Immunohistochemical (IHC) tests were required for confirmation and differentiation from other histologies (e.g., leiomyoma, schwannomas). The following antigens were assessed CD117, CD34,  $\alpha$ -SMA, S100, and Ki67, with technical details and antibody clones used presented in Table 1.

**Table 1** – Technical details and antibody clones

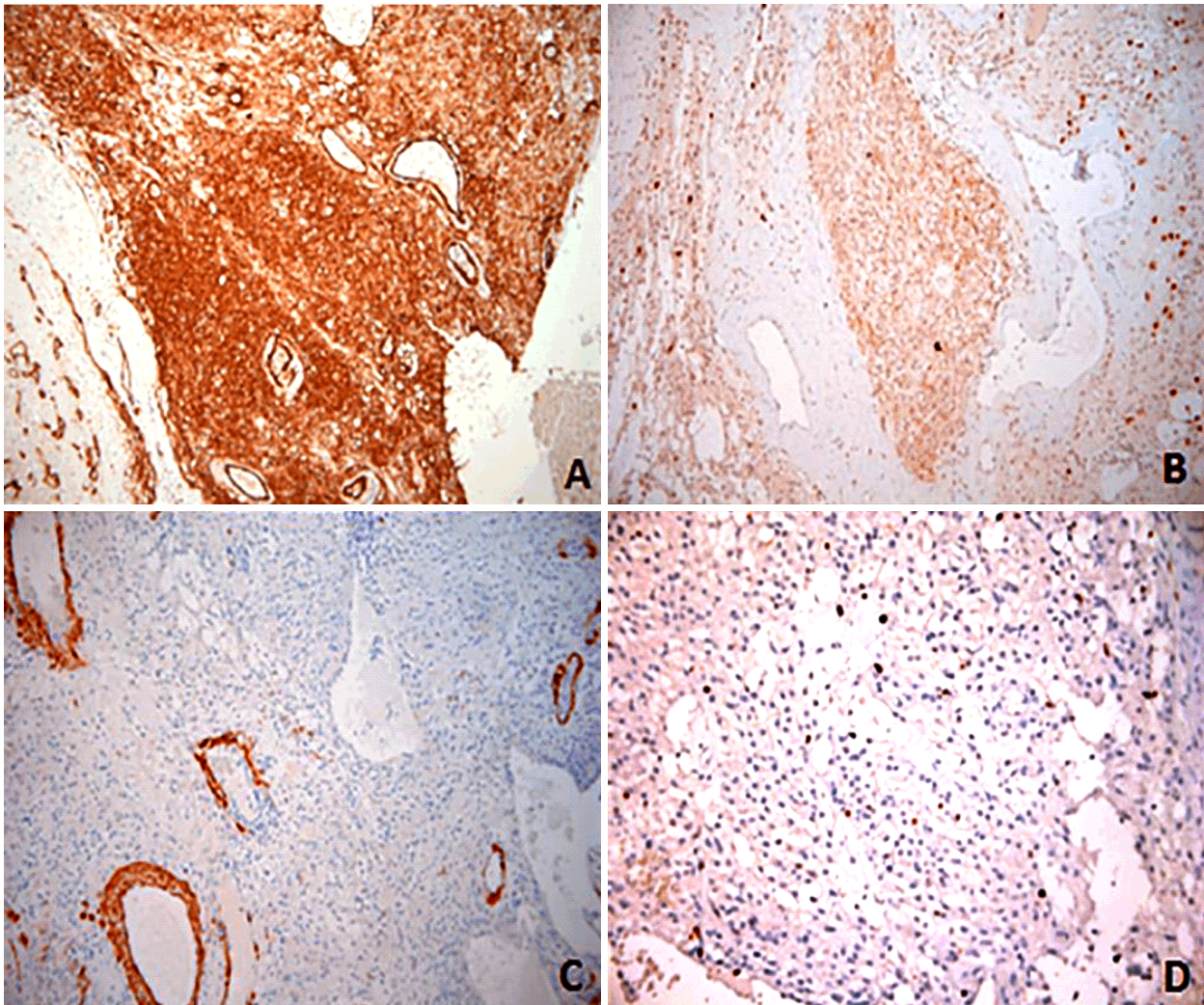
Primary antibody	Clone	Dilution	Exposure
CD117	T 595, Novocastra	1/40	pH 8, RE 7116, Novocastra
CD34	QBEnd/10, Novocastra	1/50	pH 6, RE 7113, Novocastra
$\alpha$ -SMA	S1/61/69, Novocastra	1/50	–
S100	S1/61/69, Novocastra	1/200	pH 6, RE 7115, Novocastra
Ki67	MM1, Novocastra	1/200	pH 6, RE 7113, Novocastra

IHC techniques showed strong positive marking for CD34, with vascular endothelium used as positive internal control and moderate diffuse positive for CD117, with intratumoral mast cells used as positive internal control. There were very few cells with positive marking for Ki67 (less than 3%) (Figure 4). Markings for S100 and  $\alpha$ -SMA were negative, with positive internal control in peritumoral adipocytes respectively in vascular walls. The described microscopic features, correlated with the macroscopic description, size and relative position to the digestive tract corresponds to a gastrointestinal stromal tumor with malignant behavior (high-risk EGIST, 3b prognostic group can be reported based on tumor size and mitotic counts on histology and immunohistochemistry), developed outside the digestive tract, without contact to the digestive lumen.





**Figure 3** – Optical microscopy of omental EGIST showing predominantly epithelioid tumor proliferation, moderate nuclear pleomorphism, isolated cells with voluminous nuclei, hyperchromasia and well represented cytoplasm. HE staining: (A)  $\times 100$ ; (B)  $\times 200$ .



**Figure 4** – Immunohistochemistry examination: (A) CD34 intense staining in the tumor and in the vascular endothelium,  $\times 100$ ; (B) CD117 slightly positive locally,  $\times 200$ ; (C)  $\alpha$ -SMA-negative in the tumor,  $\times 100$ ; (D) Ki67-positive  $<10\%$  of the cells,  $\times 200$ .

## Discussion

EGISTs are a group of rare tumors with similar histology and immunohistochemical features to GISTs,

occurring outside the gastrointestinal tract, majority of them in the omentum and mesentery or in the retroperitoneum [7, 11, 19]. Pathogenesis, incidence and prognosis



of EGISTs have not yet been completely defined, although these are well established in GISTs. This is due to the reduced number of cases reported in the literature. An extensive search on PubMed revealed only 82 cases of omental EGISTs being reported worldwide [7, 8, 12, 16, 20, 21]. Like their digestive counterparts, most omental tumors are typically positive for CD117 and less consistently for CD34, positive for  $\alpha$ -SMA and negative for desmin and S100 protein [7]. Our tumor exhibits a slightly different pattern with intense CD34 and slightly positive CD117 staining. These tumors have low mitotic activity and similarly to GIST present as elongated spindle cells, epithelioid cells or mix cells with high cellularity [22]. Analyzing 48 EGISTs (40 omental and mesenteric and eight retroperitoneal), Reith *et al.* found that the tumors expressed CD117 (c-kit receptor) – 100%, CD34 – 50%, neuron-specific enolase (NSE) – 44%,  $\alpha$ -SMA – 26%, desmin – 4%, and S100 protein – 4% [8]. In our case, the results of immunohistochemical evaluation revealed intense CD34 staining in the tumor and vascular endothelium, CD117 slightly positive locally,  $\alpha$ -SMA negative in the tumor and S100 negative in the tumor.

The real origin of these tumors is a subject to debate. While some authors consider that EGISTs may originate *de novo* as primary tumors from multipotent mesenchymal stem cells of the greater omentum and mesentery, others consider that these tumors derive from gastrointestinal tract and for some reason they have detached during their development, or may represent a metastatic stage of a GIST [16, 17, 23]. In their study, Sakuray *et al.* claimed that they found KIT immunoreactive CD117 and CD34 interstitial Cajal-like cells within specimens of the mesothelial cells of the omentum, supporting the theory of primary GISTs of the omentum [17]. On the other hand, the study of Miettinen *et al.* analyzing 95 GISTs located in the omentum, with 21 single tumors showing no evidence of gastrointestinal tract involvement, failed to support the presence of KIT-positive Cajal-like cells in normal omentum [12]. They concluded that omental EGIST unattached to digestive tract often resemble gastric GIST, suggesting that they may be gastric GIST directly extending or parasitically attached to the omentum, whereas multiple omental GIST more often resemble small intestinal GIST suggesting that they may be metastatic or detached from initial source. Another point of view is sustained by Agaimy & Wünsch who claimed that tumors labeled initially as primary EGISTs are in fact GISTs [21]. On a critical reevaluation of the surgical report and a careful search for residual muscular tissue from the gut wall in the tumor pseudocapsule of 14 EGISTs, it was possible to reclassify most of these cases either as GISTs with extramural growth (8/14) or as metastases from a GIST (3/11). This study emphasizes on focal attachment or adhesions to the gut wall that must be documented intraoperatively and the paramount role of the pathologist in searching for any residual muscle tissue in the tumor pseudocapsule.

The clinical presentation of EGIST depends on the primary location and its dimension, but in very large abdominal tumors, the visceral origin is almost impossible to suggest. The omental EGISTs are very rare and the only sign suggestive of omental origin is tumor mobility

even at large dimensions. There are few reports in the literature regarding omental EGISTs and all show large tumors. Reith *et al.* have examined the clinico-pathological features of 48 EGISTs arising within the abdominal cavity and the retroperitoneum [8]. The tumors ranged from 21 to 320 mm with a median size of 120 mm. Unfavorable prognostic features demonstrated in univariate analyses were high cellularity, high mitotic index ( $>2/50$  HPF), and necrosis. In multivariate analysis, the mitotic activity and necrosis appear as potential independent predictive features. The study did not show any association between tumor size and outcome. There was no clear association neither between histological pattern and outcome, nor between tumor size and outcome, but majority of EGISTs were large tumors ( $>100$  mm). Based on the histological appearance and immunophenotype authors suggest that EGISTs resemble stromal tumors originating from the small intestine rather than from the stomach.

Yamamoto *et al.* presented the clinico-pathological features, prognostic factors, as well as c-kit and PDGFRA mutations in 39 cases of EGIST, including three omental tumors [11]. They pointed out that EGISTs were often large size due to their anatomic site, having enough space to grow before producing symptoms. Therefore, a grading system defined by a combination of mitotic rate and tumor size, which is commonly used in GIST, may not be applicable in EGIST. Based on a combination of the mitotic rate and MIB-1 index, they defined three categories: the high-risk group ( $\geq 5/50$  HPF with  $\geq 10\%$  Ki67), the intermediate-risk group ( $\geq 5/50$  HPF with  $<10\%$  Ki67 or  $<5/50$  HPF with  $\geq 10\%$  Ki67), and the low-risk group ( $<5/50$  HPF with  $<10\%$  Ki67). According to this, our tumor can be defined as low risk presenting  $<5/50$  HPF with  $<10\%$  Ki67 expression. Based on the criteria advocated by Miettinen & Lasota for GIST, the tumor we reported would be included in Group 3b, having an intermediate risk [23]. According to Reith *et al.*, tumor necrosis may increase the risk for adverse outcomes for our patient [8]. Miettinen *et al.* examined nine cases of omental EGIST and seven cases of mesenteric EGIST. Omental EGISTs seemed to have a more favorable behavior, typically showing low mitotic counts, whereas mesenteric EGISTs appeared more aggressive (higher mitotic activity, frequent malignant behavior) [7]. No tumor-related deaths were documented during the follow-up in the nine patients with omental EGIST. Later, the same author analyzed 95 GISTs that were surgically identified as omental masses [12]. Single tumor cases showed a less aggressive behavior as compared to multiple tumors. Single tumors, when compared with multiple tumors showed: less median mitotic count, smaller median tumor size and better survival rate. More cases of single tumors had histological features similar to gastric GISTs as compared to multiple tumors. The authors concluded that omental GISTs are clinico-pathologically heterogeneous and patients with solitary tumors usually have gastric GIST-like morphology and a better prognosis, as compared to those with multiple tumors, which resemble usually small bowel GIST histology.

Surgery remains the standard treatment for non-metastatic EGISTs of the greater omentum [24]. There is no consensus regarding adjuvant therapy in such cases.

Chemotherapy and radiotherapy showed limited benefit [25]. Based on GIST experience and the presence of Kit alteration in EGIST, we can assume that tumors as large as those described in the literature have a high risk of relapse and patients are good candidates for Imatinib mesylate therapy. Most authors recommend Imatinib mesylate as adjuvant treatment even after complete resection [7, 8, 12, 13, 20, 26–29]. Our patient had an R0 resection and was classified as having a low or intermediate risk, and received Glivec 300 mg/day, being free of disease at six months.

## Conclusions

The location in the greater omentum of an EGIST is very unusual and the diagnostic can only be suggested by position and origin of main vascular pedicles. Surgery is the main therapeutic approach and resection poses no significant difficulties unless tumor invades adjacent organs. Adjuvant therapy with tyrosine kinase inhibitors should be advocated by extrapolating data from GIST therapy. Lack of data regarding omental EGISTs and large average size of these tumors suggest a close monitoring of these patients in order to detect local relapse or distant metastasis. Accumulating data and extended future studies are necessary to better define this type of tumor, its pathogenesis, behavior and treatment.

## Conflict of interests

The authors declare that they have no conflict of interests.

## Acknowledgments

Research financed through the project “Program of Excellence in multidisciplinary doctoral and postdoctoral research of chronic diseases”, Contract No. POSDRU/159/1.5/S/133377, beneficiary U.M.F. “Gr. T. Popa” Iasi, and co-financed by the European Social Fund through the Sectorial Operational Program for Development of Human Resources 2007–2013.

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*Received: June 17, 2015*

*Accepted: January 28, 2016*