IDH1, IDH2, JAK1, JAK2, JAK3, KIT, KRAS, MAP2K1, MAP2K2, MET, MTOR, NOTCH1, NRAS, PDGFRA, PIK3CA, PTEN, RAF1, RET, ROS1, SMAD4, SMO, STK11, and *TP53*. Furthermore, no copy number alterations were detected in *AKT1, ALK, AR, BRAF, CCND1, CDK4, CDK6, EGFR, ERBB2, FGFR1, FGFR2, FGFR3, FGFR4, KIT, KRAS, MET, MYC, MYCN, PDGFRA*, and *PIK3CA*.

The other non-Barrett's associated EAC derive from heterotopic gastric mucosa and is more frequent in males. A third actor to consider is the esophageal gland duct adenoma, located in the lower esophagus, with most published cases being in males between 40 and 60 years old, treated with endoscopic resection and with no recurrence or malignancy during follow up.[5] It is uncertain whether esophageal gland duct adenoma can be a precursor lesion of adenocarcinoma. Our case had some hyperplastic benign submucosal glands, larger than normally seen, but it is difficult to state if the tumour was originated in such a lesion, although it cannot be completely excluded (Fig. 1H).

In conclusion, it is important to identify these rare EAC arising in the submucosal gland/duct system, since they could have a different etiopathogenesis and carcinogenetic pathway. Little is known about their genetic profile as no genetic study has been performed in the few reported cases. Our case had a poor response to neoadjuvant therapy, and we did not find any mutation in any of the most frequent genes involved in gastric, esophageal or other frequent human adenocarcinomas.

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Splenosis: An underappreciated cause of gastrointestinal bleeding in splenectomized patients. Case report and literature review

Esplenosis: una causa subestimada de hemorragia gastrointestinal en el esplenectomizado. Caso clínico y revisión literaria

Splenosis is the ectopic splenic tissue autotransplanted following splenectomy or splenic trauma.[1] This tissue may give rise to a mass or masses located in the peritoneum or extraperitoneally, which may present a difficult differential diagnosis. Occasionally, splenosis may produce abdominal pain, obstruction, and gastrointestinal bleeding.[1,2]

A 55-year-old male attended the emergency room (ER) for a new episode of melena in July 2018. Previous medical history included a necrotizing pancreatitis in 2003 with a splenic vein thrombosis with collateral circulation as a sign of prehepatic portal hypertension (PPH). In 2007 spleen rupture occurred. Since then, the patient presented several episodes of upper gastrointestinal bleeding (UGIB). They were thought to be secondary to this PPH because on endoscopy an enlarged mucosal fold on the gastric fundus was found to be the source of bleeding recurrently (findings were: adherent clot to this fold, or an stomach full of blood with no alternative source). Despite different approaches (cyanoacrylate, aethoxysklerol, or arterial embolization of

Table 1 Summary of all cases reviewed.

case	Year of publication	Age (years)/sex	Reason of splenectomy	Time interval from surgery to bleeding (years)	Location	Tc99mHDES (performed yes/no)	Rebleeding[a]	Endoscopic findings	Definitive intervention	Outcome
Basile RM, et al.[9]	1989	24/M	Traumatic rupture	19	Ileon	NO (Tc99m sulfur colloid study)	NO	EGD x2: No findings	Surgical resection	Survived intervention. No follow up.
Chiarugi M, et al.[10]	1996	65/M	Gaucher disease	29	Greater curvature of the stomach	NO	YES	EGD: Ulcer 10 mm with adherent clot IIB	Surgical resection	Survived intervention. No follow up.
Laszewicz, et al.[11]	1997	40/M	NM	NM	Posterior wall of the stomach	NO	YES	EGD: Bluish semypedunculated polyp. Detachable snare.	Surgical resection	Survived intervention. No follow up.
Sikov M, et al.[6]	2000	48/M	Traumatic rupture	41	Jejunum + colon	YES (but splenosis was not found).	YES	EGD + Colonoscopy: No findings.	Surgical resection	Survived intervention. Several years (not specified) follow up: No rebleeding.
Margari A, et al.[1]	2008	47/M	Traumatic rupture	19	Gastric fundus	NO	NO	EGD: Big clot.occupying stomach.	Surgical resection	Survived intervention. No follow up.
Arroja B, et al.[7]	2011	68/M	Traumatic rupture	30	Greater curvature of the stomach	YES	NO	EGD: Ulcer over elevated formation	Medical treatment[b]	3 weeks follow up: No rebleeding.
Obokhare ID, et al.[12]	2012	41/M	Gastric varices	3	Colon (splenic flexure)	NO	YES	Colonoscopy: Polypoid ulcerated mass.	Surgical resection	Survived intervention. No follow up.
Alang N[2]	2013	54/F	NM	37	Gastric fundus	NO	NO	EGD: Fundic clot.	Surgical resection	Survived intervention. No follow up.
Alvite Canosa[13]	2013	49/M	Traumatic rupture	28	Gastric fundus	NO	YES	EGD: Fundic erosions. EUS: Perilessional tortuous vessels (varices).	Surgical resection	Survived intervention. 4 months follow up: No rebleeding.

Table 1 (*Continued*)

case	Year of publication	Age (years)/ sex	Reason of splenectomy	Time interval from surgery to bleeding (years)	Location	Tc99mHDES (performed yes/no)	Rebleeding[a]	Endoscopic findings	Definitive intervention	Outcome
Yang K, et al.[14]	2013	42/M	Traumatic rupture	17	Gastric fundus	NO	YES	EGD: Submucsal mass in fundus, bleeding ulcer on top.	Surgical resention	Survived intervention. No follow up.
Leitz EM, et al.[15]	2015	35/M	Traumatic rupture	NM	Small bowel	YES	NO	EGD + Colonoscopy: No findings.	Transarterial embolization	Survived intervention. 9 months follow up: No rebleeding.
Famà F, et al.[8]	2016	68/M	Traumatic rupture	25	Jejunum	YES	YES	EGD + Colonoscopy + VCE: No findings.	Medical treatment[b]	7 years follow up: No rebleeding.
Reinglas J, et al.[4]	2016	52/M	Traumatic rupture	38	Gastric fundus	NO	YES	EGD: Fundic clot. EUS: Perforating vessels in the gastric wall, no large varices.	Transarterial embolization	Survived intervention. 8 months follow up: No rebleeding.
Xiao SM, et al.[16]	2017	40/M	Traumatic rupture	10	Colon (splenic flexure) + stomach greater curvature	NO	YES	Colonoscopy: Neoplasia in splenic flexure	Surgical resection	Survived intervention. No follow up.
Arena R, et al.[17]	2018	58/M	Traumatic rupture	30	Ileum	NO	NO	EGD + Colonoscopy: No findings. VCE: Ulcerated lession in the ileon	Surgical resection	Survived intervention. No follow up.
Moralejo Lozano Ó, et al. (current article)	2020	55/M	Traumatic rupture	11	Gastric fundus	YES	YES	EGD: IGV-1 (EUS confirmed) + Fundic clot.	Surgical resection	Survived intervention. 18 months follow up: No rebleeding.

EGD: Esophagogastroduodenoscopy, EUS: Endoscopic ultrasound, F: Female, IGV-1: Isolated gastric varices type 1, M: Male, NM: Not mentioned, Tc-99M HDES: Technetium (Tc) 99m-labelled heat-denatured erythrocyte scintigraphy, VCE: Videocapsule endoscopy.

[a] Rebleeding: recurrent melena episodes or evidence of rebleeding during hospital admission.

[b] Medical treatment: intravenous fluids and proton-pump inhibitors (PPI).

an active leak depending on the left gastric artery), UGIB episodes continued.

This time, a new endoscopic ultrasound (EUS) revealed a 39 mm rounded, homogeneous, hypoechoic mass adjacent to the gastric fundus, with perforating vessels. A technetium (Tc) 99m-labelled heat-denatured erythrocyte scintigraphy (HDES) detected an uptake area in the gastric fundus. All this information was consistent with a diagnosis of splenosis. Selective cyanoacrylate injection under EUS guidance with disappearance of doppler uptake of the perforating vessels was done. Nevertheless, rebleeding occurred, and surgery was planned: a partial gastrectomy of the fundus was performed. In macroscopic examination, over the external surface of the gastric wall multiple solid nodular brown-violet formations are found measuring between 3 and 32 mm, corresponding in the microscopic examination to splenic tissue including white and red pulp.

After an eighteen-month follow up, no rebleeding has occurred, anaemia is solved and stable, no more transfusions or iron supplements are required, and the patient is back to an active live.

Previous published literature has been reviewed. We focused our interest on gastrointestinal bleeding due to splenosis. We conducted a search through PubMed using the MeSH terms ''splenosis'' and ''bleeding'' or ''hemorrhage'', as well as through the references of the articles found. Language was limited to English. Fifteen previously cases were found, published between 1989 and 2019 (Table 1).

Age ranged from 24 to 68 years (mean: 49.13 years; median: 48.50 years), mostly male (93.75%). Spleen rupture (75%) was the main reason for splenectomy. The interval time from splenectomy to diagnosis ranged from 3 to 41 years (mean: 24.07 years; median: 26.50 years). Most frequent location was the stomach (62.50%), followed by small intestine (31.25%) and colon (18.75%). This data contrast with the reported most frequent location of abdominal splenosis which are greater omemtum and serosal surface of small intestine.[3] Recurrence of bleeding during hospital admission was common (62.50%).

Diagnosing splenosis can be challenging. Several imaging methods can be helpful such as abdominal ultrasonography, computed tomography (CT), or standard magnetic resonance imaging (MRI) but a lack of specificity is present. Ferumoxide-enhaced MRI, Tc-99m sulphur colloid scintigraphy,[3,4] or single-photon emission computed tomography (SPECT)[5] have been described. However, technetium (Tc) 99m-labelled HDES is generally accepted as the most sensitive and specific test.[3] It is to be noted that just in 37.50% of the cases HDES was performed, with the splenosis often being diagnosed intraoperatively. This could relate to a low grade of suspicion; but also, the clinical situation of the patient often required urgent surgery.

Definitive treatment for most cases was surgical resection (75%). However, conservative approach (12.50%) and arteriography (31.25%) have also been described. Arteriography was used in 5 cases, not detecting the bleeding source in 2 of them. When embolization was performed (3 cases), it was definitive just in two of them. In 56.25% of the cases no follow-up was reported. In those with informed follow-up, it was generally short, with only three cases (including ours) overcoming one or more years.[6,8]

As a conclusion, gastrointestinal bleeding due to splenosis occurs more commonly many years after splenectomy, mostly in males, with the gastric fundus as the most common location. It is frequently recurrent, and surgical resection is often required, but other approaches such as transarterial embolization[4,15] or conservative treatment[7,8] have also been reported.

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Tocilizumab como posible causa de colitis isquémica

Tocilizumab as a possible cause of ischemic colitis

Desde diciembre de 2019, un nuevo coronavirus, llamado SARS-CoV-2, se aisló como agente causal de una nueva neumonía mundialmente extendida, denominada posteriormente por la Organización Mundial de la Salud como COVID-19[1]. En España, según los datos del Ministerio de Sanidad, el número de casos diagnosticados por PCR al 01 de mayo de 2020 supera los 215.000 y el número de fallecimientos ronda los 25.000, lo que supone una tasa de mortalidad del 11,6%[2].

En algunos pacientes se produce un síndrome de liberación de citocinas. La interleucina-6 (IL-6) es la molécula clave de esta tormenta[3]. El tocilizumab, un anticuerpo monoclonal recombinante humanizado, actúa contra el receptor de la IL-6. Es por ello que se ha convertido en un fármaco utilizado en pacientes con COVID-19 grave con IL-6 elevada. A pesar de los aparentes beneficios descritos, debemos tener presentes los posibles efectos adversos de este agente. Presentamos el caso de un paciente tratado con tocilizumab por una afectación grave por COVID-19, que presenta un cuadro compatible con colitis isquémica segmentaria.

Varón de 59 años ingresado en la UCI por neumonía bilateral por SARS-CoV-2, complicado con SDRA moderado-severo que precisa intubación orotraqueal prolongada. Como antecedentes destacan hipertensión arterial y cardiopatía isquémica revascularizada en febrero de 2020 y actualmente con doble tratamiento antiagregante. Tras tres días con bolos de metilprednisolona, el paciente cursó con mala evolución clínica, analítica y radiológica, por lo que se pautó una única dosis de tocilizumab de 600 mg intravenoso. A los 10 días de la administración de este fármaco, el paciente comenzó con rectorragias que precisaron la transfusión de cuatro concentrados de hematíes y uno de plaquetas (dos concentrados de hematíes cada 48-72 horas aproximadamente) por una anemización multifactorial, dado que se llegó a alcanzar cifras de hemoglobina de 7,2 g/dL.

Se realizó una colonoscopia a las 24 horas del primer episodio de rectorragia, en la que se objetivaron restos hemáticos digeridos (sin sangrado activo) hasta ángulo hepático y signos en la mucosa de colitis isquémica con dos úlceras con coágulo adherido entre 55 y 65 centímetros del margen anal externo (fig. 1). Dicha colonoscopia fue completa, aunque no se realizó ileoscopia. La gastroscopia visualizó varias aftas milimétricas gástricas sugerentes de lesiones agudas de la mucosa gástrica sin restos hemáticos ni signos de sangrado activo. Tras los hallazgos endoscópicos y el contexto del paciente, se instauró reposo digestivo con nutrición parenteral y antibioterapia empírica de amplio espectro. Días más tarde, ante la persistencia de la rectorragia, se solicitó una angio-TC de abdomen que descartó sangrado activo y oclusión arterial; tampoco se describía engrosamiento segmentario ni signos de mal pronóstico en la pared colónica. Desde ese día se suspendió la antiagregación y, a las dos semanas del primer episodio, la emisión de sangre a través del recto se había autolimitado, por lo que se decidió llevar a cabo una nueva colonoscopia (fig. 1). Esta prueba evidenció las mismas lesiones ulcerosas, ahora fibrinadas, y la mejoría de la afectación mucosa en el mismo segmento colónico descrito en la primera endoscopia, siendo catalogado como colitis isquémica segmentaria. En las colonoscopias no se hallaron divertículos en colon.

La forma más frecuente de isquemia intestinal es la colitis isquémica. Cursa típicamente con dolor abdominal cólico, urgencia defecatoria y sangrado rectal. La mayoría de los pacientes presentan formas leves que se resuelven en pocos días y la mucosa se recupera en dos a tres semanas. Sin embargo, en afectaciones más graves, la recuperación de las lesiones puede durar hasta seis meses, aunque el paciente persista asintomático. Tampoco hay que olvidar una posible complicación como es la perforación intestinal[4].

El reciente brote de COVID-19 ha sido considerado una emergencia sanitaria mundial. Todavía no existe un tratamiento efectivo o una vacuna disponible. El tocilizumab es útil en casos seleccionados[3]. Algunos posibles efectos adversos a nivel gastrointestinal de este fármaco son la presencia de úlcera gástrica (< 2%), diverticulitis y perforaciones gastrointestinales[5]. En nuestro caso, el paciente presentó úlceras colónicas con rectorragias anemizantes de dos semanas de duración, que se autolimitaron.

Se ha aplicado el algoritmo de Naranjo para conocer la probabilidad de la relación causal entre la administración del tocilizumab y la colitis isquémica, con resultado de cuatro puntos. Con todo esto, debemos tener en mente de que estamos ante una asociación posible. Existen otras limita-