World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v18.i23.2902

World J Gastroenterol 2012 June 21; 18(23): 2902-2908
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

Luis Bujanda, PhD, Professor, *Series Editor*

Spontaneous regression of pancreatic cancer: Real or a misdiagnosis?

Marta Herreros-Villanueva, Elizabeth Hijona, Angel Cosme, Luis Bujanda

Marta Herreros-Villanueva, Schulze Center for Novel Therapeutics, Division of Oncology Research, Department of Medicine, Mayo Clinic, Rochester, MN 55905, United States
Elizabeth Hijona, Angel Cosme, Luis Bujanda, Department of Gastroenterology, Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas, University of the Basque Country, Donostia Hospital-Biodonostia Institute, 20014 San Sebastian, Spain
Author contributions: Herreros-Villanueva M and Hijona E designed and wrote the paper; Cosme A and Bujanda L designed and reviewed the paper.
Supported by Instituto Salud Carlos Ⅲ
Correspondence to: Luis Bujanda, MD, PhD, Department of Gastroenterology, Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas, University of the Basque Country, Donostia Hospital-Biodonostia Institute, Paseo Dr. Beguiristain S/N, 20014 San Sebastian, Spain. luis.bujanda@osakidetza.net
Telephone: +34-94-3007173 Fax: +34-94-3007065
Received: January 1, 2012 Revised: March 4, 2012
Accepted: March 20, 2012
Published online: June 21, 2012

Abstract

Spontaneous tumor regression has been subject of numerous studies and speculations for many years. This phenomenon is exceptional, but well reported, in some types of tumors, but not in pancreatic cancer. Pancreatic cancer has the worst five-year survival rate of any cancer. Despite numerous molecular studies and clinical approaches, using several mouse models, this cancer responds poorly to the existing chemotherapeutic agents and progress on treatment remains elusive. Although pancreatic cancer tumors seldom undergo spontaneous regression, and some authors take that with skepticism, there are some cases reported in the literature. However, the variability in the description of the reports and technical details could make this process susceptible to misdiagnosis. Distinguishing between different types of pancreatic carcinoma should be taken with caution as they have wide differences in malignant potential. Diseases such as pancreatic benign tumors, insulinomas, or autoimmune pancreatitis could be responsible for this misdiagnosis as a pancreatic cancer. Here we review different cases reported, their clinical characteristics, and possible mechanisms leading to spontaneous regression of pancreatic cancer. We also discuss the possibilities of misdiagnosis.

Key words: Autoimmune pancreatitis; Insulinoma; Pancreatic cancer; Pancreatic ductal adenocarcinoma; Spontaneous regression

Peer reviewers: Dr. Alexander S Rosemurgy, Tampa General Medical Group, 409 Bayshore Blvd, Tampa, FL 33606, United States; Keiji Hanada, Center for Gastroendoscopy, Onomichi General Hospital, 1-10-25 Hirahara, Onomichi 722-8508, Japan; Massimo Falconi, Department of Surgery, Policlinico GB Rossi Piazzale Scuro 10, 37134 Verona, Italy

Herreros-Villanueva M, Hijona E, Cosme A, Bujanda L. Spontaneous regression of pancreatic cancer: Real or a misdiagnosis? *World J Gastroenterol* 2012; 18(23): 2902-2908 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i23/2902.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i23.2902

INTRODUCTION

Spontaneous tumor regression has been the subject of great interest and speculation for many years. It is an exceptional and well-documented biological event in some types of tumors, but not in pancreatic cancer.

Pancreatic cancer is a special form of cancer with the worst five-year survival rate of any cancer[1]. Despite numerous molecular studies and clinical approaches, using several mouse models[2], this cancer responds poorly to the existing chemotherapeutic agents and progress on

treatment remains elusive[3].

Pancreatic cancer is seldom described as undergoing spontaneous regression, but there are some cases reported in the literature.

In this review, the historical background, clinical features, and possible mechanisms are discussed for spontaneous regression of pancreatic cancer. In addition, we discuss whether it is a real phenomenon or a misdiagnosis.

Further understanding of this process and harnessing of the mechanisms involved will have significant diagnostic, preventative, and therapeutic implications.

HISTORICAL BACKGROUND AND CASES REPORTED FOR PANCREATIC CANCER

Spontaneous regression of cancer (SRC) is defined as the partial or complete disappearance of a malignant tumor in the absence of therapy that is capable of inducing anti-neoplastic effects. Although SRC has often been questioned, the literature reveals different cases showing this phenomenon. In 1966, Everson *et al*[4] published a classical monograph review describing 176 cases of SRC published from 1900 to 1964. In 1990, Challis *et al*[5] reported cases from 1900 to 1987, the majority of which occurred in renal cell carcinoma, choriocarcinoma, neuroblastoma, melanoma, breast cancer, and leukemia and lymphomas. Later, in 1993, O'Regan *et al*[6] agreed that the five most common tumors to undergo spontaneous regression are renal cell carcinoma, leukemia and lymphoma, neuroblastoma, carcinoma of breast and melanoma.

In these three main reviews, only three cases of pancreatic cancer were cited, and none of them were described in detail. Here, we review the most important cases of spontaneous regression of pancreatic cancer that have been reported in the literature. The first reported case was described in 1934 and published in 1967, describing a patient admitted to hospital presenting jaundice, severe pain, nausea, chills, and a high fever[7]. Laparotomy and biopsy confirmed pancreatic carcinoma. The patient's recovery spanned two months, after which she could return to work. She remained in good health, dying seven and a half years later of a pulmonary embolism. An autopsy did not find any tumors.

The second case was reported in 1973 by Lokich *et al*[8] and described a 42-year-old man with progressive diarrhea and weight loss. An upper image suggested a mass in the head of the pancreas. The patient underwent total pancreatectomy and microscopic examination reveled a moderately well differentiated ductal adenocarcinoma arising in the head of the pancreas. Adenocarcinoma was also found in the body of the pancreas, but the tail had only pancreatitis with fibrosis.

Although the patient was stabilized with insulin treatment, one year later he presented with rectal carcinomatosis consistent with adenocarcinoma of pancreatic cancer. Postoperatively, the patient received a combined chemotherapeutic program based on 5-fluorouracil (5-FU) and carmustine or bis-chloroethylnitrosourea, experiencing a gradual regression. Twenty-six months following onset of therapy treatment, there was no evidence of tumor recurrence.

The third case[9] was a male with a two-month history of ulcer pain and diarrhea. At exploration, he was diagnosed with a large tumor of the pancreatic head, extending into the liver with involved lymph nodes. The disease was confirmed by biopsy but no further manipulation was performed. By the fourth month following surgery, he was asymptomatic. Examined six years later, the patient remained symptom-free and a gastrointestinal exam demonstrated healing of the ulcer.

The fourth case, published in 1974, reported one case in 1962 of a 21-year-old male who presented with jaundice, anorexia, and fever of three months duration[10]. A liver biopsy was followed by abdominal pain, fever, tachycardia, and a decrease in blood pressure. Exploratory surgery to repair bile peritonitis revealed acute cholangitis and pericholangitis. When he was re-operated on seven weeks later, and was diagnosed with pancreatic adenocarcinoma. A T tube placed in the common duct improved symptoms and he made a slow recovery with no recurrence at the time of reporting. Unfortunately, details on the duration and intensity of fever or infection over the course of the illness in most of these cases were not provided.

In 2003, Hoption Cann *et al*[11] reported a case of a 50-year-old man with a three-month history of weight loss, anorexia, and discomfort after meals. By ultrasound and computed tomography (CT) identified a hypoechoic mass of 6.5 cm × 4 cm × 4 cm in the body of the pancreas. The posterior CT-guided biopsy was positive for pancreatic adenocarcinoma (T2N1M0, stage Ⅲb). A subsequent CT scan revealed a further 50%-60% increase in tumor volume and the tumor was considered inoperable. The patient received chemotherapy based on gemcitabine, mytomycin, and radiotherapy. As CA19-9 levels increased from 38 to 140 U/mL and the patient's health declined, the treatment was considered a failure. Some days later, the patient developed acute abdominal pain and fever and, after surgery, he had a perforated duodenal ulcer with contamination of the abdomen. Recovery was considered doubtful. However 90 d later, the patient's recuperation and weight gain were surprisingly rapid, while the CA19-9 level was normal and a positron emission tomography (PET) scan was negative for any focal disease. An ultrasound, however, confirmed residual tumor, although it had regressed by approximately 70%. However, five months later, an elevated CA19-9 and subsequent PET scan confirmed a relapse. Although the patient was treated with chemotherapy based on oxaliplatin and 5-FU initially, then gemcitabine, his health progressively deteriorated and he died one year later, almost two years following his febrile infection.

Apart from the infection, the authors suggested other factors could be relevant to this tumor regression. Some of them are the vegetarian diet based on Chinese herbs,

high-dose vitamin C and other antioxidant vitamins, hydrogen peroxide, and ginseng, followed by this patient. However, regression presented in this case appeared mostly to coincide with a prolonged febrile infection, similar to that often observed in many other cases of SRC[11,12].

BENIGN TUMORS

Some special types of pancreatic tumors are considered benign or their malignant potential is not well determined. Specifically, solid-pseudopapillary tumors are classified in this category and were often previously described in the literature as being related to spontaneous regression.

In 2008, Nakahara *et al*[13] described a 18-year-old healthy woman who was admitted to hospital for evaluation of a pancreatic mass. A solid-pseudopapillary tumor was suspected from the findings of diagnostic images, and surgery was recommended. However, the patient refused surgery and a later ultrasound-guided transcutaneous biopsy revealed proliferation of tumoral cells with small nuclei showing a pseudopapillary arrangement. periodic acid-Schiff positive granules and alpha-1-antitrypsin positive cells were proven, which led to confirmed diagnosis of pseudopapillary pancreatic tumor. The maximum diameter of the tumor gradually decreased over 10 years from 45 mm to 15 mm. This was the first report describing marked spontaneous shrinkage of this particular type of pancreatic tumor. The authors did not report details of whether the patient took any medication, antioxidant agent, or vitamins.

In this case, the authors showed histological findings and CT images suggesting that the shrinkage of the tumor may be attributable to continued degenerative change, including minor hemorrhage, necrosis, and absorption as the tumor was classified hypovascular.

In 2010, Suzuki *et al*[14] described a 13-year-old boy showing a demarcated hypovascular round mass of 50 mm in diameter in the head of the pancreas, presenting abdominal pain, nauseas, and elevated serum amylase and serum lipase. CT demonstrated a partially enhanced encapsulated tumoral mass with cystic components and calcification, without evidence of invasion to the surrounding organs, which was diagnosed as solid pseudopapillary tumor (SPT) and treated for acute pancreatitis. Six weeks later, the mass had decreased to 43 mm in diameter, and nine weeks after admission, concentrations of tumor markers, such as alpha-fetoprotein, carcinoembryonic antigen, carbohydrate antigen-199, and elastase-I, were not elevated, although the level of neuron-specific enolase (NSE) was slightly increased. Follow-up included routine laboratory tests and CT demonstrated that the size of the tumor slowly decreased to non-measurable size. After 4 years, the patient's NSE level was within the normal range. The authors presented CT images indicating that the tumor was highly likely to be SPT, based on the typical CT finding of a tumor bulging from the contour of the pancreas with eggshell-like calcification, the existence of both solid and cystic components with hypovascularity, and the patient's age. The rapid shrinkage of the tumor may be attributable to continued degenerative changes, including minor hemorrhage due to trauma, necrosis, and absorption. The authors did not report the administration of any medication or different agents to the patient. The authors suggest spontaneous tumor shrinkage, although they were unable to obtain pathology for the tumor and are conscious that there have been reports of recurrence and metastasis that developed more than 10 years after tumor resection in this type of neoplasm.

Considering all of the cases reported above, we can distinguish a wide variation in the description of the data presented. The first cases reported, until 1980, do not show images or acute laboratory test results that could verify the real entity of spontaneous regression of pancreatic carcinoma. In some cases, they do not specify the type of pancreatic tumor or give details about the biopsy, making it difficult to determine if it would be classified as a different entity, based in current diagnostic criteria.

However, considering the difference in the availability of medical technology more than 30 years ago compared with the present, this data should be taken with caution, and it is difficult to conclude whether these cases would be considered as genuine spontaneous regression of pancreatic adenocarcinoma today or would be considered as misdiagnoses.

The most recent cases, published since 2000, are more accurate in the presentation of images and blood test values, although they also show variability.

Finally, the most recent report concludes a diagnosis of SPT and not adenocarcinoma of pancreas. All of these data show that there are no recent cases reported of spontaneous regression of adenocarcinoma of the pancreas, unlike pseudopapillary tumors, which represent 1% of primary pancreatic tumors and are characterized by low malignant potential[13,14].

Some other types of pancreatic tumors with spontaneous regression, rather than adenocarcinomas and peudopapillary tumors, have been described. The most common neuroendocrine tumor with spontaneous regression is an insulinoma.

Insulinoma is a rare endocrine tumor developed from pancreatic beta cells. Eighty-seven percent are benign tumors, seven percent belong to multiendocrine neoplasia syndrome, and only six percent are considered malignant, as defined by the presence of metastasis[15].

The diagnosis of insulinoma is established by demonstrating inappropriately high serum insulin concentrations during a spontaneous or induced episode of hypoglycemia. Imaging techniques are then used to localize the tumor[16]. In 2008, Groselj *et al*[17] described a 64-year-old patient presenting with paroxysmal episodes. Electroencephalography finding suggested metabolic encephalopathy and laboratory tests showed hypoglycemia, and high insulin and C-peptide. Finally, ultrasonography and gagnetic resonance imaging (MRI) confirmed an

insulinoma in the head of the pancreas. The authors pointed out that the patient had a spontaneous recovery of the pancreatic tumor.

The overall survival rate of patients with benign insulinoma do not differ from that expected in the general population, and a misdiagnosis could be a reasonable justification for reporting SRC, even if it is not considered a malignant phenotype. Malignant insulinomas are rare, and patients have prolonged survival, even in the presence of liver or lymph node metastasis. It has been reported that some patients with malignant insulinoma who developed metastatic disease 4 years to 12 years after initial diagnosis, remained alive for up to 25 years[18]. This better outcome compared to the acinar or ductal adenocarcinoma could be a reason for a misdiagnosis, or it could also be reported as a spontaneous regression of pancreatic cancer.

AUTOIMMUNE PANCREATITIS MIMICKING PANCREATIC CANCER

Autoimmune pancreatitis (AIP) was described by Sarles *et al*[19] in 1961 and then proposed by Yoshida *et al*[20] in 1995 as a type of chronic pancreatitis occurring secondary to an autoimmune process, which may cause permanent structural and functional damage of the pancreas.

AIP represents approximately 6% of the patients with chronic pancreatitis[21,22] and is a heterogeneous manifestation associated with elevated serum levels of the immunoglobulin G subtype 4 (IgG4), which decreases with corticosteroid therapy. The most common site of extrapancreatic involvement is the bile duct, where distal biliary or mass-forming AIP mimics pancreatic cancer and proximal biliary involvement[23]. Recently, two types of AIP have been described, type 1 (or lymphoplasmacytic sclerosing pancreatitis) and type 2 (idiopathic duct centric pancreatitis or granulocyte epithelial lesion). Although clinically these two entities have comparable presentations, they differ significantly in their demography, serological characteristics, other organ involvement, and relapse rate[24].

While type 1 is associated with elevation of nonspecific autoantibodies and serum IgG4 levels, type 2 does not have definitive serologic autoimmune markers. In addition, high serum IgG4 may also be found in patients with pancreatic cancer[25], and tumoral markers such as CA19-9, SPAN-1, and DUPAN-2 may also be elevated in patients with AIP[26]. These findings can make the diagnosis of AIP confusing. AIP, in contrast to other benign chronic pancreatic diseases, can be cured with immunosuppressant drugs[27]; therefore, the differentiation of AIP from pancreatic cancer is of particular interest in clinical practice[28]. Two studies have also pointed out the possibility that some patients with AIP may develop pancreatic cancer[29,30], and this contributes to increasing misdiagnosis. However, the synchronous presence of adenocarcinoma and AIP can not be excluded, as some cases have been reported[31] and pancreatic cancer can develop after histologically confirmed AIP diagnosis[32].

Attempting to establish applicable diagnostic guidelines, the Japan Pancreas Society[33], the Korean Society[34], and more recently American criteria by Chari *et al*[24] in the Mayo Clinic at the Honolulu consensus proposed specific criteria to distinguished the two histological types of AIP and pancreatic cancer. The five important diagnostic criteria include imaging, histology, serology, other organ involvement and response to therapy, leading to an improvement in the diagnostic yield for AIP and avoidance of misdiagnosis of pancreatic cancer[35]. Nevertheless, several cases have been reported that suspect pancreatic cancer rather than AIP[36-38].

In 2005, Ozden *et al*[39] described a 58-year-old woman with jaundice referred for pancreatic head carcinoma and diagnosed by MRI. By laparotomy, a pancreatic head mass involving the mesocolon, pancreatic body, and tail was found. Pancreatic biopsies revealed cholecystitis and pancreatitis with lymphoplasmacytic infiltration. Two months after the surgery there was no parenchymal lesion on MRI. Serum immunoglobulin G, G4, and E levels were increased.

The authors report this as a spontaneous regression of a pancreatic head mass and biliary obstruction because of autoimmune pancreatitis. In this and other cases of a patient with autoimmune pancreatitis that were initially misdiagnosed as pancreatic cancer, the response to steroid therapy could appear to be a spontaneous resolution of a malignant pancreatic tumor. Patients operated on for pancreatic adenocarcinoma could represent a false spontaneous regression of pancreatic cancer instead of lack of malignancy.

MECHANISMS LEADING TO SPONTANEOUS REGRESSION

Most of the SRC cases reported do not provide a discussion regarding possible explanatory mechanisms. In pancreatic cancer reports, only the most recent publications show data in detail (images and laboratory test) and finally suggest some possible biological mechanisms leading to the spontaneous regression.

The prevalent hypotheses regarding mechanisms leading to spontaneous regression include the immunological response in the host as the most important factor[40-43]. Other mechanisms causing spontaneous regression include increased apoptosis and necrosis, epigenetic modifications, hormonal responses, role of oncogenes and tumoral suppressors, cytokines and growth factors, and psychological mechanisms (Table 1). All of these mechanisms were reviewed in 1996 by Papac[44], who specifically described some cancers, but not pancreatic tumors.

Today, the activation of these mechanisms in spontaneous regression of cancer occurs infrequently[5,40,45,46] and remains not well documented in pancreatic cancer. In other related tumors, like hepatocellular carcinoma, several mechanisms leading to the spontaneous regression of these tumors have been described, such as absti-

Table 1 Possible mechanisms for spontaneous regression in pancreatic cancer

Immunological response
Hormonal response
Induction of spontaneous differentiation
Elimination of the carcinogen
Modification in expression of oncogenes and tumoral suppressor genes
Angiogenesis inhibition
Apoptosis
Necrosis
Epigenetic mechanisms
Psychological mechanisms

nence from alcohol[47], persistent fever[48], withdrawal of androgen[49], blood transfusion[50], massive bleeding[51], and use of herbal medicine[52]. However, in the small number of reported pancreatic cancer cases, no evidence of clear and specific events was observed during the period of spontaneous regression.

Renal cell carcinoma accounts for the largest number of patients with spontaneous regression with acceptable histology and radiological confirmation[53,54]; therefore, this disease offers the best system to study the immunological response in spontaneous regression. The increased incidence of some tumors in immunosuppressed individuals, and regression following reduction of immunosupressive agents, suggests an important role for immunological factors[55,56]. Cytokines, interferon, and interleukin 2 (IL-2), IL-6 and IL-8[57,58], exert antitumor effects. While cytokines could activate T-lymphocytes, natural killer, lymphocyte-activated killer cells, and tumor infiltrating lymphocyte cells as a mechanism of action, interferons are capable of multiple immunomodulatory effects, involving monocytes, macrophages, and B-cells, as well as induction of IL-2 receptors[59,60].

Regression often occurs in the setting of febrile illness (bacterial or viral), other, different, cytokines associated with the host response to infections could mediate the regression as tumor necrosis factors[61]. Patients diagnosed with pancreatic cancer frequently suffer infections and all of these cytokines could play an important role in the spontaneous regression of pancreatic cancer; however, there is no evidence of this phenomena in the literature. Angiogenesis, as an essential component of the malignant process, has also been investigated as a mechanism contributing to regression. Several cytokines are known to inhibit this process, such as tumor necrosis factor-alpha and transforming growth factor beta, which could play a role in spontaneous regression[62]. Regarding hormonal mechanisms that could exert a role in pancreatic cancer, there is no data suggesting specific effects in spontaneous regression, although studies should be made because the endocrine pancreas could be exerting an important role.

A mechanism that has received more attention for spontaneous regression in the literature is the apoptotic process inside the tumor. The activation of this programmed cell death was proposed as the basis for spontaneous regression, especially in neuroblastoma[63] and renal cell carcinoma. Several authors suggest that the neoplastic cells, in response to different stimuli, such as T-cell mediated survival signals or cytokine regulation, could undergo apoptosis, followed by clinical remission.

As several data have demonstrated, vascular endothelial growth factor receptor blockade leads to rapid, robust, and progressive regression of tumor vasculature, increased intratumoral hypoxia, and apoptosis, and reduced tumor invasiveness and metastasis in pancreatic islet cancer[64]. Thus, this process could also be implicated in tumor regression. This apoptotic process is driven by oncogenes and tumoral suppressor gene expression and, although there is no specific, documented examples on the role of changes in the expression of regulator genes, this possibility has been cited in leukemia[65].

The expression of these oncogenes or tumoral suppressors could be switched by mutations and by epigenetic mechanisms, leading to apoptosis inside the tumor. The cited epigenetic changes have been demonstrated in retinoblastoma tumors[66] by abnormalities in methylation levels[67]. Some authors have suggested that loss of hypermethylation may be involved in the spontaneous regression of some retinoblastomas, but there is no confirmed evidence. In addition, repression of telomerase activity has been proposed as a possible mechanism for regression[68-70]. Some studies showed that patients whose tumors do not show telomerase activity underwent spontaneous regression, suggesting repression of telomerase activity as a possible mechanism for regression, although it has not yet been demonstrated in any type of pancreatic cancer.

Differentiation, a mechanism by which malignant cells develop a non-malignant phenotype, has been shown to occur in several types of cancer, such as retinoblastoma, neuroblastoma, choriocarcinoma, teratocarcinoma, and leukemias[71,72], where differentiation is possibly the major factor contributing to spontaneous regression, but this is still unknown in pancreatic cancer. Finally, related to the immunological response in tumors, psychological mechanisms have been proposed as a possible phenomenon in some cancers, but this is still regarded with skepticism. Although authors have reported psychological reasons, corroborating biological studies are lacking[73,74] and are not approved by most investigators.

This lack of information forces us to conclude that spontaneous regression in pancreatic cancer is not a well-documented phenomenon, the mechanisms leading to the regression remains unknown, and only hypotheses can be made based on some other types of tumors. In recent reports, where the radiological and histological confirmation of pancreatic disease are more precise, only an immunological response has been suggested as the most probable mechanism leading to regression of pancreatic cancer. Most of the causative factors leading to this phenomenon remain speculative.

In conclusion, it is very difficult to determine the characteristics of pancreatic cancer patients who experi-

ence spontaneous regression and the mechanisms leading to such spontaneous regression.

Currently, the existence of spontaneous regression of pancreatic cancer is a matter of debate. The small number of cases cited in the literature as a possible spontaneous regression could represent a nonmalignant disease, such as AIP or specific pseudopapillary tumor of the pancreas. In the cases described many years ago, the data presented make it difficult evaluate the diagnosis because of the lack of advanced images techniques or laboratory tests to distinguish pancreatic cancer from other diseases. In addition, many cases are not completely well documented, the presence of metastasis is questionable, therapy may have played a role, or the temporary or permanent regression of tumor growth was not defined.

Therefore, cases of spontaneous regression of pancreatic cancer described in the literature should be taken caution. Biological and molecular findings cannot provide a complete explanation of the underlying mechanisms and accumulation of such cases and further investigations of regression will contribute to better understanding of this intriguing phenomenon.

Elucidation of the mechanism could lead to better understanding and replication of the process, and to improved therapies for pancreatic cancer treatment.

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