

Fatal acute pulmonary embolism following endoscopic cyanoacrylate injection for gastric fundal varices

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Abstract

Acute gastric variceal bleeding is a rare but serious complication of portal hypertension. Initial therapy for bleeding gastric varices focuses on acute hemostasis. In this regard, endoscopic cyanoacrylate injection (ECI) is the first-line approach. Cyanoacrylate diluted with Lipiodol acts as a tissue adhesive that polymerizes on contact with blood. Glue-induced pulmonary embolism is a very rare but severe complication of ECI. This paper describes a case of fatal glue pulmonary embolism during ECI for prevention of bleeding from gastric fundal varices in a patient with polycythemia vera and the presence of portosystemic shunts. (*Acta gastroenterol. belg.*, 2024, 87, 531-534).

Keywords: endoscopic sclerotherapy injection, gastric varices, pulmonary embolism, polycythemia vera.

Introduction

Gastric varices (GV) occur in approximately 20% of patients with cirrhotic portal hypertension, but can also develop in patients with sinistral or segmental portal hypertension from a focal splenic vein thrombosis, stenosis of the portal or splenic vein related to inflammatory processes such as pancreatitis or a prothrombotic conditions such as Polycythemia Vera (PV) (1). Up to 36% of patients with gastric varices (GV) will bleed once in their lifetime (2-4). Therefore, the treatment and secondary prevention of variceal bleeding are important in successful patient management. Studies indicate that endoscopic cyanoacrylate injection (ECI) of GV with N-butyl-2-cyanoacrylate is both effective and safe (1). The liquid monomer polymerizes into a solid cast when in contact with ionic solutions such as blood, obturating the vessel within 10-20s. The reported primary hemostasis rate is 94-97% with few rebleeding events (3-30%) (3,5). Major complications are very rare. This paper describes a case of fatal pulmonary embolism during cyanoacrylate injection for secondary prevention of gastric variceal rebleeding.

Case history

A 48-year-old female patient was referred to our outpatient hepatology department for secondary prevention of gastric variceal rebleeding. At the age of 35 she was diagnosed with a primary Budd-Chiari syndrome (BCS) due to an underlying JAK 2 positive

prothrombotic condition PV. This led to complications of portal hypertension with ascites and esophageal varices (Child Pugh B8, MELD 18). The patient was treated for the BCS with a transjugular intrahepatic portosystemic shunt (TIPS). The patient was also treated with standard dose of Aspirin because of the underlying PV. Two months before current presentation, the patient presented at the emergency department because of hematemesis with an acute drop in hemoglobin (to 5 g/dL; normal range in females is 12 to 16 g/dL) suggestive for an upper gastrointestinal bleeding. During endoscopic examination, gastro-esophageal varices (GOV2, according to the Sarin classification) were documented. When referred to our department for elective secondary prophylaxis treatment she had not experienced any further episodes of hematemesis and had a stable hemoglobin of 9,7 g/dL. Ultrasound showed a patent TIPS and there was no evidence of ascites. Endoscopic ultrasound revealed grade II esophageal varices and two voluminous fundic varices (GOV2), without the presence of cherry red spots. The varices were treated by injection of 5ml N-butyl-cyanoacrylate mixed with Lipiodol (1ml Cyanoacrylate and 4ml Lipiodol). During the procedure, torsades de pointes were observed for several minutes which resolved after intravenous magnesium. Oxygenation appeared to be difficult. Transthoracic echocardiography showed a normal left ventricular function, but presence of a dilated right ventricle with D-shaping and severe pulmonary hypertension suggestive for saddle emboli. Thoracic radiography showed radio-opaque material perihilar bilaterally (Fig. 1), suggestive of glue-embolization. A thoracic computed tomography (CT) without contrast showed extensive glue-emboli proximally in both pulmonary arteries (Fig. 2), more extensive on the right side, and a dilated pulmonary trunk suggestive of pulmonary hypertension. The patient further deteriorated and developed a severe respiratory insufficiency necessitating intubation. She collapsed shortly after and

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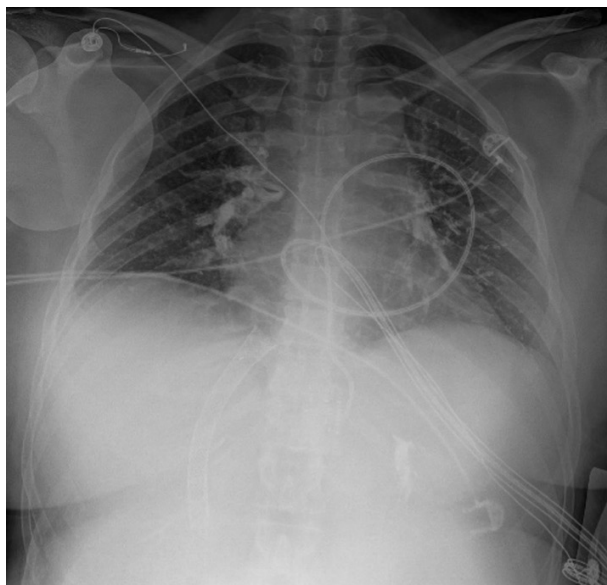


Figure 1. — Radio-opaque material perihilar bilaterally, suspected of glue-embolization.

unfortunately, after one hour of reanimation she passed away.

Discussion

GV are portosystemic collaterals that develop between the portal and the systemic circulation as a consequence of portal hypertension (1). The prevalence of GV is estimated around approximately 20% of patients with portal hypertension (2,3,6). The risk of bleeding from GV (10-36%) is lower than from esophageal varices (up to 50%), but bleeding is usually massive and more difficult to control and has a higher recurrence rate. Fundic varices have a reported 1-year death rate of 52% (3).

In patients presenting with acute bleeding from gastric fundal varices, endoscopy is performed for initial diagnosis and therapy. Endoscopic therapy is the preferred modality to achieve hemostasis with ECI as the most accepted method. ECI is a highly effective therapy at preventing both early and late rebleeding (4,6). In patients presenting with massive bleeding, balloon tamponade may serve as a bridge to more definitive treatments.

Patients who survive acute gastric fundal variceal bleeding have a high risk of rebleeding after endoscopic therapy with a rebleeding rate between 7-65% (1). Therefore, it is paramount to initiate secondary prophylaxis as soon as possible. Secondary prophylaxis may consist of TIPS or retrograde transvenous obliteration (RTO) (together with ECI with or without non-selective beta blockers (NSBB)). A recently published guidance from the AASLD recommend TIPS as a first-line therapy to prevent gastric fundal variceal rebleeding. TIPS should be placed shortly after bleeding is controlled (within 72hours). Both TIPS and RTO have been shown to be superior to ECI for the secondary prevention of gastric fundal variceal bleeding (1). In our case, the patient had already a TIPS in the context of the underlying BCS. Recent doppler ultrasound of the TIPS showed a patent portosystemic shunt. The patient also had a previously documented splenorenal shunt. Considering the patient had GOV2 varices (oesophageal and fundal varices) and for the purpose of prevention of worsening complications of portal hypertension (worsening oesophageal varices), it was opted to perform an ECI rather than RTO in secondary prevention for GV bleeding.

The best method for ECI is highly debated and influenced by choice of cyanoacrylate formulations. The most ideal formulation is the cyanoacrylate agent with the fastest polymerization time to avoid embolization (6). In our case, following routine clinical practice, a combination of 5 ml N-butyl-cyanoacrylate mixed with Lipiodol (1 ml Cyanoacrylate and 4 ml Lipiodol) was used. Lipiodol is a plant-based oily contrast agent that not only renders the mixture radiopaque to determine radiographic success of ECI, but also delays the polymerization reaction and therefore has an increased distal embolization risk (6). ECI can have specific complications including impaction of the needle into the GV, exacerbation of bleeding, embolization of the glue thrombus, portal vein thrombosis and infection. However, the most feared and important complication is displacement of the clot or its exclusion from the injected vessel. Embolism in the splenic, pulmonary, cerebral, or coronary territories after glue injection is an infrequent, but potentially fatal, complication (2-4). The reported incidence of embolization ranges from 0.5% to 4.3%

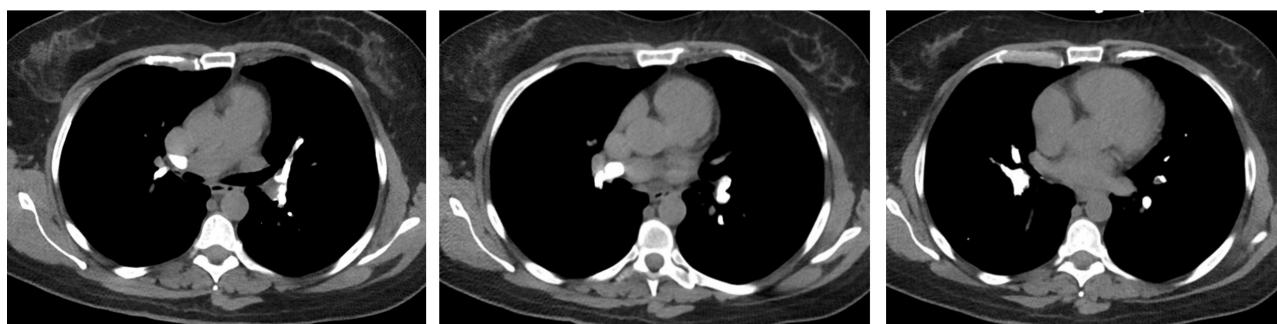


Figure 2. — Extensive glue-emboli proximally in both pulmonary arteries, more extensive on the right side, and a dilated pulmonary trunk suggestive of pulmonary hypertension.

(7). Although cases of massive or even fatal pulmonary embolism have been reported, affected patients usually have mild symptoms or are asymptomatic and therefore embolism may remain undiagnosed (2,4). In most cases emboli do not occlude the pulmonary vessels. In 15 available studies reporting 1360 patients treated by cyanoacrylate glue, 14 pulmonary embolisms were reported (1%) with no fatalities. Two individual cases reported death following pulmonary embolism occurring two and 37 days after the injection in a context of multiple organ failure (2). Tseng et al. conducted a retrospective review of 27 radiological studies reporting severe adverse events (SAE) after ECI. The majority of reported SAE were pulmonary embolism (44.4%). The overall rebleeding rate was 20% and mortality rate was 40% in the five patients who experienced SAE after cyanoacrylate injection (8). In the most extensive study of pulmonary embolism after ECI, Hwang and al. found that radiographically evident pulmonary embolism was observed in 6 (4.3%) of 140 patients (4). These patients received a higher volume of liquid Cyanoacrylate, were either mildly symptomatic or asymptomatic and in most of them the radiographic abnormalities showed complete or partial resolution (2). Although most patients remain undiagnosed, our case describes acute fatal pulmonary embolism immediately after ECI due to massive glue-emboli in the main pulmonary arteries.

The pathophysiology of pulmonary embolism during ECI is associated with the presence of a portosystemic vascular shunt, namely a gastrosplenorenal shunt. A gastrosplenorenal shunt creates an anastomosis between the portal and systemic circulation, based on the reopening of embryonic vascular pathways between the splenic vein and the left renal vein. These high blood flow shunts may develop and carry clots or embolic material from injected varices and the portal circulation to the systemic venous flow, the right heart and thus, the pulmonary circulation. Another path via the vena cava superior and the azygos vein (gastrocaval shunt) may lead to pulmonary embolism (2,3). Tseng et al. identified the presence of a spontaneous portosystemic shunt in three of the 5 patients (8). Our patient had a gastrosplenorenal shunt, proven by angiography during TIPS-placement in 2009. A second shunt from the portal circulation to the systemic circulation was created by TIPS-placement.

GV rebleeding rates after TIPS created for GV is associated with a risk ranging between 13-53%. Moreover, GVs are widely thought to remain patent and sustain bleeding at low portosystemic pressure gradients, as is the case after TIPSS. Transvenous obliteration techniques, including Balloon-occluded Retrograde Transvenous Obliteration (BRTO) and antegrade (BATO) transvenous obliteration as well as coil- (CARTO) and plug-assisted (PARTO) retrograde transvenous obliteration-have been developed with the intent of directly eradicating GV. BRTO can also be used for patients with large gastrosplenic shunt or splenorenal shunt. This procedure prevents the occurrence of systemic glue emboli for patients

with evidence of a portosystemic shunt. During BRTO assisted ECI an angiography of the portosystemic system is performed via femoral access. After the portosystemic shunt is located a balloon is deployed and secured, while the endoscopist performs the subsequent ECI (8, 9).

In our case it was opted to perform an ECI rather than RTO in secondary prevention for GV bleeding. When a patient, who receive ECI does develop respiratory symptoms, pulmonary embolism should always be considered. A thoracic CT should be performed to prove the presence of glue-emboli. The use of contrast medium for thoracic CT should be avoided when glue-embolism is suspected as the contrast masks the presence of radiopaque emboli. Clinicians should inform the radiologist about the patient's history and previous glue injections so that appropriate techniques are used to reach the correct diagnosis (2). However, if no glue-emboli are detected a thoracic CT with intravenous contrast should be considered to rule out general pulmonary emboli, especially in patients prone to develop thrombi. Possible blood clots in our patients pulmonary trunk may have been missed by not performing a CT with contrast. This could have explained the abnormalities on TTE suggestive of saddle-emboli. Moreover, one should consider the possibility of systemic embolization in case of a patent oval foramen, which occurs in 18% of the general population (4, 10).

In conclusion, the development of glue-pulmonary embolism is an uncommon but potentially life-threatening complication after ECI. Proper patient selection is key and should consist of appropriate screening for the presence of a portosystemic vascular shunt and when present, transvenous obliteration techniques should be considered to obliterate GV. When choosing ECI and a patient does develop respiratory symptoms, pulmonary embolism should always be considered and a thoracic CT without contrast should be performed.

References

1. LEE EW., EGHTEHAD B., GARCIA-TSAO G., HASKAL ZJ., HERNANDEZ-GEA V., JALAEIAN H., et al. AASLD Practice Guidance on the use of TIPS, variceal embolization, and retrograde transvenous obliteration in the management of variceal hemorrhage. *Hepatology*. 2024;79(1):224-50.
2. MARION-AUDIBERT AM., SCHOEFLER M., WALLET F., DUPERRET S., MABRUT JY., BANCEL B., et al. Acute fatal pulmonary embolism during cyanoacrylate injection in gastric varices. *Gastroenterol Clin Biol*. 2008;32(11):926-30.
3. ALEXANDER S., KORMAN MG., SIEVERT W. Cyanoacrylate in the treatment of gastric varices complicated by multiple pulmonary emboli. *Intern Med J*. 2006;36(7):462-5.
4. HWANG SS., KIM HH., PARK SH., KIM SE., JUNG JI., AHN BY., et al. N-butyl-2-cyanoacrylate pulmonary embolism after endoscopic injection sclerotherapy for gastric variceal bleeding. *Journal of computer assisted tomography*. 2001;25(1):16-22.
5. SARASWAT VA., VERMA A. Gluing gastric varices in 2012: lessons learnt over 25 years. *J Clin Exp Hepatol*. 2012;2(1):55-69.
6. HENRY Z., PATEL K., PATTON H., SAAD W. AGA Clinical Practice Update on Management of Bleeding Gastric Varices: Expert Review. *Clin Gastroenterol Hepatol*. 2021;19(6):1098-107.e1.
7. TANGCHEEWINSIRIKUL N., SUANKRATAY C. Acute pulmonary embolism following endoscopic sclerotherapy for gastroesophageal variceal hemorrhage: A case report and literature review. *SAGE Open Med Case Rep*. 2019;7:2050313x19838946.

8. TSENG Y., MA L., LUO T., ZENG X., WEI Y., LI L., et al. Thromboembolic Events Secondary to Endoscopic Cyanoacrylate Injection: Can We Foresee Any Red Flags? *Can J Gastroenterol Hepatol.* 2018;2018:1940592.
9. SHAH KY., REN A., SIMPSON RO., KLOSTER ML., MIKOLAJCZYK A., BUI JT., et al. Combined Transjugular Intrahepatic Portosystemic Shunt Plus Variceal Obliteration versus Transjugular Intrahepatic Portosystemic Shunt Alone for the Management of Gastric Varices: Comparative Single-Center Clinical Outcomes. *Journal of vascular and interventional radiology : JVIR.* 2021;32(2):282-91.e1.
10. ROESCH W., REXROTH G. Pulmonary, cerebral and coronary emboli during bucrylate injection of bleeding fundic varices. *Endoscopy.* 1998;30(8):S89-90.