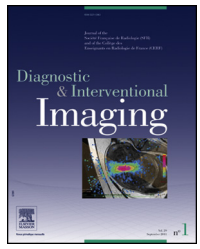
Diagnostic and Interventional Imaging (2015) **96**, 383—386



SHORT ORIGINAL ARTICLE /*Oncology*

Thrombocytopenia due to hypersplenism in oncological disease: Partial splenic embolization during palliative treatment

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KEYWORDS
Partial splenic embolization;
Hypersplenism;
Portal hypertension;
Interventional radiology;
Thrombocytopenia

Abstract Hypersplenism is excess activity of the spleen, resulting in peripheral pancytopenia that predominates in platelet cell lines. Pancytopenia can be limited by reducing the volume of the functional spleen. However, in patients in very poor general condition, a splenectomy may not be possible, due to the risks of surgery and postoperative infection. Another therapeutic alternative in these patients is to reduce the volume of the spleen by super selective percutaneous splenic embolization. We report three cases of peripheral thrombocytopenia due to hypersplenism with a platelet count between 60,000 and 80,000/mm^3, which made it impossible to continue or start a chemotherapy protocol in these patients. For these patients, super selective partial embolization of the splenic parenchyma, with uncharged microspheres (250 microns) quickly resulted in a platelet count above 150,000/mm^3 so that chemotherapy could be continued or initiated.

Thrombocytopenia is defined as a platelet count below 150,000/mm^3. One of the etiologies is splenic sequestration due to portal hypertension. If drug treatments are unsuccessful, splenectomy is often considered as a last resort to treat refractory thrombocytopenias. However, surgical treatment has both perioperative and postoperative risks [1,2]. Moreover, in patients in poor condition who cannot support general anesthesia, splenectomy is often contra-indicated and dangerous. Partial splenic embolization (PSE) may be an interesting alternative in these cases [3,4]. PSE is a non-surgical procedure performed in the interventional radiology procedure room,

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http://dx.doi.org/10.1016/j.diii.2014.08.005

which avoids the disadvantages of splenectomy, in particular, the risk of infection. We report three different cases that have the following points in common: all patients had cancer and thrombocytopenia due to hypersplenism making it impossible to begin or continue a chemotherapy protocol. The goal of our study was to describe the role of partial superselective splenic embolization, which rapidly resulted in an acceptable platelet count allowing chemotherapy to be continued or begun in these patients.

Clinical cases

Case 1

A 46-year-old patient had been followed since 2001 for intrahepatic cholangiocarcinoma that had been treated by a right hepatectomy that was extended to segment IV. In 2012, cholangiocarcinoma recurred and was exclusively intraheptatic. Hypersplenism was identified during the initial assessment before treatment was decided, associated with thrombocytopenia with a platelet count of 80,000/mm^3, which was probably secondary to the right hepatectomy. Antiangiogenic treatment was contra-indicated in this patient due to thrombocytopenia.

Because of the patient's general condition, PSE was decided during the pluridisciplinary consensus meeting with the goal of correcting thrombocytopenia to reach a count of more than 120,000/mm^3.

After careful skin preparation and local anesthesia, a femoral approach was taken. The celiac trunk and the splenic arterty were catheterized with a 5F catheter with a cobra head and a flexible guide. Embolization of the branches of the splenic artery was performed at the inferior pole and the middle third with a microcatheter. Uncharged 250 micron microspheres (Embozene, CeloNova BioSciences, headquarters San Antonio, Texas, USA) were used for embolization. Final follow-up showed significant stagnation of the contrast agent in the middle and lower territories of the splenic parenchyma. The patient was hospitalized for 48 hours after the procedure to treat post-embolization syndrome.

Seven days after embolization, control CT showed splenic ischemia of between 50 and 70%, which corresponds to the goals in the literature (Fig. 1) [3,4].

Ten days after embolization, a control visit showed a platelet count of 162,000/mm^3 so that systemic treatment could be begun. The patient presented with left upper quadrant pain for 48 hours after embolization that was successfully treated by morphine, with no other adverse effects reported.

Case 2

A 50-year-old man was being followed for adenocarcinoma of the recto-sigmoïd junction, classified as T4 N1 M0, and which was discovered during investigation of occlusion. Management included subtotal colectomy with an ileorectal anastomosis and lymph node dissection associated with FOLFOX (oxaliplatin, 5 fluoro-uracile, *acide folinique*) adjuvant chemotherapy. At 2 months, unresectable metachronous liver metastases developed. Chemotherapy was modified to a Folfox—Avastin regimen (a total of 23 rounds). The patient then developed portal hypertension with thrombocytopenia and a platelet count of 60,000/mm^3 contra-indicating the use of antiangiogenics and participation in a new treatment protocol. It was then decided to treat the thrombocytopenia with selective PSE. Embolization was identical to that in case 1, with no complications.

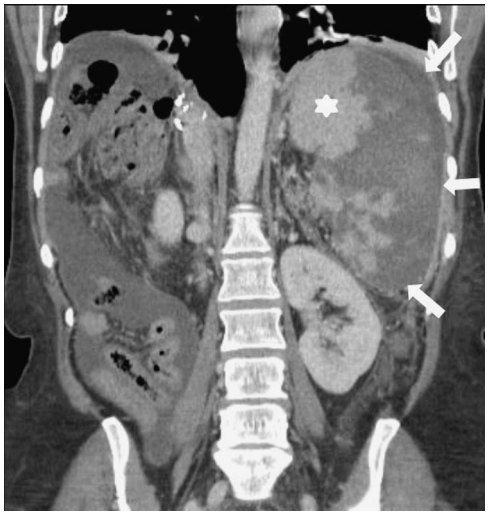

Figure 1. Coronal abdominopelvic CT with contrast injection during the portal phase 2 months after splenic embolization showing splenomegaly with a large unenhanced area of liquid (arrow) representing an area of splenic necrosis. The functional parenchyma is enhanced after contrast injection (asterisk). Ischemia involves approximately 70% of the splenic parenchyma but does not include the superior pole of the spleen to prevent post-embolization pleural reactions.

One month after embolization, the platelet count had reached 200,000/mm^3, so the patient could participate in a clinical trial that included angiogenics. At 2 months, control CT showed spenic ischemia of 50—70% of the parenchyma. At 4 months, the platelet count remained stable at 120,000/mm^3 but secondary pulmonary and vertebral lesions developed causing sleep disturbing pain that did not respond to analgesics.

Case 3

A 42-year-old patient had been followed since February 2012 for an adenocarcinoma of the left colon with synchronous liver metastases. Management included a left colectomy, resection of a left liver metastasis and radiofrequency ablation. Total portal vein thrombosis developed after surgery.

Two months after surgery, recurrent liver metastases and secondary pulmonary lesions developed. Chemotherapy with a Folfiri-Avastin regimen was decided upon. The patient then developed portal hypertension on the thrombosis resulting in hypersplenism with thrombocytopenia and a platelet count of 80,000/mm^3 contra-indicating antiangiogenics and participation in a new therapeutic trial because of tumor progression. PSE was decided upon to reach a platelet count of 120,000/mm^3 and to include the patient in a therapeutic trial.

Embolization was identical to that in case 1, with no complications and resulted in 70% splenic ischemia.

The postoperative outcome included pain that was resistant to level 3 (morphine-based) analgesics as well as 39° hyperthermia for 48 h.

Fifteen days after surgery, the platelet count had stabilized at 530,000/mm^3 so that antiangiogenic therapy was begun again and the patient could be included in a new therapeutic trial.

Discussion

This report is original because the origin of portal hypertension in these patients was non-cirrhotic. Indeed, to our knowledge, this is the first report of PSE for a palliative oncological indication with no underlying chronic liver disease. Hypersplenism is a well-known complication of portal hypertension. This may be present as thrombocytopenia and/or leukocytopenia. In certain patients with severe peripheral cytopenia, treatments such as interferon [5], antiangiogenics [6], and major surgery [7] can be contra-indicated and can, therefore, be the cause of a loss of chance for patients. Moreover, life-threatening spontaneous episodes of bleeding may also occur in these patients who are already in poor condition.

Portal hypertension with hypersplenism has many possible causes: prehepatic portal hypertension is caused by obstruction of the portal venous system (by compression, tumor invasion or thrombosis). Intrahepatic portal hypertension can be sinusoidal, or post-sinusoidal but in fact, it is often mixed. Sinusoidal portal hypertension is mainly due to cirrhosis, which accounts for 90% of the causes of portal hypertension in western countries. Post-hepatic portal hypertension is mainly secondary to Budd-Chiari syndrome. In the present study, we present a case of iatrogenic intrahepatic portal hypertension secondary to oxaliplatin [8]. This adverse effect has been described in the literature by numerous authors [9] but the physiopathology is still a subject of debate. Nevertheless, there is no oxaliplatin dose limit for the moment to limit this adverse effect.

In case 1, the cause of portal hypertension was a partial hepatectomy in a patient with liver metastases. Portal hypertension is a well-known complication of this type of surgery [10].

At present, a surgical splenectomy is the reference technique for reducing splenic cell hyperdestruction and treating cases of peripheral thrombocytopenia that do not respond to medical treatment. However, complications are severe with this type of surgery and occur in 9.6 to 26.6% of the cases including those performed by laparoscopy [1,2]. Moreover, splenectomy is often associated with an increased long-term risk of septic events [1,2], in particular encapsulated organisms such as *pneumococcus* or *meningococcus*.

Partial splenic embolization was first described by Maddison in 1973 [11], and was proposed as an effective alternative to splenectomy [12,13]. Several studies have shown that this procedure is feasible and reported effective results in particular in patients with cirrhosis, with a significant increase in both the platelet and leucocyte count [9,12—14].

The volume of the splenic infarction is an essential factor for long-term improvement in thrombocytopenia, and it should be between 50 and 70% [3,4], to ensure effective long-term management of hypersplenism and reduce severe complications such as splenic abscess or rupture, refractory ascites or pleural effusion [3,15,16]. No specific precautions against infection are needed with partial splenic embolization: no pneumococcal vaccination or specific long-term antibiotics are needed, unlike with splenectomy.

The patients in the present study were all late stage, requiring palliative treatment and in poor general condition. Successful management of their thrombocytopenia was essential to give them access to treatment and to participation in treatment protocols. However, a splenectomy was impossible because of their general condition and comorbidities. The indication of PSE was, therefore, a good alternative to splenectomy for the treatment of refractory thrombocytopenia with portal hypertension.

Morbidity following PSE is low with severe complications in less than 10% and mortality in less than 1% compared to 5% for splenectomy [17]. The main complications following PSE were left subphrenic abscess, splenic rupture, acute pancreatitis, reactional pleural effusion and thrombosis of the splenic or portal veins. The rate of severe complications varies in relation to the volume of splenic infarction [3,4]. If it is more than 70% of the splenic volume, severe complications develop in 50% compared to 8.8% if the infarctus is between 50% and 70%. In these patients who require palliative treatment, the risk-benefit ratio clearly seems to support PSE. It is associated with very few adverse events and makes it possible for patients to receive chemotherapy which increases their life expectancy and quality of life. The context of palliative care is especially interesting because this procedure is easy to perform under local anesthesia and has immediate, long-term effects. In the three reported cases, the PSE restored the platelet count enough to allow appropriate systemic treatment, with no serious complications from the procedure.

Uncharged microparticles such as microspheres were chosen in this study for embolization. Proximal agents (coils, plugs or balloons) result in occlusion of the splenic artery but with minimal change in the splenic parenchyma unless the collateral network is affected. The goal of this treatment is to superselectively destroy part of the splenic parenchyma; the intraparenchymatous branches of the splenic artery must, therefore, be occluded as distally as possible. Agents causing distal embolization such as microparticles or resorbable gelatin can therefore be used. According to Zhu et al. [3], microparticles are more effective than absorbable gelatin in increasing the platelet count, with no difference in the rate of complications. Two hundred and fifty micron microspheres were therefore used.

The good results of PSE in patients with palliative stage disease must be confirmed in a larger group of patients to better evaluate the rate of efficacy and potential complications.

Conclusion

In conclusion, partial splenic embolization successfully treated refractory thrombocytopenia in three patients

presenting with portal hypertension secondary to late stage neoplastic liver disease requiring palliative treatment. Thus, partial splenic embolization seems to be a viable option for the treatment of refractory thrombocytopenia in patients with late stage disease requiring palliative care, which does not require a pneumococcal vaccination or long term antibiotics.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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