Repetitive episodes of cryptogenic septicaemia in a patient with cirrhosis : a case of "heavy metal"

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Abstract

Endotipsitis or primary infection of a TIPS-stent, is an uncommon but possible life- threatening condition by its potential evolution to sepsis and death.

Diagnosis should be suspected in patients with a TIPS-stent presenting with stent-dysfunction associated with fever or relapsing episodes of bacteremia/sepsis without any other alternative focus.

A certain diagnosis is made by post-factum histopathological and/or microbiological examination of the TIPS-stent which is only possible after liver transplantation or at autopsy, whereas it can be highly suspected in case of repetitive positive blood-cultures without any other focus in a patient with a TIPS-stent.

The microorganisms responsible for endotipsitis are most frequently of Gram-negative enteric origin. The regimen and duration of the treatment should be individualized and depends on multiple factors like the antibiotic sensitivity of the organism and the patients condition. In case of a fungal infection, longer treatment is recommended. (Acta gastroenterol. belg., **2011**, 74, **82-87**).

Key words : TIPS, cirrhosis, sepsis.

Introduction

Insertion of a transjugular intrahepatic portosystemic shunt (TIPS) is a minimally invasive, endovascular technique used since 1991 to relieve portal hypertension and its related complications, such as refractory variceal bleeding, therapy-resistant ascites and hepatic hydrothorax. The intent of the procedure is to create an intrahepatic tract, or shunt, by means of a connecting expandable metal stent between the hepatic and portal vein via a transjugular route. As a result, the hepatic venous pressure gradient is reduced. TIPS functions as a side to side portacaval shunt but avoids the risks of major surgery (1). Its use, however, was hampered in the past by rapid occlusion leading to dysfunction and need for repeated revision and re-intervention (2). With the introduction of the polytetrafluoroethylene (PTFE)-covered TIPS stents, this problem has largely been overcome as documented by improved patency and lower re-intervention rates (2). Due to the combined improved efficacy and limited invasiveness, this procedure has taken unsurpassed heights and is more frequently being applied.

On the other hand, increasing use has led to the recognition of both expected and unexpected complications (3). Infection of the device or endotipsitis is an example of an unforeseen but rare complication.

This article documents a case of primary infection of the TIPS, also called endotipsitis, five years after its placement. We report the clinical spectrum of this condition, the means to and difficulties in diagnosis and its management taking into consideration some microbiological aspects and rescue strategies.

Case report

A 59-year old male patient, known with a post-alcoholic cirrhosis (Child C10 and MELD 9) and complicated by refractory variceal bleeding was treated with a rescue TIPS in 2003. His postprocedural course was uneventful until March 2008 when a partial thrombosis of the TIPS resulted in recurrent ascites and hydrothorax, which recovered completely after TIPS-revision. Unfortunately in April of 2008, he redeveloped progressive ascites and recurrent hepatic hydrothorax which at this point was aggravated by repetitive episodes of fever with temperature above 39°C, shivering and hypotension. Repetitive analysis of pleural and ascitic fluid could not support the presence of thoracic empyema or (spontaneous) bacterial peritonitis. Urine and sputum cultures, chest-X-ray and CT thorax-abdomen could not identify any focus of infection. No arguments could be withheld for endocarditis. Duplex of the TIPS-stent revealed rethrombosis, confirmed on CT (Fig. 1). Blood cultures with peripheral blood revealed the presence of *E. coli*. Amoxycillin-clavulanic acid was started empirically and continued based on the antibiogram. Initially, patient did well but he soon redeveloped fever and showed clinical deterioration. Antibiotics were switched to piperacillinetazobactam and a whole body scintigraphy with marked leukocytes (Tc-99m-HMPAO) was performed. This showed an aspecific spot in the left posterior upper quadrant, which could not be exposed on CT or colonoscopy. The patient was referred for further investigation.

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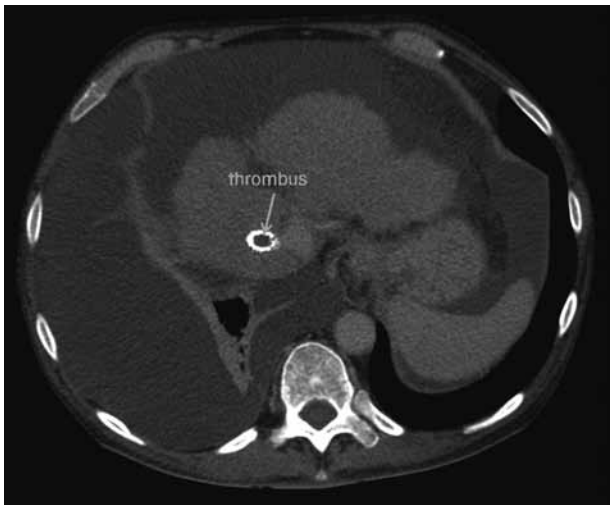

Fig. 1. — Abdominal CT showing a thrombus of the TIPS

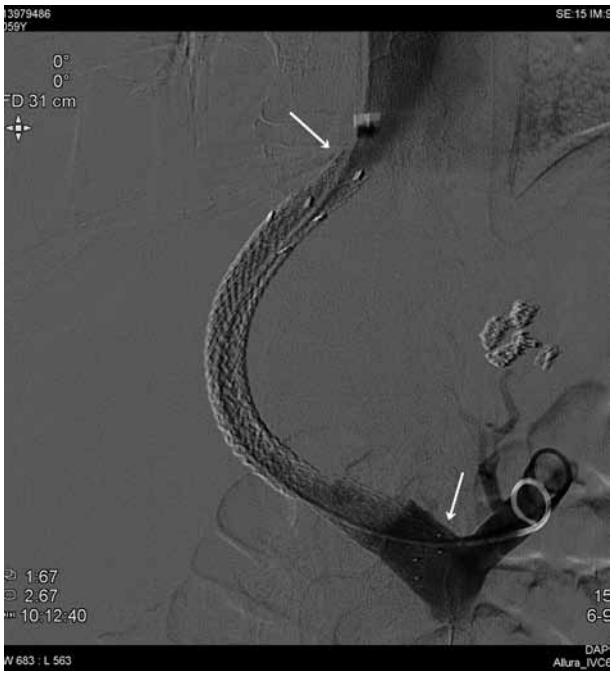

Fig. 2. — Angiography presenting several TIPS-stents extending into the portal vein (in the area between the arrows).

A revision of the TIPS confirmed the thrombosis of the endovascular prosthesis. Before obtaining recanalisation, blood cultures were taken just above the occluded stent and at an antecubital vein. After recanalisation, two additional stents were inserted through the original TIPS extending into the portal vein (Fig. 2). Almost immediately after angioplasty and stent placement, the patient developed a septic shock for which ICU admission and intensive haemodynamic support were necessary. Endotipsitis, or primary infection of the TIPS-stent, was suspected. Both peripherally drawn blood cultures and cultures taken just above the occluded TIPS-stent grew positive for *E. coli*. Interestingly, the sensitivity of *E. coli* grown from these latter cultures showed a more pronounced antibiotic resistance than the *E. coli* from peripheral blood cultures. On this basis, the treatment was switched to cefotaxim for three weeks with normalisation of the CRP, sterile hemocultures and clinical improvement.

After this episode the patient developed recurrent episodes of *E. coli* septicaemia. Since complete sterilisation of the infected stent was not to be expected, and as TIPS-stents are per definition not removable the patient was considered for liver transplantation, which was granted by means of a non-standard exception. He received an orthotopic liver transplantation in December 2008 and is still doing well.

Discussion

This case-report describes a patient with post-alcoholic cirrhosis, complicated by refractory variceal bleeding in whom a rescue-TIPS was performed in the past and who presented now with recurrent refractory ascites, hepatic hydrothorax and repetitive episodes of *E. coli*-septicaemia, based on endotipsitis or primary infection of the TIPS-stent.

There are only few reports of this condition, with the first report in 1997, several years after introduction of TIPS in 1991 (Table I) (4-12).

The real incidence of endotipsitis remains unclear because of the necessity of directly obtained histological/microbiological material to absolutely prove the presence of an infected TIPS-stent. This can only be obtained by hepatectomy at liver transplantation or by autopsy. Additionally, there is a lack of substantially tested non-invasive or indirect 'golden standard diagnostic criteria'. Based on deductions made from case series and retrospective studies, the incidence is estimated at 1-2% of all TIPS-procedures (4).

Endotipsitis can be grouped into 2 entities : early (< 3 months after insertion) and late primary (> 3 months after insertion) infection (5). An early primary infection with post-procedural bacteremia is often due to seeding at the time of insertion and related to the interventional procedure or during the initial hospital admission (skin contaminants) (9). Technical complications as portal vein-bile duct fistula or iatrogenic injury to bile ducts colonized with bacteria may also lead to early infection of the TIPS-stent (13). One series described self-limiting fever (lasting 3-5 days) after TIPS in 10% of the patients without any evidence of infection of the device. This phenomenon was considered secondary to translocation of microorganisms from the mesenteric portal circulation into the systemic blood circulation, which in fact makes it rather a post-procedural bacteraemia than an early primary infection (3).

Table I.

Reference	Number of patients	Age (Years)	Gender	Liver disease	Etiology	Diagnostic procedure	Treatment	Length of treatment	Outcome
Bouza 2004 (5)	3	50	♀	Alcoholic	MRSA	QBC	Vancomycin Fosfomycin Cotrimoxazole	6 w	Recovered (LT)
		69	♀	Cryptogenic	*E. faecalis*	Endothelial biopsy	Ampicilin	1 w / 6 w	Unrelated †
		60	♂	Cryptogenic	MRSA	QBC	Vancomycin linezolid Fosfomycin Teicoplanin	6 w	Recovered
Armstrong 2003 (6)	3	65	♀	HCV	*S. aureus*	Not reported	Vancomycin Teicoplanin	9 w	Related †
		66	♀	Alcoholic	*E. coli*	Not reported	Ticarcillin/Clavulanate Ciprofloxacin	16 w	Recovered
		55	♂	Alcoholic HBV	*P. aeruginosa*, *S. aureus*	Culture of TIPS + stenosis (US)	Ticarcillin/Clavulanate Gentamicin Amikacin	NR	Related †
DeSimone 2000 (9)	5	Median : 64 (Range : 51-70)	♂	Alcoholic	*E. faecalis*	Occluded stent	Vancomycin Gentamicin	2 w	Recovered
			♂	Sclerosing cholangitis	*Gemella morbillorum*	Not reported	Vancomycin	2 w	Recovered
			♂	Alcoholic HBV / HCV	*S. aureus*	Not reported	Vancomycin	5 d	Related †
			♂	Alcoholic HCV	*Lactobacilllus acidophilus*	Not reported	Ampicillin Gentamicin	6 w	Unrelated †
			♂	Alcoholic	*Lactobacilllus acidophilus*	Not reported	Ampicillin	4 w	Unrelated †
Eversman 1999 (10)	1	69	♀	Cryptogenic	*E. faecalis*	Thrombus (US)	Vancomycin	8 w	Recovered
Zaman 1999	1	62	♂	NR	*E. faecium* (Vancomycin resistant)	Partial occlusion TIPS (US)	Quinupristin/Dalfopristin Doxycycline Trovafloxacin	6 w / 4 w / 4 w	Recovered
Brown 1998 (7)	3	43	♂	Alcoholic HCV	*Enterococcus*	Thrombus (?)	Vancomycin Gentamicin	4 w	Related †
		57	♂	Alcoholic	*E. faecium*, *Citrobacter amalonaticus*	Thrombus (US)	Vancomycin Ceftriaxone Streptomycin	2 w / 5 w	Recovered
		66	♂	Alcoholic	*Enterococcus*	Thrombus	Vancomycin Ampicillin	2 w	Recovered
Darwin 1998	1	55	♂	Cryptogenic	*Torulopsis glabrata*	Culture of thrombus	Amphotericin B Flucytosine	26 d	Related †

Table I. — **Continued**

Reference	Number of patients	Age (Years)	Gender	Liver disease	Etiology	Diagnostic procedure	Treatment	Length of treatment	Outcome
Sanyal 1998 (13)	8	Mean : 45 ± 9	1 ♀, 7 ♂	Alcoholic	*S. sanguis*	Thrombus (US)	Penicillin	4 w	Recovered
				Alcoholic HCV	*E. coli, K. oxytoca*	Thrombus (US)	Ceftriaxone	4 w	Recovered
				Alcoholic	*E. coli*	Thrombus (US)	Ceftriaxone	4 w	Recovered
				Alcoholic HCV	*S. aureus*	Not reported	Vancomycin rifampin	6 w	Recovered
				Cryptogenic	*S. bovis*	Vegetation (US)	Vancomycin	6 w	Recovered
				Alcoholic HCV	*Acinobacter calcoaceticus, E. coli, C. albicans*	Thrombus (US)	Ceftriaxone Amphotericin Fluconazole	6 w Antifungals NR	Recovered
				Alcoholic	*K. pneumoniae*	Not reported	Ceftriaxone	4 w	Recovered
				HCV	*E. coli*	Vegetation (US)	Ceftriaxone	4 w	Recovered
Schiano 1997 (4)	1	66	♂	Alcoholic	*Torulopsis glabrata*	Culture of the TIPS thrombus	Fluconazole Flucytosine Amphotericin B	NR	Related †

NR : Not reported, HCV : Hepatitis C virus, HBV : Hepatitis B virus, QBC : Quantitative blood culture, US : Ultra sonography, w : weeks, d : days, † : died, LT : liver transplantation.

Late primary infections occur months or years after TIPS placement and are usually associated with a thrombosis of the TIPS-graft or with a recent revision or manipulation of the device (6,7,9,12,13). There are no data how these early primary or late primary infections affect the course or outcome of an infection, neither if the pathogenesis differs between the two groups.

The pathogenesis of endotipsitis is complex and is considered multi-factorial. Bacterial translocation and local factors, like thrombus formation or vegetations leading to further reduction in flow, may allow portal bacteremia with infection of the device. This condition is analogous to that of prosthetic valvular endocarditis but thrombus formation is not always necessary in case of endotipsitis (11). Many bacterial or fungal species can cause endotipsitis and most patients show polymicrobial infection. Gram-negative aerobes and Gram-positive *streptococci* of oral or enteric origin are the predominant organisms. *Enterobacteriaceae* are the most mentioned culprit organisms. This is not surprising since the gastrointestinal tract is the major source of bacteremia in cirrhotic patients which support the hypothesis that translocation might play a role in this entity (4,14). On the other hand, early re-epithelialization of the TIPS-stent after implantation is considered protective, similar to low infection rates documented in coronary stents (15,16).

The diagnosis should be suspected in patients with a TIPS-stent presenting with fever or relapsing episodes of bacteremia/sepsis with or without stent-dysfunction and in the absence of alternative foci of infection. As mentioned earlier, direct histological/microbiological sampling of the infected TIPS-stent represents the highest degree of certainty, the latter is only possible if the TIPS-stent is removed, by means of hepatectomy. For this reason, diagnostic criteria for endotipsitis were proposed by Sanyal and Reddy in 1998 (11), similar to those previously used for the diagnosis of endocarditis (14).

Endotipsitis is considered as a *definite* endovascular prosthetic-related infection when continuous and clinically significant (fever and multiple positive blood cultures) bacteremia is present with a vegetation and/or thrombi inside the TIPS. Doppler ultrasound can be helpful in this situation but the sensitivity and specificity are variable in different studies (17). A negative Doppler ultrasound can not exclude endotipsitis and clinical findings suggestive of TIPS dysfunction should always lead to revision of the TIPS. The low sensitivity of Doppler ultrasound challenges the value of radiological evidence of thrombosis or vegetations as a diagnostic criterion for 'definite' infection, as proposed by Sanyal and Reddy (11). In a retrospective study by Bouza *et al*. (4) thrombi or vegetations were observed by ultrasonography within the TIPS-graft in 16 of the 26 patients (61,5%). Conversely, the presence of a thrombus or vegetations does not imply infection until it is adequately supported by histopathological/microbiological evidence. A biopsy of the TIPS-covered endothelium is another technique which deserves further investigation but has the disadvantage that it remains technically difficult (12). Only in 2 of the 26 cases TIPS-stents were cultured ex vivo and led to the confirmation of infection (12).

An infection is considered *probable* when sustained bacteremia and unremitted fever is present in patients with an apparently normal TIPS without other potential sources of sustained bacteremia. "Sustained bacteremia" is defined as 2 blood cultures positive for the same organism, for samples obtained > 12 h apart, or 3 out of 3 blood cultures positive for the same organism (or the majority, if > 3 were performed), for samples each obtained > 1 h apart.

In this condition quantitative bacteriology can be helpful, as a substantial increase in the number of colony-forming units from hepatic venous blood compared to those in peripheral venous, and can provide important evidence of the stent as a source of infection. This technique was described by Bouza *et al*. in 2002 and has been already widely applied for the demonstration of other catheter related infections as in our case (4).

Treatment should always be individualized and depends strongly on the condition of the patient, the identification of the exact microbiological agent and its sensitivity to different antimicrobial agents. The limited experience due to small numbers of documented cases of endotipsitis, the heterogeneity of pathogens, their different sensitivity to certain agents and the variable clinical course does not allow formal recommendations about the duration of therapy. In currently available literature, it varies between 2 and 8 weeks (4,12,13). In general, broad-spectrum antibiotics (type imipenem, piperacillinetazobactam) can be empirically initiated until they can be switched to a more goal-directed therapy. Blood cultures should be performed some days after the initiation of antibiotics to ascertain efficacy of therapy.

When primary infection of the TIPS-graft can not be overcome, the patient should be considered for liver transplantation since hepatectomy (including the stent) is the only way to locally control the process. In our patient, prioritisation to transplantation was obtained by means of non-standard exception request based on similarity with patients with recurrent cholangitis in primary sclerosing cholangitis (5,9,12,15).

Remains the question of prophylaxis. Again, the absence of a true incidence of the infection makes it difficult to advise in recommendations with regard to prophylaxis in patients with TIPS undergoing revision of the TIPS. Some authors state that all patients who have a TIPS should receive prophylaxis, mainly to preclude the risk of immediate post-procedural bacteremia (3). The risk should be weighed against the possibility of resistance of the organism and the cost benefit remains to be explored (5). We recommend prophylaxis in high risk, technically complicated procedures, and in case of thrombosis of the stent.

In conclusion, this case-report reports the problem of endotipsitis, or primary infection of a TIPS-graft. It

represents, a little know and unexpected complication of TIPS-stents which should always be considered in case of unexplained and repetitive septicaemia in these patients.

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