

REVIEW

An Update of Treatment of Pancreatic Arteriovenous Malformations

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Abstract:

Pancreatic arteriovenous malformation is a rare entity (0.9%). There are about 200 articles available in PubMed. This review article includes 86 published articles, with 117 cases published after 2000. The median age at diagnosis was 51, and most of the patients were male (87.0%). The symptoms included pain, bleeding, pancreatitis, ulcers in the duodenum or stomach, varix formation, jaundice, and ascites. The diagnostic modalities were angiography, contrast-enhanced CT, MRI, and/or Ultra Sound. The most common treatments were surgery and embolization. The clinical success rate of embolization reported was 57.7%. The tailored embolization based on each agio-architecture had a clinical success rate of 80%. If embolic therapy is ineffective, surgical intervention should be considered.

Keywords:

pancreatic arteriovenous malformation, clinical features, treatments, embolization, angioarchitecture

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Introduction

In the visceral arteriovenous malformations (AVM), there are many kinds of AVMs, including renal [1], pancreatic [2], hepatic [3], intestinal [4], gallbladder [5], and duodenum [6]. Pancreatic AVM is relatively rare, with about 200 case reports or series available. Although most case reports included literature reviews in their discussion, a few focused on endovascular treatment for pancreatic AVM. Therefore, we would like to review the diagnosis and treatment of pancreatic AVM, focusing on the current endovascular treatment methods. In this review article, we searched the literature about pancreatic AVMs published from January 2000 to June 2022 through the PubMed database. The search keywords were “pancreatic arteriovenous malformation” and “treatment,” combined with “published date from January 2000 years to June 2022.” Our search included literature written in English and Japanese and excluded cases about the arteriovenous shunt after pancreatic transplantation or cases without pancreatic AVM. The final list includes 86 articles with 117 cases [7-92] with 25 additional articles [7, 9, 10, 16, 17, 24, 25, 31, 37-39, 41, 43, 46, 48, 49, 54, 57, 61, 63, 64, 66, 67, 74, 76] by hand search. Age, gender, medical history, symptoms, treatment, and follow-up periods were recorded. **Table 1** presents a review summary. Not all the

articles provided complete case information, including age, gender, treatment details, embolic materials, or follow-up period. Therefore, not all the parameters matched the number of cases.

Clinical Features of the Pancreatic AVMs

The incidence of pancreatic AVMs is reportedly about 0.9% [93]. Since the first case report of pancreatic AVM was published in 1968 by Halpern et al. [2], 201 articles are available in PubMed using the search phrase “arteriovenous pancreas malformation.” A few case series exist, but other articles are case reports with similar literature reviews. According to our literature review of articles published from January 2000 to June 2022, pancreatic AVMs mostly occurred in males (87.0%). The median age at diagnosis was 51. Most reported pancreatic AVMs cases were in Japan (52.3%), with 11 reports written in Japanese and then from other Asian countries (22.1%). The present research suggests that approximately 90% of patients have congenital pancreatic AVMs resulting from an aberrant formation of the arteriovenous plexus during embryonic development. Approximately 10% to 30% of cases are associated with Osler-Rendu-Weber syndrome, an autosomal dominant inherited disorder, which is also called hereditary hemorrhagic te-

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Table 1. Summary of 117 Cases Published from January 2000 to June 2022.

Age (y.o)	N=107	Median 51	Range 26-85
Gender	N=115	Female 15 (13.0%)	Male 100 (87.0%)
Symptoms (N=117)	Pain	54	50.5%
	GI bleeding, hemorrhage	50	42.7%
	Pancreatitis	26	22.2%
	Ulcer formation	13	11.1%
	Varix	8	6.8%
	Jaundice	7	6.0%
	Asymptomatic	6	5.1%
	Mass	6	5.1%
	Ascites	5	4.3%
	Other	19	17.8%
Territory (86 articles)	Japan	45	52.3%
	Asia except Japan	19	22.1%
	Europe	12	14.0%
	Americas	10	11.6%
Location (N=101)	Head	66	63.5%
	Body	23	22.8%
	Tail	25	24.8%
	Entire	9	8.9%
Treatment (N=97)	Surgery	43	44.3%
	Embolization alone	28	28.9%
	Embolization + Surgery	12	12.4%
	Radiation	5	5.2%
	None (follow up)	9	9.3%
Embolic materials	Coils	13	
	Ethylene vinyl alcohol copolymer	6	
	NBCA	5	
	Gelatin Sponge	5	
	Other (Microsphere, Ethanol, Polyvinyl alcohol)	4	
follow up period	Average (months)	18	
	Median	12	
	Minimum	0	
	Maximum	72	

GI: gastrointestinal, NBCA: n-butyl-2-cyanoacrylate

langiectasia (HHT) [46, 50, 52, 53, 59, 66, 86]. The other causes of acquired pancreatic AVMs include trauma, pancreatitis, medical interventions, and others [46, 50, 52, 53]. The locations of the pancreatic AVMs were in the head (63.5%), body (22.8%) and tail (24.8%), and entire pancreas (8.9%). Some pancreatic AVMs are in two or three areas of the pancreas; therefore, the total number of locations is more than 117. In some cases, portal vein thromboses were associated with pancreatic AVMs [41, 71, 84]. There were three cases in the case reports of pancreatic AVM published after 2000, which were related to the portal vein thrombus. In one case, the portal vein thrombus existed when the patient was diagnosed with pancreatic AVM [41]. Two cases developed portal vein thrombi after treatment [71, 84].

Symptoms of Pancreatic AVMs

According to our review, the most frequent pancreatic AVM symptom was abdominal pain and/or back pain (50.5%). The second most frequent symptom was gastroin-

testinal (GI) bleeding or hemorrhage (42.7%). Pancreatitis occurred in 22.2% of pancreatic AVM cases. Next to pancreatitis, ulcer formation in the duodenum or stomach (11.1%), varix formation in the esophagus or stomach (6.8%), jaundice (6.0%), and ascites (4.3%) occurred. Chou et al. reported GI bleeding was related to the pancreatic head AVM (62.7%) compared to the other location (26.7%) [52]. It was difficult to define whether the pancreatic AVMs caused pancreatitis or pancreatitis caused pancreatic AVM. There were three possible causes of GI bleeding related to the AVM:

1. Rupture of the feeding arteries or outflow vein of pancreatic AVMs located around the biliary duct or duodenal mucosa.

2. Portal hypertension, secondary to the higher inflow due to the pancreatic AVMs, could be caused by the varicose vein in the esophagus or other part of the GI tract. Portal hypertension also might cause ascites.

3. Ischemic change of the mucosa due to the steal phenomenon of the pancreatic AVM. Ischemic change of the

mucosa might cause ulcer formation, resulting in GI bleeding.

Abdominal and/or back pain was to be expected because of the ischemic change and/or ulcer formation. Pain could also be related to pancreatitis. On the other hand, there were also asymptomatic cases (5.1%). In the asymptomatic cases, pancreatic AVMs were revealed incidentally by contrast-enhanced CT, MRI, or US doppler for other reasons.

Diagnostic Methods of Pancreatic AVMs

The golden standard for diagnosing pancreatic AVM is angiography [8, 69, 94]. The celiac and superior mesenteric angiographies can demonstrate the tortuous, tangled, racemose, and wider inflow arteries around the pancreas. The main inflow arteries are the splenic artery, gastroduodenal artery, dorsal pancreatic artery, anterior or posterior superior pancreaticoduodenal arteries, transverse pancreatic artery, greater pancreatic artery, and inferior pancreaticoduodenal artery. Sometimes, other arteries around the pancreas form collateral arteries such as branches of proper, right or left hepatic arteries, right or left gastric arteries, and middle colic artery. The early visualization of the portal vein is another diagnostic feature of pancreatic AVMs. In the angiography before embolization, investigating the details of the angioarchitecture of the pancreatic AVMs is important since the Cho-Do classification [95] may help determine the treatment method. As mentioned earlier, angiography is still the gold standard method of diagnostic modality. It is an invasive method; therefore, non-invasive diagnostic methods were used in many cases beforehand. Contrast-enhanced CT is also a very important diagnosing method for pancreatic AVMs. The contrast-enhanced CT with three phases revealed the wide tortuous arteries and veins [43, 54, 66, 72, 77], with early visualization of splenic, superior mesenteric, or portal veins in the arterial phase. In some pancreatic AVM cases, the lesion mimics hypervascular tumors such as a pancreatic neuroendocrine tumor, serous cyst adenoma or adenocarcinoma, islet cell pancreatic tumors, sarcomas, metastasis, or, rarely, chronic pancreatitis [14, 27]. MRI depicts the "honeycomb" like flow void, demonstrating the abnormal high flow vascular network in T1- or T2 weighted sequences [43]. The US reveals the presence of small hypoechoic nodules in the pancreatic parenchyma. The color Doppler US shows the mosaic pattern of the arteriovenous fistulas, the direction of the blood flow in the lesion, and the relation of the pancreatic AVMs and portal vein flow [76]. In a recent development of endoscopic ultrasound, there is a case of diagnosing pancreatic AVM by endoscopic ultrasound [22].

Treatment Options for Pancreatic AVM and Post-treatment Follow-up

There were six cases of asymptomatic pancreatic AVMs reported in the literature. One patient was treated with radiation therapy because the patient was asymptomatic, but there

were visible esophageal varicose veins due to portal hypertension. The patient also suffered from liver cirrhosis. The other asymptomatic patients were followed up closely, but the AVM did not change during their follow-up periods. We recommend close follow-up for asymptomatic pancreatic AVM patients until symptoms or comorbidities worsen.

In the reviewed case reports, surgical resection was the most frequent treatment option (44.3%). The surgical resection method differed depending on the locations of the pancreatic AVMs [8]. Most patients with pancreatic head lesions underwent pylorus-preserving pancreaticoduodenectomy [8]. Those with body and tail lesions underwent a distal pancreatectomy [11, 30]. Patients with pancreatic AVMs in the entire pancreas were managed by total pancreatectomy [51]. For small or limited lesions, the surgical resection was performed successfully in the case reports without severe late complications, including diabetes mellitus, due to lack of insulin creation. However, in the entire lesion with total pancreatectomy cases, if the surgical resection was successful without early complications, late complications, including diabetes mellitus and digestive problems, could occur [51]. Next to the surgical resection, embolization alone was selected (28.9%). Embolization had been considered a short-term treatment because of early recanalization of the lesion. In the former case reports [59, 79, 96], the recurrence rate of embolization was about 37%. However, this rate reportedly occurred from embolization for the pancreatic arterial lesion for pancreatitis, with 33% (4/12 cases) of mortality due to hemorrhage within 30 days after treatment [96]. Therefore, the post-embolization recurrence rate was unclear. The details of endovascular treatments are discussed in the next section. The combination of embolization and surgical resection was also reported (12.4%) [9, 11, 26, 41]. Mainly, the embolization was performed before surgical resection to control the bleeding during the operation [11, 26, 41]. In some cases, the embolization was ineffective, and surgical resection was selected to control the bleeding [9]. On the other hand, there were five cases of radiation therapy for pancreatic AVMs [45, 50, 58, 78]. Two cases underwent intraoperative radiation therapy [45, 78], and the others were external beam radiation therapy. The median follow-up period of radiation therapy was 12 months (0 to 72 months).

In the follow-up after treatment, most of the case reports or case series, the main treatment was successful and uneventful in the follow-up without any clinical complications. The median follow-up period was 12 months (0-72 months) among reviewed cases published from January 2000 to June 2022.

Endovascular Treatment for Pancreatic AVM

The reviewed articles published from January 2000 to June 2022 reported 40 cases treated with endovascular treatment, including transarterial embolization (TAE), transvenous embolization, stent-graft insertion, sclerotherapy and/or Transjugular Intrahepatic Portosystemic Shunt (TIPS), both with and without surgery. There were 28 cases of en-

dovascular treatment alone and 12 cases with surgery. According to the reviewed series, the embolic treatment was unsuccessful in two cases [9, 10]. The median follow in embolization alone was 12 months. The used embolic materials were coil, NBCA [19, 37, 47, 44, 84], gelatin sponge [19, 34, 78, 84, 88], Onyx [7, 12, 19, 40, 53, 55], microspheres [34, 84], ethanol [34] or polyvinyl alcohol [88]. **Table 1** summarizes the endovascular therapy and the embolic materials. In some case reports or case series, the details of embolic materials of embolic technique were not described. Therefore, the TAE and the total number of embolic materials were not matched. Wu et al. summarized 26 pancreatic AVM cases treated with TAE from 1968 to 2020, 15 of which (57.7%) reported successful TAE; 12 of them were completely cured of bleeding without complications [8]. Two cases were treated by surgical resection after TAE to control the bleeding. One had mild abdominal pain after embolization. In the other 11 cases, TAE could not cure the pancreatic AVMs. Rebleeding was a major cause of TAE failure. The reported recurrence rate of TAE for AVMs in the bowel, including the pancreas, was about 37% [93]. The authors treated the pancreatic arterial lesions, including pancreatic AVMs. The potential complications due to embolization were considered acute pancreatitis due to the pancreatic parenchymal ischemia or portal vein thrombus formation because the embolic materials might pass through the AVM during the embolization. There were no case reports in which these complications occurred. There was one portal thrombus after the endoscopic sclerotherapy for esophageal varices [71].

The target vessels of TAE were feeding arteries mainly from the celiac axis or SMA, including branches of the gastroduodenal artery, anterior or posterior superior pancreaticoduodenal artery, dorsal pancreatic artery, transverse pancreatic artery, greater pancreatic artery, and the inferior pancreaticoduodenal artery. In two articles with three cases published in 2021 [10] and 2022 [7], venous embolization or venous stent-graft implantation was selected due to type 2 of Cho-Do classification [95] or type 3 of Yakes' classification [97]. Type 2 of Cho-Do classification and type 3 of Yakes' classification were similar because both types have dilated outflow veins connected by multiple branched arteries of AVMs. And both classifications recommend to embolize the dilated venous components just after arteriovenous shunts. In these two articles, the venous embolization or venous stent-graft implantation was selected for the widely dilated draining vein in the pancreatic AVMs due to the angioarchitecture. One patient underwent splenic embolization and draining the vein of the dominant outflow venous sac with coils [10]. Another patient underwent stent-graft implantation in the dilated splenic vein with embolization of the aneurysmal sac around the stent-graft with a direct puncture method with onyx and coils [7]. The other was embolized with plug and sodium tetradecyl sulfate embolization with a pressure cooker technique [7]. In each case of venous embolization, the arterial embolization was performed before the venous embolization [7, 10]. The tailored endovascular

treatment based on each angioarchitecture, like the Cho-Do classification or Yakes' classification, is considered effective in the peripheral AVMs, including the pancreatic AVMs. Classical arterial embolization could achieve a 57.7% success rate [8] for pancreatic AVM clinically. The case series employed the tailored endovascular treatment based on each angioarchitecture. The success rate of complete regression of the symptom was 80%, with 60% of technical success of embolization [7]. The tailored endovascular treatment based on each angioarchitecture might contribute to better results, and the embolization, combining the arterial and venous sides, might be effective. In cases of unsuccessful embolization, switching to surgical treatment should be considered.

Conclusion

Pancreatic AVMs are rare but sometimes encountered in clinical practice. Therefore, knowing the symptoms, diagnostic method, and treatment option is crucial for interventional radiologists. Tailored endovascular treatment based on each angioarchitecture is important using various techniques such as arterial and venous embolization and stent-grafting. Also, surgical intervention is an important option for pancreatic AVMs.

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SO, RM and MT reviewed the literatures.

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