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Single Case

Disease Control on Lanreotide Autogel[®] 120 mg in a Patient with Metastatic Gastrinoma: A Case Report

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Keywords

Gastrinoma · Gastroenteropancreatic neuroendocrine tumors · Liver metastasis · Somatostatin analogs · Lanreotide · Case report

Abstract

Gastrinomas are functionally active pancreatic neuroendocrine tumors (NETs) secreting gastrin and are associated with local or regional metastases in 60% of the cases. Somatostatin analogs (SSAs) are currently recommended as a first-line treatment for the symptomatic treatment of NETs. Although antiproliferative activity of SSAs has been demonstrated in various cancer types in several in vivo and in vitro studies, clinical benefits with SSAs have been only achieved in a small proportion of patients. We report a disease control on a long-acting SSA lanreotide in a patient with metastatic gastrinoma. A 60-year-old man, who had previously undergone a surgical resection of metastatic pancreatic gastrinoma, presented with abdominal bloating, edema in the lower limbs, fatigue, and weight loss. The gastrinoma relapse with additional metastases in the pancreas, duodenum, and liver was confirmed by positron emission tomography-computed tomography (PET-CT) scan; the patient's blood gastrin level was >5,000 ng/L. Treatment with the SSA octreotide long-acting release was initiated to treat the gastrinoma relapse. On the CT scan done in September 2011, the liver metastases were still identifiable. In December 2011, the treatment was switched to lanreotide Autogel[®] (120 mg every 2 weeks). Following the treatment, the gastrin levels were re-

duced to <1,200 ng/L in September 2013, and 812 ng/L in July 2016. Since November 2012, the gastrinoma lesions were no longer visible in abdominal CT. At the time of this report, the patient's gastrinoma was under control with lanreotide Autogel®. This case report supports the use of lanreotide Autogel® as effective treatment for metastatic gastrinoma.

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Published by S. Karger AG, Basel

Introduction

Gastrinomas are functionally active pancreatic neuroendocrine tumors (NETs) secreting gastrin and are located predominantly in the duodenum or the pancreas. The clinical manifestations of gastrinomas include gastric acid hypersecretion, abdominal pain related to peptic ulcer disease, and secretory diarrhea [1]. In about 80% of the cases, gastrinomas lead to the Zollinger-Ellison syndrome, which is characterized by pain, diarrhea, and gastroesophageal reflux disease. Gastrinomas are classified as NET G1 or G2 neoplasms according to their rate of proliferation, and present local or regional metastases in 60% of the cases [2, 3]. They typically show a proliferative activity (Ki-67 index) between 2 and 10% (closer to 2% in the majority of cases) [4]. The worldwide incidence of gastrinomas is 0.5–2/million population/year [3, 5].

The treatment of functional NETs such as gastrinomas should be aimed at controlling the tumor progression and managing the symptoms caused by the gastric acid hypersecretion. Antitumor treatments include surgery, chemo-, radio-, and biotherapy, depending on the characteristics of the tumor. Proton pump inhibitors and long-acting formulations of somatostatin analogs (SSAs) are currently recommended as a first-line treatment for the symptomatic treatment of NETs [5, 6]. Previous observational studies demonstrated tumor stabilization, besides symptomatic improvement, in patients with well-differentiated metastatic or progressive NETs treated with long-acting SSA lanreotide [7, 8]. Antiproliferative activity of SSAs has been demonstrated in breast, kidney, lung, prostate, cervix, and colon cancer in several in vivo and in vitro studies; however, clinical benefits with SSAs have been only achieved in a small proportion of patients [9]. Accumulating data indicate that SSAs are capable of inhibiting NET growth [10–12]. The phase III randomized placebo-controlled PROMID study in 85 treatment-naïve patients with disseminated well-differentiated NETs of midgut or unknown origin was the first study that demonstrated antiproliferative effect of SSAs in NETs; 6 months following the treatment with the SSA octreotide LAR, stable disease was observed in 67% of patients, as compared to 37% of patients receiving placebo [10]. In a more recent phase III CLARINET study, patients with advanced NETs treated with another SSA, lanreotide, had an improved median progression-free survival compared with placebo (progression-free survival, not reached vs. 18 months; $p < 0.001$; hazard ratio, 0.47; 95% confidence interval, 0.30–0.73); relative risk of disease progression was decreased by 53% in patients with gastroenteropancreatic (GEP)-NETs located in the pancreas, midgut, hindgut, or of unknown origin [13].

SSAs are currently recommended as first-line systemic therapy in GEP-NETs (Ki-67 <10%) in patients with G1 or a subset of G2 (equivalent to Ki-67 <10%), unresectable, locally advanced, or metastatic disease [3, 6]. Furthermore, based on the data from the CLARINET study, recent ENETS consensus guidelines recommend preferable use of lanreotide in pancreatic NETs, as prospective data on the use of octreotide in pancreatic NETs are lacking [6].

Here, we report a disease control on lanreotide in a patient with metastatic gastrinoma.

Case Presentation

In September 2010, a 60-year-old Caucasian man presented in our hospital with abdominal bloating, edema in the lower limbs, fatigue, and weight loss of 6 kg over 4 months. The timeline of the patient's outcomes and interventions is shown in [Figure 1](#).

In March 1996, the patient underwent a pancreatic biopsy and was diagnosed with pancreatic gastrinoma not associated with Zollinger-Ellison syndrome; thereafter, he underwent surgical resection of the tumor and one of the three liver metastases detected during the surgery. Following the surgery, he had been treated with proton pump inhibitors 20 mg daily to reduce the excessive gastric acid secretion. The patient's medical history included hypertension and chronic alcoholism.

In July 2004, he was hospitalized due to general worsened condition, diarrhea, and loss of appetite; the blood gastrin level was >1,000 ng/L and a probable relapse of the gastrinoma at the bulbous of the stomach was identified by abdominal computed tomography (CT) scan and magnetic resonance imaging (MRI). There was no progression of the liver metastases as assessed by CT, MRI, positron emission tomography (PET) scan, and octreotide scan. No intervention was implemented at that point due to the lack of symptoms and the slow evolution of the tumor.

In September 2010, when the patient presented to our hospital, the gastrinoma relapse was confirmed by a PET-CT scan ([Fig. 2](#)). Additional metastases were detected in the pancreas, duodenum, and liver, and the blood gastrin level was >5,000 ng/L. Decompensated liver cirrhosis (probably caused by the chronic alcoholism) was also diagnosed. Treatment with the SSA octreotide long-acting release (Sandostatin™ LAR™, Novartis; 30 mg every 4 weeks) was started to treat the gastrinoma relapse.

In January 2011 ([Fig. 2](#)), the patient's gastrin level decreased to 1,922 ng/L. In February 2011 ([Fig. 2](#)), as confirmed by MRI, the metastases in the duodenum and liver were stable and the lesions in the pancreas were not visible. On the CT scan done in September 2011, the liver metastases were still identifiable.

In November 2011, the gastrin level was still below 1,900 ng/L; at a follow-up visit in December 2011, the treatment was switched to lanreotide Autogel® (Somatuline Autogel® Injectable™ 120 mg, Ipsen) every 2 weeks. The reason for changing the treatment was to improve the ease of use, as lanreotide Autogel® does not require reconstitution and is injected deep subcutaneously, as opposed to both reconstitution and intramuscular injection required for octreotide LAR. Following the treatment, the gastrin levels were reduced to <1,200 ng/L in September 2013, and 812 ng/L in July 2016 ([Fig. 3](#)). Since November 2012, the gastrinoma lesions have no longer been visible in abdominal CT ([Fig. 2](#)). At the time of this report, the patient continued receiving his injections, and the gastrinoma was under control with lanreotide Autogel® 120 mg administered every 2 weeks.

Following one injection of lanreotide Autogel®, the patient developed erysipelas at the injection site with fever, treated with Floxapen 500 mg 4 times daily for 10 days, after which the event was resolved.

Discussion

Surgical treatment is considered a curative treatment for patients with resectable NETs and limited disease who are suitable for surgery. However, some patients cannot undergo surgery or have NETs which are nonresectable, metastatic, or with an aggressive clinical

course. For such patients, alternative treatment options include SSAs, biotherapy, targeted radionuclide therapy, locoregional treatments, and chemotherapy [3]. Furthermore, the choice of treatment depends on the symptoms, stage, and histological features of the tumor.

In this case report, the patient with metastatic gastrinoma showed stabilization of the disease upon treatment with SSAs. The patient showed some benefits upon treatment with octreotide, i.e., stability of the gastrinoma metastases and decrease in gastrin level, then switched to lanreotide Autogel® and kept on improving, as shown by the disappearance of the liver metastases and further decrease in the gastrin level. Two years following the start of treatment with SSAs, the gastrin level in blood remained stable and the gastrinoma lesions (including the liver metastases) were no longer visible. At the end of this report, the patient's treatment with lanreotide Autogel® 120 mg was still ongoing. A yearly CT scan is planned for further evaluation and follow-up.

The somatostatin receptors located on the cell membrane are expressed in about 80% of GEP-NETs, providing the basis for the use of SSAs in the treatment of these tumors [14]. The mechanisms by which somatostatin and its analogs exert their effects on the NET cells are complex and not yet fully understood; somatostatin inhibits different cellular functions such as secretion, motility, and proliferation [15]. SSAs have been used for many years in the treatment of NETs (mostly GEP-NETs) to relieve symptoms associated with functional tumors, or in inhibiting tumor progression in patients with advanced disease. However, little is known regarding the antiproliferative role of SSAs in NETs, although increasing data suggest that such analogs might exert tumorigenic effects [16]. Since the introduction of SSAs, multiple studies have demonstrated that SSA treatment is associated with prolonged survival and disease stabilization in a large proportion of patients [11]. The long-acting SSA lanreotide Autogel® is effective in controlling tumor-related symptoms in most patients with GEP-NETs [16]. In addition, several studies have investigated the antiproliferative effects of lanreotide Autogel® in patients with GEP-NETs and showed effective tumor stabilization upon treatment [7, 8, 13, 17]. The antiproliferative effect of intramuscular slow-release lanreotide 30 mg administered every 10 or 14 days was evaluated in a phase II trial in patients with carcinoid and pancreatic NETs; 2 patients (5%) achieved an objective radiographic response and 19 patients (49%) had stable disease for a mean duration of 9.5 months [18]. The pivotal CLARINET study showed a 53% reduction in the risk of tumor progression with lanreotide Autogel® 120 mg treatment in GEP-NETs compared to placebo; however, in this previous study, only 4 cases of gastrinoma were included, 2 in the treatment group and 2 in the control (of note, patients with gastrinoma were eligible for the study if gastrinomas had been adequately controlled with proton-pump inhibitors for at least 4 months) [13]. To date, the CLARINET study is considered as the most comprehensive and robust study of the antitumor effects of a SSA in patients with metastatic NETs. In addition, recently published data from the open-label extension of the CLARINET study suggest that lanreotide Autogel® 120 mg has antitumor effects in patients with progressive disease [17]. We believe our case report adds to the evidence of lanreotide Autogel® efficacy in gastrinoma tumors.

In conclusion, this case report supports the use of lanreotide Autogel® 120 mg as effective treatment for metastatic gastrinoma. Potential benefits include the ease of use, an improved adherence to treatment, symptom relief, and adequate tumor growth control.

Acknowledgements

The authors thank Urszula Micielica, PhD and Sara Rubio, PhD (XPE Pharma and Science), who provided medical writing services on behalf of Ipsen NV.

Statement of Ethics

Informed consent was obtained from the patient for publication of this case report and the accompanying CT scan images.

Disclosure Statement

The authors declare that they have no conflicts of interest.

Funding Sources

Medical writing services were funded by Ipsen NV.

Trademarks

Sandostatin LAR is a registered trademark of Novartis. Somatuline Autogel® is a registered trademark of Ipsen NV.

References

- 1 Imamura M, Nakamoto Y, Uose S, Komoto I, Awane M, Taki Y: Diagnosis of functioning pancreaticoduodenal neuroendocrine tumors. *J Hepatobiliary Pancreat Sci* 2015;22:602–609.
- 2 Bosman F, Carneiro F, Hruban R, Theise N: WHO Classification of Tumours of the Digestive System. Lyon, International Agency for Research on Cancer, 2010.
- 3 Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, Corrie P, Davar J, Davies AH, Lewington V, Meyer T, Newell-Price J, Poston G, Reed N, Rockall A, Steward W, Thakker RV, Toubanakis C, Valle J, Verbeke C, Grossman AB: Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut* 2012;61:6–32.
- 4 Jensen RT, Niederle B, Mitry E, Ramage JK, Steinmüller T, Lewington V, Scarpa A, Sundin A, Perren A, Gross D, O'Connor JM, Pauwels S, Klöppel G: Gastrinoma (duodenal and pancreatic). *Neuroendocrinology* 2006;84:173–182.
- 5 Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, Scoazec J-Y, Salazar R, Sauvanet A, Kianmanesh R; Barcelona Consensus Conference participants: ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. *Neuroendocrinology* 2012;95:98–119.
- 6 Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, Krenning E, Knigge U, Salazar R, Pape UF, Oberg K: ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. *Neuroendocrinology* 2016;103:172–185.
- 7 Bianchi A, De Marinis L, Fusco A, Lugli F, Tartaglione L, Milardi D, Mormando M, Lassandro AP, Paragliola R, Rota CA, Della Casa S, Corsello SM, Brizi MG, Pontecorvi A: The treatment of neuroendocrine tumors with long-acting somatostatin analogs: a single center experience with lanreotide autogel. *J Endocrinol Invest* 2011;34:692–697.

- 8 Martin-Richard M, Massuti B, Pineda E, Alonso V, Marmol M, Castellano D, Fonseca E, Galan A, Llanos M, Sala MA, Pericay C, Rivera F, Sastre J, Segura A, Quindos M, Maisonobe P: Antiproliferative effects of lanreotide autogel in patients with progressive, well-differentiated neuroendocrine tumours: a Spanish, multicentre, open-label, single arm phase II study. *BMC Cancer* 2013;13:427.
- 9 Keskin O, Yalcin S: A review of the use of somatostatin analogs in oncology. *Onco Targets Ther* 2013;6:471–483.
- 10 Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, Mayer C, Aminossadati B, Pape UF, Blaker M, Harder J, Arnold C, Gress T, Arnold R, Group PS: Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 2009;27:4656–4663.
- 11 Strosberg J, Kvols L: Antiproliferative effect of somatostatin analogs in gastroenteropancreatic neuroendocrine tumors. *World J Gastroenterol* 2010;16:2963–2970.
- 12 Strosberg JR, Fisher GA, Benson AB, Malin JL, Panel GTC, Cherepanov D, Broder MS, Anthony LB, Arslan B, Fisher GA, Gibbs JF, Greeno E, Iyer RV, Kim MK, Maples W, Philip PA, Strosberg J, Wolin EM: Systemic treatment in unresectable metastatic well-differentiated carcinoid tumors: consensus results from a modified Delphi process. *Pancreas* 2013;42:397–404.
- 13 Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedlackova E, Cadiot G, Wolin EM, Capdevila J, Wall L, Rindi G, Langley A, Martinez S, Blumberg J, Ruzsniowski P: Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014;371:224–233.
- 14 Appetecchia M, Baldelli R: Somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine tumours, current aspects and new perspectives. *J Exp Clin Cancer Res* 2010;29:19.
- 15 Grozinsky-Glasberg S, Shimon I, Korbonits M, Grossman AB: Somatostatin analogues in the control of neuroendocrine tumours: efficacy and mechanisms. *Endocr Relat Cancer* 2008;15:701–720.
- 16 Paragliola RM, Prete A, Papi G, Torino F, Corsello A, Pontecorvi A, Corsello SM: Clinical utility of lanreotide Autogel® in gastroenteropancreatic neuroendocrine tumors. *Drug Des Devel Ther* 2016;10:3459–3470.
- 17 Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedláčková E, Cadiot G, Wolin EM, Capdevila J, Wall L, Rindi G, Langley A, Martinez S, Gomez-Panzani E, Ruzsniowski P: Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. *Endocr Relat Cancer* 2016;23:191–199.
- 18 Ducreux M, Ruzsniowski P, Chayvialle JA, Blumberg J, Cloarec D, Michel H, Raymond JM, Dupas JL, Gouerou H, Jian R, Genestin E, Hammel P, Rougier P: The antitumoral effect of the long-acting somatostatin analog lanreotide in neuroendocrine tumors. *Am J Gastroenterol* 2000;95:3276–3281.

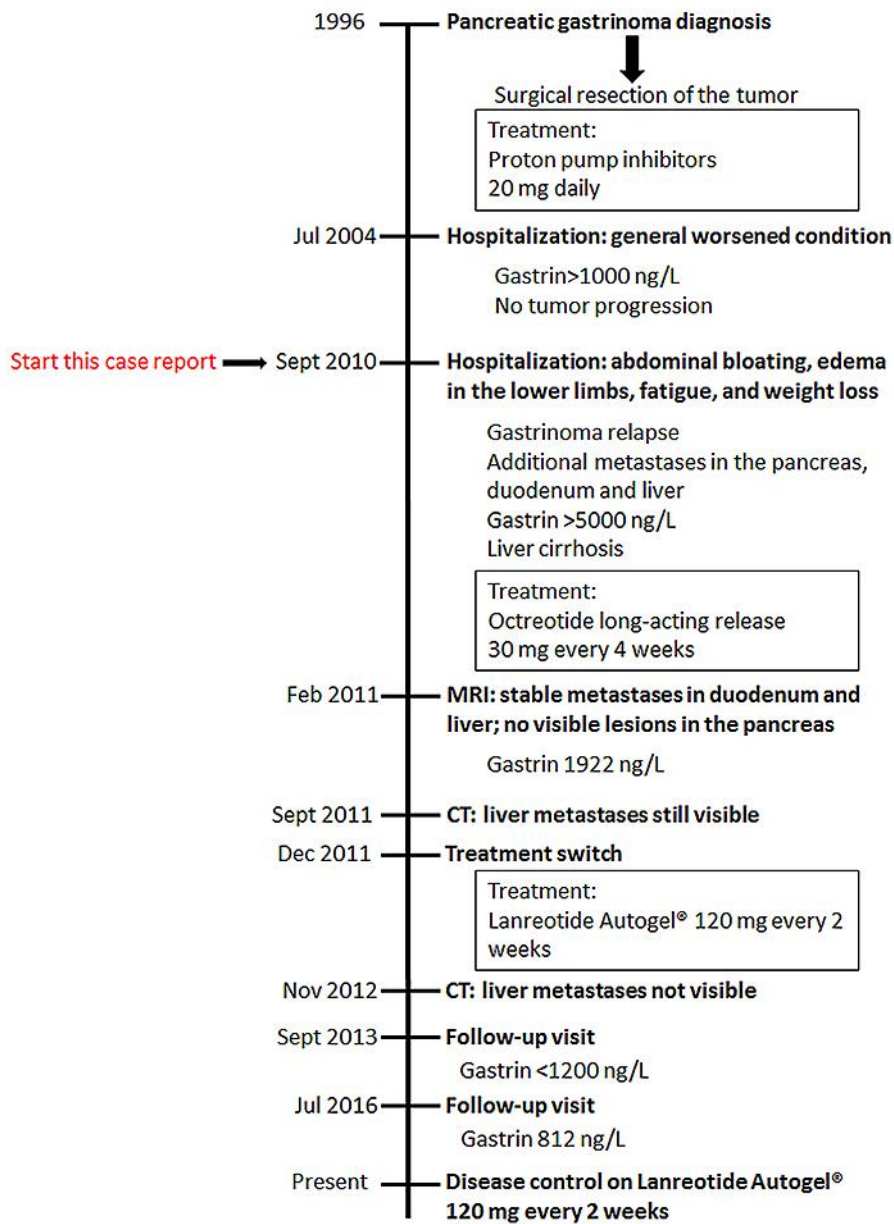


Fig. 1. Timeline of the patient's outcomes and interventions.

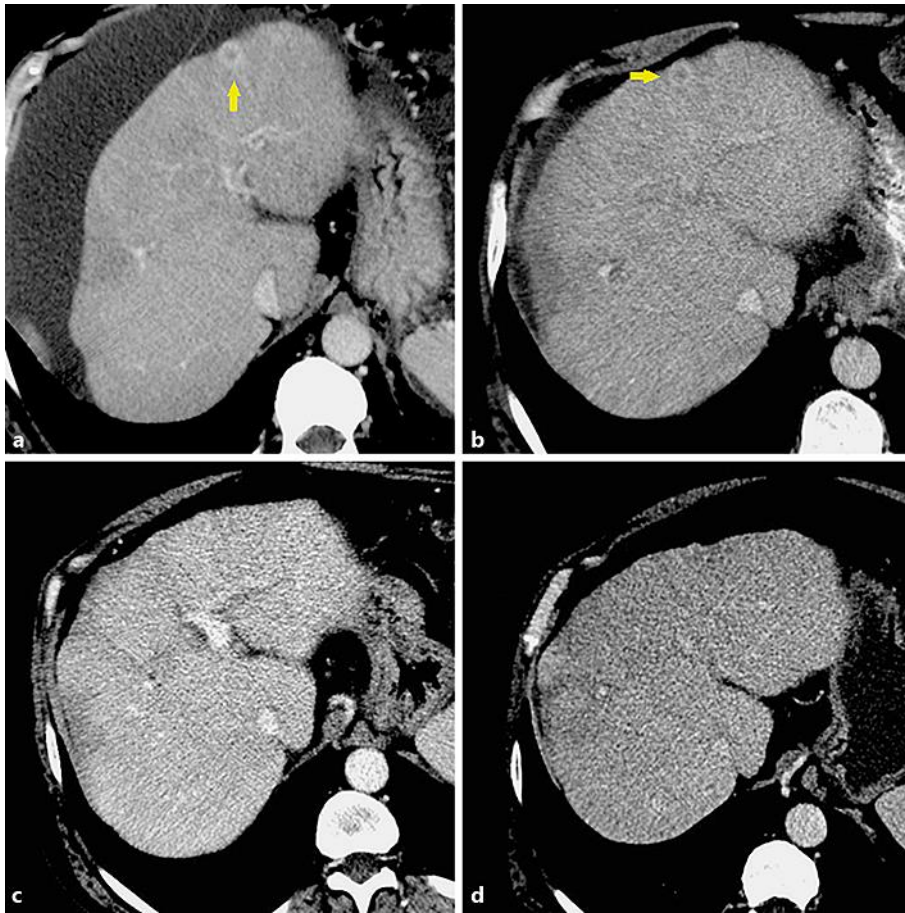


Fig. 2. a–d Transverse abdominal CT scan images showing the regression of the gastrinoma lesions in the liver after treatment with somatostatin analogs.

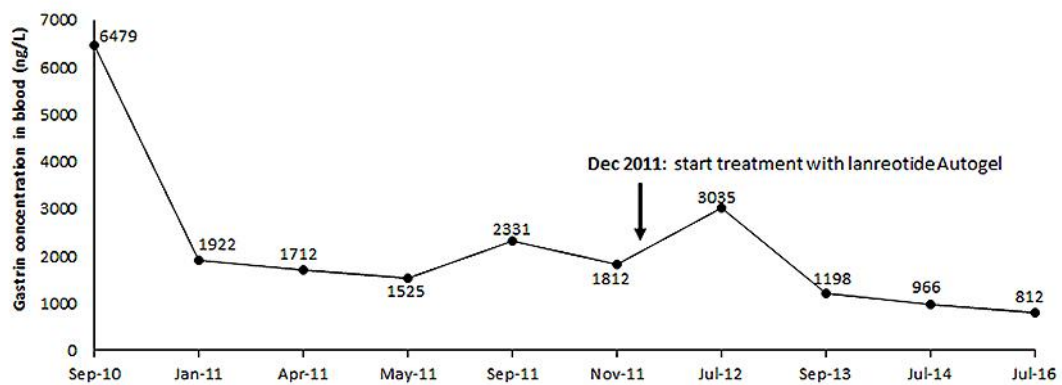


Fig. 3. Gastrin blood level of the patient throughout the treatment with lanreotide Autogel®.