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Efficacy of Cetuximab in Metastatic Colon Cancer - Case Report

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Rezumat

Eficacitatea tratamentului cu Cetuximab în cancerul de colon metastatic - prezentare de caz

În ultimii ani, terapiile țintite s-au dovedit eficiente în tratamentul cancerului de colon, dar, chiar și în aceste condiții, boala metastatică este considerată, de obicei, incurabilă. Cetuximabul este aprobat pentru tratamentul pacienților cu cancer colorectal avansat cu KRAS wild-type, cu scopul de a crește supraviețuirea și a împiedica progresia bolii. Raportăm un caz al unei femei în vârstă de 55 ani cu cancer sigmoidian stenozant și metastaze hepatice, care a beneficiat de tratament multimodal: chirurgie paliativă – colectomie segmentară Hartmann și chimioterapie adjuvantă – monoterapie de linia a doua cu cetuximab, conform protocoalelor standard. După 6 luni de chimioterapie XELOX, în care a prezentat progresia bolii metastatice, a fost trecută pe monoterapie cu cetuximab, cu rezultate favorabile. Comparând datele din literatură, în care răspunsul complet la tratamentul cu cetuximab se obține într-un procent redus (< 3%) după 3 luni de tratament cu cetuximab, pacienta prezenta răspuns clinic și paraclinic complet cu ameliorarea calității vieții. Selecția adecvată a pacienților cu cancer de colon metastatic pentru tratament cu terapie anti-EGFR poate duce la prelungirea supraviețuirii și creșterea timpului până la progresia bolii.

Cuvinte cheie: anticorp monoclonal anti-EGFR, cancer de colon metastatic, cetuximab, KRAS

Abstract

In recent years, targeted therapies have proved effective in the treatment of colon cancer, but even in these conditions, metastatic disease is generally considered incurable. Cetuximab is approved for the treatment of advanced colorectal cancer patients with KRAS wild-type, in order to increase survival and hinder progression of the disease. We report a case of a 55 year-old woman, diagnosed with stenosing sigmoid cancer and liver metastases, which

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underwent multimodal treatment: palliative surgery - Hartmann segmental colectomy, and adjuvant chemotherapy - second line monotherapy with cetuximab, according to standard protocols. After 6 months of XELOX chemotherapy, during which she showed progression of metastatic disease, she was switched to monotherapy with cetuximab, with favorable outcome. Comparing relevant literature, in which complete response to treatment with cetuximab is obtained in low percentages (< 3%) after 3 months of treatment with cetuximab the patient shows clinical and paraclinical complete response and increased quality of life. Proper selection of patients with metastatic colon cancer for treatment with anti-EGFR therapy may lead to prolonged survival and time to progression.

Key words: anti-EGFR monoclonal antibody, cetuximab, colon cancer metastases, KRAS

Background

Colorectal cancers are the second leading cause of death from cancer in Europe and the third leading cause in the USA (1). Therefore, colorectal cancer represents a challenge regarding study and implementation of new treatments in order to heal the disease and increase survival. Over the last few years, targeted therapies have proved to be effective in the treatment of colon cancer, but even in these conditions, metastatic disease is generally considered incurable and treatment is palliative, meant only to comfort symptoms, control tumor growth, hinder tumor progression and prolong overall survival (2).

The aim of chemotherapy in metastatic colon cancer is to increase quality of life by controlling symptoms and prolonging survival (3). Patients who can benefit after chemotherapy must have good performance status ECOG (Eastern Cooperative Oncology Group) = 0-2, good bone marrow reserve, and good liver, kidney, heart and lung functions. Before initiating chemotherapy for metastatic colon the cancer risks / benefits ratio must be properly assessed (2). Conventional chemotherapy in metastatic colonic cancer includes fluoropyrimidine, irinotecan, oxaliplatin. Also, lately, targeted therapies with bevacizumab, cetuximab, panitumumab and ralitrexed had been approved (3). Cetuximab is a monoclonal antibody - G1k chimerical immunoglobulin (IgG1) that recognizes and binds to the extracellular domain of EGFR (epidermal growth factor receptor) (2). Approximately 80% of colorectal cancers are EGFR positive (3) and are associated with poor prognosis (4). EGFR, also known as HER1, is a transmembrane glycoprotein-receptor. By binding to specific ligands (EGF - epidermal growth factor, TGFα - transforming growth factor alpha) dimerization of the receptor occurs in the extracellular domain of EGFR, tyrosine kinase activation in the intracellular domain initiating phosphorylation, signalling a cascade promoting proliferation, migration, aggregation and cellular differentiation (2).

By binding cetuximab to EGFR, signalling is interrupted and receptor dimerization and tyrosine kinase activation is prevented. It also stimulates internalization and degradation of EGFR (4). Thus, inhibition of pMAPK (phosphorylated mitogen - activated protein kinase) and pAkt expression, reduction of Ki 67 (cell proliferation antigen) expression and increased expression of p27 (cyclin-dependent kinase inhibitor) occurs, leading to inhibition of tumor growth, metastasis, invasion and angiogenesis (4).

KRAS is a cytoplasmic protein with low GTP (guanosine triphosphate) binding activity. This protein acts as a typical oncogene, when binding to GTP, signalling cell proliferation and inhibiting apoptosis. KRAS mutation in exon 2, by activating RAS/RAF/MAPK pathway, inhibits EGFR, making modulation therapy with anti-EGFR monoclonal antibodies irrelevant. Treatment with cetuximab and panitumumab is indicated in patients with colon cancer with KRAS wild type (without mutation), but even in these patients, the benefit is achieved in less than half of the cases (5).

Other biomarkers predictive for response to cetuximab treatment are activating mutations in BRAF and PIK3CA genes (5). Different response to treatment is explained by variable pharmacokinetics of cetuximab. It was noted that "responders" have higher amounts of serum cetuximab than "non-responders" (1,6). There is a significant association between cetuximab and body surface area and body weight and an inverse relationship between serum albumin and unsaturated elimination rate of cetuximab (1,7).

Cetuximab is approved for treatment of colorectal cancer, alone or in combination with irinotecan, in patients with disease progression under chemotherapy with oxaliplatin or irinotecan (8).

Case report

We report a case of a 55 year-old woman, admitted in June 2012 to the Department of General Surgery, Emergency Clinical Hospital Bagdasar-Arseni with constipation, accompanied by nausea and loss of appetite, with progressive onset two months before admission. Clinical exam showed a general good state (ECOG = 1), fatigue, loss of appetite, normal colored skin, firm hepatomegaly with inferior border of the liver 7 cm below the costal rim, with apparent homogeneous surface and ascites. Colonoscopy revealed an exophytic ulcerative vegetated stenosing tumor at 40 cm from the anal verge. Abdominal ultrasound revealed intraperitoneal fluid and liver metastases. Positive diagnosis, corroborating clinical and paraclinical exams, was stenosing sigmoid cancer with liver metastases and neoplastic ascites. She underwent surgery and a Hartmann segmental colectomy was performed. Histopathological exam was positive for colonic tubular adenocarcinoma, differentiation grade 2, with moderate desmoplastic aspect, necrosis (about 20% of the tumor surface), invading the pericolonic adipose tissue and with deep ulceration of the mucosal layer. Two lymph nodes presented no tumor invasion; limits of resection were free of tumor. The disease was staged as pT3N0M1HEP. Assay for KRAS detection by PCR (polymerase

chain reaction) followed by hybridization with specific molecular probes targeting 10 mutations in codons 12 and 13 of this gene was negative for KRAS mutation.

One month later she was referred to the Department of Oncology, Palliative Care for Chronic Patients, of the Chronic Disease Hospital "St. Luke", for adjuvant therapy. For 6 months she received palliative chemotherapy XELOX regimen type (oxaliplatin 150 mg/m^2 + capecitabine 1000 mg/m^2 tid, d 1-14) every 21 days. Under XELOX chemotherapy thorax, abdomen and pelvis CT-scan showed absence of pulmonary tumors, two mediastinal lymph nodes in the Barety space and aorto-pulmonary window, measuring 9 and 13 mm. The liver was inhomogeneous, and two nodules were seen inside the left lobe, one situated at the junction of segments II and IV, 14 mm in size and the second in segment III, measuring 12 mm, hypodense, hypoenhancing (suggestive for possible metastases), without abdomino-pelvine lymph node invasion or bone metastases (Fig. 1). Abdominal MRI confirmed the presence of the two subcapsular liver nodules in segment III and at the junction of segment IV and II, measuring 12 mm and 14 cm, respectively, hypointense in T1 weighted images, with initial peripheral ring enhancing in T2 weighted images, with homogenization of hyperintensity in late acquisition and fat suppression. The lesions presented intense vascularization, compared with normal liver parenchyma, being suggestive for secondary metastatic tumors. No infradiaphragmatic lymph node invasion was noted (Fig. 2).

After 6 months the treatment was switched to cetuximab. She received cetuximab 400 mg/m^2, as loading dose during the first week, followed by 250 mg/m^2/week. Due to occurrence of severe hypersensitivity reaction during administration of the first doses, cited in the literature in 3% of patients, 90% of them occurring during the first dose (9), we preferred in-hospital treatment. Follow-up and response to treatment was assessed with clinical exam, blood analysis (Table 1, Fig. 3 and Fig. 4) and CT-scan every 6 months. Also, tolerance and side effects of

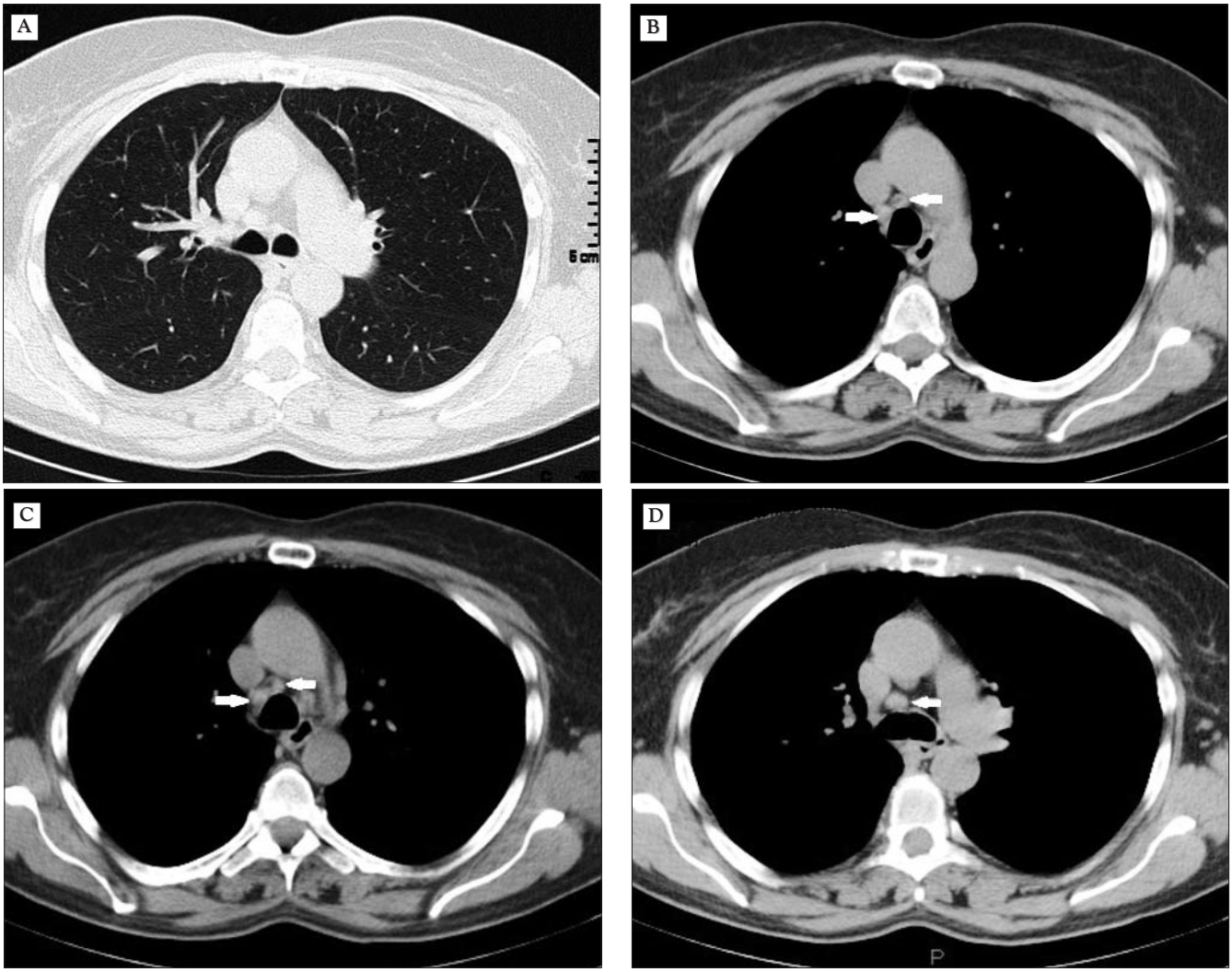

Figure 1. *Thorax, abdomen, pelvis CT-scan. No pulmonary metastases (**A**). Two mediastinal lymph nodes situated in the Barety space, pre and laterotracheal, with partial necrosis, measuring 9 and 13 mm (**B, C, D**)*

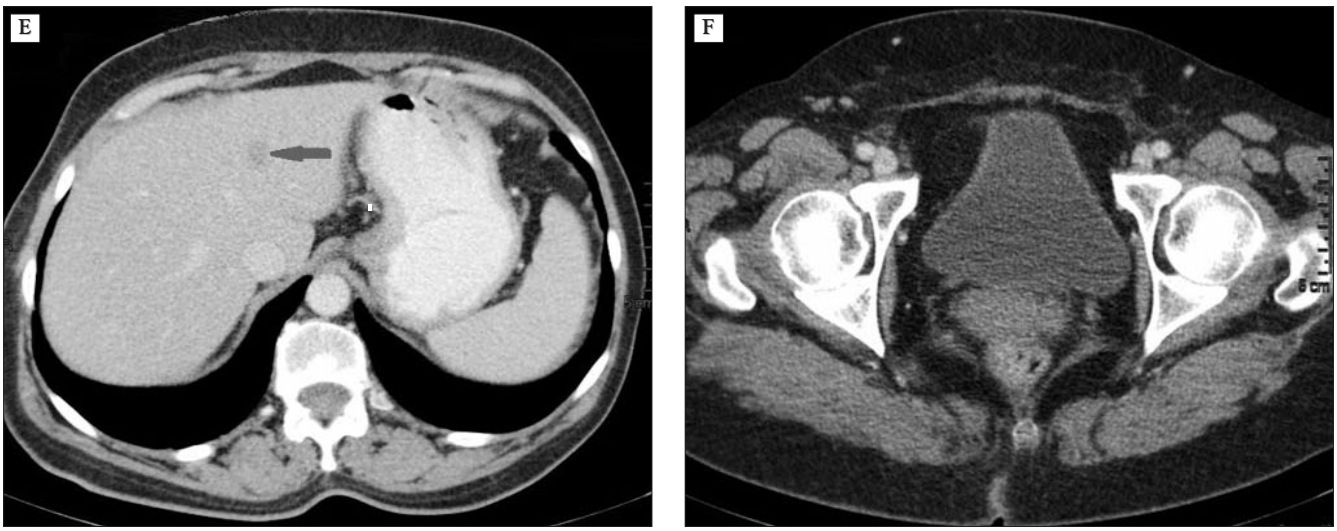

Figure 1. *Thorax, abdomen, pelvis CT-scan. Inside the left hepatic lobe there was a hypodense area, relatively well defined, hypo-enhancing, sizing 14/11 mm (**E**) without abdominopelvic lymph nodes invasion or fluid in the peritoneal cavity (**F**)*

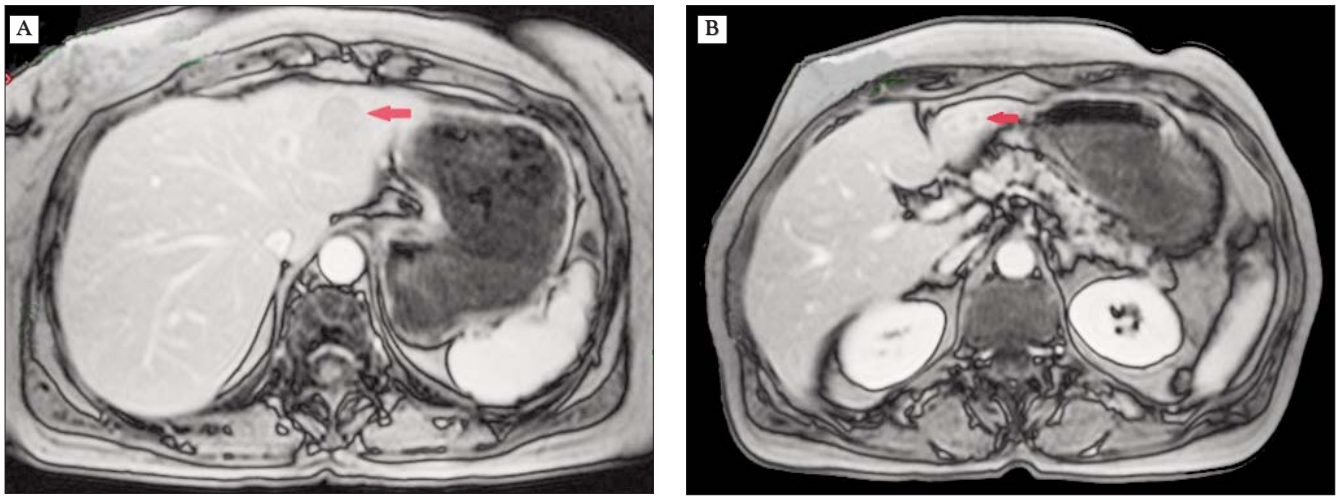

Figure 2. *Abdominal MRI (**A, B**). T2 weighted imaging*

Table 1. *Blood analysis in dynamics*

*Cht**	*Date*	*ALT (u/l)* N: 3-31	*AST† (u/l)* N: 2-31	*GGT (u/l)* N: 7-32	*ALP‡ (u/l)* N: 25-115	*Albumin (g/dl)* N: 3.4-5.6
XELOX	08/07/2012	47.8	46.2	52.5	381	4.2
	09/28/2012	49.6	48.3	56.5	384	4.18
	11/01/2012	53.7	55.9	58	394	4.8
Cetuximab	12/20/2012	53.9	57.2	59.9	400	5.2
	01/24/2013	34.1	31.8	39.7	357	4.6
	02/22/2013	29.3	31.6	31.9	324	4.6
	03/21/2013	28	29.1	3.1	317	4.9

** chemotherapy; † alanine aminotransferase; ‡ aspartate aminotransferase; § gamma-glutamyl transferase; II alkaline phosphatase*

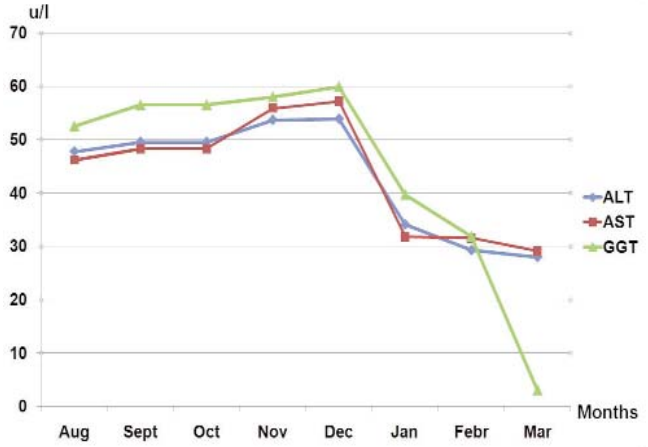

Figure 3. *Dynamics of liver tests during treatment*

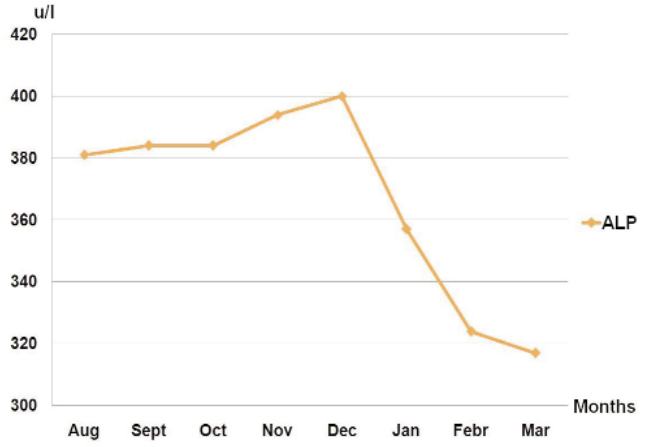

Figure 4. *Dynamics of alkaline phosphatase during treatment*

treatment were regularly evaluated. Thorax, abdomen and pelvis CT-scan revealed no pulmonary metastases, complete absence of mediastinal lymph node invasion, homogenous liver parenchyma, lacking the two nodular lesions, and no ascites fluid in the peritoneal cavity (Fig. 5).

At the last follow-up, 5 months after initiating cetuximab

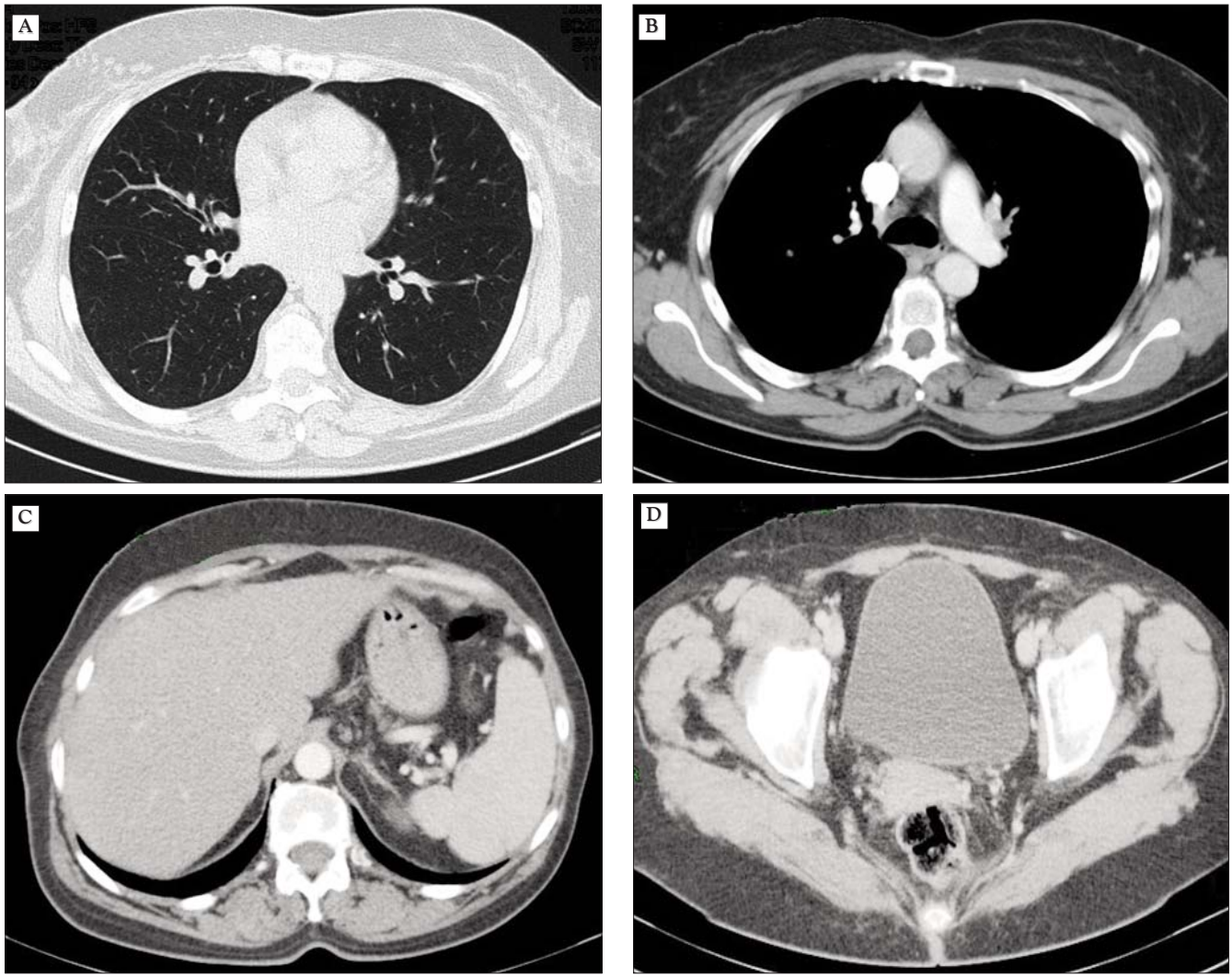

Figure 5. *Thorax, abdomen, pelvis CT-scan. No lung tumors, (fig. 5a), no mediastinal lymph nodes (fig. 5b), no intrahepatic lesions (C), without intraperitoneal fluid (**D**)*

therapy, the patient presented good general status (ECOG = 0), acneiform skin rash predominantly in the cephalic extremity, anterior chest and both forearms, soft non-tender abdomen, moderate hepatomegaly (liver 3 cm below the rim border, firm, smooth), normal bowel transit, no clinical signs of relapse. Blood analysis showed normal range parameters.

The approvals from the medical Ethical Committees of the Emergency Clinical Hospital Bagdasar-Arseni and Chronic Disease Hospital "St. Luke" were obtained.

Discussions

Efficacy of treatment with cetuximab was proved for the first time in a phase II study in patients with EGFR-positive metastatic colorectal cancer that showed tumor progression after treatment with irinotecan. Seventeen percent of 121 patients had partial response and 31% were stationary or had minimal response (4,10). In another study including 57 patients who were treated with cetuximab for the same disease, 9% had partial response and 37% had stable disease or minimal response (4,11). A study on 66 patients, with a mean age of 77 years, with metastatic colon cancer who were treated with monotherapy with cetuximab, reported 2 patients with complete response, 19 cases with partial response and 56 with stable disease (12). Also, in a study including 572 patients comparing the phase III cetuximab plus best supportive care with best supportive care alone, led by the National Cancer Institute Canada, reported 8% partial responses with association of cetuximab (2,13). In patients without KRAS mutation adding cetuximab to the standard chemotherapy failed to significantly improve the results. Evermore standard treatment was superior to combination therapy, and in elderly patients especially combination therapy had more toxic reactions and side effects, negatively influencing the quality of life and preventing completion of standard treatment" (14).

We report a case of a patient diagnosed with operated sigmoid stenosing cancer, stage T3N0M1HEP, liver metastases and neoplastic ascites, undergoing chemotherapy. The outcome of liver parameters during the first stage of chemotherapy (XELOX) suggested tumor progression, and during the second-line treatment (cetuximab) the outcome was favorable, liver parameters decreased and control imaging showed complete response after 3 months of treatment.

Reviewing relevant literature one can see that one of the most common side effects is represented by skin problems occurring in up to 80% of patients and they are mainly presented as acneiform rash, rarely with itching, scaling, hypertrichosis or paronychia. Most skin reactions occur within the first 3 weeks of treatment (8). Our patient presented only skin rash grade 2, without experiencing other side effects of treatment (fever, nausea, vomiting, shortness of breath, discomfort or diarrhea).

The case particularity is achieving complete response after 3 months of treatment with monotherapy with cetuximab, while maintaining a good quality of life, with comfort of disease-related symptoms.

Conclusions

Proper selection of patients with metastatic colon cancer for treatment with anti-EGFR therapies (considering ECOG, biological parameters, predictive biomarkers) may lead to prolonged survival and time to progression, while maintaining good quality of life.

A better knowledge of the biology of colon cancer can lead to increased treatment efficacy by decisively influencing intracellular signalling processes.

List of abbreviations

ECOG - Eastern Cooperative Oncology Group
EGRF - epidermal growth factor receptor
GTP – guanosine triphosphate

Authors' contributions

VTG established the positive diagnosis, performed surgery, participated in conception and design of the study, acquisition of data, analysis and interpretation of data, writing and reviewing the manuscript and gave final approval of the version to be published and coordinated the team; ANC conducted chemotherapy, participated in conception and design of the study, acquisition of data, analysis and interpretation of data, writing and reviewing the manuscript and gave final approval of the version to be published; GRN conducted chemotherapy, participated in conception and design of the study, acquisition of data, analysis and interpretation of data, writing and reviewing the manuscript and gave final approval of the version to be published; VS participated in conception and design of the study, acquisition of data, analysis and interpretation of data, writing and reviewing the manuscript and gave final approval of the version to be published; DNS participated in conception and design of the study, acquisition of data, analysis and interpretation of data, writing and reviewing the manuscript and gave final approval of the version to be published; MP VS participated in conception and design of the study, acquisition of data, analysis and interpretation of data, writing and reviewing the manuscript and gave final approval of the version to be published; AMS participated in conception and design of the study, acquisition of data, analysis and interpretation of data, writing, translating and reviewing the manuscript and gave final approval of the version to be published; RARN participated in conception and design of the study, acquisition of data, analysis and interpretation of data, writing and reviewing the manuscript and gave final approval of the version to be published

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Conflict of interests

We declare no conflict of interests.

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