Portal vein thrombosis as presenting feature of localized gastric adenocarcinoma

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Abstract

Background: Cancer has been widely known to grant a procoagulant state to its bearer, due to a combination of multiple local and systemic factors. Gastric adenocarcinoma is a relatively common malignancy, being one of the most prothrombotic, although rarely manifesting with portal vein thrombosis (PVT). When it occurs, it has been mainly associated with advanced disease, tumoral thrombus or an histologic hepatoid component.

Summary: We present a clinical case of a 63 year old man with PVT as presenting feature of a localized gastric adenocarcinoma (LGA) and review the existing literature on the association of both pathologies. This challenging case, besides being relevant for its rarity, brings forward the discussion about the metastatic routes, implying the importance of the hematogenous route in the absence of lymph node or hepatic metastization.

Key-messages: Upon literature review this clinical case presents itself as the first reported case of LGA presenting with PVT.

Key-words: adenocarcinoma, gastric cancer, stomach, portal vein thrombosis.

Palabras clave: Adenocarcinoma. Cáncer gástrico. Estómago. Trombosis vena porta.

Introduction

Venous thromboembolism (VTE) is a common complication in patients with malignant disease. The intrinsic relationship between cancer and thrombosis has been known for almost two centuries, first described by Bouillard in 1823 and then, by Trousseau in 1865, who largely contributed for the knowledge on the etiopathogenesis of thromboembolic phenomena.

The risk of VTE is four to seven-fold higher in patients with cancer than in those without it.

Venous manifestations of cancer-associated thrombosis include deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as visceral or splanchnic vein thrombosis and hepatic veno-occlusive disease, such as PVT, together described as VTE.

PVT related to cancer has been reported to be as high as 24%. Pancreatic and hepatocellular carcinomas, often seen in association with cirrhosis, seem to comprise the majority of the cases, although it has been also reported in carcinoma of the stomach, lung and cholangiocarcinoma[5,].

Gastric adenocarcinoma, one of the most thrombogenic malignancies (second highest incidence rate, following pancreatic cancer), comprises for 1,2% of all PVT cases, according to the *Annual Report of the pathological autopsy cases* in Japan.

Although there are very few reports on this matter, this rare event is mostly associated with advanced disease, tumoral thrombus or an histologic hepatoid component, hence its low survivability and poor prognosis.

To the best of our knowledge, we report the first case of PVT related to a LGA. Reviewing the metastatic routes for PVT, we discuss the aspects related to the hematogenic route, which seems to have an important role in PVT pathogenesis.

Case Report

We present a 63 year old man, former smoker, with known clinical history of hypertension and dyslipidemia, chronic obstructive pulmonary disease GOLD I, Stage A. He has a clinical record of a cholecystectomy at the age of 52 (due to cholelithiasis) and hepatic steatosis.

He presented at the emergency department with complaints of fever (maximum temperature of 40ºC) and low-intensity (3/10) diffuse abdominal pain for one month.

On physical examination, vital signs were normal (namely apyrexia) and the abdomen was diffusely painful to deep palpation, with an otherwise unremarkable exam.

Total blood count revealed leukocytosis (17,900 x10^3/µL WBC), neutrophilia (82,4%) and microcitic hypochromic anemia with hemoglobin=11,3 g/dL. C-Reactive protein was elevated (199 mg/L) and liver function enzymes were also altered: aspartate aminotransferase of 41 U/l (normal 10-37 U/l), gamma-glutamyl transferase of 119 U/l (normal 10-49 U/l) and alkaline phosphatase of 139 U/l (normal 30-120 U/l).

An abdominal ultrasound was performed showing severe steatosis and a left hepatic lobe prominence, suggestive of hepatopathy. Abdominal CT-scan confirmed these finds and revealed a *de novo* left branch PVT and enlargement of hilar hepatic lymph nodes (LN). (Figure 1).

Various possible etiologies for PVT were excluded, such as thrombophilic (no coagulopathy) and autoimmune disorders, such as antiphospholipid syndrome, intrabdominal infection/inflammation (no imagiologic evidence) or cirrhosis (a hepatic biopsy was performed with a METAVIR Score of Fibrosis 1 and Activity 1).

Upper gastrointestinal tract endoscopy showed two adjacent ulcers on the lesser curvature of the stomach with clean base, measuring 8 and 10 milimeters each (Figure 2).

Biopsies were performed and an histologic diagnosis of gastric adenocarcinoma (intestinal type with mucinous differentiation foci) was made.

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Cómo citar este artículo: Freitas Gonçalves F, Aguiar Almeida P, França M
Portal vein thrombosis as presenting feature of localized gastric adenocarcinoma. Galicia Clin 2018; 79 (4): 139-143

Recibido: 10/02/2018; Aceptado: 01/04/2018

Figure 1. CT-scan showing chronic hepatopathy, *de novo* left branch PVT and enlargement of hilar hepatic LN

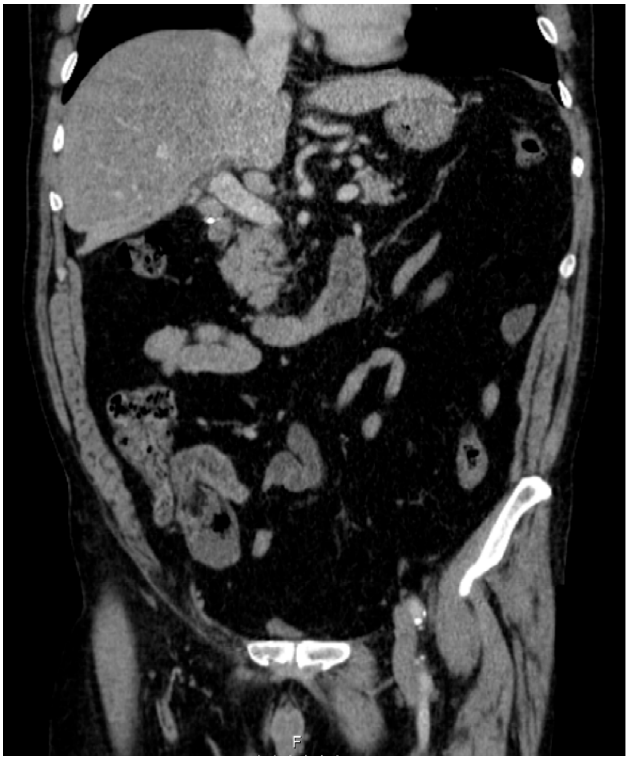
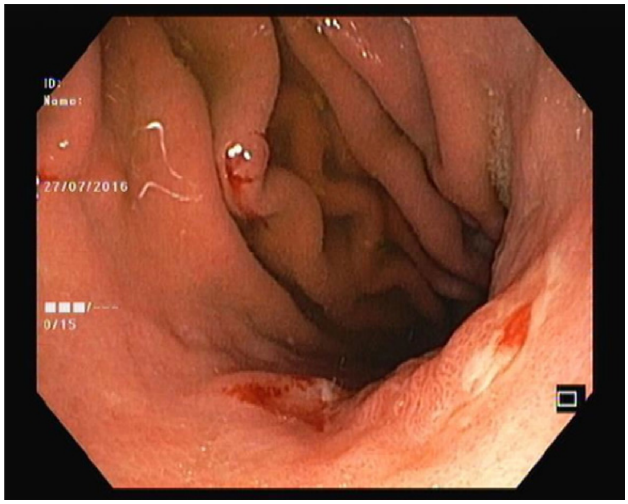


Figure 2. Upper gastrointestinal tract endoscopy showing two adjacent ulcers on the lesser curvature of the stomach



Diagnostic staging CT-Scan was performed to determine the feasibility of curative resection and it excluded extra-abdominal disease or pathologic adenopathies. The patient underwent total gastrectomy with D1 lymphadenectomy and Roux-en-Y reconstruction. Liver metastases were not detected during surgery and peritoneal carcinomatosis was excluded. The gastric lesion was not palpable and did not have macroscopic translation in the serosa.

Histological examination of the resected mass revealed a moderately differentiated adenocarcinoma, with signet ring cells. Pathological tumor stage according to the *American Joint Committee on Cancer* (AJCC), TNM Classification of Malignant Tumors was stage IA (ypT1a, pN0 [0/15], and pM0).

As surgical resection of gastric cancer, especially at early stages, is potentially curative, post-surgery clinical surveillance without adjuvant chemotherapy was decided. After 22 months follow-up, the patient has no clinical or imagiologic evidence of disease.

Literature Review

We conducted a search, on PubMed, using the keywords "portal vein thrombosis" and "gastric cancer", without restrictions on publication year. Additional studies were identified from reference lists of retrieved papers and review articles. Hematologic and neuroendocrin histology were excluded, as well as non-human subjects and non-portal vein thrombosis. One study conducted by Han JW et al, about porto-mesenteric vein thrombosis after gastric surgery was not included due to missing data in the majority of the analyzed variables on our study. Nevertheless, all the cases were post-surgical.

The search yielded, a total of 24 articles, depicting 90 cases of PVT related to gastric cancer. Patients' age, histology, LN and hepatic metastization and synchronous/methacronous status and additional causes/contributors were tabulated (Table).

There was a predominance of factors known to correlate with a poorer prognosis. Average age was 67 years old. Male gender comprised the vast majority of cases (n=75). More than one third of the cases had a poorly differentiated histology (n=36).

Most cases presented with signs of advanced disease, with lymph node metastasis in about one half of the patients (n=45) and liver metastasis in approximately two thirds of them (n=59), matching the classic known association of PVT with advanced gastric cancer.

Approximately, in one half of the patients (n=45), the thromboembolic phenomena presented synchronically with the oncologic disease.

Only five cases had no metastization, two of them directly related to major abdominal surgeries (specifically, post-gastrectomy and post-splenectomy). Kang et al case, despite not having LN or hepatic metastization, had peritoneal seeding, hallmarking advanced disease. Vanelli A. et al reported a case of LGA (pT3N0M0) with Moschcowitz's disease (thrombotic thrombocytopenic purpura), a known prothrombotic condition. The last one (Ishikawa et al), ultimately, was found to be a Borrmann type 3 advanced gastric cancer with invasion by the malignant cells into veins of the gastric wall frequently encountered in submucosal, proper and subserosal layers.

Table. PVT cases related to gastric cancer

Author	Year	Sex/ Age	Histology	Lymph node metastasis	Liver metastasis	Presentation	Another causes/ contributors
Miura S, et Al.	2016	M/75	ADC, moderate	Y	N	Met	
Sato S, et Al.	2016	M/78	ADC, moderate	Y	N	Syn	
Awazu M, et Al.	2015	M/69	ADC, poor	Y	Y	Met	
Lin YY, et Al	2015	M/64	ADC, hepatoid	6	7	N/A	
		M/69					
		M/78					
		M/63					
		F/69					
		M/60					
		M/75					
Nakao S, et Al	2015	M/63	ADC, poor	Y	N	Syn	
Uemura H, et Al.	2014	M/77	ADC, poor	Y	Y	Met	
Ebisui C, et Al	2014	M/68	ADC, poor	Y	Y	Syn	
Hata T, et Al	2014	M/58	ADC, poor	Y	Y	Met	
Ren A, et Al	2014	M/78	ADC, hepatoid	Y	Y	Syn	
		M/75					
Makino H, et Al.	2013	F/71	ADC, moderate	Y	Y	Syn	
Kang JH, et Al.	2013	F/50	N/A	N/A	N/A	Syn	
Ishigami S, et Al	2012	M/53	ADC, well	Y	N	Syn	
Eom BW, et Al[9]	2012	43 M and 8 F/ median 59 (32-79)	ADC, well 23/ poor 26	24	37	Syn 21/ Met 30	
Kagawa S, et Al	2010	F/53	ADC, poor	Y	N	Met	Post-surgery
Oishi C, et Al	2009	M/82	ADC, moderate	Y	Y	Syn	
		M/80	ADC, poor				
Lee MW, et Al	2007	M/70	ADC, hepatoid	Y	Y	Syn	
		M/65			N		
		M/46			Y		
		M/61			Y		
Vanelli A, et Al	2004	F/62	ADC, poor	N	N	Syn	Moschcowitz's disease
Tanaka A et, Al	2002	F/86	ADC, moderate	N	N	Met	Post-surgery
		M/73	ADC, well	Y	Y	Syn	
		M/68				Met	
Kogire M, et Al	1996	F/48	N/A	N	N	Met	Post-surgery
Yoshida Y, et Al	1995	M/67	N/A	N/A	Y	Syn	
Ishikawa M, et Al	1995	M/69	ADC, well	N	N	Syn	
Araki T, et Al	1990	M/68	ADC, moderate	N/A	Y	Syn	
		M/77					
		M/60					
		M/63	ADC, poor				
Takayasu K, et Al	1989	M/54	ADC, poor	Y	Y	Syn	
Aruga A, et Al	1986	M/77	ADC, moderate	N/A	Y	Syn	

ADC – adenocarcinoma; F – female; M – male; Met – Metachronous; Moderate – moderately differentiated; N – no; N/A – not available; Poor – poorly differentiated; Syn – Synchronous; Y – yes; Well – well differentiated;

Discussion

Malignancies have been widely known to grant a procoagulant state, due to a combination of multiple local and systemic factors and from the interaction between cancer cells and host factors. All the elements of the "Virchow's triad" can simultaneously account for the prothrombotic state in the same patient. These elements include: (i) stasis of the blood, due to extrinsic compression of blood vessels by the tumor or patient immobilization; (ii) vascular injury, which follows invasion of vessels by cancer cells, but also therapeutic interventions, such as insertion of central venous catheter or administration of chemotherapy toxic to endothelial cells; (iii) *blood hypercoagulability,* mostly due to release of procoagulant molecules by cancer cells (mediated by aberrant tumor cell tissue factor (TF) expression, release of tumor cell-derived, TF-expressing microparticles, cancer procoagulant, and other cell surface proteases), to increased platelet aggregation and to adhesive interactions among tumor cells, endothelium and blood cells[34,35].

In addition to these biochemical alterations, intrinsic to cancer cells, changes in portal circulation, also, play a part. Hemodynamic forces not only regulate the predilection of specific anatomic sites to thrombosis, but they strongly influence the biochemical makeup of thrombi and the reaction pathways involved in thrombus formation[36], as it happens in extrinsic compression by lymph node (LN) or hepatic metastasis.

Gastric adenocarcinoma, a highly prothrombotic malignancy, as previously discussed, is seldom related to PVT. Three main paths are thought to intervene is this pathogenesis, being: (i) the *LN* type, (ii) the *hepatic mass* type, and (iii) the *hematogenous* type. The LN type is defined when a metastatic LN is found close to the PVT, and therefore the PVT seems to originate from a metastatic LN of gastric cancer. Similarly, the hepatic mass type is defined when a metastatic hepatic mass is close to the PVT, and the PVT seems to originate from the hepatic mass. Finally, the hematogenous type is defined when the PVT occurs independently, without either an adjacent metastatic LN or an hepatic mass, as seen in the 2012 retrospective study from Eom *et al* [9].

Surgical therapy is the mainstay of treatment for LGA, either by classic surgical techniques or endoscopic removal, and no adjuvant treatment is proposed for Stage IA disease by current guidelines[37]. Complete cure can almost always be achieved by conventional gastrectomy with lymph node dissection[38].

Although the general good prognosis for LGA, there are many known poor prognosis factors. Multivariate analysis identified nodal status, vessel involvement and histological differentiation as independent prognostic factors for disease-free survival, and gender, age and differentiation were independent influencing factors for overall survival[39]. The development of VTE was an independent prognostic factor for overall survival in multivariate analysis[40].

When PVT invades the portal vein system, tumor cell spreads and distributes along with the portal vein and its branches, by hematogenous route, thus resulting in intra-hepatic micro-metastasis which contributes to early recurrence for patients following curative resection, which is specially known in hepatocellular carcinoma.

There is an ongoing clinical trial investigating the efficacy and safety of Folfox4 chemotherapy regimen to prevent early recurrence for hepatocellular carcinoma patients with PVT following curative resection (ClinicalTrials.gov **Identifier:** NCT02813096), which might, in the future, bring a new role to adjuvant treatment in the local disease setting. Unfortunately there are no ongoing trials in the setting of LGA (namely Stage IA) to reinforce this eventual data.

Conclusion

PVT is classically associated with advanced gastric cancer, with lymph node involvement, hepatic or distant metastatic disease. The authors report the first clinical case of LGA associated with PVT, with no other clinical unequivocal etiology, such as a post-surgical direct effect, inquiring the unrecognized role of the hematogenous route in the pathogenesis of PVT and adjuvant CT in LGA setting.

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